Exhibit 102

Trichloroethylene, Perchloroethylene, Benzene, Vinyl Chloride, and *trans*-1,2-Dichloroethylene Exposure and Leukemia Risk

Prepared by



Julie E. Goodman, Ph.D., DABT, FACE, ATS

February 7, 2025

GRADIENT

www.gradientcorp.com
One Beacon Street, 17th Floor
Boston, MA 02108
617-395-5000

Table of Contents

Page

1 Overview 1
- 1.1 Camp Lejeune Studies 1
- 1.2 TCE 2
- 1.3 PCE 2
- 1.4 Benzene 3
- 1.5 Vinyl Chloride 4
- 1.6 *trans*-1,2-DCE 4
- 1.7 Agency Reviews 5
- 1.8 Conclusion 5

2 Credentials 7

3 Principles and Methodology 8
- 3.1 Epidemiology 8
  - 3.1.1 Risk Ratios 8
  - 3.1.2 Study Design 11
- 3.2 Toxicology 14
- 3.3 Individual Study Reviews 16
  - 3.3.1 Epidemiology Studies 17
  - 3.3.2 Toxicology Studies 22
    - 3.3.2.1 Animal Carcinogenicity Studies 22
    - 3.3.2.2 Mechanistic Studies 25
  - 3.3.3 Study Quality and Human Relevance Evaluation 26
- 3.4 Evidence Integration 27
- 3.5 Agency Reviews 29
  - 3.5.1 Overview 29
  - 3.5.2 ATSDR (2017a) Assessment 35
    - 3.5.2.1 Resources 35
    - 3.5.2.2 Statistical Significance 36
    - 3.5.2.3 Study Quality 36
    - 3.5.2.4 Strength of Evidence 37

4 Carcinogenicity 42
- 4.1 Overview 42
- 4.2 Leukemia 43

5 Camp Lejeune Studies 46
- 5.1 Study Overview 46

5.1.1 Study Populations 46
5.1.2 Exposure Assessment 47
5.1.3 Outcome Assessment 48
5.1.4 Covariates 49
5.1.5 Temporality 50
5.2 Study Results 50
5.2.1 Bove *et al*. (2014a) 50
5.2.1.1 Leukemia 50
5.2.2 Bove *et al*. (2014b) 50
5.2.2.1 Leukemia 51
5.2.2.2 ANLL 51
5.2.3 ATSDR (2018b) 51
5.2.3.1 Leukemia 51
5.2.4 Bove *et al*. (2024a) 52
5.2.4.1 Leukemia 52
5.2.4.2 ALL and CML 52
5.2.4.3 AML 53
5.2.5 Bove *et al*. (2024b) 53
5.2.5.1 Leukemia 53
5.2.5.2 ALL, AML, CML, and MDS 53
5.3 Toxicology 54
5.4 Exposure 54
5.5 Conclusions 55

6 TCE and Leukemia 56
6.1 Epidemiology 56
6.1.1 Overview 56
6.1.1.1 Study Population 56
6.1.1.2 Exposure Assessment 56
6.1.1.3 Outcome Assessment 57
6.1.1.4 Covariates Considered 57
6.1.1.5 Temporality 58
6.1.2 Study Results 58
6.1.2.1 Leukemia 58
6.1.2.3 Acute Myeloid Leukemia 58
6.1.2.4 Chronic Myeloid Leukemia 58
6.1.3 Meta-Analyses and Pooled Analysis 58
6.1.4 Conclusions 59
6.2 Toxicology 59
6.2.1 Animal Carcinogenicity Studies 59
6.2.2 Mechanistic Studies 60
6.3 Evidence Integration 61
6.4 Agency Reviews 61
6.4.1 ATSDR 62

6.4.2 NASEM 63
6.4.3 US EPA 63
6.4.4 IARC 64
6.4.5 NTP 65
6.4.6 Conclusions 65
6.5 Conclusions 65

7 PCE and Leukemia 67
7.1 Epidemiology 67
7.1.1 Overview 67
7.1.1.1 Study Population 67
7.1.1.2 Exposure Assessment 67
7.1.1.3 Outcome Assessment 68
7.1.1.4 Covariates Considered 68
7.1.1.5 Temporality 69
7.1.2 Study Results 69
7.1.2.1 Leukemia 69
7.1.2.2 Acute Lymphocytic Leukemia 70
7.1.2.3 Acute Myelogenous Leukemia/Acute Nonlymphocytic Leukemia 70
7.1.2.4 Chronic Myeloid Leukemia 70
7.1.3 Conclusions 70
7.2 Toxicology 71
7.2.1 Animal Carcinogenicity Studies 71
7.2.2 Mechanistic Studies 71
7.3 Evidence Integration 72
7.4 Agency Reviews 73
7.4.1 ATSDR 74
7.4.2 NASEM 74
7.4.3 US EPA 75
7.4.4 IARC 76
7.4.5 NTP 76
7.4.6 Conclusions 77
7.5 Conclusions 77

8 Benzene and Leukemia 78
8.1 Epidemiology 78
8.1.1 Overview 78
8.1.1.1 Study Population 79
8.1.1.2 Exposure Assessment 80
8.1.1.3 Outcome Assessment 81
8.1.1.4 Covariates Considered 81
8.1.1.5 Temporality 82
8.1.2 Results 82

8.1.2.1 Leukemia 82
8.1.2.2 Acute Lymphocytic Leukemia 86
8.1.2.3 Acute Myeloid Leukemia/Acute Nonlymphocytic Leukemia 87
8.1.2.4 Chronic Myeloid Leukemia 89
8.1.2.5 Myelodysplastic Syndrome 90
8.1.2.6 Other Leukemia Types 91
8.1.3 Pooled and Meta-Analyses 92
8.1.4 Latency 93
8.1.5 Conclusions 94
8.2 Toxicology 95
8.2.1 Animal Carcinogenicity Studies 95
8.2.2 Mechanistic Studies 96
8.3 Evidence Integration 96
8.4 Agency Reviews 97
8.4.1 ATSDR 98
8.4.2 NASEM 99
8.4.3 US EPA 100
8.4.4 IARC 100
8.4.5 NTP 101
8.4.6 Conclusions 101
8.5 Conclusions 101

9 Vinyl Chloride and Leukemia 103
9.1 Epidemiology 103
9.1.1 Overview 103
9.1.1.1 Study Population 103
9.1.1.2 Exposure Assessment 103
9.1.1.3 Outcome Assessment 104
9.1.1.4 Covariates Considered 104
9.1.1.5 Temporality 105
9.1.2 Study Results 105
9.1.2.1 Leukemia 105
9.1.2.2 AML 105
9.1.2.3 MDS 106
9.1.3 Meta-Analysis 106
9.1.4 Conclusions 106
9.2 Toxicology 106
9.2.1 Animal Carcinogenicity Studies 106
9.2.2 Mechanistic Studies 107
9.3 Evidence Integration 107
9.4 Agency Reviews 108
9.4.1 ATSDR 109
9.4.2 NASEM 109
9.4.3 US EPA 110

9.4.4 IARC 110
9.4.5 NTP 110
9.4.6 Conclusions 110
9.5 Conclusions 111

10 *trans*-1,2-DCE 112

11 Mixtures 113

12 Conclusions 115

References 117

Attachment A Literature Search Methods
Attachment B Camp Lejeune Epidemiology Studies
Attachment C Epidemiology Study Quality Assessment
Attachment D TCE Epidemiology Studies
Attachment E TCE Animal Carcinogenicity Studies
Attachment F PCE Epidemiology Studies
Attachment G PCE Animal Carcinogenicity Studies
Attachment H Benzene Epidemiology Studies
Attachment I Benzene Animal Carcinogenicity Studies
Attachment J Vinyl Chloride Epidemiology Studies
Attachment K Vinyl Chloride Animal Carcinogenicity Studies
Attachment L *Curriculum Vitae*
Attachment M Testimony Experience

List of Tables

Table 3.1	Risk Ratios
Table 3.2	Epidemiology Study Quality Evaluation Criteria
Table 3.3	Risk Factors for Leukemia, by Subtype
Table 3.4	Animal Carcinogenicity Study Quality Evaluation Criteria
Table 3.5	Bradford Hill Considerations
Table 3.6	Agency Cancer Classification Frameworks
Table 3.7	IARC Classification Framework for Evaluating the Strength of Human, Experimental Animal, and Mechanistic Evidence of Cancer (IARC, 2019)
Table 3.8	IOM (2008) and ATSDR (2017) Hierarchies of Evidence for Causation
Table 4.1	Descriptive Statistics of Leukemia and Some Subtypes
Table 6.1	Bradford Hill Assessment of TCE and Leukemia
Table 7.1	Bradford Hill Assessment of PCE and Leukemia
Table 8.1	Bradford Hill Assessment of Benzene and Leukemia
Table 9.1	Bradford Hill Assessment of Vinyl Chloride and Leukemia

Abbreviations

1,1,1-TCA	1,1,1-Trichloroethane
ACS	American Cancer Society
ALL	Acute Lymphocytic Leukemia
AML	Acute Myeloid Leukemia
AMML	Acute Myelocytic or Acute Monocytic Leukemia
ANLL	Acute Nonlymphocytic Leukemia
APL	Acute Promyelocytic Leukemia
ARRIVE	Animal Research: Reporting of *In Vivo* Experiments
ATS	Academy of Toxicological Sciences
ATSDR	Agency for Toxic Substances and Disease Registry
CI	Confidence Interval
CIR	Confidence Interval Ratio
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
CNLL	Chronic Nonlymphocytic Leukemia
COVID-19	Coronavirus Disease 2019
DCE	Dichloroethylene
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr Virus
ERR	Excess Relative Risk
FAB	French-American-British
GD	Gestational Day
GLP	Good Laboratory Practice
HR	Hazard Ratio
HTLV-1	Human T-Cell Lymphoma/Leukemia Virus-1
IARC	International Agency for Research on Cancer
IOM	Institute of Medicine
IRIS	Integrated Risk Information System
IRR	Incidence Rate Ratio
JEM	Job-Exposure Matrix
JISA	Japan Industrial Safety Association
KCC	Key Characteristics of Carcinogens
LNT	Linear No-Threshold
MDS	Myelodysplastic Syndrome
MDS-EB	Myelodysplastic Syndrome with Excess Blasts
MDS-MLD	Myelodysplastic Syndrome with Multi-lineage Dysplasia
MNCL	Mononuclear Cell Leukemia
MoA	Mode of Action
mOR	Meta-Odds Ratio
mRR	Meta-Relative Risk
MTD	Maximum Tolerated Dose
NAM	National Academy of Medicine
NASEM	National Academies of Sciences, Engineering, and Medicine

NCI	National Cancer Institute
NCI-CAPM	National Cancer Institute-Chinese Academy of Preventive Medicine
NDI	National Death Index
NHL	Non-Hodgkin Lymphoma
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OHAT	Office of Health Assessment and Translation
OR	Odds Ratio
PCE	Perchloroethylene
PMR	Proportionate Mortality Ratio
ppb	Parts per Billion
ppm	Parts per Million
PVC	Polyvinyl Chloride
RA	Refractory Anemia
RAEB	Refractory Anemia with Excess Blasts
RCMD	Refractory Cytopenia with Multilineage Dysplasia
RCUD	Refractory Cytopenia with Unilineage Dysplasia
RR	Relative Risk
SciRAP	Science in Risk Assessment and Policy
SIR	Standardized Incidence Ratio
SMHS	Shanghai Men's Health Study
SMR	Standardized Mortality Ratio
SRR	Standardized Risk Ratio
SRRE	Summary Relative Risk Estimate
SSA	Social Security Administration
SWHS	Shanghai Women's Health Study
TCA	Trichloroacetic Acid
TCE	Trichloroethylene
TVOC	Total Volatile Organic Compound
US	United States
US EPA	United States Environmental Protection Agency
USSR	United Soviet Socialist Republics
U-TCA	Urinary Trichloroacetic Acid
VHA	Veterans Health Administration
VOC	Volatile Organic Compound
WHO	World Health Organization

1 Overview

This report was prepared at the request of counsel for Defendants in *re: Camp Lejeune Water Litigation*, Case No.: 7:23-cv-897. The Plaintiffs claim that it is at least as likely as not that exposure to trichloroethylene (TCE), perchloroethylene (PCE), benzene, vinyl chloride, and *trans*-1,2-dichloroethylene (DCE) in water caused leukemia in individuals that worked or resided at Camp Lejeune.

I analyzed relevant epidemiology and toxicology literature to assess whether it supports a causal association between exposure to these chemicals and leukemia at Camp Lejeune or more generally. My opinions are based on a review of the published literature, including a substantial number of scientific and regulatory documents, as well as my training and experience in epidemiology, toxicology, and risk assessment.

Below, I provide an overview of my opinions regarding TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE exposure and leukemia risks at Camp Lejeune and more generally. My credentials are discussed in Section 2. After describing scientific principles and my methodology in Section 3, I provide an overview of carcinogenicity generally and leukemia specifically in Section 4. I review Camp Lejeune epidemiology studies in Section 5, and analyses of chemical-specific risks at Camp Lejeune again in subsequent sections to integrate them with the larger body of evidence on each specific chemical. Section 6 describes the epidemiology, toxicology, and mode-of-action (MoA) evidence regarding TCE and leukemia, and agency reviews of this evidence. I also evaluate the available evidence as a whole in the context of Bradford Hill's considerations. Similar information is provided in Sections 7, 8, and 9 for PCE, benzene, and vinyl chloride, respectively. In Section 10, I discuss available evidence for *trans*-1,2-DCE. I discuss mixtures toxicology in Section 11. My overall conclusions on all five chemicals and leukemia are presented in Section 12. Attachment A describes my literature search methods and Attachments B through K include tables with information on epidemiology and toxicity study quality, characteristics, and results. My *curriculum vitae* and testimony experience are provided in Attachments L and M, respectively.

1.1 Camp Lejeune Studies

Five studies evaluated leukemia risks among Marines and Navy personnel stationed at Camp Lejeune or civilian workers on base who may have been exposed to contaminated water. There was variation among studies with respect to the methods used to recruit or assemble the study populations, characterize exposures, and address confounding. Overall, there were no consistent associations reported between either working or living at Camp Lejeune or TCE, PCE, benzene, or vinyl chloride exposures on base and leukemia or any leukemia subtype. Although some studies reported a few statistically significant risk estimates, they were not consistent across analyses, and several were <1. These studies also had several methodological limitations, including a high likelihood of exposure misclassification and, as noted by the National Research Council (NRC) (2009), "limitations in population size, data availability, and data quality cannot be overcome." Overall, Camp Lejeune epidemiology studies do not demonstrate that being stationed or employed at Camp Lejeune or exposure to any individual chemical at Camp Lejeune, including benzene, was sufficient to cause leukemia in general or any subtype, including acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). There are no animal carcinogenicity or mechanistic studies of Camp Lejeune drinking water, but animal carcinogenicity and mechanistic studies, in general, do not provide evidence that exposures to TCE, PCE, or vinyl chloride can cause leukemia.

Because (1) Camp Lejeune epidemiology studies are not of high quality and most analyses do not provide evidence of associations; (2) animal and mechanistic studies do not provide evidence of causation in humans for TCE, PCE, or vinyl chloride; and (3) it has not been demonstrated that benzene exposures at Camp Lejeune were sufficient to cause AML or MDS, I conclude that the currently available evidence does not support a causal association between exposure to drinking water at Camp Lejeune generally or exposure to TCE, PCE, benzene, or vinyl chloride in drinking water at Camp Lejeune and leukemia.

1.2 TCE

TCE is a colorless, nonflammable, and volatile liquid. While there are a few circumstances in which TCE can occur naturally, it is most frequently manufactured for use as a solvent to remove greases, fats, tar, oils, and waxes and to make refrigerants, adhesives, paints, pesticides, lubricants, paint strippers, and varnishes for both industrial and commercial products. TCE has also been used by the textile processing and dry cleaning industries. Impurities of commercially manufactured TCE include both PCE and 1,1,1-trichloroethane (1,1,1-TCA).

Individuals can be exposed to TCE from contaminated air, water, food, and soil. TCE can enter the body *via* inhalation, ingestion, and dermal contact. TCE has been found in prepared food at concentrations between 2 and 100 parts per billion (ppb). When TCE enters the body and reaches the bloodstream, most of it is quickly exhaled from the lungs. When TCE reaches the liver from the bloodstream, it is metabolized into breakdown products that are mostly excreted in the urine within 1 day. While repeated or high exposures to TCE can result in its storage in fat, once exposure has ceased, TCE and its breakdown products are rapidly released from fat. The half-life of TCE in the body is less than 3 days.

Despite study limitations (particularly, a high likelihood of exposure misclassification, concurrent exposures to other chemicals, a lack of adjustment for potential confounders, and changes in leukemia classifications over time), most analyses do not provide evidence of associations between or exposure-response trends for TCE and leukemia, or acute lymphocytic leukemia (ALL), AML, or chronic myeloid leukemia (CML), in cohort or case-control studies. Animal evidence does not indicate that TCE can cause leukemia, and there is no proposed MoA with sufficient scientific support.

Because the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, and animal and mechanistic studies do not provide evidence of causation in humans, I conclude that, as a whole, the currently available evidence does not support a causal association between TCE exposure and leukemia.

1.3 PCE

PCE, also known as PERC, perchloroethylene, or tetrachloroethylene, is a colorless, nonflammable, and volatile liquid. While it can occur naturally, PCE is most frequently manufactured for use as a solvent in the dry cleaning, textile, automotive, and metal industries. It is used to remove grease and oil, repel water, and finish fabric; to manufacture other chemicals; and as an ingredient in some consumer products, including adhesives, degreasers, cleaners, lubricants, sealants, and polishes. PCE can degrade in the environment to TCE, and TCE may be present as a contaminant in products containing PCE.

Individuals can be exposed to PCE from contaminated air, water, food, and soil. PCE is one of the most commonly detected chemicals in indoor environments, due to its use in consumer products, building materials, and dry-cleaning products; its presence in drinking water; and its ability to vaporize. PCE can be absorbed into the body after inhalation, ingestion, or dermal contact. PCE is quickly absorbed into the

bloodstream, and is quickly excreted *via* exhalation. PCE that is not quickly exhaled can be metabolized to breakdown products and excreted in the urine. PCE has an affinity for fat and can distribute to multiple organs, including the liver, kidney, brain, lung, and heart. The half-life of PCE in the body is about 3 days.

Despite study limitations, (particularly, a high likelihood of exposure misclassification, concurrent exposures to other chemicals, a lack of adjustment for potential confounders, and changes in leukemia classifications over time), most analyses do not provide evidence of associations between or exposure-response trends for PCE and leukemia or leukemia subtypes in cohort or case-control studies. Animal evidence does not indicate that PCE can cause leukemia in humans, and there is no proposed MoA with sufficient scientific support.

Because the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, and animal and mechanistic studies do not provide evidence of causation in humans, I conclude that, as a whole, the currently available evidence does not support a causal association between PCE exposure and leukemia.

1.4 Benzene

At room temperature, benzene is a colorless, transparent liquid with a sweet odor. In the natural environment, benzene is emitted from volcanoes and forest fires, and is present in crude oil. Benzene has been widely used in various industrial processes and as an additive to unleaded gasoline. Common anthropogenic sources of benzene exposure include tobacco smoke, automobile service stations, exhaust from motor vehicles, and industrial emissions. Automobile exhaust is the largest source of benzene in the environment. Benzene in indoor air is primarily associated with cigarette smoke. Because of its high volatility, benzene exposure mainly occurs *via* inhalation in the general population and in occupational settings.

Several high-quality occupational epidemiology studies reported that increasing cumulative benzene exposure concentrations were associated with AML and MDS, and the associations were statistically significant in meta-analyses. Most analyses do not provide evidence of associations for ALL and CML and, with few exceptions, all benzene epidemiology studies had methodological limitations, particularly with respect to exposure assessment and changes in leukemia classifications over time. Animal bioassays showed that benzene caused many types of tumors, but not leukemia. Although benzene is considered genotoxic, mechanistic evidence suggests it is not a direct-acting deoxyribonucleic acid (DNA) mutagen, but rather indirectly induces genotoxicity through a threshold-mediated MoA in which exposures below the threshold do not result in genetic toxicity. I conclude that the scientific evidence supports a causal association between benzene and AML at cumulative exposures of at least 40 to 75 ppm-years. The evidence is strongest for exposures occurring within 10 to 15 years of diagnosis. Evidence also supports an association between benzene exposure and MDS. The evidence does not indicate that benzene is associated with ALL or CML.

Because the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, and animal and mechanistic studies do not provide evidence of causation in humans, I conclude that, as a whole, the currently available evidence does not support a causal association between benzene exposure and ALL or CML. In contrast, the currently available evidence indicates that at sufficient exposures, benzene can cause AML and MDS in humans, but it has not been demonstrated that benzene exposures at Camp Lejeune were sufficient to cause AML or MDS.

1.5 Vinyl Chloride

Vinyl chloride is a colorless, flammable gas with a mild, sweet odor that is unstable at high temperatures. It does not occur naturally. It can be formed when TCE, PCE, or trichloroethane break down in the environment. It is used almost exclusively to make polyvinyl chloride (PVC), which is used to make plastic products like pipes, wire and cable coatings, and packaging materials.

Small amounts of vinyl chloride can dissolve in water. Vinyl chloride in water or soil near the surface can evaporate, while vinyl chloride in air breaks down in a few days. Individuals can be exposed to vinyl chloride in air from cigarette and cigar smoke or near plastic manufacturing facilities, hazardous waste sites, and landfills. They can also be exposed to very low levels of vinyl chloride in drinking water. Workers can be exposed by breathing vinyl chloride in air or from contact with skin or eyes in the workplace.

Despite study limitations, the epidemiology evidence does not support an association between vinyl chloride and leukemia, as studies did not consistently report associations, and there were no reported dose-response relationships. Treatment-related leukemias were not reported in any chronic vinyl chloride bioassays, and there are no proposed MoAs with scientific support.

Because the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, and animal and mechanistic studies do not provide evidence of causation in humans, I conclude that, as a whole, the currently available evidence does not support a causal association between vinyl chloride exposure and leukemia.

1.6 *trans*-1,2-DCE

DCE exists as 1,1-DCE and 1,2-DCE. *trans*-1,2-DCE was detected as a breakdown product of TCE in drinking water at Camp Lejeune. *trans*-1,2-DCE is a low molecular weight, volatile, halogenated liquid that is commonly used as a chemical intermediate or an industrial solvent. Most *trans*-1,2-DCE exposures are from anthropogenic sources. Specific industrial uses of *trans*-1,2-DCE include cleaning and degreasing, surface treatment, adhesion, spot cleaning, stain removal, and lubrication (US EPA, 2020a). Occupational exposure to *trans*-1,2-DCE most commonly occurs *via* inhalation or dermally, while the general population is exposed *via* inhalation or ingestion. The currently available scientific evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE and leukemia.

1.7 Agency Reviews

Chemical carcinogenicity is evaluated by government and scientific agencies, including Agency for Toxic Substances and Disease Registry (ATSDR); the National Academies of Sciences, Engineering, and Medicine (NASEM); the United States Environmental Protection Agency (US EPA); the International Agency for Research on Cancer (IARC); and the National Toxicology Program (NTP). Despite the goal of being systematic and objective, all of their reviews involve some degree of subjectivity. In many instances, their reviews do not fully take study quality into account and therefore conclude that the strength of the evidence is stronger than it truly is. The IARC, US EPA, and NTP carcinogenicity categories all include "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding).

The review process for the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" (ATSDR, 2017a) has even more methodological issues than other reviews conducted by ATSDR and other agencies. ATSDR (2017a) did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation. Its conclusions regarding causation for many health outcomes are inconsistent with those of several other agency reviews, including other reviews by ATSDR.

Government and scientific agency reviews either concluded that the scientific evidence is insufficient to make a determination regarding TCE and PCE exposure and leukemia causation or did not draw conclusions. Most concluded that the scientific evidence is insufficient or does not support an association between vinyl chloride and leukemia; others did not address leukemia in relation to vinyl chloride. ATSDR (2023) stated, "No studies evaluating potential carcinogenic effects of inhalation, oral, or dermal exposure of laboratory animals to trans-1,2-dichloroethene…were located."

Government and scientific agency reviews consistently concluded that evidence supports a causal association between benzene and AML. The Institute of Medicine (IOM) (2003) and NRC (2009) concluded there is limited evidence for other leukemia subtypes; only ATSDR (2017a) – but not ATSDR (2024a) – concluded there is equipoise or above evidence of causation for all leukemia subtypes, including ALL, AML, and CML.

1.8 Conclusion

I conclude that epidemiology evidence supports an association between benzene exposure and AML and MDS at cumulative exposures greater than 40 to 75 parts per million (ppm)-years. The evidence for this association is strongest for exposures occurring within 10 to 15 years of diagnosis. I am not aware of any evidence demonstrating that exposures to benzene at Camp Lejeune were sufficient to cause AML or MDS.

I did not identify any epidemiology studies of *trans*-1,2-DCE and leukemia. Many of the epidemiology studies that I reviewed are not of high quality and, apart from benzene exposure and AML and MDS, most analyses did not provide evidence of associations with leukemia or leukemia subtypes. Animal and mechanistic studies do not provide evidence of causation, and evidence for *trans*-1,2-DCE is extremely limited. The evidence does not support a causal association between benzene exposure and ALL or CML, or between TCE, PCE, vinyl chloride, or *trans*-1,2-DCE exposure and leukemia or leukemia subtypes.

Based on the currently available evidence, I conclude, to a reasonable degree of scientific certainty, that TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE in Camp Lejeune drinking water did not cause leukemia.

2 Credentials

I am an epidemiologist and board-certified toxicologist with expertise in human health risk assessment. I am a fellow of both the American College of Epidemiology and the Academy of Toxicological Sciences (ATS), and I am currently on the Board of Directors of ATS. I am a Principal at Gradient, an environmental and risk sciences consulting firm. From 2009 to 2017, I was an adjunct faculty member in the Department of Epidemiology at the Harvard T.H. Chan School of Public Health.

I received an S.B. degree in environmental engineering science from the Massachusetts Institute of Technology in 1996. I received an Sc.M. in epidemiology and a Ph.D. in environmental health sciences/toxicology from the Johns Hopkins Bloomberg School of Public Health in 2000 and 2002, respectively. From 2002 to 2004, I was a Cancer Prevention Fellow at the National Cancer Institute (NCI), where I conducted several molecular epidemiology studies on colon, breast, and prostate cancers and was instrumental in the development of "Polymorphism Interaction Analysis," a statistical tool for cancer risk assessment. In 2004, I joined Gradient. My consulting practice consists of evaluating toxicity, epidemiology, and exposure data in the context of evaluating human health risks from substances in consumer products, pharmaceuticals, and medical devices, as well as from occupational and environmental exposures.

Based on my experience and expertise, I work with several organizations on issues relating to toxicology, epidemiology, risk assessment, and public health. Since 2008, I have served as an elected member of the Board of Health in Canton, Massachusetts, the community in which I reside. In this capacity, I provide advice on a broad range of public health topics, from the evaluation of chemical risks to the prevention of coronavirus disease 2019 (COVID-19). I am also a member of the Massachusetts Medical Reserve Corps and the Massachusetts Environmental Justice Assistance Network. In May 2012, I served as a panelist at a US EPA meeting that addressed how MoA evidence should be used in assessments of exposures to and health effects caused by chemical mixtures. In 2013, I served as an expert external peer reviewer for US EPA's "Provisional Peer-Reviewed Toxicity Values for Styrene-Acrylonitrile (SAN Trimer)" report. In 2014, I served as a reviewer for research grants submitted to the National Science Foundation, the California Breast Cancer Research Program, and the John Templeton Foundation. In 2016, I served as a reviewer for a K99 research grant submitted to the National Institute for Occupational Safety and Health. In 2017 and 2018, I served as a reviewer for several R21 research grants submitted to the National Institutes of Health.

I have been active in the Society of Toxicology for many years; I was previously the treasurer/secretary of the Risk Assessment Specialty Section and an elected member of the Nominating Committee. I am also active in the American College of Epidemiology, for which I served on the Board of Directors, and the Society for Risk Analysis. I taught "Research Synthesis and Meta-Analysis," a graduate-level course at the Harvard T.H. Chan School of Public Health. As reflected in my *curriculum vitae* (Attachment L), I have authored over 150 original peer-reviewed research articles, review articles (including systematic reviews, meta-analyses, and weight-of-evidence evaluations), and book chapters on a wide variety of chemicals, including TCE, PCE, and benzene, and health outcomes in peer-reviewed journals, books, and meeting proceedings. I was on the editorial boards of *Carcinogenesis* and *The Open Biomarkers Journal* and was a managing editor of the *Journal of Environmental Protection Science*. I have been a peer reviewer for more than 35 journals.

3 Principles and Methodology

I analyzed relevant epidemiology and toxicology literature, as well as agency reviews of this literature, to assess whether it supports a causal association between TCE, PCE, benzene, vinyl chloride, or *trans*-1,2-DCE exposure and leukemia or MDS. To conduct my analysis, I considered a number of well-established epidemiology and toxicology principles. These principles are described in this section, followed by a detailed discussion of my methodology, which includes a review of individual study quality and results, as well an integration of study findings in the context of the Bradford Hill considerations (Hill, 1965; Garabrant, 2000).

3.1 Epidemiology

Epidemiology is the study of the causes, distribution, and control of disease in human populations (Lash *et al*., 2021). In epidemiology studies, both exposures and outcomes are measured or estimated, and statistical analyses are conducted to assess whether there are associations (*i.e.*, correlations) between the two. Unlike experimental animal studies, epidemiology studies involve exposure conditions relevant to humans. However, they sometimes involve very high exposures (*e.g.*, in an occupational setting) that produce effects that would not be expected to occur at lower exposures (*e.g.*, in the general population). Because these studies involve people living in the real world, study participants often have other exposures or attributes that make it difficult to determine whether an association is specific to the exposure of interest, and each epidemiology study can have other limitations that can affect the interpretation of its results. As such, associations in epidemiology studies do not always indicate causation, as they could be a result of chance, bias, or confounding.[1]

3.1.1 Risk Ratios

Epidemiology studies typically present risk ratios (often called risk estimates), including odds ratios (ORs), relative risks (RRs), standardized incidence ratios (SIRs), standardized mortality ratios (SMRs), hazard ratios (HRs), or incidence rate ratios (IRRs), depending on the study design. All are measurements or estimates of the rate of disease (*e.g.*, cancer) in people with an exposure of interest compared to the rate in unexposed people, as shown in the equation below:

$$\text{Risk Ratio} = \frac{\text{Rate of Disease in Exposed}}{\text{Rate of Disease in Unexposed}}$$

Definitions of these risk estimates are shown in Table 3.1.

[1] A confounder is associated with an exposure, but is not caused by that exposure, and can cause the disease of interest. Confounding bias can occur when a confounder is not fully accounted for in an analysis. For example, smoking is associated with alcohol consumption and can cause lung cancer. One might find an association between alcohol consumption and lung cancer because people who drink more alcohol smoke more, and not because drinking alcohol causes cancer.

Table 3.1 Risk Ratios

Risk Estimate	Definition
IRR	The ratio of the incidence rate of disease in the exposed group to the incidence rate of disease in the non-exposed group.
HR	A measure of how often a particular event happens in one group compared to how often it happens in another group, over time.
OR	The odds of disease in the exposed group divided by the odds of disease in the non-exposed group.
RR	The ratio of the risk in the exposed group to the risk of disease in the non-exposed group.
SIR	The number of people with a disease in a given population compared to what is "expected" based on the number of people with that disease in a reference population.
SMR	The number of people who die of a disease in a given population compared to what is "expected" based on the number of deaths due to that disease in a reference population.

Notes:
HR = Hazard Ratio; IRR = Incidence Rate Ratio; OR = Odds Ratio; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio.
Source: Lash *et al.* (2021).

If the rate of disease is the same in both exposed and unexposed people, then the risk ratio is 1, and there is no association between the exposure and disease. A risk ratio greater than 1 indicates there may be an increased risk for disease and a value below 1 indicates that those who are exposed have a lower risk for disease compared to those who are unexposed.[2]

A sample risk ratio on its own does not provide statistically meaningful evidence for the existence of an association between an exposure and a disease in the population. This is because, in a particular population of interest, a randomly selected study sample might not be representative of the population as a whole by chance, so the estimated risk ratio in the sample would not be representative of the true risk ratio in the population (Lash *et al.*, 2021; Ahlbom, 1993). This would also be true if a sample was selected in a biased manner.

In epidemiology studies, a confidence interval (CI; typically, 95%) is often presented for the estimated measure of association (*e.g.*, risk ratio) to reflect uncertainties in the estimation due to random error. A 95% CI is derived to indicate a range of the sample risk ratio that has a 95% probability of capturing the true population risk ratio (Lash *et al.*, 2021; Ahlbom, 1993). If a sample risk ratio's 95% CI does not contain 1, there is a 95% probability that the underlying population's risk ratio is different from 1, indicating that we can reasonably exclude chance as an explanation for the observed association (Naimi and Whitcomb, 2020). In contrast, if a sample risk ratio's 95% CI contains 1, one cannot confidently exclude the possibility that the underlying population's risk ratio is 1 (*i.e.*, there is no association) (Naimi and Whitcomb, 2020).

As noted by Savitz *et al.* (2024), "A correctly interpreted CI provides information about both the magnitude and precision of effects, indicating a range of possible parameter values that are statistically compatible with the data." This is because a CI reflects both the sample size of a study and the heterogeneity of the sample as reflected by the standard deviation or standard error of the effect being measured. The CI gives you some indication of the likelihood of the risk estimate being within a certain range with an acceptable amount of error (*e.g.*, a 95% CI reflects a willingness to be incorrect 5% of the time) (Lash *et al.* 2021).

The CI is not meaningful if it is based on a sample of the population that is not representative of the underlying population due to bias. The estimated risk from a biased or unrepresentative sample may not reflect the true risk in the underlying population and, while increasing the sample size of a study may result

[2] SIRs are typically reported as a percentage (%) but are often converted to a value based on "1," similar to an RR or an OR (*e.g.*, 100% = 1).

in increased precision, it may not reflect an increase in precision around the true effect estimate. That is, if the sample is biased or not representative of the underlying population, risk estimates for the population could be different, and may even occur outside of the original CI.

This is reflected in a relatively recent US EPA (2019) review, which stated:

> We recognized that results that failed to attain statistical significance may still indicate clinical, biological, and/or public health importance and may warrant further exploration (US EPA, 2016). We particularly noted in this review observed associations with large effects sizes (*e.g.*, OR ≥ ~ 2.5) even in the absence of significance, perhaps indicating a smaller than optimal sample size or the potential for biases. Conversely, we also recognized that statistical significance does not necessarily imply clinical or biological importance, particularly with larger than necessary sample sizes and other study elements that influence the reliability of estimated effects.

Another metric that is often reported in epidemiology studies is the *p* value, which is the probability of obtaining the observed test results, or more extreme results, assuming that the null hypothesis (*i.e.*, the supposition that there is no relationship between groups being measured) is correct (Lash *et al*., 2021; Ahlbom, 1993). A *p* value less than 0.05 is often considered statistically significant (StatsDirect Ltd., 2020). If a *p* value is less than 0.05, there is less than a 5% chance a study would have found an association between an exposure or other potential risk factor and a health outcome if they were truly unrelated, assuming the study is free from bias and confounding. However, similar to a 95% CI, the *p* value cannot address whether an association is causal (Lash *et al*., 2021).

Both the 95% CI and the *p* value are a function of sample size. That is, in some cases, a true association in a population will not be statistically significant (*e.g.*, the 95% CI includes 1 or the *p* value is ≥ 0.05) because the sample is too small to detect it. For this reason, one cannot conclude with certainty that there is no association if a result is not statistically significant, only that the study does not provide evidence that there is an association. Conversely, a statistically significant result in a large sample may not reflect a true or clinically relevant difference at the population level (Lash *et al*., 2021). As noted by Stang and Rothman (2011), "No study is completely free of systematic error; thus, as confidence intervals shrink with increasing study size, they shrink around a value that is incorrect because of the systematic error. Consequently, as study size increases, confidence intervals become less likely to contain the truth, and *P*-values become small but irrelevant because they contain little information about where the truth lies." I also note that, while both the *p* value and CI provide information on statistical significance, CIs provide more information on the precision of the estimate based on their widths (American Statistical Association, 2016).

Finally, Savitz *et al*. (2024) said, "Dichotomizing findings into 'significant' and 'not significant' reduces information, obscures biases, and often leads to misinterpreting strong associations as null and nearly identical results as conflicting." Savitz *et al*. (2024) instead suggest that one should always consider the full range of the CI, and if this range encompasses values below and above 1, one should conclude that it may support no association, a small association, or an increased risk depending on how wide this range is. Savitz *et al*. (2024) were, therefore, not opposed to testing statistical significance, but concluded that one should also consider the precision of effect estimates when interpreting results.

In this report, I consider not only statistical significance, but also the CI to get a sense of precision, and whether results are likely influenced by chance or bias, to determine how likely it is that there is an association in the population.

3.1.2 Study Design

There are several types of observational epidemiology study designs.[3] All epidemiology studies are likely subject to exposure and outcome misclassification, confounding, and bias to varying degrees. In some cases, the study limitations can be overcome with the study design (*e.g.*, matching in a case-control study to address confounding, or relying on medically confirmed disease outcomes instead of self-reported outcomes) or by using certain statistical methods (*e.g.*, adjusting for confounding). In other cases, study limitations cannot be overcome, and one must take them into account when interpreting a study's results. Below, I discuss some of the major strengths and limitations of several observational epidemiology study designs.

Cohort Studies

In prospective cohort studies, a cohort, or group of individuals who share a common characteristic (*e.g.*, birth year, place of residence, occupation) but are heterogeneous with regard to one or more exposures, is identified and detailed information on cohort members' exposures of interest and other factors (*e.g.*, demographic factors, lifestyle factors, medical history, and health conditions) is obtained at enrollment. The cohort is then followed over time, and disease outcomes, and sometimes changes in exposure and other factors, are documented (Lash *et al*., 2021). Disease risks, incidence rates, or the time to disease occurrence in exposed and nonexposed individuals are then compared.

Prospective cohort studies are often considered to have the most robust observational epidemiology study design. In these studies, exposures of interest and characteristics of the cohort members are assessed at baseline and sometimes also during follow-up, before the occurrence of any disease. This prospective feature of exposure assessment protects risk factor data from recall bias (discussed below), which can occur in case-control studies. Extensive information on known or suspected risk factors for diseases of interest is often available for well-characterized cohorts, so the results generated from studies of these cohorts can be less biased when multiple potential confounders are considered in the statistical analysis, compared to case-control studies. However, unmeasured and residual confounding cannot be ruled out completely in any observational study. Although it is possible that people who choose to participate in a cohort study do not accurately reflect the population about which inferences are being made (which can bias the study's results), selection bias is less of a concern when a prospective cohort is assembled because a person's future disease status is unknown and thus cannot influence whether they participate in the study. In contrast, during the follow-up period, there can be issues related to the attrition of study participants (*i.e.*, loss to follow-up). If the loss to follow-up is related to either an exposure or the disease of interest, it can result in biased risk estimates. In addition, changes over time in exposures or other potential risk factors and in how diseases are defined or measured can impact the results of cohort studies (Gordis, 2014).

Retrospective cohort studies are generally conceived after a group of individuals have developed the disease of interest. In these studies, the investigators identify a point in time before these individuals developed the disease and assess their exposures at that point in time (or at several points in time), often by relying on historical records. Compared to prospective cohort studies, retrospective cohort studies are more prone to confounding because information on important risk factors for the disease of interest (*e.g.*, other chemical exposures) is often not available. Retrospective studies may also be prone to selection bias because participants are recruited after their exposure and disease status are known, and individuals' knowledge about their exposures and disease status may influence whether they participate (Gordis, 2014).

[3] In observational studies, the researchers observe the effects associated with an exposure, treatment, intervention, or other factor, but do not choose who is or is not exposed/treated. In contrast, in clinical and community trials, the researchers introduce a treatment or intervention and study associated effects (Gordis, 2014).

Case-Control Studies

In case-control studies, individuals with (cases) and without (controls) a specific disease are identified, and then each person's past exposures to a substance or substances of interest are measured or estimated (Paneth *et al.*, 2002). The control group is used to estimate the distribution of exposure in the source population that gives rise to the cases. Comparing the exposure distribution in the cases to that in the controls yields direct estimates of RR measures, such as ORs.

All case-control studies can suffer from bias, including selection and recall bias. Recall bias is a type of exposure misclassification error that occurs when study participants' ability to accurately recall past exposure is associated with their disease status (Sackett, 1979; Lash *et al.*, 2009, 2021). In other words, diseased and non-diseased individuals may remember past exposures and events differently, leading to inaccurate estimates of associations between the exposure and the disease. Recall bias is not an issue in studies that use information that was collected before the disease diagnosis (*e.g.*, from medical or occupational records). Selection bias occurs when an individual's probability of being included in a study is associated with exposure or disease status (Sackett, 1979; Lash *et al.*, 2009). In a case-control study, selection bias can occur when investigators do not use the same criteria to select cases and controls, and when the criteria used are related to exposure status. Case-control studies are also vulnerable to selection bias related to nonresponse, when the decision to participate in a study is related to the case status and exposure experience, especially if the research hypothesis is known to the subjects. Case-control studies may also be subject to survivor bias if cases who have been cured or have died are excluded from the study.

Nested case-control studies and case-cohort studies are studies that are conducted within an established and often well-characterized cohort. In these studies, study participants are selected from the population of a larger cohort study, in which exposure information was collected prior to disease development. In a nested case-control study, controls are matched to cases based on follow-up time. In a case-cohort study, a sample of the total cohort is selected to be controls at baseline; however, these individuals may become cases during follow-up. Because the cases and controls are selected from the same source cohort in both nested case-control and case-cohort studies, the likelihood of selection bias is greatly diminished in studies using these designs compared to studies using the traditional case-control design (Lash *et al.*, 2021). A unique advantage of nested case-control and case-cohort study designs is that the same subcohort can serve as a control population for different sets of cases (Lash *et al.*, 2021).

Cross-Sectional Studies

In cross-sectional studies, individuals' exposure and disease status are ascertained at one point in time or over a short, defined period (Lash *et al.*, 2021). In these studies, the prevalence of disease among exposed individuals is compared to the prevalence of disease among unexposed individuals. Although many exposures and diseases can be ascertained in a cross-sectional study, it cannot be known whether an exposure is causal, because exposure during the study period may differ from exposure prior to onset of the disease. Also, because one is studying prevalent cases (the current number of people with the condition) and not incident cases (the number of new cases with the condition who will be diagnosed over a given period), individuals who were cured or died prior to the study are not included, which could affect the study's results; this is known as survivor bias. Cross-sectional studies may also be subject to selection bias if those who participate in a study differ from those who do not.

Ecological Studies

Ecological studies examine aggregates of individuals defined by units (*e.g.*, geographic region, workplace) and assess whether the overall occurrence of disease in a population correlates with the overall occurrence

of exposure (Webster, 2007). There are no individual-level data in an ecological study, so it is not possible to know which specific individuals are exposed and which individuals have a disease. Thus, it is not possible to draw conclusions with certainty regarding whether exposure is a causal factor for the disease based on the results of these studies, and group-based associations between exposure and disease outcomes may not apply to individuals.

Semi-ecological or semi-individual studies assess outcomes, and sometimes covariates, at the individual level, but exposures are aggregated, so these studies also cannot provide evidence with respect to causation (Künzli and Tager, 1997). For example, some Camp Lejeune studies (*e.g.*, Bove *et al*., 2024a,b) and analyses are semi-ecological in that the exposure is aggregated (*i.e.*, employed or stationed at Camp Lejeune) while the outcomes are specific to each individual.

Case Reports and Case Series

Case reports usually contain detailed information about individual patients. A case series is a group or series of case reports of individuals who had a similar health outcome or were given a similar treatment (Hennekens and Buring, 1987). Because there are no individuals without the outcome to consider for comparison in these studies, it is usually not possible to determine whether a particular exposure or treatment was a causal factor of the individuals' health outcomes.

Proportionate Mortality Studies

Proportionate mortality studies estimate the association between exposures to a chemical and a specific cause of death by comparing the proportion of deaths due to a specific cause in a group of individuals (*e.g.*, with a particular exposure) to the proportion in a comparison group in a proportionate mortality ratio (PMR) (Lash *et al*., 2021). These studies are often used to investigate the association between occupations and causes of death in large populations, and as such can be useful for rare diseases. However, these studies have significant methodological limitations (*e.g.*, the inability to determine whether an exposure is associated with an increase in a specific cause of death or a reduction of other causes of death; misclassification of the exposure or the cause of death). These studies cannot ascertain whether the exposure was a causal factor in the development of a fatal disease, and their results can be skewed based on other causes of death.

Pooled Analyses

A pooled analysis is a statistical analysis of individual data from primary studies (Blettner *et al*., 1999). A pooled analysis is often conducted to reconcile previous studies or may be prospectively planned, as part of the study protocol, to standardize data collection among several studies. With pooled analyses, new hypotheses may be examined, or different subgroups may be assessed, with the added sample size. Pooled analyses require that the original data characteristics be defined or planned prior to the evaluation. If similar data and models are available, heterogeneity among study populations, protocols, or results in a pooled analysis can be low. However, if heterogeneity within or among study populations, protocols, or results is high, pooled estimates may be difficult to interpret and are not appropriate to present (Blettner *et al*., 1999).

Systematic Reviews and Meta-Analyses

A systematic review evaluates a body of evidence using a systematic, reproducible, transparent approach that includes a research question, a search strategy, study inclusion and exclusion criteria, study screening methods, an evaluation of study quality, and information about data analysis and synthesis (Krnic Martinic *et al*., 2019). A meta-analysis is a type of systematic review that involves a statistical analysis of the results

of multiple independent studies, and generally aims to produce a single effect estimate (Egger *et al.*, 2001). Meta-analysis results are obtained in a two-stage process: first, a relevant summary statistic is obtained from each study; next, a weighted average is calculated. Study weights are chosen to reflect the amount of information each study contains. The number of subjects, risk of bias, and adjustment for confounders are often, but not always, considered in the assignment of weight. By statistically pooling the results from multiple studies, meta-analyses may allow for the detection of modest effects that were not observed in individual studies because of a lack of statistical power. They may also allow for the exclusion of small effects.

One issue with meta-analyses is that they may result in "over-conclusiveness," or the appearance that results are more precise and conclusive than they actually are (Lash *et al*., 2021). Also, because meta-analysis methods cannot correct the biases in the underlying study-specific results, these biases carry over to the meta-analysis results. When pooling studies with similar biases, individual study CIs and *p* values "tighten" to yield even stronger pooled values, resulting in this over-conclusiveness.

In addition, all systematic reviews and meta-analyses are subject to potential publication bias. Publication bias results when published research does not reflect the overall body of completed research studies. Typically, this occurs because journal editors are more likely to publish positive findings than null findings. As a result, the research literature becomes enriched in studies that report statistically significant results. Underrepresentation of null findings can bias the results of a systematic review or meta-analysis away from the null. One must carefully consider the issue of nonrandom sources of uncertainty when interpreting the results of systematic reviews and meta-analyses (Lash *et al*., 2021).

3.2 Toxicology

Toxicology is the study of the potentially adverse health effects of chemicals on living organisms (Hayes and Kobets, 2023). It encompasses studies of humans, laboratory animals, isolated cells, and isolated molecules, including MoA studies that assess how these chemicals may cause observed effects. An understanding of toxicology is necessary for determining how much of a chemical one can be exposed to, and under what conditions, without the likelihood of harm. In addition to an exposure assessment (*i.e.*, whether an individual had any contact with a chemical and, if so, to what degree and under what conditions, as discussed below), a determination of dose (the amount of a chemical taken into the body over time) is a key component of evaluating health effects from chemicals. Factors that may influence the toxicity of a chemical in individuals include genetic background, sex, age, health status, behavioral traits (*e.g.*, smoking and alcohol use), diet, and nutritional status (Aleksunes and Eaton, 2019).

The evaluation of the relationship between exposure to a chemical and health effects is referred to as a dose-response assessment. Although virtually every chemical can produce toxic (or adverse) effects at some dose, the range of doses necessary to produce adverse effects, injury, or death varies widely among chemicals (Aleksunes and Eaton, 2019; Faustman, 2019). The body has many biochemical and physiological processes that allow it to counteract a chemical's adverse effects, and most chemicals do not cause adverse effects unless the dose is sufficient to overwhelm the body's normal processes for a certain period of time. In other words, there is a threshold dose of most chemicals below which there is no evidence of adverse health effects (Clewell *et al*., 2019).[4]

The nature and severity of effects from a chemical can also vary with dose, and some chemicals that provide beneficial effects at low doses cause toxic effects at high doses. Aspirin, for example, provides pain relief

[4] In some cases, a threshold cannot be identified in scientific studies. The fact that a threshold cannot be identified does not mean that one does not exist.

at or below the recommended dose of two tablets per day, but increasingly higher doses of aspirin may cause adverse effects ranging from fever and acidosis to convulsions and respiratory failure (Ellenhorn and Barceloux, 1988; Grosser *et al*., 2011).

The frequency and duration of exposure to a chemical are also critical factors for determining its toxicity, and the adverse effects of a chemical can differ depending on whether exposure is to a single, large dose (acute exposure) or to lower doses over a long period of time (chronic exposure). For example, in the case of ethyl alcohol, acute exposure to a single dose can cause severe adverse effects in the central nervous system, whereas chronic exposure to lower doses can damage the liver and cardiovascular system (Bruckner *et al*., 2013). For most chemicals, acute exposures typically cause more severe health effects. With chronic exposure to sufficiently low doses, the body is able to eliminate each dose *via* excretion and repair any damage that may have occurred or adapt and find other means of accommodating each dose (Aleksunes and Eaton, 2019). Even if several individuals are exposed to a chemical at the same frequency and for the same duration, the severity of the adverse effects resulting from that exposure can vary because of differences in personal characteristics, as described above.

Finally, many chemicals can only affect tissues that they or their metabolites can physically access. The exposure route (*e.g*., ingestion, inhalation, and skin contact) and chemical and biological factors influence which tissues can be exposed to a chemical.

When animal studies are used to evaluate toxicity, study results must be extrapolated across species and often from relatively higher doses to the much lower concentrations to which humans may be exposed (US EPA, 2005). For regulatory purposes, it is generally assumed that humans are as sensitive as the most sensitive animal species and that effects observed in animals can occur in humans, even though this is not always the case owing to differences in physiology and metabolism across species (US EPA, 2005). This is because regulators do not estimate the likelihood of health effects actually occurring in a population or an individual (US EPA, 2004; ATSDR, 2018a). Rather, they use high-end estimates of exposure and toxicity (that generally result in overpredictions of potential health risks) to be protective of human health. That is, their aim is not to precisely define which health effects are expected to occur following an exposure, but to define the exposure level at which health effects are unlikely to occur (Aleksunes and Eaton, 2019).

For carcinogens, when an MoA for a particular chemical is not known, a linear approach is used for regulatory purposes to extrapolate risks at low doses from risks at high doses. A linear no-threshold (LNT) model assumes that there is no threshold exposure below which a chemical has no biological response. The LNT model also assumes that low doses over a lifetime will have the same effect as high doses over a short period of time. However, as stated by Clewell *et al*. (2019):

> Initial discovery that DNA mutation was the root of cancer led quickly to regulatory processes that assumed such a simple relationship could be described with a linear approach. This linear, no threshold approach has since become the default approach to risk assessment of chemicals with carcinogenic potential. Since then, a multitude of intrinsic processes have been identified at the molecular, cellular and organism level that work to prevent transient DNA damage from causing permanent mutations, and mutated cells from becoming cancer. Mounting evidence indicates that these protective mechanisms can prevent carcinogenesis at low doses of genotoxic chemicals, leading to non-linear dose-response. Further, a number of non-genotoxic mechanisms have demonstrated threshold-shaped dose-response for cancer outcomes.

The LNT model provides a conservative estimate of risk that is public-health protective (US EPA, 2005), and that overestimates cancer risks at low doses.

3.3 Individual Study Reviews

I conducted a systematic review of the relevant epidemiology and animal carcinogenicity studies of leukemia. I limited my epidemiology review to studies that evaluated leukemia in adult populations. First, I reviewed government and other agency assessments of TCE, PCE, benzene, vinyl chloride, and *trans*-1,2,-DCE to identify epidemiology and animal carcinogenicity studies that evaluated exposure to these chemicals and leukemia for various purposes. I also conducted literature searches using PubMed and Scopus for studies published after these assessments' literature searches were completed and reviewed the reference lists of identified studies to find additional relevant studies (Attachment A).

For all of the epidemiology and animal carcinogenicity studies included in my evaluation, I summarized relevant information on study characteristics and results, as well as study quality, in text and tables. With the exception of studies of Camp Lejeune populations (all of which I have reviewed here), if several epidemiology studies analyzed the same cohorts or population groups, I generally summarized only the most recent study (because it had longer follow-up times and/or used more reliable exposure estimates), unless older studies reported additional results (*e.g.*, dose-response relationships). I excluded studies that examined non-specific aggregations of chemical exposures (*e.g.*, solvents, hydrocarbons) or that evaluated exposures to chemicals in ambient air.[5] Finally, because some epidemiology study designs are inherently lower in quality and limited in terms of the information that they can provide regarding causal inference (*e.g.*, case reports, ecological studies, PMR studies), I only conducted formal quality assessments and detailed reviews of cohort and case-control studies. For animal carcinogenicity studies, I focused on chronic studies, because acute, subacute, and subchronic studies do not observe animals for a long enough duration to be able to evaluate the development of tumors.

I evaluated the quality of the epidemiology and animal carcinogenicity studies to determine how valid and reliable the results of individual studies are for addressing causation. The study quality criteria I used are based on those identified from several available frameworks (*e.g.*, reviewed by Lynch *et al*. [2016] and Waspe *et al*. [2021]). Although aspects of these frameworks differ, they all share common themes. For each individual epidemiology and animal carcinogenicity study, I assessed strengths and limitations for each critical quality aspect presented in Sections 3.3.1 and 3.3.2, respectively, but I focused on those aspects that were most likely to impact the validity and reliability of each study's results.

I focused my in-depth systematic review on epidemiology and animal carcinogenicity studies because these studies provide the most direct evidence for the potential of a particular agent to cause cancer. I also conducted a high-level review of available *in vitro* and *in vivo* mechanistic studies, with a specific focus on those studies that have been proposed to support specific mechanisms by which TCE, PCE, benzene, vinyl chloride, or *trans*-1,2,-DCE could cause leukemia. For these studies, I reviewed the results to determine whether they are sufficient to support a MoA for cancer, considering important factors such as assay type and the overall relevance of the results within the context of the treatment (*i.e.*, dose, route, and duration) and model system (human, non-human mammalian, non-mammalian).

Camp Lejeune epidemiology studies are reviewed in Section 5. TCE, PCE, benzene, and vinyl chloride epidemiology studies are reviewed in Sections 6.1, 7.1, 8.1, and 9.1, respectively, and TCE, PCE, benzene, and vinyl chloride animal carcinogenicity and mechanistic studies are reviewed in Sections 6.2, 7.2, 8.2, and 9.2, respectively. I review the limited evidence for *trans*-1,2-DCE in Section 10.

[5] As noted by ATSDR (2024a), which also excluded epidemiology studies of benzene exposures in ambient air, there is "great uncertainty about causality in in these studies." The agency further stated, "Major uncertainty in the interpretation of these ambient exposure studies is that benzene levels (air or biomarkers) may have been a surrogate variable for exposure to 'air pollution' in general (e.g., emissions from fuels and fuel combustion). These pollutants (e.g., BTEX, NO2, PM10) tend to be correlated."

3.3.1 Epidemiology Studies

As summarized in Table 3.2, the quality domains I considered for epidemiology studies are the study population, exposure assessment, outcome assessment, covariates considered, and temporality. Following the table, I describe in detail the key aspects of each domain and how differences in the design or execution of these key aspects can impact the quality of an epidemiology study. I consider all of these domains for each study reviewed in detail in the attachments to this report, but as suggested by Savitz *et al*. (2019), I focus my discussion on the few critical aspects that warranted detailed assessment based on their potential impact on a study's validity and reliability. For most of the epidemiology studies I reviewed, the exposure assessment is the factor most likely to critically impact the validity of results. This is because most environmental epidemiology studies do not use robust quantitative methods for estimating exposure (*i.e*., direct measurements), although some use semiquantitative methods that are more reliable than studies that use strictly qualitative methods.

Table 3.2 Epidemiology Study Quality Evaluation Criteria

Parameter	Strength	Weakness
Study Population	▪ Appropriate study and comparison groups (cohort study) or case and control selection (case-control study) ▪ ≤20% loss to follow-up/excluded or >80% enrollment ▪ Nondifferential participation rates (≤15% difference in rates between cases and controls in case-control studies)	▪ Inappropriate study and comparison groups (cohort study) or case and control selection (case-control study) ▪ >20% or unknown percentage of loss to follow-up/excluded, ≤80% or unknown percentages of enrollment/participation ▪ Differential participation rates between cases and controls (>15% difference in rates between cases and controls in case-control studies)
Exposure Assessment	▪ Direct chemical exposure measurement ▪ Quantitative or semiquantitative exposure estimate (*i.e.*, duration, frequency, or intensity) ▪ ≤5% missing data or appropriately addressed missing data (*e.g.*, MICE) ▪ Assessed the time-varying nature of exposure	▪ Indirect chemical exposure measurement (*e.g.*, job history or self-reported exposure) ▪ Qualitative exposure estimate (*e.g.*, ever/never, job title) ▪ >5% missing data that are not addressed, or amount of missing data unknown ▪ Did not assess the time-varying nature of exposure ▪ Exposure information ascertained after outcome occurred
Outcome Assessment	▪ Cases/deaths identified or validated using reliable source (*e.g.*, registry, hospital records) ▪ Assessed disease incidence ▪ ≥5 years of follow-up	▪ Assessed disease mortality only ▪ Unconfirmed self- or proxy-reported outcome ▪ <5 years of follow-up
Covariates Considered	▪ Controlled for or considered age, sex, race/ethnicity, other chemical exposures (all leukemia), family history (ALL, AML, and MDS), genetics (AML, ALL, and MDS), smoking (AML, MDS), blood disorders, and chemotherapy treatment (AML, MDS), and certain viral infections (ALL) ▪ ≤5% missing data or appropriately addressed missing data (*e.g.*, MICE) ▪ Considered time-varying nature of relevant covariates	▪ Did not control for or consider age, sex, race/ethnicity, other chemical exposures (all leukemia), family history (ALL, AML, and MDS), genetics (AML, ALL, and MDS), smoking (AML, MDS), blood disorders, and chemotherapy treatment (AML, MDS), and certain viral infections (ALL) ▪ >5% or unknown amount of missing data that were not appropriately addressed ▪ Did not consider time-varying nature of relevant covariates
Temporality	▪ Exposure measured or documented before the outcome ▪ Appropriate consideration of latency (lag ≥0.5 years or exclusion of cases occurring ≤0.5 years after exposure)	▪ Exposure not measured or documented before the outcome ▪ No/insufficient consideration of latency (<0.5 years)

Notes:
ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; JEM = Job-Exposure Matrix; MDS = Myelodysplastic Syndrome; MICE = Multiple Imputation Chained Equations.

Study Population

Selection bias is introduced when the individuals, groups, or data in an analysis are chosen in such a way that they may not be representative of the population about which researchers are making inferences. I considered cohort studies that have higher rates of enrollment or retention (>80%) (Kristman *et al*., 2004) and case-control studies with nondifferential participation rates (*i.e.*, participation rates in cases and controls differ by at most 15%) to be less likely to be subject to selection bias (Gordis, 2014).[6] If a study recruited or retained participants that systematically differ from the population of interest (*e.g*., when recruited from hospitals), or if the exposed and unexposed (cohort study) or diseased and nondiseased (case-control study) differ on important factors, risk estimates may be biased (Gordis, 2014).

Exposure Assessment

In epidemiology studies, chemical exposures are commonly estimated using job titles, job-exposure matrices (JEMs) in which exposures are linked to occupational titles or tasks by experts, air or water monitoring or modeling, biomarkers (including exhaled breath and urine metabolites), self-reported exposures, or residential proximity to chemically contaminated sites.

I considered personal or occupational monitoring with sufficient information regarding time spent near the monitor to be the strongest methods for measuring exposure. I considered other means of estimating exposure, including job titles, JEMs, biomarkers (including exhaled breath and urine metabolites), self-reported exposures, the presence of a chemical in drinking water (either measured or modeled), and residential proximity to contaminated sites, to be weaker methodologically because of the higher likelihood of misclassification. However, among these latter methods, those that are applied in a quantitative or semi-quantitative manner (*i.e*., those that consider duration, frequency, or intensity of exposure) are stronger than those that are qualitative (*e.g*., those that evaluate ever *vs.* never exposed or exposure based on job title).[7] For example, those based on JEMs with some chemical measurement data or modeled drinking water concentrations (without water consumption data) based on chemical measurements are more reliable than other methods that lack any quantitative basis for exposure estimates.

While JEMs provide an indirect measurement of exposure, they are often more reliable than qualitative methods of estimating exposure (*i.e*., ever *vs.* never exposed, or job title), but the quality of an exposure assessment based on a JEM varies based on the expertise of the person or people linking job titles to exposures, and whether the assessment is semiquantitative or not (*e.g*., whether the duration, frequency, or intensity of exposure is considered). Also, exposure estimates based solely on job titles are subject to potential exposure misclassification due to possible differences in tasks and exposure conditions for specific jobs. Using these (or other) broad categories for exposure assessments also does not account for individual job characteristics that could modify an individual's exposure potential. They also usually do not account for differences in chemical exposures in terms of the exposure route, duration, frequency, or intensity. I considered studies that estimated duration of exposure to a chemical by duration of employment, or by using information from self-reported work history, census data, or company records as proxies for exposure dose, to be of higher quality than those that did not, but these exposure estimates are still subject to the same issues discussed above, including misclassification and recall inaccuracies. Overall, estimated chemical exposure concentrations in studies that relied on JEMs or job titles more generally do not always

[6] I am not aware of any standard cutoff, so I considered a >15% difference in participation rates between cases and controls to constitute differential participation.

[7] Duration of employment is often used in studies as a proxy for exposure. However, intensity and frequency of exposure could vary dramatically over the same duration of time for different people. For example, an individual who was exposed to consistent high levels of TCE daily over 10 years would be in the same exposure category as someone exposed to intermittent low levels of TCE for 10 years, despite having very different cumulative exposure profiles.

reflect actual individual exposure levels, but are more likely to be accurate when they are based on chemical measurements.

Directly measured or modeled chemical concentrations in the environment (*e.g.*, drinking water) are more reliable than exposure estimates that are not based on any quantitative information, but with no direct link between the measurement and true individual-level exposure (*e.g.*, individual-level water consumption data), neither type of estimate is likely to be accurate and reliable with respect to individual exposures. In contrast, direct measurements of chemical concentrations in the environment (*e.g.*, drinking water) that are linked to robust individual exposure data (*e.g.*, water consumption data) can provide reliable and accurate direct exposure information. Modeled chemical concentrations in the environment (*e.g.*, in drinking water) based on chemical measurements in the environment (*e.g.*, groundwater) could similarly provide high-quality exposure data when linked to individual exposure data (*e.g.*, water consumption data); however, the quality and accuracy of estimates of modeled chemical concentrations depend on the accuracy of the model's assumptions. In addition, chemical concentration measurements or estimates in the environment that reflect contamination levels at only a single or a few points in time do not necessarily reflect long-term exposure concentrations. Also, studies that provide estimates of exposure for aggregated chemicals (*e.g.*, all chlorinated hydrocarbons) or chemicals that are highly correlated (*e.g.*, categorized TCE, benzene, vinyl chloride and total volatile organic compounds [TVOCs] in some Camp Lejeune studies), or studies in which co-exposures to other chemicals are known to occur but are not controlled for in the analysis, are of lower quality than studies that estimate exposures to individual chemicals if the goal of the study is to estimate risks of particular chemicals. This is not the case if one is interested in determining the risk of a mixture (*i.e.*, if one is interested in the risk of drinking water at Camp Lejeune, one only needs to assess exposure to drinking water).

Biomonitoring can provide high-quality exposure measurements in epidemiology studies, particularly when risks from recent exposures are of interest or if exposures were relatively constant over an extended period of time. However, biomonitoring does not provide accurate estimates of past exposures when measured chemicals or metabolites reflect only recent or non-specific exposures. As described below, biomarkers for the volatile organic compounds (VOCs) at issue in this matter are not robust measures of exposure.

- TCE and PCE are rapidly absorbed into the bloodstream and are quickly excreted *via* exhalation (ATSDR, 2019a; US EPA, 2011, 2012). TCE and PCE that are not quickly exhaled can be metabolized to breakdown products and excreted in the urine (ATSDR, 2019a; US EPA, 2011, 2012). Trichloroacetic acid (TCA) is a metabolite of TCE, PCE, and other chlorinated hydrocarbons, and can be measured in blood and urine, but it is not specific and only represents recent exposure (IARC, 2014a; Cichocki *et al.*, 2016; ATSDR, 2019a). As a result, it is generally not feasible to measure long-term TCE or PCE exposure using biomonitoring.
- Benzene and several benzene metabolites can be measured in urine, but the only benzene-specific metabolite is S-phenylmercapturic acid (Arnold *et al.*, 2010). Benzene can also be detected in blood as a marker of recent exposure (CDC, 2017). Smoking and exposures to gasoline and petroleum products can result in higher concentrations of benzene in blood (CDC, 2017), so it can be difficult to assess exposures to a specific source of benzene exposure if these other factors are not well controlled for.
- Vinyl chloride can be measured in exhaled breath but is of limited use for biomonitoring because it is only an indicator of recent exposure. Thiodiglycolic acid and N-acetyl-S-(2-hydroxyethyl)-cysteine are metabolites of vinyl chloride in urine but they are not specific, so they have limited utility for biomonitoring (ATSDR, 2024b).

With respect to missing data, I found that studies that were missing exposure data on <5% of the study population or that used appropriate analytical methods to address the missing exposure data (*e.g.*, multiple

imputation) are stronger than studies that had ≥5% missing data and did not account for missing data with appropriate methods (Jakobsen *et al*., 2017; Perkins *et al*., 2018).

Finally, self-reported exposure information is subject to potential recall inaccuracy, particularly when there are long time periods between exposures and study participant interviews. It is also subject to bias, particularly in case-control studies, when cases and controls may systematically recall prior exposures differently.

Outcome Assessment

I determined that studies that included a diagnosis or confirmation of leukemia by a medical professional or a histological evaluation, or that included leukemia cases identified from a disease registry, provide stronger outcome data than studies that relied on self- or proxy-reports of leukemia, because the latter are more likely to be subject to misclassification.

Because leukemia is not always fatal and fatality rates have changed over time, and because data from death certificates are not always reliable (*e.g*., contributing causes of death are not always reported), I considered studies that only evaluated leukemia mortality to be weaker than those that evaluated leukemia incidence (NCI, 2024a; McGivern *et al*., 2017). Studies that evaluated leukemia subtypes are stronger than those that evaluated all types of leukemia combined because each subtype has a different underlying etiology.

I considered cohort studies that followed participants for a long enough duration (≥5 years) to be able to capture a sufficient number of disease cases for analysis, particularly for rare outcomes (*e.g*., ALL), to be stronger.

Covariates

A covariate is an independent variable that can influence the outcome of interest, but that is not of direct interest itself; it may be a confounder but does not have to be (Porta, 2014). Age, sex, race/ethnicities, and other chemical exposures are risk factors for all types of leukemia (NCI, 2023a), but each type of leukemia also has unique risk factors (Table 3.3). All of these factors should be considered as potential confounders in studies of leukemia, even if they are not confounders, because including them in statistical models increases the precision of effect estimates without increasing bias (Velentgas *et al*., 2013). I therefore considered studies to be stronger if they controlled for at least some of these factors in the study design or analysis.

Table 3.3 Risk Factors for Leukemia, by Subtype

Leukemia Type	Risk Factors	References
All Leukemias	Age and sex, race/ethnicity, other chemical exposures	NCI (2023a)
CML	Age, sex, and ionizing radiation	ACS (2018a)
AML	Age, sex, genetics, smoking, family history of AML, some blood disorders, and certain types of chemotherapy treatments	NCI (2023b); ACS (2018b)
ALL	Age, sex, family history (*e.g*., sibling with ALL), genetics, and certain viral infections	ACS (2018c, 2024); NCI (2023c)
MDS	Age, sex, family history of MDS, genetics, smoking, some blood disorders, and certain types of chemotherapy treatments	ACS (2018d)

Notes:
ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; CML = Chronic Myeloid Leukemia; MDS = Myelodysplastic Syndrome.

Studies that assessed covariates that can vary over time (*i.e.*, other chemical exposures) and considered changes over time in their analyses are stronger than studies that only assessed these covariates at a single time point. Studies with <5% missing covariate data or that used appropriate analytical methods to address missing data (*e.g.*, imputation) are stronger than studies with ≥5% missing data that did not account for missing data with appropriate methods (Jakobsen *et al.*, 2017; Perkins *et al.*, 2018).

Temporality

I considered studies that measured or documented exposures prior to diagnoses to be of higher quality than those that measured or documented exposures at the time of or after diagnoses, because the former are more likely to have appropriately captured the temporal relationship between the exposure and the outcome (Gordis, 2014). Similarly, studies that incorporated a lag (either by design or in their analysis) in the time between the exposure and the outcome are stronger than studies that did not, particularly considering the latency period for cancer. Studies with an insufficient duration of time between the exposure and leukemia development (<0.5 years) (CDC, 2015) are weaker than those with sufficient time between the exposure and leukemia development (≥0.5 years). While this period of time might not be sufficient for cancer to develop, I felt it was appropriate, as it allowed me to err on the side of overestimating quality.

3.3.2 Toxicology Studies

3.3.2.1 Animal Carcinogenicity Studies

Studies in rodents can be classified based on their duration as acute (less than 24 hours), subacute (24 hours to less than 1 month, although most last 28 days), subchronic (1 to 3 months, although most last 13 weeks), and chronic (typically 6 months to 2 years) (Aleksunes and Eaton, 2019; OECD, 2024). I focused my analysis on chronic studies because those with shorter durations may not be sufficient for cancers to develop. I discuss subchronic studies only if they are the basis of any agency conclusions. The endpoints I considered in animal bioassays included acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, and malignant mononuclear cell leukemia (MNCL). I did not identify animal studies that addressed MDS.

I assessed animal carcinogenicity study strengths and weaknesses based on several formal quality and risk-of-bias frameworks, including the Integrated Risk Information System (IRIS) (US EPA, 2022; NRC, 2014), NTP Office of Health Assessment and Translation (OHAT) (NTP, 2019), Science in Risk Assessment and Policy (SciRAP) (Molander *et al.*, 2014), and "Animal Research: Reporting of *In Vivo* Experiments" (ARRIVE) (Percie du Sert *et al.*, 2020; Batke *et al.*, 2023) frameworks. I also considered whether the studies were consistent with the Organisation for Economic Co-operation and Development (OECD) "Guidelines for the Testing of Chemicals" (OECD, 2024) (referred to hereafter as the OECD Guidelines).

In Table 3.4, I summarize the key aspects of the quality domains I considered for animal carcinogenicity studies: reporting, allocation, bias, sample, chemical administration and characterization, exposure conditions, and outcome evaluation. I considered all of these factors in detail in the attachments to this report, but only those factors that are likely to have a considerable impact on the validity and reliability of a study's results are discussed in the text. For most of the animal carcinogenicity studies, the background tumor rate, the general health of the study animals, and the observation period can have the biggest impact on the reliability of their results. If the study animals have a high background cancer rate, are generally unhealthy, or are observed over their lifespan, it is more likely that cancers observed following an exposure are not related to that exposure.

Table 3.4 Animal Carcinogenicity Study Quality Evaluation Criteria

Parameter	Strength	Weakness
Reporting	For each outcome, report: (1) animal species; (2) test article name; (3) experimental design; (4) levels, duration, and route of exposure; (5) outcome evaluation methods; and (6) qualitative or quantitative results.	Do not report all these aspects.
Allocation	Random allocation of animals to experimental groups.	Do not specify whether allocation to experimental groups was random.
Bias	No indication that there were differences across treatment groups that could bias results (*e.g.*, co-exposures, vehicle, diet, gavage error, palatability, husbandry, health status).	Variables not adequately balanced across experimental groups, potentially biasing the results.
Sample	Adequate sample size; all animals were accounted for throughout the study.	Inadequate sample size; animals not all accounted for throughout the study.
Chemical Administration and Characterization	Chemical source, purity, and composition were adequate, chemical purity was independently verified, and steps were taken to ensure reported exposure levels were accurate.	Chemical source, purity, or composition were inadequate, chemical purity was not independently verified, or no steps were taken to ensure reported exposure levels were accurate.
Exposure Conditions	Several doses were tested, tested doses were below levels that can cause early mortality (unless early mortality was caused by the health outcome of interest), and the duration of exposure was appropriate for assessing the outcome of interest.	Only one dose tested, tested doses were too high and caused early mortality not caused by the health outcome of interest, or the duration of exposure was inappropriate for assessing the outcome of interest.
Outcome Evaluation	Valid, reliable, sensitive, and specific outcome evaluation method and appropriate observation period.	Invalid, unreliable, insensitive, or nonspecific outcome evaluation method or inappropriate observation period.

Note:
These criteria are based on the Integrated Risk Information System (IRIS) (US EPA, 2022; NRC, 2014), National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) (NTP, 2019), Science in Risk Assessment and Policy (SciRAP) (Molander *et al.*, 2014), and "Animal Research: Reporting of *In Vivo* Experiments" (ARRIVE) (Percie du Sert *et al.*, 2020; Batke *et al.*, 2023) study quality/risk-of-bias frameworks.

Reporting

I considered studies to be stronger if they clearly reported the species and strain of animals; the identity, source, and purity of the test chemical; the experimental design; the levels, duration, timing, frequency, and route of exposure; the outcome evaluation method; and qualitative and quantitative results for all the outcomes outlined in the methods of the study report or article. I assessed whether a study's reporting was adequate by considering whether all the elements of the study are described well enough that the study could be reproduced, and whether the methodological rigor and reliability of the authors' conclusions can be evaluated (US EPA, 2022).

Allocation

I determined that studies that randomly allocated animals to experimental groups are stronger than those that did not, as random allocation helps to minimize selection bias and systematic differences in animals among treatment groups. Employing appropriate randomization techniques ensures that each animal has an equal chance of receiving a particular treatment. Merely selecting an animal "at random," based on arbitrary judgment, does not constitute statistical randomization. Ideal methods for randomization include weight randomization or utilizing random number generators. Studies that did not randomize animals are more prone to reporting exaggerated results that meet conventional statistical significance thresholds (Percie du Sert *et al*., 2020; Batke *et al*., 2023; Haseman, 1984).

Bias

Bias refers to a systematic error or deviation from the truth in a study's results or in the interpretation of its results, potentially leading to an inaccurate estimation of the true effect. The impact of bias can range from trivial to substantial, with the latter resulting in a finding that may be completely attributed to bias (Percie du Sert *et al*., 2020). Often the impact of a bias on the study results is unknown, making the interpretation of study results difficult. Common types of bias include selection bias, performance bias, detection bias, and attrition bias.

In animal carcinogenicity studies, factors such as co-exposures to multiple chemicals, diet, palatability, and husbandry practices (*e.g*., light-dark cycles, caging variables) can contribute to variability within groups. I considered stronger studies to be those that reported the strategies taken to mitigate potential discrepancies between treatment groups throughout the entire experimental period and lower-quality studies to either have differences between treatment groups or a lack of sufficient information to enable a reliable assessment of bias.

Sample

I considered stronger studies to be those that specified the exact number of experimental animals allocated to each treatment group, the total number of animals in each experiment, and the total number of animals used in the entire study. This information is critical when assessing the validity of a study's statistical analyses and the reliability of its experimental results. It is also preferable for studies to justify how the sample size was chosen, and to ensure the bioassay has sufficient statistical power (Percie du Sert *et al*., 2020). The appropriate sample size also depends on the endpoint being studied. For carcinogenicity assays, the OECD Guidelines state that chronic studies should test at least 50 male and 50 female rodents per dose, subchronic studies should test at least 10 male and 10 female rodents per dose, and subacute studies should test at least 5 male and 5 female rodents per dose (OECD, 2018, 2024). Studies with too few animals have low statistical power and may not produce reliable information on chemical carcinogenesis (Percie du Sert *et al*., 2020; OECD, 2018, 2024).

The starting sample size is also necessary to estimate attrition (*i.e*., the number of animals that have been excluded from analysis) and identify in which groups attrition occurred. I concluded that stronger studies accounted for all the animals throughout the experiment, and reported all animals that were excluded from analyses, along with the rationale for their exclusion. A high attrition rate that is not described or accounted for, particularly when the attrition rate differs across treatment groups, can result in unsupported conclusions (Percie du Sert *et al*., 2020).

Chemical Administration and Characterization

I concluded that stronger studies provided comprehensive information about the test substance, including its purity and source, verified the purity of the test substance, and took steps to ensure the accuracy of reported exposure levels or doses. Using a high-purity (*i.e.*, ≥95%) chemical in carcinogenicity studies can help ensure that the observed responses are caused by the chemical itself, rather than contaminants (OECD, 2018, 2024). Chemical stability should also be confirmed (OECD, 2018, 2024).

Exposure Conditions

I considered stronger studies to be those that used a sensitive exposure protocol, including the use of several doses below that associated with early mortality, and an appropriate exposure duration for the outcome of interest. The maximum tolerated dose (MTD), which is the highest dose that does not cause toxicity, can be determined from subchronic studies and then used in a chronic study, along with lower doses (half of the MTD and a quarter of the MTD, for example), in case the highest dose selected leads to excessive mortality. This approach also contributes information on dose-response relationships.

Ideally, carcinogenicity bioassays in rats and mice begin at 6 weeks of age and span 104 or 78 weeks, respectively, which includes early adulthood through what would be analogous to a significant part of the occupational lifespan in humans (OECD, 2018, 2024). Longer exposure durations may mask effects due to background tumor incidence, while shorter exposure durations reduce sensitivity in detecting late-appearing tumors related to the chemical exposure (OECD, 2018, 2024).

Outcome Evaluation

The outcome measures in a bioassay include any information recorded to evaluate the chemical's effects. I considered studies to be stronger if they evaluated each outcome of interest using established, standardized methods over an appropriate observation period, *i.e.*, 24 months (104 weeks), representing the majority of the rodent lifespan (OECD, 2018). Histopathology is the primary method for evaluating outcomes in carcinogenicity bioassays. A proper assessment includes a thorough evaluation of all organs and tissues in each animal to detect neoplastic and non-neoplastic lesions. Moribund animals should be removed from the study to prevent tissue autolysis (OECD, 2018, 2024). Autolysis can interfere with the detection of neoplastic and non-neoplastic lesions, reducing the power of the study (NTP, 2006). When mortality rates differ between dose groups, comparisons and tumor trend analyses should be conducted using survival-adjusted tumor rates. Failing to adjust for survival differences could yield unreliable cancer risk estimates and potential misinterpretations of site-specific effects. Studies that sacrificed animals when moribund, or at the end of their natural lifespans, are less reliable than those studies that sacrificed animals at scheduled time points, due to late-life background pathology (OECD, 2018, 2024).

3.3.2.2 Mechanistic Studies

Several mechanisms have been proposed by which TCE, PCE, benzene, and vinyl chloride could cause cancer generally or leukemia specifically. I conducted a high-level review of relevant mechanistic evidence to determine whether it supports any biologically plausible mechanism or MoA for cancer with respect to any of these chemicals. I identified relevant mechanistic studies from agency documents (discussed above), recent literature reports, and Plaintiff expert reports (Flesher, 2024; Gilbert, 2024; Bird, 2024; Gondek, 2024; Mallon, 2024).

I considered the quality of *in vivo* mechanistic studies in a similar manner to the way in which I considered the quality of animal carcinogenicity studies. For *in vitro* studies, I focused on factors that generally have

a large impact on the interpretation of the results, including the consistency and reliability of the reported results and the overall relevance of the treatment (*i.e.*, dose, route, and duration) and model system (human, non-human mammalian, non-mammalian) used, with consideration for whether there were any factors that may have biased the results (*e.g.*, differences in culture conditions, high levels of non-specific cytotoxicity, increased cell passages, lack of relevant detoxification pathways, co-exposures, reagent production lots, and infections).

3.3.3 Study Quality and Human Relevance Evaluation

As discussed in Sections 3.3.1 and 3.3.2, I conducted a formal quality assessment of cohort and case-control studies and chronic animal carcinogenicity studies. Because the cutoffs for higher and lower quality are subjective, I did not simply categorize studies as higher or lower quality, but rather reviewed each study with the above quality aspects in mind and determined how each aspect impacted the interpretation of both the individual study's results and the body of literature as a whole.

The quality criteria for animal carcinogenicity studies are focused on internal validity, or the degree to which the results are free from bias and are not due to methodological limitations. I also considered external validity, which is whether an animal study's results have human relevance (Aleksunes and Eaton, 2019). If a study has poor internal validity, then it cannot have external validity. Thus, low-quality animal studies, as determined generally based on exposure conditions and the outcome evaluation, both of which are likely to impact the interpretation of a study's results, have limited human relevance. Also, by design, animal toxicity studies test high doses of chemicals that are generally not directly relevant to human environmental or occupational exposures (Goodman *et al*., 2020). Regardless, I considered animal carcinogenicity studies to have adequate human relevance if they tested more than one dose; evaluated an inhalation, oral, or dermal route of exposure; and provided relevant data. Finally, F344 rats have a high spontaneous background incidence rate of MNCL, and these tumors are not predictive of human health risks (Maronpot *et al*., 2016). Thus, I do not consider MNCL findings in F344 rats to be relevant to humans.

Although I did not conduct a formal quality assessment of *in vivo* and *in vitro* mechanistic evidence, I considered the overall biological plausibility and relevance of this evidence to humans, including the dose levels at which the mechanistic event was observed, whether the observed mechanistic event represents an adverse effect, whether this adverse effect is relevant to a cancer pathway, and any fundamental differences between the test systems and humans. I also considered whether events were consistent with and specific for carcinogenesis generally and leukemia or leukemia subtypes specifically (*e.g.*, while a biologically plausible mechanism exists for benzene and AML at exposures greater than 40 to 75 ppm-years, this mechanism may not be relevant to other leukemia subtypes). For example, changes in gene and protein levels may represent normal biological responses of cells to their environment and are not necessarily associated with adverse effects. In addition, *in vitro* studies typically use experimental systems that lack the normal suite of detoxification pathways (*e.g.*, DNA repair) present in whole organisms and often use high doses that are not relevant to humans. As a result, chemicals can produce false positive results in *in vitro* assays for cancer related mechanisms (*e.g.*, genotoxicity) due to the absence of normal detoxification and repair processes and/or non-specific effects related to the high doses used (US EPA, 2022).

Similarly, with respect to the key characteristics of carcinogens (KCCs) paradigm, which is based on the concept that human carcinogens often demonstrate activity for at least one of ten key characteristics (*i.e.*, has electrophilicity, has genotoxicity, alters DNA repair or causes genomic instability, induces epigenetic alterations, induces oxidative stress, induces chronic inflammation, causes immunosuppression, modulates receptor-mediated effects, causes immortalization, and alters cell proliferation, cell death, or nutrient supply), the observed effects from exposure to a given compound may not be evidence of an adverse effect and activity, for a given KCC does not necessarily mean that the compound could produce cancer through

this activity. For example, increased oxidative stress can be the result of normal physiological processes and is not specific to carcinogens, as numerous compounds that do not cause cancer have been shown to cause oxidative stress. Further, not all genotoxicants are carcinogens. Whether a chemical is capable of causing cancer cannot be conclusively determined without carcinogenicity testing in animals. Thus, KCC activity should not be relied upon in isolation to determine whether a chemical poses a carcinogenic risk to humans (Goodman and Lynch, 2017; Goodman *et al*., 2018; Becker *et al*., 2017).

3.4 Evidence Integration

To determine whether an exposure is causally associated with a health outcome, it is critical to integrate the evidence across scientific disciplines. It is only by considering the available evidence as a whole that an informed conclusion regarding disease causation can be made. There are a number of methods for evaluating scientific evidence (*e.g.*, Rhomberg *et al*., 2011; Adami *et al*., 2011), all of which emphasize a systematic and transparent approach to the analysis.

Perhaps the most widely used approach for assessing general causation (either as proposed or with slight modifications), including by many regulatory agencies, is that outlined by Sir Austin Bradford Hill in his address to the British Royal Academy of Medicine in 1965 (Hill, 1965; Garabrant, 2000; US EPA, 2005). Dr. Hill put forth several considerations to help address, as he stated, "In what circumstances can we pass from observed association to a verdict of causation? Upon what basis should we proceed to do so?" (Hill, 1965). These considerations are described in Table 3.5, below.

Table 3.5 Bradford Hill Considerations

Aspect	Analysis
Strength of Association	Although a modest risk does not preclude a causal association, I considered an observed risk less likely to be due to chance, bias, or other factors if it was large and precise.
Consistency	Consistency refers to the reproducibility of findings within and across studies. Discordant results may indicate that findings of effect in certain studies are likely due to chance, bias, or confounding factors. If results are consistent only among studies with similar designs, people, places, circumstances, or times, I concluded that this evidence of association is not as strong as consistent results among studies of different designs, or of different people, places, circumstances, and times.
Specificity	Hill (1965) noted that if "the association is limited to specific workers and to particular sites and types of disease and there is no association between the work and other modes of dying, then clearly that is a strong argument in favour of causation." This is true for any type of exposure. I concluded that, as noted by Hill (1965), "if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence."
Temporality	I concluded that a causal interpretation is strengthened when an exposure is known to precede the occurrence of a disease. Temporality is the least definitive (but 100% necessary) of the Bradford Hill considerations, because many events occur prior to the development of a disease that may have nothing to do with its cause.
Dose-Response	To determine whether a dose-response relationship exists, I compared risks across exposure groups and related exposure to dose. I did this using risk estimates based on internal comparisons (*e.g.*, RRs or ORs) or risk estimates based on populations with similar age distributions.

Aspect	Analysis
Biological Plausibility	I concluded that if the available evidence indicates there is a biological mechanism for an adverse effect to occur under relevant exposure conditions, and this is sufficient to allow a scientifically defensible determination for causation in humans, this can add weight to an association reported in epidemiology studies. For example, if a chemical causes cancer in animal models, then it may be biologically plausible that it can also cause cancer in humans. Similarly, data regarding specific MoAs may also provide evidence that carcinogenicity in humans is biologically plausible, particularly in a particular organ. Conversely, if the evidence indicates that a biological mechanism is not plausible in humans, that places doubt on the epidemiology findings.
Coherence	To address coherence, I evaluated whether all of the known facts related to a chemical exposure and leukemia, particularly with respect to epidemiology, animal carcinogenicity, and MoA evidence, fit together in a consistent manner.
Experiment	If a substance is a causal factor in a disease process, then the association between an exposure and an effect should be altered by an experiment of preventative action. However, it is often not possible or practical to conduct such experiments. If such experiments have been conducted, I concluded causality was more likely if preventive action altered associations.
Analogy	The final consideration is often difficult to meet. I concluded that if there is evidence for a similar effect after exposure to a similar chemical, this also adds support for a causal association.

Notes:
MoA = Mode of Action; OR = Odds Ratio; RR = Relative Risk.

These considerations have been interpreted in various ways since they were first promulgated in the 1960s. With respect to strength of association, there is no specific cutoff for a strong association that has been generally accepted. US EPA (2019) characterized risk estimates between 1 and 1.3 as indicting a slight positive association, from 1.3 to <2 as indicating a positive association, from 2 to <3 as indicating a moderately strong association, and >3 as indicating a strong association. I am not aware of any framework that suggests a risk estimate of 1.1 indicates a strong association, except for ATSDR (2017a), as discussed in Section 3.5.2. In contrast, it is possible that a risk estimate >3 in an environmental epidemiology study, particularly if it has wide CIs, quite likely resulted from chance due to a small number of exposed cases. Because of this, only if the preponderance of high-quality epidemiology studies reports associations that cannot be explained by non-causal alternatives (*i.e.*, only if results are consistent), is a causal association supported. If studies are of low quality or if results are generally not consistent across studies, then it is more likely that positive associations are a result of chance, bias, or confounding.

This is also true for dose-response relationships. Only consistent evidence of similar dose-response relationships in high-quality epidemiology studies supports causation. That is, if some studies suggest a monotonic dose response and others support a non-monotonic dose response relationship, this is not consistent evidence of a dose-response relationship. If dose-response relationships are not found consistently across high-quality studies, this suggests non-causal explanations are more likely.

Dr. Bradford Hill (1965) noted that there might be occasions when information on biological plausibility is not available. If data are available, however, they should not be ignored or, conversely, overinterpreted. In some cases, there may be evidence to demonstrate that a carcinogenic MoA is not plausible. In other cases, if there is evidence that an agent can cause an effect on an organism, but there is no evidence that the magnitude of the effect is sufficient to lead to cancer, or if the effect is something common to carcinogens and noncarcinogens, this should not be considered evidence of biological plausibility. This concept should also be considered when evaluating coherence.

Keeping these caveats in mind, I note that the Bradford Hill considerations are not intended as a checklist from which causality can be concluded, but rather, they allow for drawing informed conclusions based on

available evidence. Overall, I relied on these considerations to determine whether an association is likely to be causal or whether other explanations are more likely (Ward, 2009). As stated by Dr. Hill (1965):

> None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as *sine qua non.* What they can do, with greater or less strength, is to help us make up our minds on the fundamental question – is there any other way of explaining the facts before us, is there any other answer equally, or more, likely than cause and effect?

I evaluated study quality to determine how reliable the results of individual studies were for addressing causation, and then considered individual study results in the context of study quality. I then integrated epidemiology, toxicology, and MoA evidence, with a particular focus on higher-quality studies, in the context of the Bradford Hill considerations for TCE, PCE, benzene, and vinyl chloride in Sections 6.3, 7.3, 8.3, and 9.3, respectively, to evaluate whether the evidence as a whole supports causality. Too few studies were available to conduct this type of assessment for *trans*-1,2-DCE.

3.5 Agency Reviews

3.5.1 Overview

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct evaluations of chemical carcinogenicity. IARC, US EPA, and NTP all classify chemicals according to how likely it is that they are human carcinogens, each using a unique framework, as shown in Table 3.6. NASEM and ATSDR do not classify agents according to their human carcinogenicity potential (an exception being ATSDR [2017a], as discussed below). NASEM, ATSDR, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Table 3.7.

Table 3.6 Agency Cancer Classification Frameworks

Agency/ Source	Classification	Description[a]
IARC (2019)	Group 1 (carcinogenic to humans)	[A]pplies whenever there is *sufficient evidence of carcinogenicity* in humans. In addition, this category may apply when there is both *strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens* and *sufficient evidence of carcinogenicity* in experimental animals.
	Group 2A (probably carcinogenic to humans)	[G]enerally applies when the Working Group has made at least *two of the following* evaluations, *including at least one* that involves either exposed humans or human cells or tissues: ▪ *Limited evidence of carcinogenicity* in humans, ▪ *Sufficient evidence of carcinogenicity* in experimental animals, ▪ *Strong evidence that the agent exhibits key characteristics of carcinogens.* If there is *inadequate evidence regarding carcinogenicity* in humans, there should be *strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens*. If there is *limited evidence of carcinogenicity in humans*, then the second individual evaluation may be from experimental systems.
	Group 2B (possibly carcinogenic to humans)	[G]enerally applies when only one of the following evaluations has been made by the Working Group: ▪ *Limited evidence of carcinogenicity* in humans, ▪ *Sufficient evidence of carcinogenicity* in experimental animals, ▪ *Strong evidence that the agent exhibits key characteristics of carcinogens.*
	Group 3 (not classifiable as to its carcinogenicity to humans)	Agents that do not fall into any other group are generally placed in this category. This includes when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites in experimental animals, the remaining tumour sites do not support an evaluation of *sufficient evidence in experimental animals*, and other categories are not supported by data from studies in humans and mechanistic studies. An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that the agent is of unknown carcinogenic potential and that there are significant gaps in research.
IARC (2018)	Group 4 (probably not carcinogenic to humans) [Eliminated in 2019]	This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

Agency/ Source	Classification	Description[a]
US EPA IRIS (US EPA, 1986)	Group A (carcinogenic to humans)	[T]here is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer.
	Group B (probably carcinogenic to humans)	[T]he weight of evidence of human carcinogenicity based on epidemiologic studies is "limited" and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient." The group is divided into two subgroups.... Group B1 is reserved for agents for which there is limited evidence of carcinogenicity from epidemiologic studies.... Agents for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies would usually be categorized under Group B2.
	Group C (possibly carcinogenic to humans)	[L]imited evidence of carcinogenicity in animals in the absence of human data.
	Group D (not classifiable as to human carcinogenicity)	[A]gents with inadequate human and animal evidence of carcinogenicity or for which no data are available.
	Group E (evidence of non-carcinogenicity for humans)	[N]o evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.
US EPA (2005)	Carcinogenic to humans	[C]onvincing epidemiologic evidence of a causal association between human exposure and cancer.... It can be used when all of the following conditions are met: (a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, and (b) there is extensive evidence of carcinogenicity in animals, and (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information.
	Likely to be carcinogenic to humans	[T]he weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans."
	Suggestive evidence of carcinogenic potential	[T]he weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species.
	Inadequate information to assess carcinogenic potential	[A]vailable data are judged inadequate for applying one of the other descriptors. Additional studies generally would be expected to provide further insights.

Agency/ Source	Classification	Description[a]
	Not likely to be carcinogenic to humans	[T]he available data are considered robust for deciding that there is no basis for human hazard concern. In some instances, there can be positive results in experimental animals when there is strong, consistent evidence that each mode of action in experimental animals does not operate in humans. In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic.
NTP (2023)	Known to be a human carcinogen	There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.
	Reasonably anticipated to be a human carcinogen	There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR [T]here is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, type of tumor, or age at onset, OR [T]here is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Notes:
IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NTP = National Toxicology Program; US EPA = United States Environmental Protection Agency.
(a) Description text taken directly from the cited sources. All emphasis is in the original source.

Table 3.7 IARC Classification Framework for Evaluating the Strength of Human, Experimental Animal, and Mechanistic Evidence of Cancer (IARC, 2019)

Realm	Classification	Description[a]
Cancer in Humans	Sufficient evidence of carcinogenicity	A causal association between exposure to the agent and human cancer has been established. That is, a positive association has been observed in the body of evidence on exposure to the agent and cancer in studies in which chance, bias, and confounding were ruled out with reasonable confidence.
	Limited evidence of carcinogenicity	A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.
	Inadequate evidence of carcinogenicity	The available studies are of insufficient quality, consistency, or statistical precision to permit a conclusion to be drawn about the presence or the absence of a causal association between exposure and cancer, or no data on cancer in humans are available.
	Evidence suggesting lack of carcinogenicity	There are several high-quality studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and the studied cancers at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit below or close to the null value (e.g. a relative risk of unity). Bias and confounding were ruled out with reasonable confidence, and the studies were considered informative. Evidence is limited to the cancer sites, populations and life stages, conditions and levels of exposure, and length of observation covered by the available studies.
Cancer in Experimental Animals	Sufficient evidence of carcinogenicity	A causal relationship has been established between exposure to the agent and cancer in experimental animals based on an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories and/or under different protocols. An increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in both sexes of a single species in a well-conducted study, ideally IARC Monographs Preamble conducted under Good Laboratory Practices (GLP), can also provide sufficient evidence. A single study in one species and sex may be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour, or age at onset, or when there are marked findings of tumours at multiple sites.
	Limited evidence of carcinogenicity	The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, for example, (a) the evidence of carcinogenicity is restricted to a single experiment and does not meet the criteria for sufficient evidence; (b) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; (c) the agent increases tumour multiplicity or decreases tumour latency but does not increase tumour incidence; (d) the evidence of carcinogenicity is restricted to initiation-promotion studies; (e) the evidence of carcinogenicity is restricted to observational studies in non laboratory animals (e.g. companion animals); or (f) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the available studies.

Realm	Classification	Description[a]
	Inadequate evidence of carcinogenicity	The studies cannot be interpreted as showing either the presence or the absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data are available on cancer in experimental animals.
	Evidence suggesting lack of carcinogenicity	Well-conducted studies (e.g. conducted under GLP) involving both sexes of at least two species are available showing that, within the limits of the tests used, the agent was not carcinogenic. The conclusion of evidence suggesting lack of carcinogenicity is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure covered by the available studies.
Mechanistic Evidence	Strong evidence	Results in several different experimental systems are consistent, and the overall mechanistic database is coherent. Further support can be provided by studies that demonstrate experimentally that the suppression of key mechanistic processes leads to the suppression of tumour development. Typically, a substantial number of studies on a range of relevant end-points are available in one or more mammalian species. Quantitative structure-activity considerations, in vitro tests in non-human mammalian cells, and experiments in non-mammalian species may provide corroborating evidence but typically do not in themselves provide strong evidence. However, consistent findings across a number of different test systems in different species may provide strong evidence.
	Limited evidence	The evidence is suggestive, but, for example, (a) the studies cover a narrow range of experiments, relevant end-points, and/or species; (b) there are unexplained inconsistencies in the studies of similar design; and/or (c) there is unexplained incoherence across studies of different end-points or in different experimental systems.
	Inadequate evidence	Common findings that lead to a determination of inadequate mechanistic evidence include: (a) few or no data are available; (b) there are unresolved questions about the adequacy of IARC Monographs Preamble the design, conduct, or interpretation of the studies; (c) the available result are negative.

Notes:
IARC = International Agency for Research on Cancer.
(a) Description text taken directly from IARC (2019).

The methods by which these agencies conduct their reviews vary, though all strive to use an objective systematic approach to review the scientific literature. These reviews generally involve many researchers and peer-reviewers and take years to complete. For example, ATSDR generates Toxicological Profiles, which reflect "a comprehensive and extensive evaluation, summary, and interpretation of available toxicological and epidemiological information on a substance" (ATSDR, 2024a).

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, these reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. This is sometimes a result of the frameworks themselves. For example, IARC (2019) concludes that an agent is a possible carcinogen (Group 2B) if there is "limited evidence of carcinogenicity in humans," "sufficient evidence of carcinogenicity in experimental animals," *or* "strong evidence that the agent exhibits key characteristics of carcinogens."

Limited evidence in humans means that "chance, bias, or confounding could not be ruled out with reasonable confidence" (IARC, 2019). If this is the case, one should not conclude the agent is a possible carcinogen, but that the data are not sufficient to make a scientifically informed judgment. This is consistent

with the IOM (2008) hierarchy, which states that "if there are several high-quality epidemiologic studies, the preponderance of which show evidence of an association that cannot readily be explained by plausible noncausal alternatives (e.g., chance, bias, or confounding), and the causal relationship is consistent with the animal evidence and biological knowledge, then the overall evidence might be categorized as Equipoise and Above."

Similarly, as noted above, the 10 KCCs on their own are not informative with respect to cancer risk, as many chemicals that are not carcinogenic share these characteristics (Goodman and Lynch, 2017; Goodman *et al*., 2018; Becker *et al*., 2017).

The US EPA and NTP carcinogenicity categories include ones similar to IARC's Group 2B ("possibly carcinogenic to humans"): "possibly carcinogenic to humans" and "reasonably anticipated to be a human carcinogen," respectively (US EPA, 2005; NTP, 2023). As with agents categorized in IARC's Group 2B, the available evidence for agents placed into the equivalent US EPA and NTP categories is generally not sufficient to make a scientifically informed judgment regarding their ability to cause cancer in humans. As such, for agents in IARC's Group 2B, US EPA's "possibly carcinogenic to humans" category, and NTP's "reasonably anticipated to be a human carcinogen" category, it is **not** always the case that the scientific evidence demonstrates that the agents are at least as likely as not to be human carcinogens. Rather, these classification categories indicate that additional evidence is required to make a scientifically informed conclusion regarding the carcinogenicity of the agent.

Regardless of the classification, it is important to note that classifications for all agents are based on specific cancer types. When an agency classifies a chemical as to its likelihood of being carcinogenic to humans, this classification does not apply to all cancer types.

3.5.2 ATSDR (2017a) Assessment

The review process for the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases" (ATSDR, 2017a) was quite different than those discussed above. ATSDR (2017a) stated, "The purpose [of this report] was to assess the strength of the evidence supporting causality of adverse health effects from exposures to the drinking water contaminants at Camp Lejeune. This report represents ATSDR's assessment of the state of evidence at this time." This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation. Its conclusions regarding causation for many health outcomes are inconsistent with those of several other agency reviews, including those by ATSDR.

3.5.2.1 Resources

In his recent deposition, Dr. Bove (2024a) indicated that he was the sole author of this report. He noted that a few senators requested that he conduct this review over a 6-week period. He stated, "During that period, I had enough material together so that it was peer-reviewed by two people to give their advice. One person liked it, one person didn't like it, but that – so – and I took their comments into account. And we briefed the VA [Veterans Affairs] researchers/scientists… And for the most part, they agreed with what my -- with what my assessment was. There were some disagreements."

It is simply not possible to conduct an objective, systematic review of four chemicals with a considerable amount of data and 16 health outcomes in 6 weeks. Systematic reviews can take months or years for teams of researchers to complete, and they then generally undergo a rigorous peer-review process. Bove (2024a) even acknowledged that this type of review was unusual to conduct at ATSDR.

3.5.2.2 Statistical Significance

With respect to evaluating individual studies, ATSDR (2017a) did not "use significance testing to assess the evidence for causality." ATSDR (2017a) stated, "There are several limitations to the use of statistical significance testing (Rothman et al. 2008, Goodman 2008, Stang et al 2010). Moreover, a finding that does not achieve statistical significance nonetheless can provide important evidence for a causal association, while a finding that achieves statistical significance can often lack scientific and public health significance." ATSDR (2017a) instead relied heavily on a concept later defined by Bove *et al*. (2024a,b) as a confidence interval ratio (CIR). This is the ratio of the upper 95% confidence limit to the lower 95% confidence limit. This is not a generally accepted metric in the field of epidemiology.

The report states that in a high-quality epidemiology study, "the effect of biases on the study's findings was probably low and the precision of the effect estimate was adequate, e.g., the width of the 95% confidence interval as measured by the ratio of the upper to lower limit is ≤ 3." Elsewhere the report states that "an effect estimate (e.g., risk ratio, odds ratio, or standardized mortality ratio) was considered to have good precision (or less uncertainty) if the ratio of the upper limit to lower limit of its 95% confidence interval was ≤ 2." It is not clear what the basis of these cutoffs were or why they were not the same.

While it is true that statistical significance should not be the only consideration for whether an association is causal, it is not appropriate to simply ignore it. As noted in Section 3.1.1, a 95% CI is derived to indicate a range of the sample risk ratio that has a 95% probability of capturing the true population risk ratio. If a sample risk ratio's 95% CI does not contain 1, there is a 95% probability that the underlying population's risk ratio is different from 1, indicating that we can reasonably exclude chance as an explanation (Naimi and Whitcomb, 2020). In contrast, if a sample risk ratio's 95% CI contains 1, one cannot confidently exclude the possibility that the underlying population's risk ratio is 1 (*i.e.*, there is no association). In other words, the sample risk ratio on its own does not provide statistically meaningful evidence for the existence of an association in the population.

In some cases, a true association in a population will not be statistically significant (*e.g.*, the 95% CI includes 1 or the *p* value is ≥ 0.05) because the sample is too small to detect it or other factors are masking the association (*e.g.*, exposure misclassification). For this reason, one cannot conclude with certainty that there is no association if a result is not statistically significant, only that the study does not provide evidence that there is an association. Conversely, a statistically significant result may not reflect a true or clinically relevant difference at the population level. However, if one were simply to ignore statistical significance, every single association studied would either support causation or a protective effect; there would be few true null results. I also note that the CIR is completely dependent on significance testing, only with less stringent criteria for what is considered "significant." That is, it appears to be a work-around for when statistical significance is not achieved, even though it is based on the same statistics.

Flaws with this reasoning are evident in the number of health conditions that ATSDR (2017a) concluded are causally associated with VOC exposure. Every chemical has some degree of specificity with respect to the health conditions it can cause, and it defies logic that the chemicals discussed in this report can cause many health conditions known to have very different MoAs.

3.5.2.3 Study Quality

ATSDR (2017a) discussed several limitations of the studies it evaluated but appears to downplay the impact of these limitations on the interpretation of these studies' results. For example, the report stated, "Drinking water studies included in this review based their exposure assessments on modeled historical estimates of

contaminant levels in the drinking water serving residences or workplaces. Information on the amount of water consumed by individuals was either limited (due to likely inaccuracies in the recall of past consumption habits) or unavailable." This can result in major exposure misclassification, but that is not adequately considered in this report.

Similarly, ATSDR (2017a) discussed confounding, but tends to downplay its impact, for example, indicating that "substantial confounding due to smoking or any other risk factor is rare in occupational and environmental epidemiology." However, smoking is a major confounder for several cancers. Even if smoking or another factor is not a confounder *per se*, but is associated with a health outcome, it should be considered in a rigorous manner.

In addition to these issues, ATSDR (2017a) did not review studies in a systematic manner. It is not clear how studies were selected to be discussed. Study quality is not evaluated in a systematic manner, and sometimes is not discussed at all.

3.5.2.4 Strength of Evidence

Perhaps most importantly, the criteria used in the ATSDR (2017a) report are not appropriate. ATSDR (2017a) claimed that it based its criteria on those put forth by IOM in its report, "Improving the Presumptive Disability Decision-Making Process for Veterans" (IOM, 2008). The requirements for categorizing levels of evidence for causation by IOM (2008) and ATSDR (2017a) are shown in Table 3.8. For each category, IOM (2008) requires more scientific evidence than ATSDR (2017a) does. For example, for the causal category, ATSDR (2017a) indicated that consistent positive associations >1.1 provide evidence for causation. The report does not discuss whether study quality needs to be considered when determining causality – only study utility (though utility is not defined in the report). In addition, ATSDR (2017a) does not cite a source for the cutoff of 1.1. A risk estimate of 1.1 is generally considered quite weak, and even a small amount of bias or confounding could influence a risk estimate by 10%. For example, in a recent review, US EPA (2019) characterized risk estimates from epidemiology studies as follows:

- no evidence of a positive association between exposure and outcome (*e.g.*, OR = 1.00; OR < 1.00);
- no evidence of a significant positive association (*e.g.*, OR > 1.00 but not significant);
- evidence of a slight positive association (*e.g.*, 1.00 < OR < 1.30 and significant);
- evidence of a positive association (*e.g.*, 1.30 ≤ OR < 2.0 and significant); and
- evidence of a moderately strong (*e.g.*, 2.0 ≤ OR < 3.0 and significant) or strong (*e.g.*, OR ≥ 3.0 and significant) positive association.

The criteria listed by ATSDR (2017a) for classifying evidence as "equipoise and above" are more consistent with the IOM (2008) criteria for "below equipoise" in that only one "high-utility" epidemiology study with a risk estimate of 1.1 or above is required. What constitutes a "high-utility" study is not clearly defined, and there is no indication that results of this one required study must be consistent with other studies, or that this risk estimate even needs to be statistically significant. ATSDR (2017a) also considers evidence above equipoise if "[t]he 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." There is no requirement that these experimental studies be high quality or relevant to humans. ATSDR (2017a) does not provide any criteria for evidence against causation.

It is notable that several other agency reviews include an analysis of the level of evidence for causation for the health conditions evaluated by ATSDR (2017a). While some of these reviews reach similar conclusions

for certain health outcomes (*e.g.*, benzene and leukemia/AML), as a whole, ATSDR (2017a) tends to conclude the evidence is stronger than other agency reviews do, including other reviews by ATSDR. For example, most government and scientific agency reviews either concluded that the scientific evidence is insufficient to make a determination regarding TCE and leukemia causation (IOM, 2003; NRC, 2009; US EPA, 2011, 2020b), or did not draw any conclusions regarding their potential association (ATSDR, 2019b; IARC, 2014a; IOM, 2015; NTP, 2015). In contrast, ATSDR (2017a) concluded that the evidence for TCE and leukemia was "sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists."

I provide brief summaries of leukemia assessments in agency reviews of TCE, PCE, benzene, and vinyl chloride in Sections 6.4, 7.4, 8.4, and 9.4, respectively.

Table 3.8 IOM (2008) and ATSDR (2017) Hierarchies of Evidence for Causation[a]

Level of Evidence	IOM (2008)	ATSDR (2017a)
Sufficient	If the overall evidence for a causal relationship is categorized as Sufficient, then it should be scientifically compelling. It might include • replicated and consistent evidence of a causal association: that is, evidence of an association from several high-quality epidemiologic studies that cannot be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding), or • evidence of causation from animal studies and mechanistic knowledge, or •compelling evidence from animal studies and strong mechanistic evidence from studies in exposed humans, consistent with (*i.e.*, not contradicted by) the epidemiologic evidence.	[T]he evidence is sufficient to conclude that a causal relationship exists. This category would be met, for example, if: 1. There is sufficient evidence from human studies in which chance and biases (including confounding) can be ruled out with reasonable confidence, or 2. There is less than sufficient evidence from human studies but sufficient evidence in animal studies and strong evidence that the agent acts through a relevant mechanism in humans. Sufficient evidence from human studies can be provided by a meta-analysis and/or by several studies considered to have high utility. Considerations in assessing the evidence include several of Hills viewpoints: (1) temporal relationship, (2) consistent positive associations (*e.g.*, risk ratio or odds ratio greater than 1.1), (3) magnitude of the effect estimate (*e.g.*, risk ratio, odds ratio), (4) exposure-response relationship, and (5) biological plausibility (Hill 1965).

Level of Evidence	IOM (2008)	ATSDR (2017a)
Equipoise and above	To be categorized as Equipoise and Above, the scientific community should categorize the overall evidence as making it more confident in the existence of a causal relationship than in the non-existence of a causal relationship, but not sufficient to conclude causation. For example, if there are several high-quality epidemiologic studies, the preponderance of which show evidence of an association that cannot readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding), and the causal relationship is consistent with the animal evidence and biological knowledge, then the overall evidence might be categorized as Equipoise and Above. Alternatively, if there is strong evidence from animal studies or mechanistic evidence, not contradicted by human or other evidence, then the overall evidence might be categorized as 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. 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.

Level of Evidence	IOM (2008)	ATSDR (2017a)
Below Equipoise	To be categorized as Below Equipoise, the overall evidence for a causal relationship should either be judged not to make causation at least as likely as not, or not sufficient to make a scientifically informed judgment. This might occur 1. when the human evidence is consistent in showing an association, but the evidence is limited by the inability to rule out chance, bias, or confounding with confidence, and animal or mechanistic evidence is weak, or 2. when animal evidence suggests a causal relationship, but human and mechanistic evidence is weak or inconsistent, or 3. when mechanistic evidence is suggestive but animal and human evidence is weak or inconsistent, or 4. when the evidence base is very thin.	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. This is a rather broad category that encompasses: • evidence sufficient to conclude an association exists but where there is some doubt that biases can be ruled out and the animal and mechanistic evidence is weak, or • evidence for an association that is so limited that there is substantial doubt that biases can be ruled out, or • insufficient evidence to determine whether an association exists.
Against	To be categorized as Against, the overall evidence should favor belief that there is no causal relationship from exposure to disease. For example, if there is human evidence from multiple studies covering the full range of exposures encountered by humans that are consistent in showing no causal association, or there is animal or mechanistic evidence supporting the lack of a causal relationship… then the scientific community should categorize the evidence as Against causation	The evidence suggests the lack of a causal relationship.

Notes:
(a) Text taken directly from IOM (2008) and ATSDR (2017a).

4 Carcinogenicity

4.1 Overview

Cancer is a term used to describe a group of over 100 chronic diseases that can develop in almost every part of the body (ACS, 2019a). Because organs and tissues are made up of several types of cells, several different types of cancer can arise in the same organ or tissue (ACS, 2019a). The "defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, which can then invade adjoining parts of the body and spread to other organs" (WHO, 2018). Chemical carcinogens impact specific biological pathways and can only cause specific cancer types (ACS, 2019b; Meek *et al*., 2014; US EPA, 2005). For example, radiation from sun exposure has been shown to cause various types of skin cancer (Berwick *et al*., 2005; Fartasch *et al*., 2012) but not any other type of cancer.

Carcinogenic substances can only affect cells by specific MoAs. The MoAs of known or suspected carcinogens are investigated based on physical, chemical, and biological information that explains key events in the development of tumors. While some carcinogens may have more than one MoA, as indicated by Meek *et al*. (2014), "In general, mode of action analysis applies to a single effect in a single tissue. In essence, there is one mode of action leading to an effect of interest in the relevant organ for a given substance." It is also important to note that carcinogens can only affect tissues that they, or their metabolites, can physically access. A carcinogenic substance cannot cause cancers in tissues that it cannot reach (US EPA, 2005).

In addition, in order for a substance to cause cancer, there must be sufficient exposure to that substance (Wolf *et al*., 2019). For example, high doses of ionizing radiation can cause cancer, but low doses cannot (ATSDR, 1999; Dobrzynski *et al*., 2015; HPS, 2020).

One of the primary characteristics of cancer is the latency period. According to NRC:

> For cancers, there is generally a period of time, which may be as long as several decades, between a critical molecular interaction of a carcinogen within a single cell and the first appearance of a malignant cell. The length of this period will vary based on the nature of the cancer and whether the molecular interaction occurs early or late in the chain of events leading to the cancer. That period between the critical exposure to the carcinogenic agent and the occurrence of the cancer is referred to as the latency period. Latency is usually estimated by determining the period between the time of first exposure to the carcinogen and the clinical detection of the cancer. (NRC, 2001)

Latency periods are disease specific and, for cancer, can range from <1 year (*e.g*., leukemias following low-level ionizing radiation [CDC, 2015]) to several decades (*e.g*., lung cancer development from smoking [CDC, 2014; Weisenburger, 1992; Weiss, 1997; Smith, 2001; Bilello *et al*., 2002; US PHS, 2004]). If a chemical exposure can cause cancer, it is often necessary for the exposure to occur repeatedly over a long period of time that is sufficiently before disease onset (*i.e*., at the beginning of the latency period).

In some cases, there is evidence that a chemical can only cause cancer within a certain time frame. For example, evidence suggests that benzene most likely only causes cancer within 10 to 15 years of exposure (Rhomberg *et al*., 2016).

It is often not known what the cause of cancer in a specific individual is or why one person develops cancer while another does not (NCI, 2015). While some researchers have suggested that extrinsic risk factors may play a large role in cancer causation (*e.g.*, McGuinn *et al.*, 2012; Whiteman and Wilson, 2016; Wu *et al.*, 2016), others conclude that the majority of cancers are due to random mutations in DNA that can arise during normal cell division (Tomasetti and Vogelstein, 2015). In these cases, mutations arise normally as errors in cell division and are not associated with specific chemicals or physical agents (meaning they occur naturally, not as a result of an exogenous exposure). Most of these mutations are repaired by the body, but some escape normal repair mechanisms, in some cases due to immune system irregularities (Johns Hopkins Medicine, 2019).

According to the American Cancer Society (ACS), "having a risk factor, or even several, does not mean that you will get the disease. Many people with one or more risk factors never get cancer, while others who get cancer may have had few or no known risk factors" (ACS, 2019c). Increasing age is considered the most important cancer risk factor, though cancer may develop at any age (NCI, 2015). Genetic changes that cause cancer can be inherited; therefore, a family history of cancer can indicate that a person may be genetically predisposed to develop cancer (NCI, 2017). There are also common, modifiable lifestyle factors that contribute to the development of cancer. For example, people who smoke or who are exposed to secondhand smoke have an increased risk of cancer. In fact, Johns Hopkins Medicine states that "cancerous tumors from the use of tobacco are the leading cause of deaths from cancer" (Johns Hopkins Medicine, 2019). In addition to smoking, being overweight or obese increases a person's risk of developing certain types of cancer (NCI, 2015). Other common risk factors for cancer include radiation and extreme sun exposure (Johns Hopkins Medicine, 2019).

4.2 Leukemia

Leukemia, which starts in the tissues that form blood, is the 11th most common cancer in the United States (US), accounting for about 3% of all cancers (NCI, 2023a). This cancer generally develops from myeloid cells or lymphocytes in the bone marrow. Leukemias are categorized based on the time-course of disease development (*i.e.*, chronic *vs.* acute) and the type of white blood cells affected (*i.e.*, myeloid *vs.* lymphoid) (ACS, 2019d).

The two main categories of leukemia based on cell type are myeloid leukemias (*i.e.*, affecting the progenitors of other cell types in the hematopoietic system, such as red blood cells, other types of white blood cells, and platelets) and lymphoid leukemias (*i.e.*, affecting the cells that form lymphocytes, a type of infection-fighting immune cell) (Eastmond *et al.*, 2014). The two main leukemia categories based on the time-course of disease development are acute and chronic leukemias (Eastmond *et al.*, 2014; Lightfoot *et al.*, 2008). In the acute forms of the disease, the buildup of abnormal cells, as well as the disease progression, typically takes place more rapidly than in the chronic forms of the disease. In chronic leukemias, more mature forms of blood cells are present (Lightfoot *et al.*, 2008). In leukemia, blasts are immature white blood cells that develop abnormally and multiply uncontrollably. Blasts are also known as leukemia cells when leukemia is diagnosed. "The number of leukemic cells in the blood is highly variable. Occasionally, blasts are entirely absent from the blood (aleukemic leukemia [also called aleukemia])" (Kumar *et al.*, 2021). The three major types of leukemia are ALL, AML, and CML (Eastmond *et al.*, 2014). Each leukemia subtype is further classified based on morphological, cytochemical, and immunophenotypic features (ACS, 2018e,f). MDS is a group of blood disorders that are associated with a high risk of developing AML (Loscalzo *et al.*, 2022). It is also considered a type of leukemia.

The classification of lymphoid and hematological malignancies has evolved over time, which leads to some difficulties in evaluating specific lymphoid or hematological cancers in older and newer studies combined.

For example, chronic lymphocytic leukemia (CLL) was historically classified as a type of leukemia, but in recent classification schemes, it is more often classified as a subtype of non-Hodgkin lymphoma (NHL) (Loscalzo *et al*., 2022). As such, I do not review CLL in this report, unless epidemiology studies included CLL in their definition of leukemia. In addition, AML is currently called acute nonlymphocytic leukemia (ANLL) (ACS, 2019d). Historically, ANLL also included some other leukemias in addition to AML, although even then most ANLLs were AMLs.

NCI estimated that, in 2023 in the US, there would be 59,610 new cases and 23,1710 deaths due to leukemia. Leukemia was expected to represent approximately 3.0% of all new cancer cases in 2023 in the US and, in 2020, there were an estimated 490,875 people in the US living with leukemia. NCI reported an overall lifetime risk of being diagnosed with this cancer of 1.6% for people in the US, based on data from 2017-2019. Leukemia is more common in men than women. For the period of 2016-2020, the overall age-adjusted incidence rate was 17.8 per 100,000 men and 10.9 per 100,000 women in the US. About 64.1% of all new US leukemia cases are diagnosed in people between the ages of 55 and 84 years, with a median age at diagnosis of 67 years (NCI, 2023a). Descriptive statistics by leukemia subtype are in Table 4.1.

AML is a relatively rare disease; NCI estimated that AML would make up 1% of all new cancer cases in 2023 (NCI, 2023b). AML is more common in older adults, with a median age at diagnosis of 69 years and 66.4% of cases occurring between age 55 years and 84 years in 2016-2020 (NCI, 2023b). However, younger people can get AML; one subtype, acute promyelocytic leukemia (APL), is most often diagnosed in people between the ages of 20 and 50, with a median age of 40 to 47 years. The multiple subtypes of AML that are defined by the type and maturity of the cells from which AML develops and factors that affect prognosis, like certain genetic mutations. There are two main systems that are used to classify AML, the French-American-British (FAB) classification and the World Health Organization (WHO) classification (ACS, 2018e).

Among demographic risk factors, being male and older make it more likely that an individual will develop AML. Other risk factors include exposure to high-dose radiation, a family history of AML, certain genetic syndromes (*e.g*., Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, Li-Fraumeni syndrome, neurofibromatosis type, Kostmann syndrome, Down syndrome, and trisomy 8), and some blood disorders (*e.g*., chronic myeloproliferative disorders). Among potentially modifiable AML risk factors, the strongest evidence is for smoking (ACS 2018b; US PHS, 2004). Long-term exposure to benzene and certain chemotherapy drugs (*e.g*., alkylating agents and topoisomerase II inhibitors) have also been linked to AML (ACS, 2018b).

Most cases of ALL occur in children, with a median age at diagnosis of 17 years and 53.5% of cases being diagnosed in patients under 20 years of age (ACS, 2024; NCI, 2023c). Children under 5 years of age are at the highest risk of ALL, with risk declining until the mid-20s, and starting to rise again slowly after 50 years of age (ACS, 2024). There's some overlap in risk factors between AML and ALL. Demographic risk factors for ALL include age, male sex, and white race. Having an identical twin with ALL and certain genetic syndromes (*e.g*., Down syndrome, Klinefelter syndrome Fanconi anemia, Bloom syndrome, Ataxia-telangiectasia, Neurofibromatosis, and Li-Fraumeni syndrome) also increase the risk of developing ALL (ACS, 2018c). Other risk factors include exposure to high-dose radiation, infection with human T-cell lymphoma/leukemia virus-1 (HTLV-1), and Epstein-Barr virus (EBV). However, these two viral infections are associated with types of ALL that are not common in the US (ACS, 2018c).

"CML is distinguished from other myeloproliferative neoplasms by the presence of a chimeric BCR-ABL gene…. In more than 90% of cases, BCR-ABL is created by a reciprocal (9;22)(q34;q11) translocation (the so-called 'Philadelphia Chromosome')" (Kumar *et al*., 2021). CML is more common in older adults. Diagnoses of CML is highest in the fifth and sixth decades of life (Kumar *et al*., 2021), and the median age at diagnosis is 66 years (NCI, 2023d). In 2016-2020 only 2.1% of new cases occurred in people under

20 years of age (NCI, 2023d). Known risk factors for CML include older age, male sex, and exposure to high-dose radiation (ACS, 2018a).

MDS (formerly known as "preleukemia") are a diverse collection of conditions characterized by ineffective production of blood cells, leading to cytopenia, and varying risks of transformation to AML (Loscalzo *et al*., 2022). There are several subtypes of MDS, which have been historically identified according to the FAB system and more recently under the WHO classification system (Loscalzo *et al*., 2022). The most common form is MDS with multi-lineage dysplasia (MDS-MLD), which was previously referred to as refractory cytopenia with multilineage dysplasia (RCMD) (ACS, 2018g). The second most common form, MDS with excess blasts (MDS-EB), occurs in approximately 25% of MDS cases; this form was previously known as refractory anemia with excess blasts (RAEB) (ACS, 2018g). MDS-EB/RAEB is the most common form that can develop into AML (ACS, 2018g). RAEB is subdivided into RAEB1 and RAEB2, which have very different prognoses in terms of transformation to AML. Since the 2008 WHO classification, refractory anemia (RA) has been included in the more general classification of refractory cytopenia with unilineage dysplasia (RCUD) (IARC, 2008a). MDS is considered a "disease of the elderly," and the average age of diagnosis is over 70 (Loscalzo *et al*., 2022). In addition to age, risk factors for MDS include sex, prior cancer treatment, genetics, a family history of MDS, smoking, and occupational/chemical exposures (ACS, 2018d).

Table 4.1 Descriptive Statistics of Leukemia and Some Subtypes

Statistic	Leukemia	AML	ALL	CML	MDS[a]
New cases (n)[b]	62,770	20,800	6,550	9,280	15,529[c]
New deaths (n)[b]	23,670	11,220	1,330	1,280	–
Percent of new cancers (%)[d]	3.1%	1.0%	0.3%	0.5%	–
Prevalence (n)[d]	508,796	75,266	115,294	66,366	60,253
Lifetime risk (%)[e]	1.5%	0.5%	0.1%	0.2%	–
Rate in men[f]	17.9	5.1	2.1	2.5	5.4
Rate in women[f]	11.0	3.5	1.6	1.5	2.9

Notes:
ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; CML = Chronic Myeloid Leukemia; MDS = Myelodysplastic Syndrome; SEER = Surveillance, Epidemiology, and End Results Program.
Sources: Leukemia = NCI (2024b); AML = NCI (2024c-e); MDS = NCI (2023e); Leukemia & Lymphoma Society (2024).
– = Not Reported.
(a) SEER does not provide detailed data on MDS (NCI, 2024f).
(b) Estimated number of new cases or deaths for 2024.
(c) Average of new MDS cases diagnosed from 2016-2020 (Leukemia & Lymphoma Society, 2024).
(d) Estimated number of people living with this cancer in 2021.
(e) Based on 2018-2021 data, excluding 2020.
(f) Age-adjusted rate (per 100,000) of new cases based on data from SEER 22 from 2017-2021.

5 Camp Lejeune Studies

NRC (2009) produced the report, "Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects." The report concluded, "The available scientific information does not provide a sufficient basis for determining whether the population at Camp Lejeune has, in fact, suffered adverse health effects as a result of exposure to contaminants in the water supplies." NRC (2009) went on to say:

> Additional research on potential health effects of water contamination at Camp Lejeune are unlikely to provide definitive information on whether exposure to it resulted in adverse health effects. Limitations in population size, data availability, and data quality cannot be overcome. Those limitations are due in part to the lack of documentation of exposure and the difficulty in assessing the health events that residents experienced after they were exposed. Even if ATSDR's planned work goes forward successfully, the outcome of the efforts is unlikely to determine conclusively whether Camp Lejeune residents were adversely affected by exposure to water contaminants.

Despite this, several Camp Lejeune epidemiology studies were conducted after the NRC (2009) report. Below I review five cohort studies that evaluated leukemia risks in US Marines and Navy personnel or civilian employees at Camp Lejeune (Bove *et al*., 2014a,b, 2024a,b; ATSDR, 2018b).[8] The characteristics and results of these studies are detailed in Attachment B and the quality is detailed in Attachment C. Below, I provide brief summaries of each study and describe important quality considerations that impact the interpretation of study results, followed by a discussion of the study results.

5.1 Study Overview

5.1.1 Study Populations

The study populations examined in the five Camp Lejeune studies overlap but are not identical. All studies used appropriate comparison groups. The three mortality studies (Bove *et al*., 2014a,b, 2024b) had low loss to follow-up, largely because of their reliance on historical records for enrollment and outcome ascertainment. Bove *et al*. (2024a) did not report on loss to follow-up. The cohort study conducted by ATSDR (2018b) reported low response rates to the health survey among military personnel and civilian employees at Camp Lejeune and Camp Pendleton (31% overall). It is not known how those who did not participate differed from those who did.

[8] ATSDR (2018b) analyzed Marine and Navy personnel and civilian employee cohorts, as well as ATSDR 1999-2002 survey respondents (described in Ruckart *et al*., 2013), which included Marines and their spouses and children. The 1999-2002 survey was conducted to investigate health outcomes in children born at Camp Lejeune before 1985. Marines who responded to the 1999-2002 survey who were stationed at Camp Lejeune after March 1975 were included in the Marine cohort in ATSDR (2018b). Marines stationed at Camp Lejeune before March 1975 and their spouses and children were analyzed separately in ATSDR (2018b), because there was no available comparison group so the results were necessarily qualitative, and are not included in my report. Ruckart *et al*. (2013) evaluated childhood leukemia and NHL combined as "childhood hematopoietic cancers." Because I do not evaluate childhood leukemia and the results are not specific to leukemia, I do not discuss this study here. I also do not discuss Rosenfeld *et al*. (2024a,b) because this is a cancer risk assessment and not specific to leukemia, and is outside the scope of my report.

The compilation of the study cohorts in the four Bove *et al*. (2014a,b, 2024a,b) studies relied on historical records, which likely did not result in any selection bias. ATSDR (2018b) actively recruited participants *via* mail surveys. At the time of recruitment, the contamination at Camp Lejeune was well known. ATSDR (2018b) stated that:

> [S]election bias could have impacted analyses comparing Camp Lejeune to Camp Pendleton, likely biasing results away from the null (potentially overestimating the effect of the exposures) because those at Camp Lejeune with health problems may have been more likely to participate than those at Camp Pendleton with health problems. The Camp Lejeune participants with health problems may have been more likely to participate because they were aware of the contaminated drinking water and believed they were affected by their exposures.

This is supported by the fact that civilian employees at Camp Lejeune had a higher participation rate than civilian employees at Camp Pendleton and Marines at either base (see Table 1 of ATSDR, 2018b).

5.1.2 Exposure Assessment

All five studies included at least some comparisons of leukemia risks in Camp Lejeune populations to risks in Camp Pendleton populations without consideration of chemical specific exposures or doses. Two of the studies (Bove *et al*., 2024a,b) considered disease risk by duration of assignment or employment on base, but this did not account for chemical concentrations in the water during each individual's assignment or individual water consumption.

Some studies conducted analyses of Marines and Navy personnel who began active duty before 1975. There are no data available on military unit codes for Marines and Navy personnel who began active duty prior to 1975. These individuals could have been stationed at Camp Pendleton, Camp Lejeune, or elsewhere prior to 1975, leading to exposure misclassification.

Bove *et al*. (2014a,b) and ATSDR (2018b) estimated individual exposures at Camp Lejeune based on modeled average monthly levels of chemicals in drinking water on base. These levels were estimated based on ATSDR (2007a, 2013) groundwater fate and transport models and data on historical occupation codes, workplace or residence, and period and duration of employment or residence.

Modeled exposure estimates are generally less reliable than direct measurements, particularly when modeled estimates are only based on limited or sparse quantitative information or are not based on any quantitative information. Also, modeled exposure estimates based on chemical concentrations in the groundwater supplying different locations on base depend on the accuracy of the model's assumptions, and, while the time-varying nature of the water concentrations of chemicals were considered in the ATSDR model, the modeled estimates are constrained by the limited timing and frequency of measurements and do not necessarily reflect long-term or even average concentrations.

Drs. Hennet's and Spiliotopoulos's reports show that, for several reasons, including the lack of chemical concentration data prior to 1980 and the lack of reliable data on the start and quantity of contaminant source releases, ATSDR's modeled exposure estimates are biased high, raising questions about quantitative exposure estimates derived from this model (Hennet, 2024; Spiliotopoulos, 2024). Furthermore, without a direct link between measurements or modeled exposure estimates and individual-level water consumption/exposure data, exposure estimates are likely to be even less accurate with respect to individual exposures. Similarly, the ATSDR (2017b) "Public Health Assessment for Camp Lejeune Drinking Water" stated:

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

Finally, Bove *et al*. (2014a) and ATSDR (2018b) reported near perfect correlations between the TCE, benzene, vinyl chloride, and total VOC categorical exposure variables among Marines and Navy personnel. For civilian employees, Bove *et al*. (2014b) reported high correlations between TCE, PCE, benzene, and vinyl chloride, while ATSDR (2018b) reported that categorical exposure variables for TCE and PCE were nearly perfectly correlated. Therefore, results from these studies are not specific to individual chemical exposures.

With respect to exposure misclassification, ATSDR (2018b) stated:

> Additionally, the study results could have been impacted by exposure misclassification bias. Exposure misclassification bias could have resulted because of errors in base assignments, limited information on each unit's barrack location, lack of information on how much drinking water was consumed at the Marine's residence, lack of data on where a Marine at Camp Lejeune trained on-base and drinking water use during training, inability to accurately capture time spent away from the base for training or deployment, uncertainty about the drinking water use of civilian workers at Camp Lejeune, and uncertainty about workplace locations (*e.g.*, during the workday, a worker might have been assigned to multiple locations at the base). The exposure misclassification bias is likely non-differential because the errors in exposure assignments should be unrelated to diseases status.

Nondifferential exposure measurement error can, but does not always, bias results towards the null (*i.e*., towards a lack of effect). It is only guaranteed to bias associations towards the null under specific conditions (Van Smeden *et al*., 2020). It has been demonstrated that when evaluating multiple exposure categories (Dosemeci *et al*., 1990; Van Smeden *et al*., 2020) or categories formed from continuous exposure measurements (Flegal *et al*., 1991), non-differential misclassification can result in bias either toward or away from the null.

5.1.3 Outcome Assessment

Bove *et al*. (2014a,b, 2024b) evaluated mortality among Marines and Navy personnel who were stationed at Camp Lejeune between 1975 and 1985 and civilian workers at Camp Lejeune who were employed full-time between 1972 or 1973 and 1985.

ATSDR (2018b) and Bove *et al*. (2024a) evaluated disease incidence. ATSDR (2018b) examined incidence among Marines and Navy personnel and civilian employees stationed or employed at Camp Lejeune between 1972 and 1985. Bove *et al*. (2024a) evaluated disease incidence among Marines and Navy

personnel stationed at Camp Lejeune between 1975 and 1985 and among civilians employed at Camp Lejeune between 1972 and 1985.

All four Bove *et al*. (2014a,b, 2024a,b) studies used reliable sources to identify cases or deaths (*i.e*., Social Security Administration [SSA], commercial tracing services, National Death Index [NDI], cancer registries). ATSDR (2018b) confirmed cases using medical records or death certificates, but initially relied on self-reports to identify cases, which could have resulted in some missed cases. All studies had sufficient follow-up time for cancer to develop (range: 22-41 years) but, because leukemia is not always fatal, analyses evaluating incidence are more informative than those evaluating mortality.

All of the studies evaluated leukemia overall, and some of the studies also evaluated leukemia subtypes. Bove *et al*. (2014b) estimated ANLL risks comparing rates in Camp Lejeune civilian employees to Camp Pendleton civilian employees. Bove *et al*. (2024a) provided results for ALL, AML, and CML. Bove *et al*. (2024b) provided results for ALL, AML, CML, and MDS. Bove *et al*. (2014a) and ATSDR (2018b) only provided results for all leukemias combined.

5.1.4 Covariates

ATSDR (2018b) controlled for age, or age and sex, in analyses of Marines and Navy personnel. The study either controlled for age or did not control for any covariates in analyses of civilian employees. All four Bove *et al*. (2014a,b, 2024a,b) studies controlled for age, sex, race, and education in some analyses. Bove *et al*. (2014b, 2024a,b) also controlled for occupation (blue *vs.* white collar) as a proxy for other chemical exposures when comparing risks to those civilians employed at Camp Pendleton and in analyses within the civilian Camp Lejeune cohort. No Camp Lejeune study controlled for other important covariates, including smoking (for which no data were available), family history of leukemia, genetics, blood disorders, chemotherapy treatment, and certain viral infections.

Two of the Camp Lejeune studies (Bove *et al*., 2014a,b) considered smoking indirectly. Bove *et al*. (2014a,b) evaluated whether the risk of smoking-related diseases that were not associated with solvents were different in the Camp Lejeune and Camp Pendleton populations. Bove *et al*. (2014a) concluded that there was minimal confounding from smoking in their study of Marines and Navy personnel because the "HRs for other smoking-related diseases such as cardiovascular disease, and cancers of the bladder, esophagus, stomach, pancreas, and liver were <1.0 in the Camp Lejeune cohort." Similarly, Bove *et al*. (2014b) stated:

> Among the smoking-related diseases not known to be associated with solvent exposure, only COPD [chronic obstructive pulmonary disease] was elevated in the Camp Lejeune cohort with HR of 1.21. Using the HR for COPD to adjust for the possible confounding effects of smoking would reduce the HRs for the diseases of primary and secondary interest by approximately 17.5%.

While smoking increases the risk of AML and MDS, it does not increase the risk of all smoking-related diseases equally (American Lung Association, 2024). The degree to which smoking contributed to these smoking-related diseases in study participants is unknown, and this analysis is not informative with respect to the degree of confounding from smoking in other cancer risk estimates.

Finally, the amount of missing covariate data reported varied by study, but none reported having no missing data, which limits the ability to fully interpret the results.

5.1.5 Temporality

All studies had documented exposures prior to the onset of disease, and Bove *et al*. (2014a,b, 2024a) appropriately considered disease latency by incorporating 10-year lags in some analyses. Bove *et al*. (2024b) did not consider disease latency in their analyses but noted that 75% of the deaths occurred more than 10 years after the water contamination ended. ATSDR (2018b) also did not consider disease latency in their analyses, but stated that, "virtually all participants with a confirmed cancer of interest developed their cancers ten years or more after they were first stationed or worked at either base."

5.2 Study Results

5.2.1 Bove *et al*. (2014a)

Bove *et al*. (2014a) retrospectively evaluated leukemia deaths among 154,932 Marines and Navy personnel who were stationed at Camp Lejeune between 1975 and 1985 and potentially exposed to contaminated drinking water on base. Between 1979 and 2008, there were 66 leukemia deaths in this cohort.

5.2.1.1 Leukemia

The authors observed fewer leukemia deaths among Camp Lejeune Marines and Navy personnel than expected based on US general population rates (SMR = 0.78, 95% CI: 0.60-0.99). There was no difference between leukemia mortality in Camp Lejeune Marines and Navy personnel and that of 154,969 Marines and Navy personnel at Camp Pendleton (10-year lag HR = 1.11, 95% CI: 0.75-1.62).

There were no trends of increasing leukemia mortality risks with increasing cumulative exposures (based on fate and transport models) to TCE, PCE, benzene, or vinyl chloride when Marines and Navy personnel at Camp Lejeune were compared to those at Camp Pendleton (HR range: 0.73-1.47). Similarly, there were no observed trends of increasing risks with increasing cumulative exposures to TCE, PCE, or vinyl chloride within the Camp Lejeune cohort, though HRs were consistently above 1 (HR range: 1.27-2.00). However, there was an increased risk of leukemia death for those in the "low" benzene exposure group (*i.e*., 2-45 µg/L-months) when compared with those with exposures <2 µg/L-months within the Camp Lejeune cohort (HR = 2.54, 95% CI: 1.27-5.08), but this was not the case for higher exposed groups, indicating a lack of dose response. The authors also evaluated exposure-response relationships and found an association in the $\log_{10}$ continuous cumulative benzene exposure model ($p = 0.05$), but not in models for any other chemical ($p > 0.05$). As discussed in Section 5.1.2, the estimated water concentrations of benzene and other chemicals were not likely accurate or reliable.

5.2.2 Bove *et al*. (2014b)

Bove *et al*. (2014b) retrospectively evaluated leukemia and ANLL deaths among 4,647 civilian workers at Camp Lejeune who were employed full-time between 1973 and 1985 and potentially exposed to contaminated drinking water on base. Between 1979 and 2008, there were 12 leukemia deaths in this cohort.

5.2.2.1 Leukemia

The authors did not observe more leukemia deaths among Camp Lejeune civilian employees than expected based on rates in the US general population (SMR = 1.55, 95% CI: 0.80-2.71). This was also true based on rates among 4,690 civilian employees at Camp Pendleton (10-year lag HR = 1.59, 95% CI: 0.66-3.84).

There were no trends of increasing mortality risks with increasing cumulative exposures to TCE, PCE, benzene, or vinyl chloride (based on fate and transport models) when civilian employees at Camp Lejeune with medium (10-year lag HR range: 0.36-1.01) or high exposure (10-year lag HR range: 1.25-1.82) were compared to those with no or low exposures. In comparisons between civilian employees with greater than or equal to the median maximum cumulative exposure level of TCE, PCE, benzene, or vinyl chloride and those with less than the median level, risk estimates were consistently above 1 but low in magnitude and none were statistically significant (10-year lag HR range: 1.30-1.44). The authors also evaluated exposure-response relationships using both continuous and $\log_{10}$ continuous cumulative exposure models for each chemical and did not report any statistically significant trends with leukemia mortality for any chemical (all $p > 0.05$). As discussed in Section 5.1.2, the estimated water concentrations of benzene and other chemicals were not likely accurate or reliable.

5.2.2.2 ANLL

The number of ANLL diagnoses among Camp Lejeune civilian employees was not higher than expected based on the rate in Camp Pendleton employees (10-year lag HR = 2.13, 95% CI: 0.57-7.95, exposed cases = 6).

5.2.3 ATSDR (2018b)

ATSDR (2018b) retrospectively evaluated leukemia incidence among 50,684 Marines and Navy personnel stationed at Camp Lejeune between 1975 and 1985 and 2,168 civilian employees employed at Camp Lejeune between 1972 and 1985 and potentially exposed to contaminated drinking water on base. A health survey was administered between 2011 and 2012 that collected information on cancer and lifestyle and demographic factors. Between 1975 and 2012, there were 125 leukemia cases among Marines and Navy personnel and between 1972 and 2012, there were 8 cases among civilian employees at Camp Lejeune.

5.2.3.1 Leukemia

The risk of leukemia among Camp Lejeune Marines and Navy personnel and civilian employees at Camp Lejeune was similar to that in Camp Pendleton Marines and Navy personnel (OR = 0.97, 95% CI: 0.61-1.52) and civilian employees (OR = 1.10, 95% CI: 0.36-3.38).

The categorized levels (low, medium, high) of TCE, benzene, vinyl chloride, and total VOCs for the Marines and Navy personnel analyses were almost completely correlated in this study ($\gamma = 0.99$), so results were only presented for TCE and PCE ($\gamma = 0.88$). For male Marines and Navy personnel and all civilian employees, cut points at the 50th ("medium exposure") and 90th ("high exposure") percentiles of estimated TCE and PCE exposure levels were used to categorize the exposures. For female Marines and Navy personnel, cut points at the 75th and 90th percentiles were used to categorize exposures because the 50th percentile was 0 ppb for each contaminant. Compared to those at Camp Pendleton, Marines and Navy personnel at Camp Lejeune had a lower risk of leukemia incidence associated with highest level of cumulative exposure to TCE (*i.e.*, ≥11,030 µg/L-months; OR = 0.28, 95% CI: 0.09-0.83). This association

was similar when comparing those with high TCE exposure to those with low TCE exposure (<110 μg/L-months) at Camp Lejeune (OR = 0.26, 95% CI: 0.09-0.72), but trend tests were not reported. No associations were observed with increasing cumulative PCE exposure in either external or internal analyses.

The correlation between TCE and PCE in civilians was approximately equal to one, so results were reported for TCE and PCE combined. Compared to civilian employees at Camp Pendleton, no associations or trends were observed with increasing cumulative TCE/PCE exposure among civilian employees at Camp Lejeune. Similarly, no associations were observed when comparing those civilian employees with medium (OR = 1.69, 95% CI: 0.38-7.57) or high TCE/PCE exposure (OR = 1.58, 95% CI: 0.16-15.30) at Camp Lejeune with those employees with low TCE/PCE exposure. As discussed in Section 5.1.2, the estimated water concentrations of benzene and other chemicals were not likely accurate or reliable.

5.2.4 Bove *et al*. (2024a)

Bove *et al*. (2024a) retrospectively evaluated leukemia, ALL, CML, and AML incidence among 154,821 Marines and Navy personnel who began service and were stationed at Camp Lejeune between 1975 and 1985 and 6,494 civilians employed at Camp Lejeune between 1972 and 1985, all of whom may have been exposed to contaminated drinking water on base. Between 1996 and 2017, there were 314 leukemia cases among Marines and Navy personnel and 36 cases among civilian employees at Camp Lejeune.

5.2.4.1 Leukemia

Leukemia incidence among Marines and Navy personnel at Camp Lejeune who began active duty between 1975 and 1985 was similar to that among Marines and Navy personnel at Camp Pendleton (HR = 1.07, 95% CI: 0.91-1.25); this was also true for all Marines and Navy personnel, regardless of start date (HR = 1.05, 95% CI: 0.93-1.18). No associations or trends were observed when comparing Camp Lejeune Marines and Navy personnel with increasing durations of assignment to Camp Pendleton Marines and Navy personnel.

Among civilian employees at Camp Lejeune, leukemia incidence was not different from that among Camp Pendleton civilian employees (HR = 0.86, 95% CI: 0.54-1.36). No associations were observed when comparing Camp Lejeune civilian employees with increasing duration of assignment to Camp Pendleton civilian employees.

5.2.4.2 ALL and CML

The authors observed 23 ALL and 39 CML cases among Marines and Navy personnel at Camp Lejeune. There were no associations between being assigned, or duration of assignment, at Camp Lejeune and ALL or CML incidence when rates were compared to those in Camp Pendleton Marines and Navy personnel. Among civilian employees at Camp Lejeune, only 1 ALL case and 6 CML cases were observed, and there were no associations reported when compared to Camp Pendleton civilian employees (HR = 0.27, 95% CI: 0.03-2.63 for ALL, and HR = 0.69, 95% CI: 0.24-2.01 for CML). No associations between duration of employment at Camp Lejeune as a civilian employee and CML incidence were observed in analyses using Camp Pendleton civilian employees as a reference.

5.2.4.3 AML

The authors reported an increased risk of AML when incidence rates in Marines and Navy personnel at Camp Lejeune who began service between 1975 and 1985 were compared to those in Camp Pendleton Marines and Navy personnel (HR = 1.38, 95% CI: 1.03-1.85). This was also true for the full cohort of Camp Lejeune Marines and Navy personnel (*i.e.*, not just those who began service between 1975 and 1985) (HR = 1.34, 95% CI: 1.07-1.67). When comparing Camp Lejeune Marines and Navy personnel with increasing duration of assignment to Camp Pendleton Marines and Navy personnel, there was a statistically significant increased risk in the highest duration of assignment (*i.e.*, >10 quarter years; HR = 1.90, 95% CI: 1.12-3.21), but not for the lower durations (low [1-6 quarter years] HR = 1.36, 95% CI: 0.97-1.90; medium [7-10 quarter years] HR = 1.11, 95% CI: 0.66-1.87). Among civilian employees, the authors observed 14 AML cases, and there were no associations with AML risk overall or by duration of employment compared to civilian employees at Camp Pendleton.

5.2.5 Bove *et al*. (2024b)

Bove *et al*. (2024b) retrospectively evaluated leukemia, ALL, AML, CML, and MDS mortality among 159,128 Marines and Navy personnel stationed or employed at Camp Lejeune between 1975 and 1985 and 7,332 civilians employed at Camp Lejeune between 1972 and 1985, all who had been potentially exposed to contaminated drinking water on base. Between 1979 and 2018, there were 142 leukemia deaths among Marines and Navy personnel and 31 leukemia deaths among civilian employees at Camp Lejeune.

5.2.5.1 Leukemia

The number of observed leukemia deaths among Marines and Navy personnel at Camp Lejeune were not different than expected based on US general population rates (SMR = 0.87, 95% CI: 0.73-1.02). When compared with Camp Pendleton Marines and Navy personnel, there was no increase in leukemia mortality risk observed among Camp Lejeune Marines and Navy personnel (HR = 1.10, 95% CI: 0.87-1.40) and no trends or associations were observed based on increasing duration of assignment.

The number of observed leukemia deaths among civilian employees at Camp Lejeune was what was expected based on US general population rates (SMR = 0.98, 95% CI: 0.67-1.39). Risks were also similar to those in Camp Pendleton civilian employees (HR = 1.00, 95% CI: 0.61-1.64). No associations were observed among Camp Lejeune civilian employees with increasing durations of employment when compared with Camp Pendleton civilian employees.

5.2.5.2 ALL, AML, CML, and MDS

The authors observed 20 ALL, 62 AML, 11 CML, and 11 MDS deaths among Marines and Navy personnel at Camp Lejeune. No associations between being assigned, or duration of assignment, at Camp Lejeune and mortality from any of these leukemia subtypes were observed when rates were compared with those among Camp Pendleton Marines and Navy personnel. Among civilian employees at Camp Lejeune, the authors observed 15 AML and 8 CML deaths. ALL and MDS deaths among civilian employees were not investigated. No associations or trends between being employed, or duration of employment, at Camp Lejeune and AML or CML mortality were observed when compared with Camp Pendleton civilian employees.

5.3 Toxicology

No animal carcinogenicity or mechanistic studies have investigated exposures to Camp Lejeune drinking water. As discussed in Sections 6.2, 7.2, 8.2, and 9.2, respectively, toxicity studies of TCE, PCE, benzene, and vinyl chloride either do not support causation at all, or do not provide evidence for a casual association with leukemia at Camp Lejeune. I did not identify any chronic *trans*-1,2-DCE animal toxicity studies.

5.4 Exposure

TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE concentrations in the water supply at Camp Lejeune have been modeled by ATSDR (2007a, 2013). As noted in Section 5.1.2, these values are unreliable and biased high. Still, in its assessment of potential health effects from contaminated drinking water at Camp Lejeune, NRC (2009) stated:

> Because of the historical and complex nature of the contamination that occurred at Camp Lejeune and the availability of few empirical data on concentrations in water supplies, only crude estimates of exposure can be obtained. Even with the use of reasonable and, in some cases, advanced approaches, limitations in data availability and quality cannot be overcome. Thus, only a general conclusion can be drawn that the Tarawa Terrace and Hadnot Point water-supply systems were contaminated and that residents and workers were exposed to the contaminants in a highly variable manner. Additional work should make it possible to assign exposure categories of exposed and unexposed based on time and residence with reasonable certainty.

To calculate VOC exposures at Camp Lejeune, NRC (2009) stated:

> Standard assumptions commonly used for hazard evaluations are that adults weigh an average of 70 kg and drink an average of 2 L of water per day and that children weigh an average of 10 kg and drink 1 L of water per day. Exposure via inhalation and dermal absorption of VOCs from water during showering, bathing, dishwashing, and other household activities has been shown experimentally to account for as much exposure as that from drinking water that contains the chemicals (see Chapter 3). Therefore, to account for potential inhalation and dermal uptake in addition to ingestion in drinking water, an intake of 4 L/day is assumed for adults and 2 L/day for children. This calculation, therefore, takes into account all three routes of exposure—ingestion, inhalation, and dermal—of both adults and children.

Assuming a person was exposed to twice the highest measured TCE and PCE concentrations in drinking water at Camp Lejeune (2,800 and 400 µg/L, respectively), NRC (2009) calculated TCE and PCE exposure levels of 0.2 and 0.02 mg/kg-day, respectively. NRC (2009) did not calculate benzene, vinyl chloride, or *trans*-1,2-DCE exposure levels.

NRC (2009) noted, "The lowest doses at which adverse health effects have been seen in animal or clinical studies are many times higher than the worst-case (highest) assumed exposures at Camp Lejeune."

5.5 Conclusions

Five studies evaluated leukemia risks among Marines and Navy personnel stationed at Camp Lejeune or civilian workers on base who may have been exposed to contaminated water. There was variation among studies with respect to the methods used to recruit or assemble the study populations, characterize exposures, and address confounding. Overall, there were no consistent associations reported between either working or living at Camp Lejeune or TCE, PCE, benzene, or vinyl chloride exposures on base and leukemia or leukemia subtypes. Although some studies reported a few statistically significant risk estimates, they were not consistent across analyses of the Camp Lejeune population, and several were <1. These studies also had several methodological limitations, including a high likelihood of exposure misclassification. There are no toxicity or mechanic studies of Camp Lejeune drinking water, but toxicity and mechanistic studies do not provide evidence that exposures to TCE, PCE, or vinyl chloride can cause leukemia, and the epidemiology studies at Camp Lejeune do not demonstrate that being stationed or employed at Camp Lejeune or exposure to any individual chemical at Camp Lejeune, including benzene, was sufficient to cause leukemia in general or any subtype, including AML or MDS.

Overall, (1) Camp Lejeune epidemiology studies are not of high quality, (2) most epidemiology analyses do not provide evidence of associations, and (3) animal and mechanistic studies do not provide evidence of causation in humans for TCE, PCE, benzene, or vinyl chloride. Thus, I conclude that the currently available evidence does not support a causal association between exposure to drinking water at Camp Lejeune generally or exposure to TCE, PCE, benzene, or vinyl chloride in drinking water at Camp Lejeune and leukemia.

6 TCE and Leukemia

In this section, I describe epidemiology and toxicity studies that assessed TCE exposure and leukemia, and government and other agency reviews of this evidence. I conclude that the scientific evidence does not support a causal association between TCE exposure and leukemia overall, or AML, or CML.

6.1 Epidemiology

6.1.1 Overview

I identified 23 cohort studies (in 18 unique populations) and 5 case-control studies (in 5 unique populations) that evaluated TCE exposure and leukemia. Most studies were conducted in the US and Europe, and two studies were conducted in Taiwan. I review here all studies in populations at Camp Lejeune if TCE exposures were specified, even if overlapping, for completeness. If several studies analyzed the same cohorts or population groups, I summarize only the study with the longest follow-up or that used more reliable exposure estimates, unless another study reported additional results (*e.g.*, dose-response relationships). I provide an overview, including a brief discussion of cohort and case-control study characteristics and quality, below and in Attachment D, Tables D.1 and D.5, and Attachment C, respectively. Study results are discussed in Section 6.1.2 and in Attachment D, Tables D.2, D.3, and D.4 for cohort studies and Tables D.6, D.7, and D.8, for case-control studies. Epidemiology evidence is integrated with experimental evidence in Section 6.3.

6.1.1.1 Study Population

In all cohort studies, exposed and unexposed participants were selected from appropriate source populations. Individuals with and without leukemia were also drawn from appropriate source populations in all case-control studies. Most cohort studies reported low rates of loss to follow-up and exclusion (<20%), though some studies did not specify how many people were excluded or lost to follow-up. All but one case-control study (Greenland *et al*., 1994) reported high participation rates (≥80%), that were similar between cases and controls. Two cohort studies (Chang *et al*., 2003; Silver *et al*., 2014) had a relatively young study population, as the mean age at the end of follow-up was <50 years. In their cohort study utilizing urinary TCA (U-TCA) and occupational air TCE measurements, Hansen *et al*. (2001) could not match 36% of U-TCA or 48% of air monitoring samples with individuals, so these samples were not included.

6.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to TCE *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation of all the cohort and case-control studies was how exposures were estimated. The epidemiology studies examining TCE exposure and leukemia were largely conducted among populations that represented specific occupational groups (*e.g.*, aircraft manufacturing workers in Lipworth

et al. [2011]). Almost all the studies estimated individual exposures to TCE in an indirect manner, usually based on a JEM, occupational categories (*e.g*., mechanics), or self-reported exposures, all of which were likely subject to varying degrees of exposure misclassification. One cohort study utilized data on U-TCA (*i.e*., Anttila *et al*., 1995), but this metabolite is not specific to TCE.

Bove *et al*. (2014a,b) and ATSDR (2018b) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on ATSDR (2007a, 2013) groundwater fate and transport models, along with historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). None of these studies had individual water consumption/exposure data, so individual exposures were likely misclassified to some degree. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014a,b) and ATSDR (2018b), which limits the interpretation of the TCE-specific results.

Most case-control studies characterized exposure based on self-report or occupational information, which was often collected after leukemia had been diagnosed (*e.g*., Costantini *et al*., 2008). Self-reported exposure information is subject to potential recall inaccuracy due to the long time period between chemical use or exposure and interviews, and potential recall bias can occur in case-control studies when cases recall exposures differently than controls.

Most studies considered frequency, duration, or intensity of potential exposures. The studies that aimed to account for exposure levels did so based on modeled contamination in drinking water (with no individual consumption data), JEMs, expert opinion, or duration of/time since first employment; these indirect measurements are at best crude estimates of actual exposures with an unknown amount of error. Most studies did not consider the time-varying nature of potential exposures (*e.g*., exposure was measured or estimated at a single time point or incorporated into a statistical model as a single value).

6.1.1.3 Outcome Assessment

Leukemia diagnoses were obtained or confirmed using reliable and complete methods in most cohort and case-control studies, as cases were mostly identified using medical records, registries, or government or national databases (*e.g*., NDI, SSA). A few studies did not validate self-reported cases using more reliable methods (*e.g*., Greenland *et al*. [1994] did not validate all leukemia-related deaths identified from company pension office records). Most studies reported on leukemia incidence or mortality, while a few reported on specific leukemia subtypes (*i.e.*, AML, CML), and some reported on leukemia and aleukemia combined. I did not identify any cohort or case-control studies that evaluated TCE exposure and ALL.

6.1.1.4 Covariates Considered

Almost all epidemiology studies have some residual or uncontrolled confounding, which can bias the results in either direction. All cohort and case-control studies controlled for age and sex, while race/ethnicity was controlled for less consistently; other chemical exposures, smoking, and a family history of leukemia were rarely controlled for. Notably, most of the studies evaluating AML did not control for smoking. No studies controlled for high-dose radiation, genetic syndromes disorders, or viral infections. Even when data on these covariates were collected, most cohort studies did not account for their time-varying nature. Most cohort and case-control studies also did not provide information on the degree or impact of missing covariate data.

6.1.1.5 Temporality

All cohort and case-control studies assessed or considered exposures prior to leukemia diagnosis, but many did not ensure an appropriate period of time between exposure and diagnosis, either in the design or the analysis (*i.e.*, ≥0.5 years for leukemia [CDC, 2015]). Many studies may have included cases that could have occurred <0.5 years after the exposure began in their analyses, undermining the ability to properly assess associations.

6.1.2 Study Results

Risk estimates reported in cohort and case-control studies of TCE and leukemia, AML, and CML ranged from 0.26-3.1.[9] Most risk estimates were between 1 and 2 and not statistically significant. Below, I discuss results for leukemia (overall) and then for AML and CML.

6.1.2.1 Leukemia

Most cohort studies did not report any statistically significant associations between TCE and leukemia, including leukemia and aleukemia combined. ATSDR (2018b) observed lower risks of leukemia incidence associated with TCE exposure (OR = 0.28, 95% CI: 0.09-0.83, and OR = 0.26, 95% CI: 0.09-0.72, for high cumulative exposure groups when compared with Camp Pendleton Marines and Navy personnel and Camp Lejeune Marines and Navy personnel with low cumulative exposure, respectively).

None of the three case-control studies reported a significant association between TCE and leukemia (Wilcosky *et al*., 1984; Greenland *et al*., 1994; Costantini *et al*., 2001, 2008).

6.1.2.3 Acute Myeloid Leukemia

Two cohort studies in European populations reported null results or a significant decrease in AML incidence associated with TCE exposure (Pukkala *et al*., 2009, 2008; Saberi Hosnijeh *et al*., 2013). Two case-control studies also found no significant associations between TCE and AML (Costantini *et al*., 2008; Talibov *et al*., 2014).

6.1.2.4 Chronic Myeloid Leukemia

In a study of the EPIC project cohorts, Saberi Hosnijeh *et al*. (2013) found no significant association between TCE exposure and CML incidence. No other studies investigated the potential relationship between TCE and CML.

6.1.3 Meta-Analyses and Pooled Analysis

I identified three meta-analyses (Wartenberg *et al*., 2000; Alexander *et al*., 2006; Karami *et al*., 2013) and one pooled study (Hansen *et al*., 2013) that evaluated TCE exposure and leukemia risk. Alexander *et al*. (2006) identified seven studies and did not find an association with leukemia (summary relative risk estimate [SRRE] = 1.11, 95% CI: 0.93-1.32). Karami *et al*. (2013) meta-analyzed 10 cohort and case-control studies of occupational TCE exposure and leukemia, and similarly found no association (RR = 1.10,

[9] Bahr *et al*. (2011) reported risk estimates of 0 in some analyses where there were no cases reported. These estimates are not included in this range.

95% CI: 0.94-1.28). Wartenberger *et al*. (2000) identified 14 cohort studies and did not report an association between TCE and leukemia for any tier of study quality (*e.g*., for the highest quality studies, SIR = 1.0, 95% CI 0.5-2.1). Hansen *et al*. (2013), a pooled analysis of 3 cohort studies, did not observe an increase in leukemia incidence in their analysis of men and women combined (SIR = 1.06, 95% CI: 0.67-1.60).

6.1.4 Conclusions

Very few associations between TCE exposure and leukemia in epidemiology were statistically significant, and risk estimates were both above and below 1. None of the studies that evaluated leukemia risk by level of TCE exposure reported trends of increasing risk with increasing exposure. No significant associations were reported in studies that investigated TCE and ALL, AML, or CML subtypes.

Given the lack of a consistent association between TCE and leukemia (overall), AML, or CML and the high likelihood of exposure measurement error across studies, I conclude that the epidemiology evidence does not support a causal association between TCE exposure and leukemia.

6.2 Toxicology

6.2.1 Animal Carcinogenicity Studies

I identified ten oral and five inhalation chronic TCE bioassays for which it was stated that the hematopoietic system was examined. The results of these studies are reported in Attachment E, Tables E.1 and E.2; an overview of chronic study quality is described in Attachment E, Table E.3 and individual chronic study quality is shown systematically in Attachment E, Table E.4. All studies are described briefly below. Experimental evidence is integrated with epidemiology evidence in Section 6.3.

Among the 10 chronic oral TCE bioassays in rats and mice, a statistically significant positive trend for all leukemias combined was observed in female August rats (0 ppm: 1/50; 500 ppm: 0/50; 1,000 ppm: 5/50; $p_{trend} < 0.05$) in NTP (1988). A few leukemias were reported in the remaining three rat strains, but none were significantly elevated in either sex at any dose. NTP (1988) concluded, "The studies are considered inadequate for either comparing or assessing trichloroethylene-induced carcinogenesis in these strains of rats," due to "chemically induced toxicity, reduced survival, and deficiencies in the conduct of the studies." In a subsequent study, NTP (1990) stated that "[l]eukemia occurred in reduced ([*p*]<0.05) incidence in the low dose female [rat] group compared with controls. Both leukemia and leukemia or lymphoma (combined) occurred in reduced but not statistically significant proportions in the high dose male and high dose female groups." A statistically significant increase in lymphoma or leukemia (combined) was observed in TCE-exposed female mice. However, NTP (1990) noted that "[t]he increased incidence of dosed female mice with malignant lymphoma (P<0.05) and lymphoma or leukemia (P<0.05) are not considered to be related to the administration of TCE. The incidence in the concurrent control group was somewhat lower than that in the historical controls, and the incidences in dosed females were within the ranges of historical incidences."

Maltoni *et al*. (1986a) reported, "A borderline higher frequency of leukemias was observed in treated males [Sprague-Dawley rats] (NS) [not significant], mainly due to lymphoblastic lymphosarcomas, but not in females." None of the leukemia incidences were statistically significant. Gift *et al*. (2013) re-analyzed the results from several oral and inhalation bioassays conducted by this lab, including the chronic inhalation studies by Maltoni *et al*. (1986a, 1988a). Gift *et al*. (2013) stated, "The spontaneous (control) rate of these tumors in RI Sprague-Dawley rats has been reported to be higher than in Sprague-Dawley rats from other

sources (Cruzan 2009)," and concluded that the proper health status of experimental animals may not have been maintained. In the remaining chronic oral studies in rats and mice (NCI, 1976; Henschler *et al*., 1984), leukemia was not reported at any dose, species, or sex.

I identified five chronic inhalation TCE bioassays conducted in rats and mice (Table E.2). Fukuda *et al*. (1983) did not report any leukemias in female Sprague-Dawley rats or female ICR mice exposed to up to 450 ppm TCE for 104 weeks. Maltoni *et al*. (1986a, 1988a) reported leukemia incidences in three bioassays in rats and mice, except for one dose group in B6C3F1 male mice. Maltoni *et al*. (1986a, 1988a) observed leukemias in controls and exposed groups across all species and sex, but no results were statistically significant. Overall, none of the chronic inhalation bioassays reported statistically significant increases of leukemia (Maltoni *et al*., 1986a, 1988a).

6.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which TCE could cause leukemia (US EPA, 2020b; ATSDR, 2019b; Zhu *et al*., 2024; Rusyn *et al*., 2014). In humans and animals, TCE is metabolized *via* oxidation and glutathione conjugation, mainly in the liver and kidney, but also in the lung and testes (IARC, 2014a; Cichocki *et al*., 2016). Some TCE metabolites can enter systemic circulation and have been detected in urine, but the liver and kidney have the highest concentrations of TCE metabolites due to local formation in these organs (IARC, 2014a).

While the major oxidative metabolites of TCE are not mutagenic in most studies, there is evidence that some reactive glutathione conjugation pathway metabolites (*e.g*., dichlorovinyl cysteine, dichlorovinyl glutathione) are mutagenic (IARC, 2014a; Cichocki *et al*., 2016), and they form the basis of the proposed genotoxic MoA for kidney cancer (US EPA, 2020b; ATSDR, 2019b; IARC, 2014a; Cichocki *et al*., 2016). However, metabolism through the oxidation pathway greatly exceeds metabolism through the glutathione conjugation pathway, and it remains unclear whether human metabolism through the minor glutathione pathway is sufficient to support this MoA for kidney cancer (Chiu *et al*., 2009; IARC, 2014a; Cichocki *et al*., 2016; US EPA, 2011, 2020b). In the kidney, reactive metabolite formation in rodents may be an order of magnitude greater than that in humans, with the evidence overall indicating faster metabolism through both the oxidative and glutathione conjugation pathways (US EPA, 2011, 2020b). In the liver, TCE is metabolized to chloral hydrate, a reactive intermediate that may be genotoxic. However, the data overall are considered insufficient to support any particular MoA for liver tumorigenesis (US EPA, 2020b).

Although MoAs have been proposed for liver and kidney cancer as a result of TCE exposure – including those involving reactive metabolites, genotoxicity, oxidative stress, inflammation, immune-mediated effects, and gene expression alterations – mechanistic evidence is sparse for hematopoietic cancers such as leukemia (US EPA, 2020b; Zhu *et al*., 2024; Lash, 2024). Limited data from human occupational studies have suggested that TCE exposure may cause epigenetic changes such as altered DNA methylation (Phillips *et al*., 2019) and affect biomarkers and proteins related to inflammation and immunity (Lee *et al*., 2019a,b; NTP, 2021a; Hosgood *et al*., 2022; US EPA, 2020b; ATSDR, 2019b); however, the exact mechanisms by which TCE exposure may result in these alterations, whether these changes represent adverse effects, and any etiologic relevance to cancer risk, including to hematologic cancers such as leukemia, are unknown.

Although there is uncertainty regarding the contribution of TCE genotoxicity to carcinogenicity in humans (US EPA, 2020b), scientific and regulatory agencies have concluded that there is sufficient evidence to support a genotoxic MoA for TCE and kidney cancer *via* the formation of reactive glutathione metabolites, but that the MoA for liver cancer is unclear, and there is insufficient evidence to support MoAs for other etiologically distinct cancer types, including leukemia (ATSDR, 2019b; IARC, 2014a; US EPA, 2011,

2020b). Overall, there is no compelling or consistent evidence to support a biologically plausible MoA by which TCE could cause leukemia.

6.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated TCE and leukemia (see Sections 6.1 and 6.2). Most epidemiology studies accounted for temporality and had higher-quality outcome assessments (*e.g.*, confirmed cases), but the changing classification of leukemia subtypes overtime makes it difficult to directly compare results of studies using classification schemes from different eras (*e.g.*, some studies included CLL in analyses of all leukemias or all myeloid leukemias, while others classified CLL as a type of NHL). Control for potential confounders varied across studies, but none sufficiently controlled for all important potential confounders. Most importantly, none of the studies adequately assessed TCE exposures, calling into question the validity of reported risk estimates. Although limited in number, animal studies do not provide consistent evidence for causation. Keeping these study strengths and limitations in mind, I evaluated the available evidence in the context of Bradford Hill's considerations, in Table 6.1. I conclude that the evidence does not support a causal association between TCE exposure and leukemia.

Table 6.1 Bradford Hill Assessment of TCE and Leukemia

Aspect	Analysis
Strength of Association	Epidemiology evidence does not support a strong association between TCE exposure and leukemia or leukemia subtypes.
Consistency	Risk estimates for leukemia and leukemia subtypes were not consistently elevated.
Specificity	There is no currently available evidence to suggest that there is a specific relationship between TCE and leukemia.
Temporality	Temporality was adequately addressed in some cohort studies and case-control studies, as many did not ensure an appropriate latency period between exposure and diagnosis (*i.e.*, ≥0.5 years).
Dose-Response	There were no trends of increasing risk with increasing exposures across the studies that considered multiple exposure levels.
Biological Plausibility	Evidence does not support a biologically plausible MoA by which TCE could cause leukemia.
Coherence	Collectively, the evidence does not support a causal association between TCE exposure and leukemia. There were no consistent strong associations between TCE and leukemia overall, AML, or CML across cohort and case-control studies, and most associations were null. There were no dose-response relationships reported, and each epidemiology study had several methodological limitations that impacted the interpretation of its results. There is no consistent evidence that TCE causes leukemia in animal models and toxicokinetic and MoA studies do not support a biologically plausible MoA for leukemia.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compounds to TCE with respect to leukemia risk.

Notes:
AML = Acute Myeloid Leukemia; CI = Confidence Interval; CML = Chronic Myeloid Leukemia; MoA = Mode of Action; TCE = Trichloroethylene.

6.4 Agency Reviews

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct chemical carcinogenicity evaluations. IARC, US EPA, and NTP all classify agents according to whether they are likely to cause cancer in humans, each using a unique framework, as described in Section 3.5.1 and Table 3.5. ATSDR, NASEM, US EPA, and NTP evaluate cancer risks, while IARC

classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Tables 3.6 and 3.7.

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, the reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. Also, IARC, US EPA, and NTP carcinogenicity categories all include ones called "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data for the agent at all, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding). The review process for ATSDR (2017a) had even more methodological issues than those discussed above (see Section 3.5.2 and Table 3.8). This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation.

Most government and scientific agency reviews either concluded that the scientific evidence is insufficient to make a determination regarding TCE and leukemia causation (IOM, 2003; NRC, 2009; US EPA, 2011, 2020b), or did not draw any conclusions (ATSDR, 2019b; IARC, 2014a; IOM, 2015; NTP, 2015). These agency assessments of TCE carcinogenicity are described below.

6.4.1 ATSDR

In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) concluded there was "sufficient evidence for causation" for TCE and kidney cancer, NHL, and cardiac defects; "equipoise and above evidence for causation" for TCE and multiple myeloma, all types of leukemia, liver cancer, Parkinson's disease, end-stage renal disease, and systemic sclerosis/scleroderma; and "below equipoise evidence for causation" for TCE and pancreatic cancer, prostate cancer, breast cancer, bladder cancer, esophageal cancer, rectal cancer, and brain/central nervous system cancers.

ATSDR (2017a) discussed the scientific evidence regarding TCE and leukemia in the Camp Lejeune review. ATSDR (2017a) determined the evidence for causation for TCE and leukemia is "equipoise and above…for TCE and all adult leukemias, including AML, ALL, CML, and CLL." This determination was based on positive but inconsistent findings in human studies for each leukemia type (ATSDR, 2017a) including two meta-analyses with summary RRs of about 1.10 for leukemias and TCE exposure (Alexander *et al*., 2006; Karami *et al*., 2013). ATSDR (2017a) described two additional cohort studies (Hansen *et al*., 2013; Silver *et al*., 2014) and two case-control studies (Cocco *et al*., 2013; Talibov *et al*., 2014) published after the Karami *et al*. (2013) meta-analysis that provided support for an association. ATSDR (2017a) also determined that supporting evidence was provided by studies in both animals and humans that indicate TCE causes immune disorders that are associated with leukemias, citing US EPA (2011) and NTP (2015), and by one study that indicates that factory workers exposed to TCE have reduced lymphoid cell types (Bassig *et al*., 2016). Limitations of the ATSDR (2017a) analysis are discussed in more detail in Section 3.5.2.

In its "Toxicological Profile for TCE," ATSDR (2019b) stated that there is "strong evidence that trichloroethylene can cause kidney cancer in people and some evidence that it causes liver cancer and malignant lymphoma (a blood cancer)." The agency further noted, "Lifetime exposure to trichloroethylene resulted in increased liver cancer in mice and increased kidney cancer in rats at relatively high exposure

levels. There is some evidence for trichloroethylene-induced testicular cancer and leukemia in rats, and lymphomas and lung tumors in mice."

ATSDR (2019b) listed several epidemiology studies that addressed TCE and leukemia, but no conclusions were presented regarding an association (ATSDR, 2019b). With respect to TCE-induced leukemia in rats, ATSDR (2019b) cited only two studies: one study showed a positive association in male rats but not in female rats, and another study by the same group showed a negative association in male mice (Maltoni *et al*., 1986b, 1988a). The agency stated that the mechanism for immunological effects (including hematopoietic cancers) is unknown but may involve oxidative damage *via* reactive TCE metabolites (ATSDR, 2019b).

6.4.2 NASEM

Subcommittees of NASEM reviewed the associations between solvent exposures and various cancers in the contexts of the Gulf War and Camp Lejeune. Most of the studies included in NASEM's reviews were not specific to TCE. IOM, now called the National Academy of Medicine (NAM) and one of three NASEM operating units, conducted the first evaluation of insecticides and solvents in the context of the Gulf War (IOM, 2003). In 2003, IOM (2003) did not conclude that TCE was associated with any cancer type in humans. IOM (2003) concluded there was insufficient evidence to determine whether there was an association between TCE and any leukemia, based on small numbers of studies and a lack of consistent positive findings. IOM (2003) did not discuss any animal or mechanistic data. IOM (2003) did not discuss any conclusions regarding MDS.

In an assessment of potential health effects at Camp Lejeune, NRC (2009), the operating and principal programmatic arm of NASEM, concluded that there was "limited/suggestive evidence of an association" for TCE and kidney cancer in humans, but "inadequate/insufficient" evidence for other cancers evaluated. NRC (2009) also noted, "TCE was reported to cause kidney and testicular cancers in rats and liver and lung cancers in mice."

NRC (2009) conducted an updated review with several additional epidemiology studies (Morgan and Cassady, 2002; Raaschou-Nielsen *et al*., 2003; Boice *et al.*, 2006; Sung *et al.*, 2007; Chang *et al*., 2003; Seidler *et al*., 2007). Some of these studies did not make a distinction between TCE and PCE. NRC (2009) noted that none of these additional studies showed an association between TCE and adult leukemia. NRC (2009) concluded that there was "inadequate/insufficient evidence to determine whether an association exists" between TCE and leukemia. NRC (2009) did not discuss any animal or mechanistic studies.

In 2012, US Congress passed the Honoring America's Veterans and Caring for Camp Lejeune Families Act, also known as the Janey Ensminger Act (Public Law 112-154) (IOM, 2015). The Veterans Health Administration (VHA) drafted clinical guidance to help determine which medical conditions should be covered by the act. IOM (2015) conducted and published a "Review of the VA Clinical Guidance for the Health Conditions Identified by the Camp Lejeune Legislation." In its 2015 review, the IOM committee noted that the epidemiology literature reported associations between "chronic exposure to solvents" and multiple myeloma, adult leukemia, and MDS, but did not discuss these diseases in relation to TCE or any specific solvent, and did not cite any epidemiology, animal, or mechanistic data (IOM, 2015).

6.4.3 US EPA

US EPA (2011) has characterized TCE as "carcinogenic in humans by all routes of exposure" based on "convincing evidence from epidemiological studies that reported an association with kidney cancer." US EPA (2011) stated that evidence from epidemiology studies "is strong for non-Hodgkin Lymphoma but

less convincing than for kidney cancer, and more limited for liver and biliary tract cancer." US EPA (2011) further stated, "less human evidence is found for an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia" Regarding evidence from animal studies, US EPA (2011) noted chronic TCE exposure caused "low, but biologically and sometimes statistically significant, increases in the incidence of kidney tumors" and "statistically significant increases in TCE-induced liver tumors" in mice (but not rats or hamsters). US EPA (2011) concluded that "there is more limited evidence for TCE-induced lymphohematopoietic cancers in rats and mice, lung tumors in mice, and testicular tumors in rats."

US EPA (2011) described the evidence for an association between TCE and childhood leukemia as "limited" and "suggestive" based on four case-control studies (Costas *et al*., 2002; Shu *et al.*, 1999; McKinney *et al*., 1991; Lowengart *et al*., 1987) and four ecological studies (ATSDR, 2006a; ADHS, 1990, 1995; Cohn *et al*., 1994; Aickin *et al.*, 1992). US EPA (2011) also stated the overall evidence was "not robust or conclusive." US EPA (2011) discussed several other epidemiology studies of TCE and leukemia in general but did not present any conclusions regarding an association. The agency discussed a limited amount of animal data, noting that three studies reported "positive trends" (Maltoni *et al*., 1986b, 1988a; NTP, 1988), but also stated, "Due to study limitations, these trends cannot be determined to be TCE-induced" (US EPA, 2011). No mechanistic evidence specific to leukemia was discussed.

In its most recent evaluation of TCE, US EPA (2020b) upheld its conclusion that TCE is "Carcinogenic to Humans" based on "positive associations of NHL, kidney cancer and liver cancer with exposure to TCE." With respect to ecological studies of leukemia, US EPA (2011) stated:

> The geographic-based studies for adult lymphopoietic (see Table 4-74) or childhood leukemias (see Table 4-75) do not greatly contribute to the overall weight of evidence. While some studies observed statistically significantly elevated risks for NHL or childhood cancer, these studies generally fulfilled only the minimal of evaluation criteria with questions raised about subject selection (Morgan and Cassady, 2002), their use of less sophisticated exposure assessment approaches and associated assumption of an average exposure to all subjects (all studies), and few cases with high level parental exposure (all studies).

US EPA (2020b) did not discuss other leukemias, or any potential modes of action, but noted that animal studies reported increased incidence of lymphomas and/or leukemias with TCE exposure.

6.4.4 IARC

In 2014, IARC evaluated TCE and cancer, and concluded TCE is "carcinogenic to humans (Group 1)" (IARC, 2014a). Regarding epidemiology evidence, IARC (2014a) concluded there is "sufficient evidence" in humans that TCE "causes cancer of the kidney," and that there is a "positive association" with liver cancer and NHL. Regarding evidence in experimental animals, the IARC Working Group indicated there is "sufficient evidence" supporting the carcinogenicity of TCE with respect to liver and kidney cancer (IARC, 2014a).

IARC (2014a) described several epidemiology studies on TCE exposure and leukemia, and a few animal studies that evaluated leukemia. However, the agency did not offer any evaluation of the evidence, discuss mechanistic data, or draw any conclusions regarding whether evidence supports a causal association between TCE and leukemia.

6.4.5 NTP

In its 2015 "Report on Carcinogens Monograph on Trichloroethylene," NTP (2015) conducted a cancer hazard assessment focused on kidney cancer, NHL, and liver cancer only. NTP (2015) classified TCE as "known to be a human carcinogen," based on "sufficient evidence of carcinogenicity from studies in humans." NTP (2015) did not discuss leukemia in relation to TCE exposure in humans. The agency noted that leukemia was observed in female rats exposed to TCE and that, "[a]lthough the modes of action of trichloroethylene-induced NHL and related neoplasms are unknown, the key events may be related to effects of trichloroethylene on the immune system." (NTP, 2015). NTP (2015) also noted that several immunomodulatory effects were reported in several rodent studies after TCE exposure, including changes in leukocyte numbers, proliferation, activation, and function, and that these effects may be precursors to hematopoietic cancers.

NTP (2021a) classified TCE as "known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans." NTP (2021a) stated:

> This conclusion is based on epidemiological studies showing that it causes kidney cancer in humans, together with supporting evidence from toxicological, toxicokinetic, and mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. Epidemiological studies also provide limited evidence that trichloroethylene causes non-Hodgkin lymphoma (NHL) in humans. Supporting evidence is provided by studies in experimental animals demonstrating that trichloroethylene causes cancer at several tissue sites, including some of the same sites as seen in humans.

6.4.6 Conclusions

Most government and scientific agencies either concluded that the scientific evidence is insufficient to make a determination regarding TCE and leukemia causation (IOM, 2003; NRC, 2009; US EPA, 2011, 2020b), or did not draw any conclusions (ATSDR, 2019b; IARC, 2014a; IOM, 2015; NTP, 2015). The exception was ATSDR (2017a), which determined the evidence for TCE and general leukemia was "sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists." The determinations by ATSDR (2017a) were based on a limited number of epidemiology studies with inconsistent results, and three animal studies that reported positive trends but had many study limitations. Some agency reviews discussed mechanistic evidence regarding immunological effects of TCE that were potential precursors to hemopoietic cancers but noted that these effects are not specific to leukemia.

6.5 Conclusions

Most government and scientific agency reviews either concluded that the scientific evidence is insufficient to make a determination regarding TCE and leukemia causation (IOM, 2003; NRC, 2009; US EPA, 2011, 2020b), or did not draw any conclusions (ATSDR, 2019b; IARC, 2014a; IOM, 2015; NTP, 2015). Most analyses do not provide evidence of associations between or exposure-response trends for TCE and leukemia, AML, or CML in cohort or case-control studies; all epidemiology studies had several methodological limitations that impact the interpretation of their results (particularly a high likelihood of exposure misclassification, concurrent exposures to other solvents, and a lack of adjustment for potential confounders). Animal evidence does not provide compelling evidence that TCE can cause leukemia, and there is no proposed MoA with sufficient scientific support.

Because (1) the epidemiology studies are not of high quality and most analyses do not provide evidence of associations or a dose-response relationship, (2) animal studies do not provide evidence of causation in humans, and (3) there is no proposed MoA with sufficient scientific support, I conclude that, as a whole, evidence does not support a causal association between TCE exposure and leukemia.

7 PCE and Leukemia

7.1 Epidemiology

Below I describe epidemiology and toxicity studies that assessed PCE exposure and leukemia, and government and other agency reviews of this evidence. I conclude that the scientific evidence does not support a causal association between PCE exposure and leukemia overall, or ALL, AML, or CML.

7.1.1 Overview

I identified 18 cohort studies (in 11 unique populations) and 7 case-control studies (in 7 unique populations) that evaluated PCE exposure and leukemia. Most studies assessed leukemia in aggregate (*i.e.*, leukemia overall or leukemia and aleukemia combined). Two cohort studies assessed specific types of leukemia (*i.e.*, ALL, AML, or CML), and two case-control studies assessed a specific type of leukemia (*i.e.*, AML). Most of the epidemiology studies were conducted in the US and Europe; one study was conducted in Taiwan and one in New Zealand. I review here all Camp Lejeune studies if PCE exposures were specified, even if populations overlapped, for completeness. Otherwise, if several studies analyzed the same cohorts or population groups, I summarize only the study with the longest follow-up or that used the most reliable exposure estimates, unless another study reported additional results (*e.g.*, dose-response relationships). I provide a brief discussion of cohort and case-control characteristics and quality below and in Attachment F, Tables F.1 and F.6 and Attachment C, Table C.1. Study results are discussed briefly in Section 7.1.2 and in Attachment F, Tables F.2-F.5 and F.7-F.8. Epidemiology evidence is integrated with experimental evidence in Section 7.3.

7.1.1.1 Study Population

In all cohort studies, exposed and unexposed participants were selected from appropriate source populations. Some cohort studies did not report the number of subjects lost to follow-up or the number exclusions. About half of the cohort studies had low rates of loss to follow-up and six studies reported no or low exclusions. The cohort study conducted by ATSDR (2018b) reported low response rates to the health survey among military personnel and civilian employees at Camp Lejeune and Camp Pendleton (31% overall). Two studies followed relatively young subjects, with a mean age of <50 years at the end of follow-up (Chang *et al.*, 2003; Silver *et al.*, 2014). All case-control studies used appropriate methods for selecting cases. Three case-control studies reported low participation rates (*i.e.*, <80%) (Aschengrau *et al.*, 1993; Costantini *et al.*, 2008; McLean *et al.*, 2009), especially among controls, which also increased the potential for selection bias. All of the case-control studies reported similar participation rates between cases and controls.

7.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to PCE *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation of the cohort and case-control studies was how exposures were estimated. The epidemiology studies examining PCE exposure and leukemia were largely conducted among populations that represented specific occupational groups (*e.g.*, dry cleaning or manufacturing). Most studies estimated individual exposures to PCE in an indirect manner; usually based on a JEM, employment history, facility records, occupational categories (*e.g.*, dry cleaning workers), or self-reported exposures, all of which are subject to varying degrees of exposure misclassification. Only one study that was conducted in Massachusetts had direct chemical measurements. Aschengrau *et al*. (1993) modeled participants' PCE exposures based on an algorithm of PCE leaching from vinyl-lined asbestos cement pipes into water and their residence on streets with vinyl-lined asbestos cement pipes. However, this study did not have individual water consumption data, so individual exposures were likely subject to some misclassification.

Bove *et al*. (2014a,b) and ATSDR (2018b) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on groundwater fate and transport models calculated in ATSDR (2007a, 2013) along with historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). None of these studies had individual water consumption data, so individual exposures were likely misclassified to some degree. There was also a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014b) and ATSDR (2018b), which limits the interpretation of the PCE-specific results.

Most case-control studies characterized exposure based on self-reported or occupational information collected after leukemia had been diagnosed (*e.g.*, Miligi *et al*., 1999). Self-reported exposure information is subject to potential recall inaccuracy due to the long period between chemical use or exposure and interviews, and potential recall bias can occur when cases recall exposures differently than controls in case-control studies. Most studies did not consider the time-varying nature of potential exposures (*e.g.*, exposure was measured or estimated at a single time point or incorporated into the statistical model as a single value).

Frequency, duration, or intensity of potential exposures were assessed in about half of the studies. The studies that attempted to account for exposure levels did so based on modeled contamination in drinking water (with no individual consumption/exposure data), JEMs, expert opinion, or duration of/time since first employment; these indirect measurements are at best crude estimates of actual exposures with an unknown amount of error.

7.1.1.3 Outcome Assessment

Information on leukemia diagnoses was obtained or confirmed using reliable and complete methods for all cohort and case-control studies, but initial case identification relied on self-report in one study (ATSDR, 2018b). Leukemia cases and deaths were typically identified using medical records, registries, or government or national databases (*e.g.*, NDI, SSA) in both cohort and case-control studies. Most cohort studies assessed mortality, while most case-control studies assessed incidence. Only four studies reported risks of specific leukemia subtypes (*e.g.*, ALL, AML, CML) (Travier *et al*., 2002; Pukkala *et al*., 2009; Costantini *et al*., 2008; Talibov *et al*., 2014), and some reported risks of leukemia and aleukemia combined.

7.1.1.4 Covariates Considered

All epidemiology studies have some residual or uncontrolled confounding, which can bias the results in either direction. All cohort and case-control studies controlled for age and sex, while race/ethnicity was controlled for less consistently; other chemical exposures, smoking, and a family history of leukemia, and radiation were rarely controlled for. Notably, none of the studies evaluating AML controlled for smoking. No studies controlled for genetic syndromes disorders (*e.g.*, chronic myeloproliferative disorders) or viral

infections. None of the cohort studies accounted for the time-varying nature of relevant covariates. Many cohort and case-control studies did not report on missing covariate data, but most that did reported that <5% of covariate data were missing.

7.1.1.5 Temporality

All cohort and case-control studies assessed or considered exposures prior to leukemia diagnosis, but many did not ensure an appropriate period of time between exposure and diagnosis, either in the design or the analysis (*i.e.*, ≥0.5 years for leukemia [CDC, 2015]). Many studies could have included cases that occurred <0.5 years after the exposure began in their analyses, undermining the ability to properly assess an exposure-response relationship.

7.1.2 Study Results

Overall, cohort and case-control studies reported a wide range of risk estimates for PCE and leukemia or leukemia subtype (range: 0.3-8.33), but most risk estimates were between 1 and 2 and not statistically significant.

Below, I discuss results for leukemia overall, and then those for ALL, AML, and CML subtypes.

7.1.2.1 Leukemia

In the cohort studies that examined qualitative measures of PCE exposure (*e.g.*, ever *vs.* never, by occupation), and leukemia, aleukemia, lymphoid or myeloid leukemias and leukemias other than CLL, most results were not statistically significant and ranged from 0.40 to 2.53. One study reported statistically significant increases in risk of leukemia incidence (Travier *et al.*, 2002) and one reported a statistically significant decreased risk of leukemia incidence (Pukkala *et al.*, 2009).

In an analysis in Sweden, Travier *et al.* (2002) reported an increased risk of leukemia incidence among all workers who had been employed as dry cleaning, laundry, or ironing workers compared to workers who had never been employed as dry cleaning, laundry or ironing workers as reported in both 1960 and 1970 censuses (RR = 1.84, 95% CI: 1.11-3.06). However, there was no increased risk in workers who had been employed in one of these occupations on one or both censuses (RR = 1.06, 95% CI: 0.85-1.31). This association was also statistically significant among female workers who had reported been employed as dry cleaning, laundry, or ironing workers on both censuses (RR = 2.53, 95% CI: 1.44-4.46) but not among male workers (RR = 0.93, 95% CI: 0.30-2.88). Both statistically significant risk estimates were based on only a small number of cases and exposure was based on self-reported job code at the time of the census. Pukkala *et al.* (2009), a study of launders and dry cleaners from five Nordic countries, reported a lower-than-expected rate of incident leukemia among male workers when compared to rates in the general populations in these countries (SIR = 0.71, 95% CI: 0.50-0.99). They did not report an association in female workers (SIR = 1.03, 95% CI: 0.88-1.19). However, these estimates were based on indirect exposure assessments (*i.e.*, job titles).

Six cohort studies evaluated leukemia risks based on semiquantitative levels of PCE exposure (*i.e.*, considering intensity or duration of exposure) (Blair *et al.*, 1989; Bove *et al.*, 2014a,b; Silver *et al.*, 2014; ATSDR, 2018b; Callahan *et al.*, 2019). None of these studies reported statistically significant associations between PCE exposure and leukemia incidence or mortality.

None of the case-control studies that examined qualitative measures of PCE exposure (*e.g.*, ever *vs*. never, by occupation) and leukemia or acute leukemias reported an association with PCE, though risk estimates were all above 1 (range: 1.1-3.3). Two case-control studies evaluated leukemia risks using semiquantitative levels of PCE exposure (Aschengrau *et al*., 1993; Costantini *et al*., 2008).

Neither Aschengrau *et al*. (1993) or Costantini *et al*. (2008) reported p_{trends}, but Aschengrau *et al*. (1993) reported an increased risk of incident leukemia among individuals with the highest levels of exposure and a 5-year latency period (OR = 5.84, 95% CI: 1.37-24.91). The authors did not report statistically significant increases in risks with any PCE exposure (OR = 1.96, 95% CI: 0.71-5.37). Aschengrau *et al*. (1993) modelled PCE exposure based on residence on streets with vinyl-lined/asbestos cement pipes but did not have any information on individual water consumption/exposure, likely resulting in exposure misclassification. Also, about 24% of eligible controls and 20.5% of eligible cases did not participate, and no details were provided on how those who participated differed from those that did not, potentially resulting in selection bias.

7.1.2.2 Acute Lymphocytic Leukemia

One cohort study (Travier *et al*., 2002) examined the relationship between PCE and ALL. This study reported five cases of ALL in dry-cleaning workers in Sweden and did not find an association between dry-cleaning work and ALL (RR = 1.95, 95% CI: 0.80-4.75).

7.1.2.3 Acute Myelogenous Leukemia/Acute Nonlymphocytic Leukemia

Two cohort studies (Travier *et al*., 2002; Pukkala *et al*., 2009) and two case-control studies (Costantini *et al*., 2008; Talibov *et al*., 2014) examined the relationship between qualitative measures of PCE exposure and AML or ANLL. Neither of the studies reported any statistically significant associations (Travier *et al*., 2002; Pukkala *et al*., 2009). Two other studies relied on semiquantitative measures of PCE exposure (Costantini *et al*., 2008; Talibov *et al*., 2014), but neither reported a statistically significant difference in the risk of AML or ANLL incidence.

7.1.2.4 Chronic Myeloid Leukemia

Only one cohort study (Travier *et al*., 2002) evaluated the relationship between PCE exposure and chronic nonlymphocytic leukemia (CNLL) incidence. The authors observed an increased risk of CNLL among female workers who reported being employed as dry cleaning, laundry, or ironing workers compared to workers who had never reported being employed as dry cleaning, laundry or ironing workers on 1960 and 1970 censuses in Sweden (RR = 4.43, 95% CI: 1.42-13.81). However, this risk estimate was based on only 3 workers with CNLL. No male workers were diagnosed with CNLL.

7.1.3 Conclusions

Associations between PCE exposure and leukemia, ALL, and AML risk in epidemiology studies were both above and below 1 and mostly not statistically significant. No study reported a dose-response trend. Only one study evaluated PCE exposure and CML. This study reported a statistically significant association, but this was based on only three cases and exposure was assumed based on occupation reported on two censuses.

Given that most analyses do not provide evidence of associations between PCE exposure and leukemia or leukemia subtypes, and the methodological limitations of these epidemiology studies, particularly the high likelihood of exposure measurement error, I conclude that the epidemiology evidence does not support a causal association between PCE exposure and leukemia, ALL, AML, or CML.

7.2 Toxicology

7.2.1 Animal Carcinogenicity Studies

I identified two oral and four inhalation chronic bioassays that stated they evaluated PCE and the hematopoietic system. The results of the chronic studies are reported in Attachment G, Tables G.1 and G.2; an overview of chronic study quality is described in Attachment G, Table G.3 and individual chronic study quality is shown systematically in Attachment G, Table G.4. All studies are described briefly below. Experimental evidence is integrated with epidemiology evidence in Section 7.3.

Neither of the two chronic oral PCE bioassays (Attachment G, Table G.1) reported any leukemias (NCI, 1977).

NTP (1986a) reported reduced survival in male rats at the high dose, but not in female rats at any dose in a chronic inhalation bioassay (Attachment G, Table G.2). Survival was also reduced in male mice at both doses, and in females at the high dose only. NTP (1986a) reported a significant increase in the incidence of stage-3 MNCL in males and female rats in the high dose groups only. In addition, there were significant positive trends for stage-3 MNCL in males ($p = 0.024$) and females ($p = 0.027$). Based on MNCL incidences, the authors concluded there was "clear evidence of carcinogenicity of tetrachloroethylene" in male F344/N rats, and "some evidence of carcinogenicity" in female rats (NTP, 1986a). No leukemia was reported in mice of either sex.

Similarly, in a second chronic inhalation study, the Japan Industrial Safety Association (JISA) (1993) reported significantly increased incidence of MNCL in male rats in the high-dose group (600 ppm), and significant dose-dependent increases were observed in both male ($p < 0.01$) and female ($p < 0.05$) rats. No significant increase of leukemia was observed in mice of either sex.

NTP (1986a) and JISA (1993) reported chronic PCE inhalation exposure was associated with MNCL in F344 rats. As noted by Maronpot *et al*. (2016), this is an inappropriate tumor type "for human health risk assessment and lack[s] relevance in predicting human carcinogenicity." This is primarily because there is a high variable background incidence of MNCL in F344 rats (Caldwell, 1999; Ishmael and Dugard, 2006; Thomas *et al*., 2007; US EPA, 2012; Maronpot *et al*., 2016). US EPA (2012) stated that Caldwell (1999) and Ishmael and Dugard (2006) noted that "the high background rate of M[N]CL in control (untreated) rats can limit the ability to separate the background response from possible chemically induced responses, particularly when the chemically induced response above background is low." Finally, Caldwell (1999) stated, "The weight of evidence strongly supports MNCL being an F-344 rat strain-specific tumor with questionable biological relevance for humans."

7.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which PCE could cause leukemia (US EPA, 2020c; ATSDR 2019a). Animal and human studies indicate that PCE metabolism is relatively limited, particularly at higher exposures (US EPA, 2012, 2020c), but it can occur *via* both oxidation and glutathione conjugation pathways, mainly in the liver and kidney, but also in the lung (US

EPA, 2012, 2020c; IARC, 2014b; Cichocki *et al*., 2016). Some PCE metabolites can enter systemic circulation and have been detected in urine, but the liver and kidney have the highest relative concentrations of PCE metabolites due to local formation in these organs (IARC, 2014b).

In both humans and animals, metabolism through the oxidation pathway exceeds the conjugation pathway, and the major oxidative metabolites of PCE are not mutagenic in most studies. In contrast, there is evidence that some glutathione conjugation metabolites of PCE are mutagenic (IARC, 2014b; Cichocki *et al*., 2016), and they form the basis of the potential mutagenic MoA for kidney cancer as a result of PCE exposure. However, evidence is inconsistent with respect to whether PCE metabolite genotoxicity could result in blood cell carcinogenesis (US EPA, 2020c), and substantial uncertainty exists regarding the contribution of the glutathione conjugation pathway to PCE metabolism, including the extent to which humans form reactive glutathione metabolites (US EPA, 2012, 2020c; Chiu and Ginsberg, 2011; IARC, 2014b; Cichocki *et al*., 2016).

There is some evidence that chronic inhalation exposure (NTP, 1986a; JISA, 1993) to PCE causes MNCL in F344 rats; however, US EPA concluded that the data were inadequate to establish an MoA for MNCL in rats exposed to PCE (US EPA, 2012). In addition, this tumor type is not predictive of leukemia risks in humans (Caldwell, 1999; Ishmael and Dugard, 2006; Thomas *et al*., 2007; US EPA, 2012; Maronpot *et al*., 2016) and therefore does not provide support for biological plausibility.

Limited data from immunotoxicity studies have suggested that PCE exposure may increase oxidative stress and alter white cell counts and immune system markers in humans and mice (US EPA, 2012, 2020c; Li *et al*., 2024; Ghahri *et al*., 2022), but some of these changes were observed at cytotoxic concentrations and reported effects were inconsistent across studies (*e.g*., both anti-inflammatory and inflammatory changes were observed). Whether immune system alterations are involved in carcinogenicity induced by PCE is unknown (US EPA, 2020c).

Scientific and regulatory agencies have concluded that there is some evidence to support potential MoAs for PCE and liver and kidney cancer (although evidence is insufficient to establish definitive MoAs), but not other cancer types, including hematologic cancers such as leukemia (ATSDR, 2019a; IARC, 2014b; US EPA, 2012, 2020c). Overall, there is no compelling or consistent evidence to support a biologically plausible MoA by which PCE could cause leukemia.

7.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated PCE and leukemia (see Sections 7.1 and 7.2). Most of relevant epidemiology studies accounted for temporality and had higher-quality outcome assessments (*e.g*., confirmed cases), but the changing classification of leukemia subtypes overtime makes it difficult to directly compare results of studies using classification schemes from different eras (*e.g*., some studies included CLL in analyses of all leukemias or all myeloid leukemias, while others classified CLL as a type of NHL). Most importantly, none of the studies adequately assessed PCE exposures, calling into question the validity of reported risk estimates. Although limited in number, animal studies do not provide consistent evidence for causation. Keeping these study strengths and limitations in mind, I evaluated the available evidence in the context of Bradford Hill's considerations, in Table 7.1. I conclude that the evidence does not support a causal association between PCE exposure and leukemia.

Table 7.1 Bradford Hill Assessment of PCE and Leukemia

Aspect	Analysis
Strength of Association	Epidemiology evidence does not support a strong association between PCE exposure and leukemia or leukemia subtypes.
Consistency	Risk estimates for leukemia and leukemia subtypes were not consistently elevated.
Specificity	There is no currently available evidence to suggest that there is a specific relationship between PCE and leukemia.
Temporality	Temporality was adequately addressed in all cohort and case-control studies, though many did not consider an appropriate latency period between exposure and diagnosis (*i.e.*, ≥0.5 years).
Dose-Response	There were no reported trends of increasing risk with increasing exposures in any study that considered multiple exposure levels.
Biological Plausibility	Overall, evidence does not support a biologically plausible MoA by which PCE could cause leukemia.
Coherence	Collectively, the evidence does not support a causal association between PCE exposure and leukemia. Most associations between PCE and leukemia in epidemiology studies were null, no dose-response relationships were reported, and each epidemiology study had several methodological limitations that impacted the interpretation of its results. Chronic animal studies do not provide evidence of increased leukemia incidence associated with exposure to PCE that is relevant to humans. There is insufficient data to establish a MoA for leukemia.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compounds to PCE with respect to leukemia.

Notes:
CI = Confidence Interval; MoA = Mode of Action; PCE = Perchloroethylene.

7.4 Agency Reviews

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct chemical carcinogenicity evaluations. IARC, US EPA, and NTP all classify agents according to whether they are likely to cause cancer in humans, each using a unique framework, as described in Section 3.5.1 and Table 3.5. ATSDR, NASEM, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Tables 3.6 and 3.7.

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, the reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. Also, IARC, US EPA, and NTP carcinogenicity categories all include ones called "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data for the agent at all, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding). The review process for ATSDR (2017a) had even more methodological issues than those discussed above (see Section 3.5.2 and Table 3.8). This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation.

Government and scientific agencies either concluded that the scientific evidence is insufficient to make a determination regarding PCE and leukemia causation in humans (ATSDR, 2017a, 2019a; IOM, 2003; NRC, 2009; US EPA, 2012), or did not draw any conclusions (US EPA, 2020c; IARC, 2014b; IOM, 2015; NTP, 2021b). These agency assessments of PCE carcinogenicity are described below.

7.4.1 ATSDR

In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) concluded there was "sufficient evidence for causation" for PCE and bladder cancer, "equipoise and above evidence for causation" for PCE and NHL and end-stage renal disease, and "below equipoise evidence for causation" for PCE and kidney cancer, multiple myeloma, leukemias, liver cancer, pancreatic cancer, prostate cancer, breast cancer, Parkinson's disease, esophageal cancer, rectal cancer, brain/central nervous system cancers, systemic sclerosis/scleroderma, and cardiac defects.

With respect to PCE and leukemia, ATSDR (2017a) concluded that the evidence for causation was below equipoise based on a limited number of epidemiology studies with mixed results, including inconsistent results in dry-cleaning workers who would be expected to have the highest exposures. ATSDR (2017a) also noted that, although there was evidence that PCE was associated with mononuclear-cell leukemia in rats, the relevance of this finding to humans is uncertain. The agency did not discuss any mechanistic evidence. Limitations of the ATSDR (2017a) analysis are discussed in Section 3.5.2.

In its "Toxicological Profile for Tetrachloroethylene," ATSDR (2019a) stated, "Available human data provide suggestive, but weak evidence for [PCE]-induced non-Hodgkin's lymphoma, multiple myeloma, and bladder cancer in humans." Regarding evidence from animal studies, ATSDR (2019a) noted that "[i]ncreased incidences of tumors in the kidney, liver, and lymphoid tissues have been reported in chronic bioassays of rats and mice exposed to tetrachloroethylene *via* inhalation and oral exposure routes." ATSDR (2019a) presented several epidemiology studies that evaluated inhalation and oral PCE exposure and leukemia. Most of these studies were not specific to PCE exposure, and many did not distinguish between leukemias and lymphomas. ATSDR (2019a) noted that studies that evaluated cancer types including leukemia have limitations such as possible exposure misclassification, concurrent exposure to other solvents, and lack of adjustment for smoking and socioeconomic status.

ATSDR (2019a) cited an animal study by NTP (1986a), in which F344 rats exposed to PCE by inhalation at 200 or 400 ppm exhibited a dose-dependent increase in incidence of MNCL. ATSDR (2019a) noted that MNCL occurs spontaneously in F344 rats, and that the incidence in controls in this study was higher than historical control incidences. ATSDR (2019a) cited another similar study (JISA, 1993) in which exposed male rats exhibited a dose-related trend in monocytic leukemia of the spleen. The agency did not draw any conclusions regarding PCE and leukemia, but did note that "additional mechanistic data to aid interpretation of the…rat mononuclear cell leukemias and their relevance to humans would be useful" (ATSDR, 2019a).

7.4.2 NASEM

In 2003, IOM (2003) did not conclude that PCE was associated with any cancer type in humans. IOM (2003) concluded there was "limited/suggestive evidence of an association between chronic exposure to tetrachloroethylene and dry-cleaning solvents and bladder cancer" based mainly on two cohort studies of dry cleaning workers that showed positive associations (Blair *et al*., 1990; Ruder *et al*., 2001) and several case-control studies that reported positive associations that were not statistically significant (Schoenberg *et al*., 1984; Teschke *et al*., 1997; Smith *et al*., 1985). IOM (2003) also considered a study of PCE in drinking water (Aschengrau *et al.*, 1993) and a worker study that showed an increased bladder cancer risk in men but not in women (Pesch *et al*., 2000). In its 2003 review, an IOM committee concluded there was

insufficient evidence to determine whether there was an association between PCE and any leukemia. IOM (2003) did not discuss any animal or mechanistic data.

In an assessment of potential health effects at Camp Lejeune, NRC (2009) concluded that there was "limited/suggestive evidence of an association" between PCE and esophageal, lung, breast, and bladder cancer in humans and that "PCE was reported to cause liver cancer in mice and mononuclear cell leukemia and kidney cancer in rats." Regarding leukemia, NRC (2009) identified four additional studies of PCE exposure and adult leukemia (Morgan and Cassady, 2002; Blair *et al*., 2003; Chang *et al*., 2003; Seidler *et al*., 2007). NRC (2009) found that these studies had mostly null results and concluded that there is "inadequate/insufficient evidence to determine whether an association exists" between PCE and leukemia. The agency also cited the NTP (1986a) study described above in Section 7.4.1 that found an increased incidence of MNCL in F344 male and female rats chronically exposed to PCE at 200 or 400 ppm by inhalation. NRC (2009) noted, however, that this rat strain has high spontaneous rates of this disease, that there was no apparent dose-response relationship, and that this form of leukemia in rats has been judged not to be relevant to humans. No mechanistic data were discussed.

In its 2015 review, an IOM committee reiterated the conclusions of prior NASEM reports. IOM (2015) stated that the epidemiology literature reported associations between "chronic exposure to solvents" and multiple myeloma, adult leukemia, and MDS, but did not discuss these diseases in relation to PCE or any specific solvent, and did not cite any epidemiology, animal or mechanistic data.

7.4.3 US EPA

US EPA (2012) concluded that PCE is "'Likely to be Carcinogenic to Humans' by all routes of exposure" based on "suggestive evidence of carcinogenicity in epidemiologic studies and conclusive evidence that the administration of tetrachloroethylene, either by ingestion or by inhalation to sexually mature rats and mice, increases tumor incidence," citing JISA (1993), NTP (1986a), and NCI (1977) as support for this conclusion. Regarding epidemiology evidence, US EPA (2012) stated that there is "a pattern associating tetrachloroethylene exposure and several types of cancer, including bladder cancer, non-Hodgkin lymphoma and multiple myeloma," and that, "for other sites, including esophageal, kidney, lung, cervical and breast cancer, more limited data suggestive of an effect are available." Regarding animal evidence, US EPA (2012) stated:

> [T]etrachloroethylene increased the incidence of liver tumors (hepatocellular adenomas and carcinomas) in male and female mice and of mononuclear cell leukemia (MCL) in both sexes of rats…. Additional tumor findings in rats included significant increases in the NTP bioassay of testicular interstitial cell tumors and kidney tumors in males, and brain gliomas in males and females. In mice, hemangiosarcomas in liver, spleen, fat, and subcutaneous skin were reported in males in the JISA study.

Regarding leukemia, US EPA (2012) stated that there is little evidence for an association between PCE exposure and leukemia in humans. US EPA (2012) placed most weight on two cohort studies with exposure methodologies that the agency considered relatively high-quality (Boice *et al*., 1999; Costantini *et al*., 2008). The agency also considered several other occupational cohort studies of dry cleaner workers with less specific exposure classifications (Pukkala *et al*., 2009; Travier *et al*., 2002; Sung *et al*., 2007; Blair *et al*., 2003; Andersen *et al*., 1999; Lynge and Thygesen, 1990; Ji and Hemminki, 2005; Travier *et al*., 2002), most of which did not show an increase in risk.

US EPA (2012) also cited and analyzed in detail the same animal studies described above in Section 7.4.1 showing increased incidences of MNCL (NTP, 1986a; JISA, 1993). The agency concluded that PCE caused

MNCL in the F344 rat, there was little information on the MoA, and that "[n]o mechanistic or other data are available that would rule out the relevance of the F344 [mononuclear leukemia] for assessing potential carcinogenic hazard to humans" (US EPA, 2012).

US EPA (2020c) conducted its most recent review of PCE in 2020 and, similar to its 2012 review, concluded that:

> There is a pattern of epidemiological evidence associating PCE exposure with NHL. There is some evidence for bladder cancer and multiple myeloma (MM) but results are mixed. Additional epidemiological data were available showing weaker support for cancers at other sites, including esophageal, lung, and blood (lymphoma). Studies provide more limited support for associations with breast cancer, with little or no support for associations with kidney, esophagus, or liver cancer, and no useful information for cervical cancer.

Regarding rodents, US EPA (2020c) concluded there is "conclusive evidence of the carcinogenicity of PCE" for liver cancer, testicular cancer, MNCL, renal tubular adenomas and adenocarcinomas, brain gliomas, hemangiosarcomas/hemangiomas, and adenomas of the Harderian gland. Overall, US EPA (2020c) concluded that "PCE is considered 'likely to be carcinogenic in humans' by all routes of exposure based on conclusive evidence in animals and suggestive evidence in humans."

US EPA (2020c) identified three additional epidemiology studies of leukemia (Bove *et al*., 2014a; Ruckart *et al*., 2013; Talibov *et al*., 2014), but did not present any conclusions about an association in humans (US EPA, 2020c). The agency also discussed the two rat studies that showed increased incidences of MNCL (NTP, 1986a; JISA, 1993) and noted that the data are inadequate to establish an MoA for this outcome in rats. US EPA (2020c) did not comment on the relevance of this outcome in humans.

7.4.4 IARC

In 2014, IARC did not conclude PCE is a known human carcinogen, but rather "probably carcinogenic to humans (Group 2A)" (IARC, 2014b). Regarding evidence in humans, IARC (2014b) stated, "There is limited evidence in humans for the carcinogenicity of tetrachloroethylene. Positive associations have been observed for cancer of the bladder." IARC (2014b) further concluded, "Several studies evaluated exposure to tetrachloroethylene and the risk of cancers at other sites, including oesophagus, kidney, cervix, and non-Hodgkin lymphoma. No consistent patterns were seen across studies." Regarding animal evidence, IARC (2014b) concluded, "There is sufficient evidence in experimental animals for the carcinogenicity of tetrachloroethylene" based on evidence related to MNCL, testicular cancer, kidney cancer, fibroadenomas of the mammary gland, and brain gliomas in rats, and liver cancers, hemangiomas/hemangiosarcomas, and Harderian gland adenomas in mice.

IARC (2014b) described several epidemiology studies that evaluated PCE and leukemia, but did not draw any conclusions regarding an association in humans. IARC (2014b) also described the animal studies by NTP (1986a) and JISA (1993) and determined that there was a causal association between PCE and MNCL in rats. The agency stated, "Although there is a well established connection between immune status and carcinogenesis in general, overall the evidence was not sufficiently strong to support a conclusion about a mechanism for tetrachloroethylene-induced carcinogenesis in cells of the immune system" (IARC, 2014b).

7.4.5 NTP

NTP (2021b) noted that PCE caused MNCL in rats after inhalation exposure, but did not discuss any human studies of PCE and leukemia, and did not discuss any mechanistic studies. NTP (2021b) concluded that

PCE is "reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals." NTP (2021b) stated that PCE caused liver tumors in mice, and MNCL in rats, and increased the incidence of benign and malignant kidney tumors in rats. Regarding epidemiology evidence, NTP did not present its own conclusions, but rather stated that the 1995 volume of the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, titled "Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals," concluded that there was "limited evidence" for the carcinogenicity of PCE in humans "based mainly on evidence of consistent associations between tetrachloroethylene exposure and esophageal cancer, cervical cancer, and non-Hodgkin lymphoma," but that "confounding by exposure to other chemicals could not be ruled out, and the total numbers in the combined cohort studies were small" (NTP, 2021b). NTP (2021b) did not discuss conclusions with respect to leukemia.

7.4.6 Conclusions

All government and scientific agencies acknowledged that PCE caused MNCL in rats. NRC (2009) stated that this form of leukemia in rats has been judged not to be relevant to humans, but US EPA (2012) did not rule out the possibility of human relevance. Most agency reviews noted that mechanistic information that would support the human relevance of this outcome in rats is lacking. These agencies either concluded that the scientific evidence is insufficient to make a determination regarding PCE and leukemia causation in humans (ATSDR, 2017a, 2019a; IOM, 2003; NRC, 2009; US EPA, 2012), or did not draw any conclusions (US EPA, 2020c; IARC, 2014b; IOM, 2015; NTP, 2021b).

7.5 Conclusions

Government and scientific agencies either concluded that the scientific evidence is insufficient to make a determination regarding PCE and leukemia causation in humans (ATSDR, 2017a, 2019a; IOM, 2003; NRC, 2009; US EPA, 2012), or did not draw any conclusions (US EPA, 2020c; IARC, 2014b; IOM, 2015; NTP, 2021b). The associations between PCE exposure and leukemia or leukemia subtypes in epidemiology studies were both above and below 1, mostly modest, and either not statistically significant or statistically unstable (*i.e.*, had wide CIs). None of the epidemiology studies reported a dose-response relationship between PCE and leukemia. All epidemiology studies had several methodological limitations that impact the interpretation of their results (particularly a high likelihood of exposure misclassification, concurrent exposures to other solvents, and a lack of adjustment for potential confounders). There is no animal evidence indicating PCE can cause leukemia in humans, or any proposed MoA with sufficient scientific support.

Because (1) the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, (2) animal studies do not provide evidence of causation in humans, and (3) there is no MoA with sufficient scientific support, I conclude that, as a whole, evidence does not support a causal association between PCE exposure and leukemia.

.

8 Benzene and Leukemia

In this section, I describe epidemiology and toxicity studies that assessed benzene exposure and leukemia, and government and agency reviews of this evidence. I conclude that the scientific evidence supports a causal association between benzene and AML at cumulative exposure concentrations greater than 40 to 75 ppm-years and is strongest for exposures that occurred within 10 to 15 years of diagnosis. Benzene exposure is also associated with MDS at cumulative exposure concentrations greater than 40 ppm-years. Evidence does not support a causal association between benzene exposure and leukemia overall or other leukemia subtypes (*i.e.*, ALL or CML).

8.1 Epidemiology

8.1.1 Overview

I identified 70 cohort studies (in 36 unique populations) and 23 case-control studies (in 21 unique populations), and 2 case-cohort studies (in 1 unique population) that evaluated benzene exposure and leukemia.[10] Most studies assessed leukemia overall or leukemia and aleukemia combined. Three cohort and two case-control studies evaluated total lymphoid leukemias, five cohort studies and one case-control study evaluated total myeloid leukemias, and one cohort study evaluated monocytic leukemia. ALL was assessed in 10 cohort, 1 case-cohort, and 3 case-control studies; AML in 22 cohort studies, 1 case-cohort, and 10 case-control studies; CML in 10 cohort, 1 case-cohort, and 6 case-control studies; and MDS in 2 cohort, 1 case-cohort, and 5 case-control studies. Most of the epidemiology studies were conducted in the US, Europe, and China, but six studies were conducted in Canada, two in South Korea, and one each in Turkey, Russia, Australia, Thailand, and Pakistan.

Eleven studies evaluated the association between benzene exposure and leukemia, AML, acute myelocytic or acute monocytic leukemia (AMML), or ANLL risk in rubber workers from three plants in Ohio. In these studies, workers were involved in the "Pliofilm" process, during which natural rubber was dissolved in refined benzene and processed by being spread out on a conveyor belt system (Infante *et al.*, 1977; Rinsky *et al.*, 1981, 1987, 2002; Crump, 1994; Paxton *et al.*, 1994a,b, Wong, 1995; Silver *et al.*, 2002; Rhomberg *et al.*, 2016; Finkelstein *et al.*, 2000). This cohort included workers exposed to benzene for at least 1 day between 1940 and 1975. Studies of the Pliofilm cohort are of particularly high quality because the participants were exposed to a wide range of benzene exposure levels and had minimal occupational co-exposures to other potential carcinogens (ATSDR, 2024a). I relied on Rhomberg *et al.* (2016) for its evaluation of ANLL and AML mortality because it had the longest duration of follow-up and the most robust exposure estimates (discussed in detail in Section 8.1.2), and Rinsky *et al.* (2002) for its evaluation of all leukemias because, aside from Rhomberg *et al.* (2016), it has the longest follow-up and, while exposure estimates were not as robust as those in Rhomberg *et al.* (2016), this study incorporated cumulative exposure levels. Silver *et al.* (2002), Finkelstein *et al.* (2000), and Rhomberg *et al.* (2016) evaluated leukemia risk by time windows of benzene exposure (*e.g.*, lagged exposure analyses), so I relied on these studies to evaluate latency (Section 8.1.4).

[10] There are both cohort and case-cohort studies (included in the case-control study tables) from the National Cancer Institute-Chinese Academy of Preventive Medicine (NCI-CAPM) cohort in my review, therefore there are 57 unique populations when considering both cohort and case-control studies combined.

Five studies evaluated the association between benzene exposures and leukemia, ALL, AML or ANLL, CML, MDS, and AML/MDS risk in in workers in 672 factories across 12 Chinese cities in the collaborative National Cancer Institute-Chinese Academy of Preventive Medicine (NCI-CAPM) study (Hayes *et al*., 1997, 2000; Linet *et al*., 2015, 2019, 2020). Cohort participants had a wide variety of occupations, allowing for an evaluation of a wide range of benzene exposures. In these studies, up to 74,828 benzene-exposed workers were followed from 1972-1999. The cohort also consists of an unexposed group of up to 35,805 workers employed in work units or factories where benzene was not used. One limitation of the NCI-CAPM study is that, unlike the Pliofilm cohort, other exposures that might have co-occurred in these occupational settings were not controlled for, which may have impacted observed associations between benzene and leukemia.

Hayes *et al*. (1997, 2000) estimated exposures in this cohort based on air measurements and benzene-use data, considering the time-varying nature of exposure; they followed participants through 1987. Linet *et al*. (2015) expanded follow-up through 1999, but only used information on job histories and employment records to identify individuals as exposed to benzene. Linet *et al*. (2019, 2020) conducted a case-cohort study using more refined exposure assessment methods than prior evaluations did, including modeled exposures from available monitoring data, occupational records, and a study-specific JEM that allowed them to better account for possible chemical co-exposures; they included participants followed through 1999 and evaluated risk of myeloid and lymphoid leukemias, respectively. I considered the exposure characterization in Linet *et al*. (2019, 2020) to be of the highest quality and relied on Linet *et al*. (2019) for estimates of AML, MDS, AML and MDS combined, and CML risks and Linet *et al*. (2020) for estimates of ALL risk. I relied on Hayes *et al*. (1997) for risk estimates of all leukemias, ANLL, and ANLL and MDS combined because this study provided the most comprehensive evaluation of leukemia risk overall, including several estimates of dose (*e.g*., cumulative exposure, average intensity of exposure) and provided these estimates for ANLL and ANLL and MDS, as well.

I also review here all Camp Lejeune studies if benzene exposures were specified, even if populations overlapped, for completeness. Otherwise, if several studies analyzed the same cohorts or population groups, I summarize only the study with the longest follow-up or that used more reliable exposure estimates, unless another study reported additional results (*e.g*., dose-response relationships).

I provide an overview, including a brief discussion of cohort and case-control study characteristics and quality, below, and in Attachment H, Tables H.1 and H.7, and Attachment C, Table C.1. Cohort and case-control study results are discussed briefly in Section 8.1.2 and reviewed in Attachment H, Tables H.2-H.6 and H.8-H.12, and results from pooled and meta-analyses are discussed briefly in Section 8.1.3 and reviewed in Attachment H, Table H.13. Epidemiology evidence is integrated with experimental evidence in Section 8.3.

8.1.1.1 Study Population

In all cohort studies, exposed and unexposed participants were selected from appropriate source populations. Individuals with and without leukemia were also drawn from appropriate source populations in most case-control studies, although seven studies used hospital-based control groups, which may have increased the risk of selection bias. Most cohort studies that provided data on loss to follow-up and exclusions reported low rates for both (*i.e*., <20%), but many studies did not provide this information. Most case control-studies reported similar participation rates among cases and controls, but many reported low participation rates overall (*i.e*., <80%), particularly among control groups, which also increased the potential for selection bias.

8.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to benzene *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation of the cohort and case-control studies was how exposures were estimated. The epidemiology studies examining benzene exposure and leukemia were largely conducted among populations that represented specific occupational groups (*e.g.*, refinery and petrochemical workers or workers in other industries with benzene exposure). Almost all studies estimated individual exposures to benzene in an indirect manner, usually based on company records, a JEM, expert opinion, and/or self-reports, all of which may have been subject to varying degrees of exposure misclassification.

A few cohort studies used direct chemical exposure measurements (Hayes *et al*., 1997, 2000; Collins *et al*., 2003, 2015; Bloemen *et al*., 2004; Bove *et al*., 2014a,b; Rhomberg *et al*., 2016; ATSDR, 2018b). Using air measurements and job titles, Hayes *et al*. (1997, 2000) and Bloemen *et al*. (2004) assigned individual exposures to workers based on industrial hygienists' expert opinions along with air monitoring and benzene-use data. Information on work process changes and some work area and individual air samples were available in Collins *et al*. (2003), and individual exposures were assigned based on an industrial hygienist's expert opinion. Collins *et al*. (2015) used employee work history information with some historical department-specific benzene exposure measurements to estimate individual exposures. Rhomberg *et al*. (2016) used Monte-Carlo techniques to assign exposures based on area air measurements and employment information.

Bove *et al*. (2014a,b) and ATSDR (2018b) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on groundwater fate and transport models calculated in ATSDR (2007a, 2013), along with information on historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). None of these studies had individual water consumption data, so individual exposures were likely misclassified to some degree. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014a,b) and ATSDR (2018b), which limits the interpretation of the benzene-specific results.

Most case-control studies characterized exposure based on self-reported or workplace information collected after leukemia had been diagnosed. Self-reported exposure information is subject to potential recall inaccuracy due to the long period between chemical use or exposure and interviews, and potential recall bias can occur when cases recall exposures differently than controls.

Several studies in oil and petroleum industry workers evaluated leukemia risk with estimated benzene exposures (*e.g.*, Wong *et al*., 1993; Schnatter *et al*., 1996a). These workers were also exposed to other hydrocarbons, however, so it was not possible to attribute any estimated risks to benzene.

Most studies considered frequency, duration, or intensity of potential exposures. These studies often did so based on modeled contamination in drinking water (with no individual consumption data), JEMs, expert opinion, or duration of/time since first employment; these indirect measurements are at best crude estimates of actual exposures with an unknown amount of error. Most studies, however, did not consider the time-varying nature of potential exposures (*e.g.*, exposure was measured or estimated at a single time point or incorporated into the statistical model as a single value).

As noted in Section 8.1.1, Pliofilm cohort studies are high quality mostly due to the robustness of the exposure data (*i.e*., minimal co-exposures and a wide range of exposure levels). Different evaluations of the cohort have used different methods and assumptions to estimate exposures. According to Williams and Paustenbach (2003), Rinsky *et al*. (2002) likely underestimated exposures for most job categories, while Crump (1994) underestimated exposures for some job categories and overestimated exposures for others. In addition, all studies used fixed cutoffs for exposure categories except Rhomberg *et al*. (2016), but these cutoffs do not properly reflect the frequency distribution of exposure magnitudes among workers. This approach may have resulted in unstable risk estimates and obscured information on dose-response relationships. Williams and Paustenbach (2003) updated the benzene exposure estimates for the Pliofilm cohort by incorporating more complete employment data, additional industrial hygiene air monitoring data, and Monte Carlo techniques. Their revised exposure estimates likely provide a more accurate range of plausible exposures, which were used by Rhomberg *et al*. (2016) in an evaluation of AML and ANLL risks. Rinsky *et al*. (2002) included the longest follow-up period aside from Rhomberg *et al*. (2016) and, although exposures were likely underestimated, this study incorporates cumulative exposures, unlike prior studies.

Similar to the Pliofilm studies, the Chinese worker studies also have high quality exposure data. Hayes *et al*. (1997, 2000) estimated exposures based on air measurements and benzene use data, and considered the time-varying nature of exposure, while Linet *et al*. (2019, 2020) used semi-quantitative exposure estimates.

Because of these robust exposure estimates across a wide range of exposure levels, I consider the Pliofilm and Chinese cohort studies to be the most reliable epidemiology studies of benzene and leukemia with respect to exposure assessment.

8.1.1.3 Outcome Assessment

Leukemia diagnoses were obtained and/or confirmed using reliable and complete methods for most cohort and case-control studies. Four studies were unable to confirm or validate reported leukemia outcomes for all study subjects (*i.e*., Blair *et al*., 1989; Greenland *et al*., 1994; Sorahan *et al*., 2005; Saberi Hosnijeh *et al*., 2013) and one study did not report how leukemia outcomes were identified (Fu *et al*., 1996). Leukemia cases and deaths were typically identified using medical records, registries, or government or national databases (*e.g*., NDI, SSA) in both cohort and case-control studies. Most studies reported on leukemia incidence or mortality, many reported on leukemia subtypes (*e.g*., ALL, AML, CML), and a few reported on leukemia and aleukemia combined. Most cohort studies assessed leukemia mortality only, which I consider weaker than those studies that evaluated leukemia incidence.

8.1.1.4 Covariates Considered

Almost all epidemiology studies have some residual or uncontrolled confounding, which can bias the results in either direction. All cohort and case-control studies controlled for age and sex, while race/ethnicity was controlled for less consistently; other chemical exposures, smoking, family history of leukemia, high-dose radiation, genetic disorders (*e.g.*, chronic myeloproliferative disorders), and blood disorders were rarely controlled for. Notably, most of the studies evaluating AML did not control for smoking. No studies controlled for viral infections. None of the cohort studies accounted for the time-varying nature of relevant covariates (*e.g*., other chemical exposures) and, while many studies reported minimal or no missing covariate data, some failed to address missing covariate data altogether.

8.1.1.5 Temporality

Most cohort and case-control studies assessed or considered exposures for a period prior to leukemia diagnosis, but many did not ensure an appropriate period of time between exposure and diagnosis, either in the design or the analysis (*i.e.*, ≥0.5 years for leukemia [CDC, 2015]). Many studies appeared to include cases in the analysis that could have occurred <0.5 years after the exposure began, undermining the ability to properly assess an exposure-response relationship.

8.1.2 Results

Overall, cohort and case-control studies reported a wide range of risk estimates for benzene and leukemia or leukemia subtypes (range: 0.18-98.2),[11] although the range varied greatly by subtype. Most risk estimates for leukemia, ALL and CLL were >1 but not statistically significant. Similarly, risk estimates were generally >1 for AML and MDS, and strong statistically significant risk estimates were reported in the highest quality studies of the Pliofilm and Chinese cohorts. Below I discuss study results for leukemia, and then for ALL, AML, CML, and MDS.

8.1.2.1 Leukemia

Cohort Studies

Thirty-six cohort studies evaluated benzene and leukemia or leukemia and aleukemia combined and reported a wide range of risk estimates (0.22-23.96); most estimates were >1. Twenty-one cohort studies reported no association between benzene and leukemia or leukemia and aleukemia combined (Blair *et al*., 1989; Dagg *et al.*, 1992; Tsai *et al.*, 1993, 2003, 2007; Wong *et al*., 1993, 2001a,b; Collingwood *et al.*, 1996; Lynge *et al*., 1997; Pukkala, 1998; Bulbulyan *et al*., 1999; Consonni *et al*., 1999; Collins *et al*., 2003, 2015; Lewis *et al.*, 2003; Bloemen *et al*., 2004; Sorahan *et al*., 2005; Koh *et al.*, 2011; Bove *et al*., 2014b; Koh *et al*., 2014), while fifteen reported an association (Wong, 1987a,b; Schnatter *et al.*, 1993; Honda *et al.*, 1995; Fu *et al*., 1996; Hayes *et al*., 1997; Consonni *et al*., 1999; Divine *et al.*, 1999a; Lewis *et al*., 2000a; Rinsky *et al*., 2002; Costantini *et al.*, 2003; Huebner *et al.*, 2004; Kirkeleit *et al.*, 2008; Bove *et al*., 2014a; ATSDR, 2018b).

An increased risk of leukemia was associated with benzene exposure in the Pliofilm and Chinese cohorts, both of which had the highest quality exposure estimates. In the Chinese cohort, Hayes *et al*. (1997), reported an increased risk of leukemia in benzene-exposed workers compared to workers not exposed to benzene (RR = 2.5, 95% CI: 1.2-5.1). For "other" leukemias (defined as leukemias other than ANLL or of a not specified type) there was no increased risk (RR = 2.0; 95% CI: 0.7-5.4). These risk estimates were based on time-weighted mean exposure levels of 22.5 ppm, incorporating a 1.5-year lag over an average of 9 exposure years. When considering risks based on cumulative benzene exposure, there was a statistically significant dose-response reported for leukemia (p_{trend} = 0.04) and increased risks reported for exposure at levels ≥40 ppm-years (<40 ppm-years: RR = 1.9, 95% CI: 0.8-4.7; 40-99 ppm-years: RR = 3.1, 95% CI: 1.2-8.0; and ≥100 ppm-years: RR = 2.7, 95% CI: 1.2-6.0). There was no association with any cumulative exposure category for "other" leukemias, including in the highest exposure category (≥100 ppm-years, RR = 1.9, 95% CI: 0.6-6.0).

[11] Several studies reported risk estimates of 0 among strata with no cases and Linet *et al*. (2019) report some negative and some infinite excess risk ratios. I do not include these estimates in this range.

Rinsky *et al*. (2002), reported a higher rate of leukemia deaths in the Pliofilm cohort compared to expected based on rates in the US general population (SMR = 2.47, 95% CI: 1.38-4.07). A prior study, Rinsky *et al*. (1987), reported that almost none of these cases were CML and that leukemia mortality in Pliofilm workers with exposures of <400 ppm-years was not different than expected based on rates in the US general population (1-39.99 ppm-years: SMR = 1.45, 95% CI: 0.53-3.31, n = 6; 40-199.99 ppm-years: SMR = 3.21, 95% CI: 0.86-8.89, n = 4; 200-399.99 ppm-years: SMR = 5.55, 95% CI: 0.62-24.08, n = 2). However, the authors reported higher leukemia mortality rates among workers with exposures ≥400 ppm-years than expected based on rates in the US general population (SMR = 23.96, 95% CI: 4.82-78.51, n = 3). The number of exposed cases in each strata of exposure was small. The authors also reported small increased risks with increased exposure in analyses considering each year increase in duration of exposure (RR = 1.392, 95% CI not reported), per ppm increase in average exposure (RR = 1.076, 95% CI not reported), and per ppm-year increase in cumulative exposure with a 2.5-year lag (RR = 1.025, 95% CI not reported).

Two studies evaluated leukemia risk in populations working in the shoe industry, where benzene exposures could have occurred from benzene-based glues used in shoe manufacturing. The highest quality study of shoe workers was conducted by Costantini *et al.* (2003), who evaluated risks associated with levels of exposure estimated using detailed occupational histories and a JEM linked to air concentrations in each department room based on empirical modeling. They reported that rates of leukemia mortality in Italian shoe workers with a cumulative exposure <200 ppm-years were similar to those expected based on Italian regional rates (<40 ppm-years SMR = 1.3, 95% CI: 0.3-3.7; 40-99 ppm-years SMR = 4.1, 95% CI: 0.5-14.7; 100-199 ppm-years SMR = 2.5, 95% CI: 0.3-9.1). However, they reported a higher-than-expected leukemia mortality rate among those with ≥200 ppm-years benzene exposure (SMR = 5.1, 95% CI: 1.4-13.0). In analyses using the lowest exposed group (<40 ppm-years of cumulative exposure) as the reference, risks were elevated but not statistically significant for any level of exposure (40-99 ppm-years: RR = 3.0, 95% CI: 0.5-19.6; 100-199 ppm years: RR = 2.1, 955 CI: 0.3-13.6; ≥200 ppm-years: RR = 4.7, 95% CI: 0.9-24.0), but there was a small number of exposed cases in each exposure category (*i.e.*, <5). Fu *et al*. (1996) evaluated leukemia risk among British shoe manufacturers and reported an increased risk among those involved in manufacturing of women's shoes (SMR = 2.45, 95% CI: 1.06-4.82) but not among those involved in other tasks. They did not report an increasing risk with an increasing probability of exposure.

Several studies evaluated leukemia risks in studies of workers in the chemical industry or people exposed to benzene at work (*e.g.*, printing plant employees in Bulbulyan *et al*. [1999]). None of these studies reported an association between benzene and leukemia. Sorahan *et al*. (2005) reported no increased risk of leukemia, lymphoid leukemia, or myeloid leukemia mortality in benzene-exposed workers compared to what would be expected based on the England and Wales general population. The authors also reported no difference in rates of incident leukemia cases compared to what would have been expected (SIR = 1.20, 95% CI: 0.78-1.77). Bulbulyan *et al*. (1999) reported similar rates of leukemia mortality in printing plant employees compared to what would be expected in the Moscow general population.

Two other studies evaluated several levels of benzene exposure among chemical workers and leukemia risk. Collins *et al.* (2003) examined cumulative exposure and number of days with peak exposure >100 ppm and Collins *et al.* (2015) evaluated cumulative exposure. Neither of these studies reported any risks associated with any level of benzene exposure, and Collins *et al.* (2015), which was the only study to evaluate a dose-response trend, reported all $p_{trends} > 0.15$.

Three studies evaluated overall risk in oil and petroleum workers (Tsai *et al.*, 1993; Koh *et al.*, 2011, 2014). Compared to appropriate reference populations (*e.g.*, national or regional general populations), none reported a higher-than-expected rate of leukemia mortality or incidence.

Several studies evaluated risk by time period of employment, time period of first employment, or duration of employment, and reported mixed results. Compared to a referent group of general population workers in Norway, Kirkeleit *et al.* (2008) reported an increased risk of leukemia incidence in offshore upstream operators (RR = 2.49, 95% CI: 1.30-4.78) and all offshore workers combined (RR = 1.84, 95% CI: 1.05-3.22) who were first employed from 1981 to 1985, but not for those first employed from 1986 to 2003.

Huebner *et al*. (2004) reported a higher-than-expected rate of leukemia in employees at a Baton Rouge oil refinery and petrochemical plant (SMR = 1.69, 95% CI: 1.19-2.33), and among employees hired before 1944 (SMR range: 1.96-2.41), and those with at least 30 years of employment (SMR = 1.75, 95% CI: 1.13-2.59). The risks of leukemia mortality were not different than expected based on national or regional reference population rates overall in workers at the facilities in Baytown, Texas (Huebner *et al.*, 2004), Bayway, New Jersey (Lewis *et al*., 2000a), by timing of first employment (pre- or post-1950), or duration of employment at Baytown, Texas (Huebner *et al.*, 2004). Divine *et al.* (1999a) reported no association between leukemia and duration of employment, or job type, but they reported a *lower* rate of leukemia deaths among white male employees who were employed after 1950 than expected based on the US general population (SMR = 0.50, 95% CI: 0.23-0.94).

Honda *et al*. (1995) evaluated leukemia risk among white male workers at petroleum plants. They reported an increased risk of leukemia mortality among those who died prior to 1980 (SMR = 1.68, 95% CI: 1.19-2.30) and a *decreased* risk among those who died during the most recent time period analyzed (*i.e*., 1985-1989, SMR = 0.26, 95% CI: 0.03-0.94). Honda *et al.* (1995) reported an increased risk of leukemia mortality among hourly workers who died before 1979 (SMR = 1.88. 95% CI: 1.15-2.90), or who had worked for 10 to 39 years (SMR = 1.54, 95% CI: 1.02-2.22), and among salaried workers for all time periods of death and duration of employment (SMR range: 2.16-3.06).

Consonni *et al*. (1999) reported a higher rate of leukemia mortality in workers with the longest duration of employment (at least 15 years, SMR = 3.77, 95% CI: 1.01-9.65) than expected based on rates in the Italian and Lombardy general populations. They reported no association with time since first employment or year of first employment. Wong *et al.* (2001b) reported a statistically significant trend of increased leukemia mortality with increasing duration of employment among male US oil and refinery process employees ($p_{trend} < 0.05$) compared to what would be expected based on the US general population. Pukkala (1998), Lewis *et al.* (2003), Wong *et al.* (2001a), and Schnatter *et al*. (1993) did not report any associations between duration of employment in the oil or petroleum industry and leukemia.

The three studies in Camp Lejeune populations reported mixed results. Bove *et al*. (2014a) reported an increased risk of leukemia among Marines and Navy personnel with the lowest cumulative benzene exposures (2-45 µg/L-months) compared to those exposed to <2 µg/L-months (HR = 2.54, 95% CI: 1.27-5.08), but no increased risk in higher exposure groups. ATSDR (2018b) reported a *decreased* risk of leukemia among Marines and Navy personnel at Camp Lejeune in the highest exposure category compared to those at Camp Pendelton (OR = 0.28, 95% CI: 0.09-0.83) or those at Camp Lejeune with low exposures (OR = 0.26, 95% CI: 0.09-0.72). They reported no association at lower levels of exposure. Bove *et al*. (2014b) reported no association between any level of benzene exposure and leukemia in civilians working at Camp Lejeune.

Nine cohort studies examined benzene exposure and the risk of leukemia and aleukemia combined (Wong, 1987a,b; Dagg *et al*., 1992; Wong *et al*., 1993, 2001a,b; Collingwood *et al*., 1996; Tsai *et al*., 2003; Bloemen *et al*., 2004; Tsai *et al*., 2007). Risk estimates varied greatly (0.22-3.09),[12] and none of these studies reported any statistically significant associations, except Wong (1987a,b). Wong (1987a,b) reported

[12] Collingwood *et al*. (1996) and Bloemen *et al*. (2004) reported risk estimates of 0 in strata with no cases. These estimates are not included in this range.

no increased rate of leukemia and aleukemia combined among continuously exposed chemical workers compared to what would be expected based on rates in the US general population. Rates were similar when analyses were stratified by duration of exposure and cumulative exposure; however, they reported a significant dose-response relationship between cumulative exposure and leukemia and aleukemia (p_{trend} = 0.01).

The cohort studies all had appropriate study and comparison groups and most had high retention. While all the studies used reliable sources to identify cases and deaths, only some evaluated leukemia incidence. Most studies appropriately considered disease latency and none of the studies adequately controlled for all important covariates, so uncontrolled confounding is likely.

Most cohort studies reporting leukemia risks assessed benzene exposure indirectly, inferring exposure from employment records, JEMs, or interviews. All of the oil and petroleum studies used employment in that industry as a surrogate for exposure, and none used direct measurements or estimates of benzene exposures. Of the studies that reported an increased risk of leukemia with any level of exposure, most used direct exposure measurements in some capacity (*i.e.*, measurements in water or air), although none had direct measurements in individuals or data to link direct measurements (Hayes *et al.*, 1997; Rinsky *et al.*, 2002; Costantini *et al.*, 2003; Bove *et al.*, 2014a; ATSDR, 2018b). As noted above, Hayes *et al.* (1997) and Rinsky *et al.* (2002) had the most robust exposure estimates, and both estimated individual exposures using available facility air sampling and employment information data. Costantini *et al.* (2003) based individual exposure estimates partly on seven measurements collected during one month in 1961, near the end of the investigated exposure period. Bove *et al.* (2014a) and ATSDR (2018b) had access to drinking water concentrations, but information on water consumption/exposure at Camp Lejeune was not available for exposed individuals.

Case-Control Studies

Ten case-control studies evaluated benzene and leukemia and reported a wide range of risk estimates (0.18-98.2), most were between 1 and 4, and most were not statistically significant. Seven studies reported no association between benzene and leukemia overall (Ciccone *et al.*, 1993; Greenland *et al.*, 1994; Schnatter *et al.*, 1996a; Nilsson *et al.*, 1998; Blair *et al.*, 2001; Costantini *et al.*, 2008; Forsell *et al.*, 2020).

Adegoke *et al.* (2003) reported an increased risk of leukemia associated with self-reported occupational benzene exposure among all participants (OR = 1.7, 95% CI: 1.1-2.6), and similar elevated risks for men and women analyzed separately. When they combined self-reported exposure with a JEM, the risk was still significant (OR = 1.6, 95% CI: 1.2-4.6). This study had appropriately selected cases and controls, identified cases using reliable sources, and evaluated disease incidence, but did not have direct exposure measurements. Adegoke *et al.* (2003) appropriately considered latency in at least some analyses, but did not fully consider important covariates, so uncontrolled confounding is likely.

Two case-control studies reported no association between increasing benzene exposure and increasing leukemia risk (Schnatter *et al.*, 1996a; Costantini *et al.*, 2008). Three case-control studies report an increased risk of leukemia with increasing benzene exposure (Guenel *et al.*, 2002; Adegoke *et al.*, 2003; Glass *et al.*, 2003). Guenel *et al.* (2002) examined leukemia risk among gas and electric utility workers in France and reported no association with total leukemia. When they looked specifically at benzene exposure from solvent use, the authors reported an increased risk of leukemia with increasing duration of exposure (p = 0.02), intensity of exposure (p = 0.05), and cumulative exposure with a 2-year lag (p = 0.01). Adegoke *et al.* (2003) reported an increased risk of leukemia associated with self-reported occupational benzene exposure among participants with ≥15 years of self-reported exposure (OR = 3.3, 95% CI: 1.6-6.9). Glass *et al.* (2003) evaluated leukemia risk in a case-control study nested in the Health Watch cohort, a prospective cohort of Australian petroleum workers. They reported an increased risk in the two highest

levels of lifetime cumulative exposure to benzene (>8-16 ppm-years, OR = 5.9, 95% CI: 1.3-27.0; >16 ppm-years, OR = 98.2, 95% CI: 8.8-1,090) compared to those with ≤1 ppm-years of exposure. The number of exposed cases was less than 10, resulting in very imprecise estimates. The authors did not report a p_{trend}, but reported no increased risk of leukemia by duration of employment or exposure intensity. All these studies had appropriate cases and controls, and high participation rates. None had direct exposure measurements, but the occupational records and task-based exposure estimates used in Guenel *et al*. (2002) and Glass *et al*. (2003) are of higher quality than the exposure estimates based on recall of occupational benzene exposure after diagnosis that was used in Adegoke *et al*. (2003). All three studies used reliable sources to identify incident leukemia cases, considered exposures prior to diagnosis and addressed an appropriate latency period. None of the studies fully controlled for important covariates increasing the likelihood of uncontrolled confounding.

Three studies that evaluated benzene exposures and leukemia risk were discussed by Plaintiffs' experts and were published after I completed my literature search (Attachment A). Two of these studies evaluated leukemia risks in population-based cohorts in Shanghai and estimated benzene exposures using JEMs. Demoulin *et al*. (2024) reported an increased risk of leukemia associated with cumulative benzene exposure greater than 550 mg/m^3-years (HR = 2.3, 95% CI: 1.1-4.5) in the Shanghai Men's Health Study (SMHS), but not with lower levels of exposure, and there was no dose-response trend (all participants p_{trend} = 0.054; exposed participants only p_{trend} = 0.157) and no associations in analyses that included a 5-year lag. Bassig *et al*. (2024) pooled data from the Shanghai Women's Health Study (SWHS) and SMHS and evaluated lymphoid leukemia risks. There was no association with any benzene exposure (HR = 2.0, 95% CI: 0.9-4.4) and no trend with duration of exposure (p_{trend} = 0.20) or cumulative exposure (p_{trend} = 0.10). Andersson *et al*. (2024) assessed the association between leukemia and working at Swedish oil refineries, where workers had low to moderate levels of benzene exposure. There was no increased risk in the overall cohort (SIR = 1.62, 95% CI: 0.78-2.98), but a higher rate of leukemia was reported in refinery operators than expected based on rates in the Swedish general population (SIR = 2.45, 95% CI: 1.18-4.51). This association was no longer statistically significant after applying a 5-year lag (SIR = 2.08, 95% CI: 0.90-4.10). None of these studies evaluated specific leukemia subtypes and, like most of the studies I reviewed, all have major methodological limitations, including the potential for exposure misclassification and residual and uncontrolled confounding.

8.1.2.2 Acute Lymphocytic Leukemia

ALL was assessed in 10 cohort studies, 3 case-control studies, and 1 case-cohort study. No cohort study reported statistically significant results overall (Collingwood *et al.*, 1996; Wong *et al*., 1993, 2001a,b; Divine *et al.*, 1999b; Tsai *et al.*, 2007; Kirkeleit *et al*., 2008; Lewis *et al*., 2003; Huebner *et al*., 2004; Sorahan *et al*., 2005). Half of the cohort studies either reported no risk estimates or risk estimates of zero because there were either no (Wong *et al.*, 2001a,b; Sorahan *et al*., 2005) or very few exposed cases (n ≤4) (Lewis *et al*., 2003; Huebner *et al*., 2004) in analyses. Risk estimates reported in the cohort studies reporting non-zero estimates ranged from 0.795-2.8; most were >1. None of the three cohort studies that evaluated levels of exposure reported an association with any level of exposure, although none evaluated the magnitude of exposure and none reported a p_{trend} (Wong *et al*., 2001a,b; Lewis *et al*., 2003).

Case-control studies reported risk estimates for ALL and benzene that ranged from 0.6 to 3.9; most were >1 but not statistically significant. Linet *et al*. (2020) did not report an association with ALL overall. Blair *et al*. (2001) examined ALL risk by intensity of exposure and Guenel *et al*. (2002) and Linet *et al*. (2020) examined risk associated with cumulative exposure concentrations; none reported any statistically significant dose-response associations. Only one study (Adegoke *et al*., 2003) reported any statistically significant associations between benzene and ALL.

Adegoke *et al*. (2003) reported an increased risk of ALL incidence associated with self-reported lifetime occupational benzene exposure ≥15 years (OR = 3.9, 95% CI: 1.3-11.8). They did not report an association when analyses were based on self-reported exposures combined with a JEM. Adegoke *et al*. (2003) appropriately selected cases and controls and had a high participation rate but did not assess direct chemical exposure measurements and had the potential for recall bias because exposures were self-reported after diagnosis. The authors also did not fully control for all important covariates, increasing the likelihood of confounding.

8.1.2.3 Acute Myeloid Leukemia/Acute Nonlymphocytic Leukemia

ANLL and AML are currently used synonymously (ACS, 2019d). Historically, ANLL also included some other leukemias in addition to AML, although even then most instances of ANLL were AML. AML and ANLL were assessed in 17 cohort studies, 10 case-control studies, and 1 case-cohort study.

Cohort Studies

With respect to the highest quality studies, Rhomberg *et al*. (2016) found that ANLL and AML mortality risks were only higher than expected based on rates in the US general population in Pliofilm workers with cumulative exposures > ~75 ppm-years. For example, in analyses incorporating a 5-year lag, cumulative exposures ≥78.07 ppm-years were associated with an increase of both ANLL (SMR = 10.21, 95% CI: 4.1-21.04) and AML mortality (SMR = 10.27, 95% CI: 3.77-22.36). The authors also reported, "Exposure within 10 years of cancer onset appears most relevant for leukemia induction" (Rhomberg *et al*., 2016).

In a case-cohort study of Chinese workers in various industries exposed to benzene, Linet *et al*. (2019) reported an increased risk of AML per 100 ppm-years of cumulative benzene exposure (excess relative risk [ERR] = 1.16, 95% CI: 0.07-5.0, p_{trend} = 0.02) or per 10 ppm average intensity of benzene exposure (ERR = 0.93, 95% CI: 0.11-3.78, p_{trend} = 0.007), when the first exposure occurred before 30 years of age and the exposures occurred between 2 and 10 years before diagnosis. There was also an association between AML per 10 ppm-years of average intensity of exposure when the first exposure occurred after 30 years of age and the exposures occurred between 2 and 10 years before diagnosis (ERR = 1.16, 05% CI: 0.07-5.0, p_{trend} = 0.02), but this was not the case for cumulative exposures (ERR = -0.14, 95% CI: < -0.14-0.24, p_{trend} = 0.36). In categorical analyses, there were no associations between any level of cumulative exposure and AML (RR range: 0.80-2.41). In analyses of AML and MDS combined, there were no consistent associations with cumulative or average intensity of exposure with first exposure at any age or in those over 30 years old when exposures occurred between 2 and 10 years before diagnosis. However, there were associations between AML and MDS combined with cumulative (>0 to <40 ppm-years RR = 1.12, 95% CI: 0.27-4.29; 40 to <100 ppm-years RR = 5.58, 95% CI: 1.65-19.68; ≥100 ppm-years RR = 4.50, 95% CI: 1.22-16.68; p_{trend} = 0.004; per 100 ppm-years ERR = 1.45, 95% CI: 0.21-5.70) and average intensity of exposure (>0 to <5 ppm RR = 0.68, 95% CI: 0.10-3.18; 5 to<40 ppm RR = 4.18, 95% CI: 1.03-15.95; 40 to <100 ppm RR = 3.44, 95% CI: 0.84-13.12; ≥100 ppm RR = 6.58, 95% CI: 1.80-24.15 p_{trend} = 0.002; per 100 ppm ERR = 1.09, 95% CI: 0.19-4.14) when the first exposure occurred before 30 years of age and between 2 and 10 years before diagnosis.

As discussed in greater detail in Section 8.1.1.2, there have been several analyses of leukemia risk in the NCI-CAPM cohort. Hayes *et al*. (1997) is a historically important paper with results similar to those reported by Linet *et al*. (2019). I do not report the Hayes *et al*. (1997) study results on ANLL or ANLL and MDS combined in Attachment H because Linet *et al*. (2019) conducted a more robust exposure assessment and had longer follow-up with more cases. Hayes *et al*. (1997) reported increased risks of ANLL or ANLL and MDS combined only with cumulative exposures > 40 ppm-years. Hayes *et al*. (1997) stated, "In our study, ANLL/MDS was linked to recent benzene exposure, and additional distant exposure

did not appear to further increase risk." In this study, the difference between recent and distant exposure was 10 years.

Other cohort studies reported a wide range of risk estimates (0.3-10.27).[13] Most were >1 but not statistically significant. Eleven cohort studies reported no statistically significant increased risk of AML associated with any benzene exposure overall (Wong *et al*., 1993, 2001a,b; Collingwood *et al.*, 1996; Lynge *et al*., 1997; Divine *et al.*, 1999b; Lewis *et al.*, 2003; Tsai *et al.*, 2007; Saberi Hosnijeh *et al*., 2013; Collins *et al*., 2015; Stenehjem *et al*., 2015).

Among the 10 cohort studies that evaluated levels of benzene exposure (Wong *et al.*, 2001a,b; Collins *et al*., 2003; Lewis *et al*., 2003; Bloemen *et al*., 2004; Heubner *et al*., 2004; Tsai *et al*., 2007; Saberi Hosnijeh *et al*., 2013; Collins *et al*., 2015; Stenehjem *et al*., 2015), only Heubner *et al*. (2004) reported associations. Only three cohort studies evaluated dose response and none reported a statistically significant trend (Saberi Hosnijeh *et al*., 2013; Collins *et al*., 2015; Stenehjem *et al*., 2015).

Three cohort studies reported increased risk of AML associated with benzene exposure (Huebner *et al.*, 2004; Sorahan *et al*., 2005; Kirkeleit *et al.*, 2008). Wong *et al.* (2001b) reported an increased AML mortality risk among male oil refinery employees with 10 to 29 years of employment (SMR = 2.768, 95% CI: 1.113-5.704) when compared with the US general population, but not in analyses considering other exposure durations, specific job titles, time since first employment, or year of hire. Huebner *et al.* (2004) reported an increased risk of ANLL among oil refinery and petrochemical employees in Baytown, Texas (SMR = 2.13, 95% CI: 1.10-3.73), in employees of Baytown, Texas (SMR = 2.67, 95% CI: 1.22-5.07) and Baton Rouge, Louisiana (SMR = 2.15, 95% CI: 1.03-3.95) that were employed for over 30 years, and among those hired before 1940 in Baton Rouge, Louisiana (SMR = 3.12, 95% CI: 1.01-7.28), but not in all Baton Rouge employees (SMR = 1.52, 95% CI: 0.76-2.72). Sorahan *et al*. (2005) reported 14 cases of ANLL, 12 of which were AML, among benzene exposed workers. They reported a statistically significant increased risk of ANLL mortality among all exposed workers (SMR = 1.83, 95% CI: 1.00-3.07), but not AML mortality (SMR = 1.82, 95% CI: 0.94-3.18) or ANLL incidence (SMR = 1.65, 95% CI: 0.85-2.88). Kirkeleit *et al.* (2008) reported an increased risk of AML among petroleum industry workers in upstream offshore operating jobs (RR = 2.89, 95% CI: 1.25-6.67). Risk did not differ by period of first employment for upstream operators offshore. Risk was increased among all offshore workers who were first exposed between 1981 and 1985 (RR = 2.24, 95% CI: 1.00-5.01), but not among those first exposed between 1986 and 2003. All four studies used appropriate comparison groups but information on loss-to-follow-up, exclusions, and consideration for latency varied.

Several of the cohort studies had a small number of exposed cases (*e.g.*, Collins *et al.*, 2003, 2015; Bloemen *et al.*, 2004; Stenehjem *et al*., 2015), which may have impacted their analytical power and precision around risk estimates, particularly when analyses were stratified by level of exposure.

Case-Control Studies

Case-control studies reported a wide range of risk estimates (0.2-7.17), and 4 out of 10 studies reported at least some statistically significant increased risks (Adegoke *et al*., 2003; Glass *et al*., 2003; Kaufman *et al*., 2009; Wong *et al*., 2010). Four case-control studies reported no association between any benzene exposure overall and AML (Ciccone *et al*., 1993; Adegoke *et al*., 2003; Wong *et al*., 2010; Forsell *et al*., 2020), and one (Kaufman *et al*., 2009) reported a statistically significant increased risk of AML incidence among cases who self-reported prior occupational exposure to benzene in Thailand (OR = 4.9, 95% CI: 1.4-17). This study relied on hospital-based controls and, like most of the case-control studies, had the potential for recall bias, as exposures were reported after diagnoses. The authors also did not account for disease latency.

[13] Several studies reported risk estimates of 0 among strata with no cases. I do not include these results in this range.

With respect to dose response, half of the case-control studies that evaluated AML risk by level of benzene exposure reported no association (Blair *et al*., 2001; Guenel *et al*., 2002; Costantini *et al*., 2008; Talibov *et al*., 2014; Forsell *et al*., 2020), and three studies reported at least some statistically significant increased risk with higher levels of exposure (Adegoke *et al*., 2003; Glass *et al*., 2003; Wong *et al*., 2010). Adegoke *et al*. (2003) reported an increased risk of AML incidence associated with self-reported occupational benzene exposure for ≥15 years (OR = 2.9, 95% CI: 1.2-7.0). Glass *et al*. (2003) evaluated ANLL risk in a case-control study nested in the Health Watch cohort, a prospective cohort of Australian petroleum workers. They reported an increased risk in the highest level of lifetime cumulative exposure to benzene (>8 ppm-years) compared to those with ≤4 ppm-years of exposure (OR = 7.17, 95% CI: 1.27-40.4). They did not report an increased risk among those with 4-8 ppm-years of exposure (OR = 0.52, 95% CI: 0.05-5.0). Wong *et al*. (2010) reported an increased risk of AML incidence among those with >10 mg/m^3 maximum exposure (OR = 2.05, 95% CI: 1.05-3.98), but not among those with lower exposures, and they reported a significant dose-response relationship (p_{trend} = 0.01). They also reported increased risk among those who were first exposed in 2000 or later (OR = 4.18, 95% CI: 1.56-11.15) but not in earlier decades. There were no consistent increased risks of AML with increasing duration of employment in exposed jobs (p_{trend} = 0.84).

Most case-control studies that assessed benzene exposure and AML appropriately selected cases and controls and had high participation rates, however, three studies (Ciccone *et al*., 1993; Kaufman *et al*., 2009; Wong *et al*., 2010) used hospital-based controls, and three studies either reported low participation rates among controls (Blair *et al*., 2001; Costantini *et al*., 2008) or did not report on participation rates among controls (Wong *et al*., 2010). These limitations could have resulted in selection bias. None of these studies had direct chemical exposure measurements and more than half of these studies had potential recall bias because exposures were self-reported after diagnosis. Outcomes were all identified using reliable sources, and all the studies evaluated AML incidence. None of the studies that examined AML and benzene fully controlled for all important covariates, increasing the likelihood of confounding. Most case-control studies appropriately considered latency in either their analyses or study design.

8.1.2.4 Chronic Myeloid Leukemia

CML was assessed in 9 cohort studies, 5 case-control studies, and 1 case-cohort study. No cohort study had more than 5 exposed cases in any exposure category, and most of the case-control studies were also limited by small numbers of exposed cases. Cohort studies reported a wide range of risk estimates (0.258-7.295);[14] most were >1, but CIs were very wide, and no study reported statistically significant results for CML and any benzene exposure (Wong *et al*., 1993, 2001a,b; Collingwood *et al.*, 1996; Huebner *et al*., 2004; Sorahan *et al*., 2005; Tsai *et al.*, 2007) or with any level of exposure (Wong *et al*., 2001a,b; Tsai *et al*., 2007; Saberi Hosnijeh *et al*., 2013). Saberi Hosnijeh *et al*. (2013) was the only cohort study that evaluated dose response and they reported no significant trend (p_{trend} = 0.30). Lewis *et al.* (2003) said they evaluated CML risks in workers at oil refineries and petrochemical facilities, but did not report any results because the numbers of cases and deaths were <5 and not statistically significant. Notably, although some cohort studies evaluated duration of exposure, only Saberi Hosnijeh *et al*. (2013) examined magnitude of exposure.

The case-control and case-cohort studies reported a wide range of risk estimates (0.9-5.0),[15] and most were >1 but not statistically significant. Two studies reported no increased risks for CML incidence with any

[14] Wong *et al*. (2001a,b) reported risk estimates of 0 among strata with no cases and Lewis *et al*. (2003) and Huebner *et al*. (2004) did not report risk estimates in several analyses. These estimates are not included in this range.
[15] Glass *et al*. (2003) did not report a risk estimate in one analysis and Linet *et al*. (2019) reported ERRs. These are not included in this range.

benzene exposure overall (Bjork *et al*., 2001; Kaufman *et al*., 2009). Blair *et al*. (2001) and Linet *et al*. (2019) examined CML incidence risk by intensity of exposure, and Guenel *et al*. (2002), Glass *et al*. (2003), and Linet *et al*. (2019) examined CML incidence and cumulative exposure. None of these studies reported an association with any level of exposure and the two that evaluated dose response did not report significant trends (Guenel *et al*., 2002; Linet *et al*., 2019). Only one case-control study (Adegoke *et al*., 2003) reported statistically significant increased risks.

Adegoke *et al*. (2003) reported an increased risk of CML incidence associated with self-reported lifetime occupational benzene exposure combined with a JEM assessment (OR = 2.4, 95% CI: 1.3-4.7) and an increased risk with increasing self-reported duration of exposure (p_{trend} = 0.01). Adegoke *et al*. (2003) appropriately selected cases and controls and had high participation rates. The authors did not assess direct chemical exposure measurements, and the study had the potential for recall bias because exposures were self-reported after diagnosis. None of the studies that examined benzene and CML fully controlled for all important covariates, increasing the likelihood of confounding.

8.1.2.5 Myelodysplastic Syndrome

MDS was assessed in two cohort studies, seven case-control studies, and one case-cohort study. The two cohort studies reported a wide range of risk estimates (0.41-25.05);[16] most were close to 1 and not statistically significant (Collins *et al*., 2015; Sorahan and Mohammed, 2016).

Linet *et al*. (2019) evaluated the risk of MDS incidence in the NCI-CAPM cohort. They reported an increased risk with increasing cumulative exposure among those who were first exposed before they were 30 years of age (p = 0.03) and with increasing average exposure intensity in those either younger or older than 30 when first exposed ($p \leq 0.05$). These findings were observed in analyses limited to exposures occurring from 2 to 10 years before diagnosis. The authors did not report an increased risk of MDS based on exposures that occurred ≥ 10 years before diagnosis. Results from Linet *et al*. (2019) on AML and MDS combined are discussed in more detail in Section 8.1.2.3. Linet *et al*. (2019) used an appropriate source of controls (*i.e*., from an occupational cohort), had high participation rates, and used reliable sources to identify cases.

Collins *et al*. (2015) reported MDS mortality rates among benzene exposed chemical workers were not different than expected based on rates in the US general population overall (SMR = 6.48, 95% CI: 0.17-38.15) or by level of cumulative exposure (p = 0.11), but these risk estimates were based on only a single exposed case. Sorahan and Mohammed (2016) reported incidence rates of MDS in petroleum distribution workers (standardized risk ratio [SRR] = 0.73, 95% CI: 0.43-1.18) or oil refinery workers (SRR = 0.81, 95% CI: 0.54-1.16) 15 to 84 years of age were not different than expected based on rates in the general populations of England, Wales, and Scotland. There were no associations with time period of enrollment in the study or date of hire in either population, or with duration of employment in petroleum distribution workers. The authors reported a *lower* rate of MDS incidence in oil refinery workers aged 15 to 99 with the longest duration of employment than expected (≥20 years SRR = 0.44, 95% CI: 0.19-0.87), and there was a statistically significant *decreased* risk with increased duration (p_{trend} = 0.05).

The case-control studies that examined benzene and MDS reported a wide range of risk estimates (0.58-12.54)[17]; most were >1. Two case-control studies (Albin *et al*., 2003; Yarosh *et al*., 2021) reported no association between MDS and any benzene exposure overall, while three others (Irons *et al*., 2010; Lv *et al*., 2011; Anwar *et al*., 2022) reported increased risks. Irons *et al*. (2010) evaluated MDS risk in a hospital-

[16] Collins *et al*. (2015) and Sorahan and Mohammed (2016) reported risk estimates of 0 in strata with no cases. These estimates are not included in this range.
[17] ERRs are not reported in this range.

based case-control study in Shanghai. Exposed signal cases were defined as those with benzene exposures of >67 mg/m^3 for at least 6 months. The average duration of exposure was 12 years. The authors reported an association with the unclassifiable form of MDS (U-MDS) (OR = 11.12; CI: 1.34-92.4), but not RCMD (OR = 0.58, 95% CI: 0.24-1.4), RAEB (OR = 1.4, 95% CI: 0.19-11.1), RCUD (OR = 1.0, 95% CI: 0.18-5.46), or RA (OR = 0.67, 95% CI: 0.13-3.3). Anwar *et al*. (2022) reported an increased risk of MDS incidence among patients who self-reported ever being exposed to benzene (OR = 1.564, 95% CI: 1.077-2.272) compared to those who reported no exposure. Lv *et al*. (2011) reported an increased risk of MDS (OR = 4.33, 95% CI: 1.88-10.00) and RCMD incidence (OR = 5.66, 95% CI: 1.81-17.64), but not RAEB incidence (OR = 3.00, 95% CI: 0.5-17.95), among patients who self-reported prior benzene exposure compared to those reporting none. All three case-control studies that reported an association with any benzene exposure used hospital-based controls (Irons *et al*., 2010; Lv *et al*., 2011; Anwar *et al*., 2022). Anwar *et al*. (2022) did not consider disease latency.

Four case-control studies evaluated MDS risk by level of benzene exposure (Blair *et al*., 2001; Lv *et al*., 2011; Copley *et al*., 2017; Linet *et al*., 2019) and reported mixed results. Blair *et al*. (2001) reported no association between MDS incidence and increasing benzene exposure intensity based on self-reported occupational history linked to a JEM. Lv *et al*. (2011) and Copley *et al*. (2017) evaluated risk by various levels of exposure (*i.e*., duration of exposure, average exposure intensity, weekly frequency) and both reported an increased risk of MDS ($p_{trend} < 0.01$) and RCMD incidence ($p_{trend} < 0.01$) with all metrics of increasing benzene exposure. Neither study reported an increased risk of RAEB incidence with increasing benzene exposure. Both Lv *et al*. (2011) and Copley *et al*. (2017) conducted their studies in Shanghai-based hospitals, recruited controls from the hospitals, and based-their analyses on self-reported prior benzene exposure after diagnosis, increasing the likelihood of exposure misclassification and recall bias. Lv *et al*. (2011) considered disease latency but Copley *et al*. (2017) did not. None of the studies that examined benzene and MDS fully controlled for all important covariates, increasing the likelihood of confounding.

8.1.2.6 Other Leukemia Types

Three cohort studies (Sorahan *et al*., 2005; Saberi Hosnijeh *et al*., 2013; Collins *et al*., 2015) and two case-control studies examined total lymphoid leukemias (Bernard *et al*., 1984; Wilcosky *et al*., 1984) and none reported an association with benzene.

Five cohort studies examined myeloid leukemia and none reported an association with benzene (Sorahan *et al*., 2005; Saberi Hosnijeh *et al*., 2013; Bassig *et al*., 2015; Collins *et al*., 2015; Stenehjem *et al*., 2015). Two case-control studies examined all myeloid leukemias (Kaufman *et al*., 2009; Forsell *et al*., 2020) and reported mixed results. Forsell *et al*. (2020) did not report an association among Swedish seafarers employed on tankers. Kaufman *et al*. (2009) reported an increased risk of myeloid leukemia among cases who self-reported prior occupational exposure to benzene in Thailand (OR = 3.9, 95% CI: 1.3-11) compared with those with no prior occupational exposure. This study relied on hospital-based controls and had a potential for recall bias, as exposures were reported after diagnoses. They also did not account for disease latency.

One cohort study (Schnatter *et al*., 1993) investigated mortality rates for myeloid and lymphatic leukemia combined among petroleum distribution workers and did not observe any difference in rates when compared with the Canadian general population.

One cohort study (Sorahan *et al*., 2005) examined monocytic leukemia mortality. There were no cases among benzene exposed workers.

Two cohort studies (Aksoy *et al*., 1974; Divine *et al.*, 1999b) evaluated risks of acute leukemias. Aksoy *et al*. (1974) reported an increased incidence of acute leukemia and preleukemia combined in Turkish shoe, slipper, and handbag industry workers compared to what would have been expected based on rates in the Turkish general population ($p > 0.02$). Divine *et al.* (1999b) reported a higher mortality rate of acute unspecified leukemia than would have been expected based on rates in the US general population (SMR = 2.76, 95% CI: 1.54-4.55). They also reported an association in workers who were employed before 1950 (SMR = 2.76, 95% CI: 1.47-4.72) but not after (SMR = 2.73, 95% CI: 0.30-9.86).

Guenel *et al*. (2002) was the only case-control study that evaluated benzene exposure and acute and chronic leukemias separately. The authors observed an increased risk of acute leukemia incidence among electric utility workers with increasing benzene exposure ($p_{trend} = 0.05$) and in the highest exposure group (≥16.8 unit-years OR = 4.6, 95% CI: 1.2-17.4) when compared with those never exposed, but not for other exposure categories. They did not observe any associations between benzene exposure and chronic leukemia.

Tsai *et al*. (2007) did not observe any differences in mortality rates for other leukemias when compared with the US general population, and Hayes (1997) did not report any differences in risk for other leukemias (*i.e*., non-ANLL and undefined) based on any exposure or duration of exposure. Divine *et al*. (1999b) observed an increased mortality rate for cell-type-unspecified leukemia among all white, male, petrochemical employees (SMR = 2.31, 95% CI: 1.29-3.81), and particularly among those employed before 1950 (SMR = 2.62, 95% CI: 1.43-4.40) and in 1950 or later (SMR = 0.87, 95% CI: 0.01-4.86).

8.1.3 Pooled and Meta-Analyses

I identified one pooled analysis and six meta-analyses of benzene and leukemia or leukemia subtypes. Overall, these analyses support an association between benzene exposure and leukemia, AML and MDS, but not CML or ALL.

Raabe and Wong (1996) conducted a meta-analysis of 19 petroleum worker cohort studies from the US and UK. Individual mean and cumulative exposures from the highest-exposed jobs were 1 ppm and <45 ppm-years, respectively. There were no increased risks reported for AML, CML, or ALL mortality.

Lamm *et al*. (2009) conducted a meta-analysis of six case-control studies that estimated the association between benzene and CML. Their exposure assessments were based on job histories, JEMs, or industrial hygiene assessments. The authors found no evidence of an association using a fixed-effects model (meta-odds ratio [mOR] = 1.003, 95% CI: 0.94-1.07).

Khalade *et al*. (2010) meta-analyzed 15 cohort and case-control studies that assessed occupational exposure to benzene and the risk of leukemia and leukemia subtypes, including AML and CML, in 15 cohort and case-control studies (no ALL studies were identified). They reported an association with leukemia overall (meta-relative risk [mRR] = 1.72, 95% CI: 1.37-2.17) and with increasing cumulative exposure (*i.e*., <40, 40-<100, and >100 ppm-years, $p_{trend} = 0.015$, n = 9). AML risks were significant in the highest exposure category only (mRR = 3.20, 95% CI: 1.09-9.45, $p_{trend} = 0.813$). Summary effect estimates also increased with increasing cumulative benzene exposure categories for AML (range = 1.94-3.20), though this trend was not statistically significant. There was no increase in CML risk associated with any benzene exposure (mRR = 1.05, 95% CI: 0.83-1.34, n = 6).

Vlaanderen *et al*. (2011) evaluated occupational exposure to benzene from any industry and AML and ALL risk in a meta-analysis of 21 and 17 cohort studies, respectively. Occupational benzene exposure was associated with increased risk of AML (mRR = 1.68, 95% CI: 1.35-2.10) and ALL (mRR = 1.44, 95%

CI: 1.03-2.02) in analyses that included all relevant studies. In similar analyses by Vlaanderen *et al*. (2012), the authors did not find any relationship between benzene exposure and CML.

One of the most recent meta-analyses of benzene and several myeloid malignancies, including AML, CML, and MDS, was conducted by Mundt *et al*. (2021). These authors reported benzene was associated with increased risks of AML based on 27 estimates reported in 26 publications (mRR = 1.30, 95% CI 1.09-1.55) with similar increases across exposure categories, but risks for low or any benzene exposure were not statistically significantly elevated. Based on 18 estimates from 17 studies, benzene was not associated with an increased risk of CML overall (mRR = 1.25, 95% CI 1.00-1.55), and there was a large variation in the summary RRs across exposure categories. However, risk was increased in high exposure subcategories (mRR = 2.79, 95% CI: 1.44-5.40) based on three studies. There was an increased risk of myeloid leukemias combined, based on seven studies (mRR = 1.56, 95% CI: 1.10-2.20) with wide variability across exposure categories. Risks of MDS were estimated based on nine studies and were also increased (mRR = 1.87, 95% CI: 1.39-2.52). Mundt *et al*. (2021) concluded:

> The interpretation of results on risk of specific leukemia types from exposure to benzene is complicated by the heterogeneity in exposure circumstances. However, the evidence indicates a similar association between occupational exposure to benzene and specific myeloid neoplasms, but the association appears strongest for MDS, especially among more recent studies. This raises the question of whether earlier studies identifying associations between generally very high benzene exposure and AML might have reflected the occurrence of secondary AML following unrecognized (or misdiagnosed) primary cases of MDS. It is noteworthy that a very large record linkage study from the Nordic countries reported no association between benzene exposure and AML incidence.

Schnatter *et al*. (2012) conducted a pooled analysis of three nested case-control studies from Australia, Canada, and the United Kingdom with 370 potential cases and 1,587 matched controls among petroleum distribution workers and follow-up through 2006. Benzene exposure was reconstructed using historical monitoring data and pathological diagnoses were redefined from the available medical records. This study reported that cumulative exposures of >2.93 ppm-years were associated with a statistically significant increase in MDS (OR = 4.33, 95% CI: 1.31-14.3) but not of AML (OR = 1.39, 95% CI: 0.68-2.85) when compared with the lowest tertile of exposure (≤0.348 ppm-years). The risk was also increased for CML incidence and cumulative exposures 0.348-2.93 (OR = 5.04, 95% CI: 1.45-17.5) but not based on tertile of exposure (OR = 2.20, 95% CI: 0.63-7.68). Analyses based on tertiles of other exposure metrics (*i.e*., average exposure intensity, maximum exposure intensity, and duration of employment) did not yield any associations. The authors reported that there "was little evidence of dose-response relationships for" AML or CML.

8.1.4 Latency

Several studies reported that evidence was strongest for benzene exposures less than 10 or 15 years before the development of leukemia. Silver *et al*. (2002) analyzed "exposure windows" for benzene in the follow-up of the Pliofilm cohort through 1996 and found that exposures 15 or more years prior to death from leukemia did not contribute to risk. Finkelstein (2000) analyzed data for the earlier follow-up through 1987 from Rinsky *et al*. (1987), including additional cases provided by the National Institute for Occupational Safety and Health (NIOSH) after this publication. Finkelstein (2000) stated that, "The coefficients for those windows more than 14 years before the death of the case were not statistically significant; that is, there were no significant differences between the exposures of the case subjects and their controls more than 14 years before the death of the case." Using updated exposure estimates, Rhomberg *et al*. (2016) found that exposures within 10 years were the most important for induction of ANLL/AML.

As noted in Section 8.1.2.3, Hayes *et al*. (1997) compared death rates in Chinese factory workers exposed to benzene to unexposed workers and stated that, "In our study, ANLL/MDS was linked to recent benzene exposure, and additional distant exposure did not appear to further increase risk." In this study the difference between recent and distant exposure was 10 years.

In an evaluation of an Australian petroleum worker cohort, Glass *et al.* (2004) reported similar findings. These authors stated, "We found that leukemia was most strongly associated with benzene exposures in the period 15 years prior to diagnosis and exposures more than 15 years prior to diagnosis made little contribution to the risk."

Triebig (2010) presented the data of 537 confirmed cases of leukemia as an occupational disease in Germany from 1978 to 2007 and concluded that the epidemiology findings demonstrated a smaller or even absent risk of leukemia 10 to 15 years after exposure to benzene had ceased.

8.1.5 Conclusions

There is a wide range of risk estimates for benzene and leukemia and leukemia subtypes (range: 0.18-98.2). Most estimates for leukemia were greater than 1 but, as noted by IARC (2018), "Treating all leukaemias as a single entity is a limitation of several…studies, given the evidence of etiological heterogeneity." ALL and CML were occasionally, but not consistently, associated with benzene exposure, but most risk estimates were not statistically significant, and there were no consistent dose-response trends. In most studies of AML and MDS, risk estimates tended to be >1. Two cohorts with high-quality exposure assessments reported an association between benzene exposure and AML (Rhomberg *et al*., 2016) and AML or ANLL and MDS (Linet *et al*. 2019). Rhomberg *et al*. (2016) reported an increased risk of ANLL and AML among Pliofilm workers exposed to the highest cumulative benzene exposures (≥40-75 ppm-years), and Linet *et al*. (2019) reported increased risks of MDS and AML combined with exposures >40 ppm-years in the NCI-CAPM cohort. Hayes *et al*. (1997) reported an increased risk of ANLL in NCI-CAPM factory workers with ≥40 ppm-years of cumulative exposure, but no increased risk of non-ANLL leukemias with any level of exposure. The NCI-CAPM studies demonstrate how reported associations between benzene exposure and leukemia overall may be driven by the association between benzene and ANLL or AML and MDS.

The exact level of benzene exposure required to cause ANLL, AML, or MDS is not clear. Increased risks of ANLL and AML in the Pliofilm cohort were only observed at benzene exposures greater than ~75 ppm years respectively, but there were very few exposed cases overall (ANLL n = 8, AML n = 6) (Rhomberg *et al*., 2016). There were more cases of ANLL and AML in the NCI-CAPM cohort, particularly at lower ranges of exposure (*e.g*., < 40 ppm-years), but there were no associations between ANLL, AML, or AML and MDS at exposure levels <40 ppm-years in this cohort.

Most epidemiology studies of benzene exposure and leukemia, including leukemia subtypes, had several methodological limitations, particularly a high likelihood of exposure measurement error and co-exposures to other chemicals in most studies. However, given the relative consistency of associations and dose-response relationships reported in studies with high quality exposure estimates, I conclude that the epidemiology evidence supports an association between benzene exposures above 40 to 75 ppm-years and AML. The evidence is strongest for exposures that occurred within 10 to 15 years before diagnosis. The evidence also supports an association with MDS at exposures above 40 ppm-years. The evidence does not support a causal association between benzene and leukemia overall or ALL or CML.[18]

[18] The results of the three studies I identified after the completion of my literature search (Section 8.1.2.1), do not change my conclusions regarding benzene exposure and leukemia risk.

8.2 Toxicology

8.2.1 Animal Carcinogenicity Studies

I identified seven chronic oral gavage benzene bioassays, all of which reported results for leukemia generally or MNCL specifically in both control and treated animals. The results of these studies are reported in Attachment I, Table I.1; an overview of study quality is described in Attachment I, Table I.3, and individual chronic study quality is shown systematically in Attachment I, Table I.4. Experimental evidence is integrated with epidemiology evidence in Section 8.3.

Maltoni *et al*. (1983, 1985, 1988b, 1989) and Maltoni and Scarnato (1979) exposed Sprague-Dawley rats *via* oral gavage to 0, 50, or 250 mg/kg-d for either 52 or 104 weeks, Wistar rats to 0 or 500 mg/kg-d for 104 weeks, Swiss mice to 0 or 500 mg/kg-d for 78 weeks, and RF/J mice to 0 or 500 mg/kg-d for 52 weeks. There was a significant increase in the number of both male and female RF/J mice with leukemia (as reported by IARC [2018]) but both control (males: 17 of 45, females: 14 of 40) and treated animals (males: 26 of 45, females: 24 of 40) had high incidences of leukemia, indicating that tumors may not have been treatment related. It is also possible that some tumors were misdiagnosed (Gift *et al*., 2013).

In a good laboratory practice (GLP)[19] study, researchers dosed male F344/N rats with 0, 50, 100, and 200 mg/kg-d and male and female B6C3F1 mice and female F344/N rats with 0, 25, 50, and 100 mg/kg-d benzene *via* gavage (Huff *et al*., 1989/NTP, 1986b). MNCL incidence was significantly elevated in female F344/N rats only (9 of 50 at 100 mg/kg-d *vs*. 6 of 50 controls). The authors concluded that the MNCL incidence in female F344/N rats was within the range of historical controls and were therefore not treatment related.

All 12 of the chronic inhalation benzene bioassays I identified reported leukemia data for rats or mice exposed to 100-300 ppm benzene (Attachment I, Table I.2). CMLs and AMLs were reported in a single animal exposed to 100 or 300 ppm benzene in several bioassays, but the only statistically significant finding was reported by Snyder *et al*. (1988); an increase in leukemia/lymphoma combined was reported in male CD-1 mice, but not male C57BL/6 mice, exposed to 300 ppm benzene (7 of 54 *vs*. 1 of 46 controls). Because Snyder *et al*. (1988) treated animals over their lifespan, late-life pathology cannot be ruled out.

Because US EPA (1998) also relied on subchronic benzene studies, I review them here. I identified eight subchronic oral bioassays with benzene exposure durations of 8-27 weeks (Stoner *et al*., 1986; French and Saulnier, 2000; NTP, 2007) and 19 subchronic inhalation bioassays with benzene exposure durations of 10-26 weeks (Maltoni *et al*., 1982, 1983, 1985; Cronkite *et al*., 1984, 1985, 1989; Cronkite, 1986; Ward *et al*., 1985; Snyder *et al*., 1988; Farris *et al*., 1993; Li *et al*., 2006; Kawasaki *et al*., 2009). The findings from these studies are inconsistent. None of the eight subchronic oral bioassays reported significant increases in leukemia at benzene doses ranging from 100-200 mg/kg-d. Only 1 of the 19 subchronic inhalation bioassays reported significant increases in leukemia in male and female CBA/Ca mice treated with 300 ppm benzene (Cronkite *et al*., 1989). Farris *et al*. (1993) used the same strain of mice as Cronkite *et al*. (1989) and investigated the potential of benzene to induce carcinogenicity, with a particular focus on the potential induction of granulocytic leukemia, but did not find that exposure at 300 ppm benzene over 16 weeks caused granulocytic leukemia.

[19] GLP is defined as "a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported" (WHO TDR, 2009).

In conclusion, while Maltoni *et al*. (1983, 1985, 1988b, 1989) and Maltoni and Scarnato (1979) reported an increase in leukemias in one of five bioassays, animals were observed until spontaneous death (increasing the likelihood of late-life pathology) and leukemias may have been misdiagnosed. In GLP bioassays, MNCL incidence was only significantly elevated in female F344/N rats, and the authors concluded that this was not treatment-related (Huff *et al*., 1989/NTP, 1986b). With the exception of leukemias and lymphomas combined in one study, no increases in leukemia incidence were reported in any chronic inhalation bioassay, and results from subchronic bioassays were inconsistent. Overall, animal bioassay findings do not support benzene as a cause of leukemia in humans.

8.2.2 Mechanistic Studies

Although animal bioassay findings do not support benzene as a cause of leukemia, epidemiology studies support associations with AML and MDS, and there is a biologically plausible MoA for these leukemia subtypes. In animals and humans, benzene is primarily metabolized in the liver, and secondarily in the bone marrow, to reactive metabolites that are electrophilic, pro-oxidant, genotoxic, and immunosuppressive (IARC, 2018; ATSDR, 2007b, 2024a; US EPA, 1998). The toxicity of benzene is dependent on the formation of these reactive metabolites, with evidence suggesting that they may induce AML and MDS *via* a genotoxic MoA. Although the precise mechanisms have not been fully elucidated, various processes are believed to be involved, including oxidative stress, protein and DNA damage, disruption of gene expression, genomic instability, decreased DNA repair, enzyme inhibition, inflammation, chromosome damage, epigenetic changes, and altered cell functions, including proliferation, cell death, and receptor-mediated effects (IARC, 2018; ATSDR, 2007b, 2024a; US EPA, 1998; North *et al*., 2020). Reactive metabolites generated in the liver can also be transported to the bone marrow (ATSDR, 2024a).

Cytogenetic abnormalities, including chromosomal aberrations (hypo- and hyperdiploidy, deletions, breaks, and gaps) in peripheral lymphocytes and bone marrow cells are commonly observed in benzene-exposed humans (ATDSR, 2007b). Although benzene is considered genotoxic, mechanistic evidence suggests it is not a direct-acting DNA mutagen, but rather indirectly induces genotoxicity through a threshold-mediated process in which exposures below the threshold do not result in genetic toxicity (North *et al*., 2020). Evidence from epidemiology studies also provides support for a threshold below which benzene does not cause cancer (Rhomberg *et al*., 2016).

Because a causal association has not been demonstrated for benzene and other types of leukemia, including ALL and CML, and every cancer is etiologically distinct, it is unclear whether the MoA for AML and MDS would be applicable to other types of leukemia that originate in different cell populations (lymphoid *vs*. myeloid cells) or follow different disease progressions (*e.g*., acute *vs*. chronic).

8.3 Evidence Integration

Several epidemiology and toxicity studies have evaluated benzene and leukemia (see Sections 8.1 and 8.2). Most relevant epidemiology studies had higher-quality outcome assessments (*e.g*., confirmed cases), but the changing classification of leukemia subtypes over time makes it difficult to directly to compare results of studies using classification schemes from different eras (*e.g*., some studies included CLL in analyses of all leukemias or all myeloid leukemias, while others classified CLL as a type of NHL). Appropriate consideration of temporality, latency period, and control for potential confounders varied across studies, but almost none sufficiently controlled for all important potential confounders. The characterization of exposure varied across studies. Most studies did not adequately assess benzene exposure, but a few occupational studies estimated exposures based on detailed job histories, monitoring data, expert opinions, and JEMs, and adequately assessed risks associated with average or cumulative benzene exposure

concentrations into their analyses. The strongest evidence was provided by studies of the Pliofilm and Chinese cohorts, both of which had high quality exposure estimates. In addition to being limited in quality, animal studies do not provide consistent evidence for causation. Keeping these study strengths and limitations in mind, I evaluated the available evidence in the context of Bradford Hill's considerations, Table 8.1. I conclude that the evidence supports a causal association between benzene exposure and AML and MDS, but not ALL or CML.

Table 8.1 Bradford Hill Assessment of Benzene and Leukemia

Aspect	Analysis
Strength of Association	There is evidence of a strong association between high benzene exposures (*i.e.*, greater than 40-75 ppm-years) and leukemia, AML, and MDS. Studies with the highest quality exposure estimates consistently reported strong associations.
Consistency	Risks for leukemia, AML, and MDS were consistently >1. Studies with higher quality exposure estimates consistently reported increased risks of AML and MDS associated with higher levels of benzene exposure. Meta-analyses (*e.g.*, Mundt *et al.*, 2021) also reported increased risks of AML and MDS, but not other subtypes.
Specificity	There is no currently available evidence to suggest that there is a specific relationship between benzene and leukemia.
Temporality	Temporality was adequately addressed in most cohort studies but not in most case-control studies. Most cohort and case-control studies assessed exposures prior to leukemia diagnosis, but many did not ensure an appropriate period of time between exposure and diagnosis, either in the design or the analysis (*i.e.*, ≥0.5 years).
Dose-Response	Dose-response trends were found in higher-quality studies of benzene and AML and MDS, but there were no consistent trends for leukemia, ALL, or CML.
Biological Plausibility	There is a biologically plausible MoA by which benzene can cause AML and MDS, but it is unclear if the genotoxic MoA is applicable to other types of leukemia that follow different etiological pathways.
Coherence	Collectively, the evidence supports a causal association between benzene exposure and AML and MDS, but not ALL or CML. Animal bioassay findings do not consistently support benzene as a cause of leukemia in humans, but there is evidence to suggest that reactive metabolites of benzene may induce AML and MDS *via* a genotoxic MoA, or through alterations in cell proliferation, cell death, or receptor-mediated effects (IARC, 2018; ATSDR, 2007b; US EPA, 1998). Epidemiology studies support associations with AML and MDS, but not ALL or CML.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compound to benzene that cause leukemia.

Notes:
ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; CML = Chronic Myeloid Leukemia; MDS = Myelodysplastic Syndrome; MoA = Mode of Action.

8.4 Agency Reviews

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct chemical carcinogenicity evaluations. IARC, US EPA, and NTP all classify agents according to whether they are likely to cause cancer in humans, each using a unique framework, as described in Section 3.5.1 and Table 3.5. ATSDR, NASEM, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Tables 3.6 and 3.7.

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, the reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. Also, IARC, US EPA, and NTP carcinogenicity categories all include ones called "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data for the agent at all, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding). The review process for ATSDR (2017a) had even more methodological issues than those discussed above (see Section 3.5.2 and Table 3.8). This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation.

Government and scientific agencies concluded that evidence supports a causal association between benzene and AML. IOM (2003) and NRC (2009) concluded there is limited evidence for other leukemia subtypes. Only ATSDR (2017a) concluded there is sufficient evidence of causation for all leukemia subtypes, including ALL, AML, and CML, but ATSDR (2024a) concluded there was clear evidence for causality only for ANLL/AML. These agency assessments of benzene carcinogenicity are described briefly below.

8.4.1 ATSDR

In its 2007 toxicological profile, ATSDR concluded there was "clear evidence of a causal relationship between occupational exposure to benzene and benzene-containing solvents and the occurrence of ANLL, particularly the myeloid cell type (acute myelogenous leukemia, AML)" (ATSDR, 2007b). Regarding epidemiology evidence, ATSDR (2007b) stated that the strongest evidence for the leukemogenic potential of benzene was based primarily on a series of occupational mortality studies on workers exposed to benzene in Ohio (the Pliofilm study) and China (the NCI-CAPM study). ATSDR (2007b) noted, "The epidemiological studies are generally limited by confounding chemical exposures and methodological problems, including inadequate or lack of exposure monitoring and low statistical power, but a consistent excess risk of leukemia across studies indicates that benzene is the causal factor." ATSDR (2007b) discussed several studies in which hematopoietic cancers (leukemias or lymphomas) were observed in animals exposed to benzene by inhalation or ingestion. The agency discussed mechanisms of toxicity for the hematotoxic and leukemogenic effects of benzene, and noted that there is evidence to support an MoA where reactive benzene metabolites are transported to and/or formed in the bone marrow and cause oxidative damage to stem cells and early progenitor cells (ATSDR, 2007b).

In its "Addendum to the Toxicological Profile for Benzene," ATSDR (2015) reviewed additional epidemiology studies with mixed results for NHL, ALL, CLL, and multiple myeloma; it determined that the evidence was "sufficient to consider the associations positive, although in most cases, observed associations did not reach the level of statistical significance" (ATSDR, 2015). The agency did not make a causal determination for leukemia in humans. With regard to animal evidence, ATSDR (2015) stated that there was "sufficient evidence for the carcinogenicity of benzene in experimental animals."

In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) concluded there is "sufficient evidence for causation for benzene and all leukemia types, i.e., ALL, CLL, AML, and CML"; "equipoise and above evidence for causation" for multiple myeloma; and "below equipoise evidence for causation" for liver cancer, pancreatic cancer, bladder cancer, esophageal cancer, and breast cancer. Conclusions for leukemia were based on positive findings in a meta-analysis and more recently published cohort studies. ATSDR (2017a) also cited supporting evidence of decreased lymphoid and myeloid cell

types in factory workers exposed to benzene in one study. The agency did not discuss any animal or mechanistic studies. Limitations of the ATSDR (2017a) analysis are discussed in Section 3.5.2.

ATSDR (2024a) released a "Toxicological Profile for Benzene (Draft for Public Comment)." In this updated toxicological profile, ATSDR (2024a) stated, "Collectively, available epidemiological and meta-analyses studies show clear evidence of a causal relationship between occupational exposure to benzene and benzene-containing solvents and the occurrence of acute nonlymphocytic leukemia (ANLL), particularly the myeloid cell type (i.e., AML)." The agency further noted:

> It must be noted that available epidemiological studies are generally limited by confounding chemical exposures and methodological problems, including inadequate or lack of exposure monitoring and low statistical power (due to small numbers of cases). Many of the earlier studies are additionally limited by a lack of information on leukemia cell types other than AML, because leukemia used to be considered a single diagnostic category for epidemiological purposes, due in part to historical nomenclature, small numbers of deaths by cell type, and unavailability of cell-type-specific rates for comparison. (ATSDR, 2024a)

With respect to experimental evidence, ATSDR (2024a) stated, "Studies in laboratory animals show that exposure to benzene induced tumors at multiple sites in rats and mice, with a tendency towards induction of lymphomas in mice."

8.4.2 NASEM

IOM (2003) concluded that there is "sufficient evidence of a causal relationship between chronic exposure to benzene and acute leukemia" (as a broad category of all subtypes including AML and ALL). The agency based this conclusion on what it considered was "consistently high relative risks in studies in which the exposure to benzene is well known," citing Albin *et al*. (2000), Ciccone *et al*. (1993), Crump (1994), Ireland *et al*. (1997), Richardson *et al*. (1992), Rushton and Romaniuk (1997),[20] Wong (1995), and Yin *et al*. (1996a,b). The agency also cited supporting evidence from animal studies that showed dose-dependent effects of benzene in the bone marrow resulting in anemia, leukopenia, thrombocytopenia, aplasia, and pancytopenia, as well as increased incidence of malignant lymphoma and some solid tumors (IOM, 2003).

IOM (2003) concluded that there was "sufficient evidence of an association between chronic exposure to benzene and adult leukemia" (broadly defined as all subtypes and CLL), but that the evidence was not strong enough to warrant a conclusion of causation. This was based on "consistently positive findings in the cohort of workers with known exposures to benzene and evidence of a dose-response relationship," with the agency citing Crump (1994), Rinsky *et al*. (1981, 1987), Hayes *et al*. (1997), Yin *et al*. (1996a,b), Bond *et al*. (1986), Ireland *et al*. (1997), Wong (1987a,b), Rushton and Alderson (1981), Wong *et al*. (1993), Schnatter *et al*. (1996a,b), Rushton and Romaniuk (1997).[20]

NRC (2009) stated, "Acute myelogenous leukemia is the predominant cancer found in humans exposed to benzene and has been documented in studies of workers exposed to benzene in rubber hydrochloride manufacturing plants (Rinsky et al. 1981, 1987) and in factories in China (Yin et al. 1987b, 1989, 1996; Hayes et al. 1996, 1997)." The agency also noted that many epidemiology studies have found benzene exposure is associated with increased incidences in leukemia in general, total lymphatic and hematopoietic cancers, and specific leukemias such as CLL (Savitz and Andrews, 1997; NTP 2005). NRC (2009) also cited several animal studies that showed hematologic and immune effects from benzene exposure, including

[20] IOM (2003) cited this reference with the year 1996.

lymphoid tumors in mice, and described severe damage to the bone marrow resulting in pancytopenia and aplastic anemia, conditions that have been shown to be associated with leukemia (Snyder *et al.*, 1980, 1984, 1988; Cronkite *et al.*, 1984, 1985, 1989; Maltoni *et al.*, 1989; Farris *et al.*, 1993).

IOM (2015) noted that leukemia was associated with chronic exposure to solvents but did not include any discussion of benzene and leukemia specifically.

8.4.3 US EPA

US EPA (1998) concluded that benzene is a known human carcinogen and stated "benzene can cause acute nonlymphocytic (myelogenous) leukemia" based on evidence from epidemiology, animal, and mechanistic studies. US EPA (1998) cited several epidemiology and case studies that "provide clear evidence of a causal association between exposure to benzene and leukemia, especially ANLL and, to a lesser extent, chronic nonlymphocytic leukemia as well as chronic lymphocytic leukemia (CLL) (Vigliani and Saita, 1964; Aksoy et al., 1974; Aksoy, 1976, 1977; Infante et al., 1977; Rinsky et al., 1981, 1987; IARC, 1982; ATSDR, 1997)." US EPA (1998) also noted that the "Rinsky et al. (1987) Pliofilm cohort is currently the best set of data available for estimating exposure and the risk of leukemia." The agency also cited studies in rats and mice that reported increased cancer incidence at multiple sites, including lymphocytic leukemia, and evidence for potential mechanistic pathways involving the formation of reactive metabolites and subsequent damage and genotoxicity in the bone marrow (ATSDR, 1997). US EPA (1998) stated:

> It is noted that in humans the cancer induced by benzene exposure is predominantly acute nonlymphocytic leukemia, while in rodents lymphocytic leukemia was observed in two series of experiments in C57BL/6 mice (Snyder et al., 1980) and CBA/Ca mice (Cronkite et al., 1989). The difference in induction of hematopoietic cancers in mice and humans is not fully understood, but it may be related to species-specific differences in hematopoiesis…. The animal bioassay results may have some relevance to human leukemia, but it should be emphasized that there is no well-demonstrated and reproducible animal model for leukemia resulting from benzene exposure. The mechanism of leukemia development following exposure to benzene is not well understood (Low et al., 1989, 1995).

8.4.4 IARC

IARC (2012a) concluded that "There is sufficient evidence in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia/acute non-lymphocytic leukaemia." IARC (2018) concluded that there is "[s]ufficient evidence of an association between benzene exposure and risk of acute myeloid leukaemia (AML) and/or acute non-lymphocytic leukaemia (ANLL)." IARC (2018) stated, "There is sufficient evidence in experimental animals for the carcinogenicity of benzene" and the "Group 1 evaluation was supported by mechanistic data."

This determination was based on several occupational studies that included quantitative exposure data and reported exposure-response trends with benzene exposure and AML and/or ANLL. IARC (2018) stated there is evidence from mouse and rat studies that reported multiple tumor sites in animals exposed to benzene, including leukemias and lymphomas, but IARC (2018) did not discuss the inconsistency of lymphoma findings across animal studies. The agency also cited what it considered strong evidence of benzene metabolism to reactive species, and subsequent induction of oxidative stress and genotoxicity in the bone marrow, as well as immunosuppression, cell death, cell proliferation, and receptor-mediated effects (IARC, 2018).

8.4.5 NTP

NTP concluded "benzene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans" (NTP, 2021c). NTP (2021c) indicated that the strongest evidence was from occupational cohort studies that found associations with leukemia – "mainly acute myelogenous leukemia." NTP (2021c) noted that case-control studies were "limited by poorly defined exposures and mixed exposure patterns."

NTP (2021c) further stated that "benzene causes cancer at numerous tissue sites in rodents." NTP (2021c) indicated that this includes malignant lymphoma in mice of both sexes after oral exposures in the Huff *et al*. (1989)/NTP (1986b) study and "a tendency towards induction of lymphoid tumors in mice," citing subchronic studies (reviewed in IARC [1982, 1987]). NTP (2021c) did not consider the lack of consistent results across bioassays or that some of the studies on which it relied were subchronic, or the possibility for species-specific differences in hematopoiesis.

NTP (2021c) did not cite any mechanistic data.

8.4.6 Conclusions

Overall, government and scientific agencies concluded there was clear and sufficient evidence for a causal association between benzene and AML based on human, animal, and mechanistic evidence. In addition, ATSDR (2017a) concluded there is sufficient evidence of causation for benzene and all leukemia types, including ALL, CLL, AML, and CML, but ATSDR (2024) did not. Some other agencies noted limited or suggestive evidence of an association with leukemia types other than AML but did not conclude that the evidence was sufficient for a determination of causality (IOM, 2003; NRC, 2009).

8.5 Conclusions

Government and scientific agencies concluded that evidence supports a causal association between benzene and AML. IOM (2003) and NRC (2009) concluded there is limited evidence for other leukemia subtypes. Only ATSDR (2017a) concluded there is sufficient evidence of causation for all leukemia subtypes, including ALL, AML, and CML, but ATSDR (2024a) concluded there was clear evidence for causality only for ANLL/AML.

Several high-quality occupational epidemiology studies reported that increasing average and cumulative benzene exposure concentrations were associated with AML and MDS, and the association was statistically significant in meta-analyses. In contrast, most analyses in epidemiology studies do not provide evidence of associations for ALL and CML and benzene exposure; with few exceptions, all benzene epidemiology studies had methodological limitations, particularly with respect to exposure assessments.

Animal bioassay data are not consistent, but there is an MoA by which benzene can cause cancer. Metabolic activation in the liver and bone marrow, followed by various downstream effects resulting in genotoxicity, is generally accepted as the biologically plausible MoA for the association between benzene and AML and MDS; however, whether this MoA is applicable to other types of leukemia that are etiologically distinct is unknown.

I conclude that the scientific evidence supports a causal association between benzene exposures and AML at exposures greater than 40 to 75 ppm-years, particularly for exposures within 10 to 15 years of diagnosis. Evidence also supports an association with MDS at exposures greater than 40 ppm-years. Epidemiology

studies do not provide consistent or compelling evidence that benzene exposure is associated with ALL or CML.

Because the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, and animal studies do not provide evidence of causation in humans, I conclude that, as a whole, the scientific evidence does not support a causal association between benzene exposure and leukemia except for AML and MDS in humans, but there is no evidence that it caused AML and MDS at Camp Lejeune.

9 Vinyl Chloride and Leukemia

Below I describe epidemiology and toxicity studies that assessed vinyl chloride exposure and leukemia, and government and other agency reviews of this evidence. I conclude that the scientific evidence does not support a causal association between vinyl chloride exposure and leukemia AML or MDS.

9.1 Epidemiology

9.1.1 Overview

I identified 14 cohort studies (in 8 unique populations), 1 case-control study, and 1 meta-analysis that evaluated vinyl chloride exposure and leukemia. Most studies were conducted in the US, two studies were conducted in Europe, one study was conducted in the United Soviet Socialist Republics (USSR), and one study was conducted in Canada. I review here all studies in populations at Camp Lejeune if vinyl chloride exposures were specified, even if overlapping, for completeness. Otherwise, if several studies analyzed the same cohorts or population groups, I summarize only the study with the longest follow-up or that used more reliable exposure estimates, unless another study reported additional results (*e.g.*, dose-response relationships). I provide an overview, including a brief discussion of cohort and case-control study characteristics and quality, below and in Attachment J, Tables J.1, J.3, and Attachment C, Table C.1. Cohort and case-control study results are discussed in Section 9.1.2 and in Attachment J, Tables J.2, J.4, and J.5, and meta-analysis results are discussed in Section 9.1.3 and in Attachment J, Table J.6. Epidemiology evidence is integrated with experimental evidence in Section 9.3.

9.1.1.1 Study Population

In all cohort studies, exposed and unexposed participants were selected from appropriate source populations. Most cohort studies reported low rates of loss to follow-up (≤3%), but one study had unknown loss to follow-up (Smulevich *et al*., 1988). Overall, participant exclusion rates were low in most studies that reported this metric, ranging from 0-10%. The cohort study conducted by ATSDR (2018b) reported low response rates to the health survey among military personnel and civilian employees at Camp Lejeune and Camp Pendleton (31% overall). In the single case-control study, individuals with and without AML and MDS were drawn from appropriate source populations, but this study had low participation rates among the cases (42%) and controls (36%) (Poynter *et al*., 2017).

9.1.1.2 Exposure Assessment

I assume that most participants in occupational studies were exposed to vinyl chloride *via* inhalation or dermally, while participants in the Camp Lejeune studies could have been exposed *via* ingestion, inhalation, or dermal absorption.

The most critical limitation of all cohort and case-control studies was the manner by which exposures were estimated. The epidemiology studies examining vinyl chloride exposure and leukemia were largely conducted among populations that represented specific occupational groups (*e.g.*, workers in the vinyl chloride industry). Almost all the studies estimated individual exposures to vinyl chloride in an indirect manner, usually based on a JEM, employment history, or facility records, all of which were likely subject to varying degrees of exposure misclassification.

Bove *et al*. (2014a,b) and ATSDR (2018b) estimated individual exposures at Camp Lejeune using modeled average monthly levels of chemicals in drinking water on base, based on groundwater fate and transport models calculated in ATSDR (2007a, 2013) along with historical occupation codes, workplace or residence, and period and duration of employment or residence. As discussed in Section 5.1.2, these estimates are unreliable and biased high (ATSDR, 2017b; Hennet, 2024; Spiliotopoulos, 2024). None of these studies had individual water consumption/exposure data, so individual exposures were likely misclassified to some degree. In addition, there was a high correlation between some of the chemical-specific categorical exposure variables in Bove *et al*. (2014a,b) and ATSDR (2018b), which limits the interpretation of the vinyl chloride-specific results.

The case-control study by Poynter *et al*. (2017) characterized exposure based on self-reported information that was collected after AML or MDS had been diagnosed. Self-reported exposure information is subject to potential recall inaccuracy due to the long time period between chemical use or exposure and interviews, and potential recall bias can occur when cases recall exposures differently than controls. In addition, while this study considered duration of exposure, the amount of missing data was unknown.

Most studies considered frequency, duration, or intensity of potential exposures. The studies that aimed to account for exposure levels did so based on modeled contamination in drinking water (with no individual consumption data), JEMs, expert opinion, or duration of/time since first employment; these indirect measurements are at best crude estimates of actual exposures with an unknown amount of error.

9.1.1.3 Outcome Assessment

Leukemia diagnoses were obtained or confirmed using reliable and complete methods in most cohort and case-control studies, as cases were mostly identified using medical records, registries, or government or national databases (*e.g.*, NDI, SSA). Most of the cohort studies only assessed mortality, while a few studies assessed disease incidence. Importantly, only one case-control study (Poynter *et al*., 2017) reported on leukemia subtypes (*i.e.*, AML or MDS), while all other studies assessed leukemia overall.

9.1.1.4 Covariates Considered

Almost all epidemiology studies have some residual or uncontrolled confounding, which can bias results in either direction. Most cohort and case-control studies controlled for age and sex, while race/ethnicity was controlled for less consistently, and smoking and other potential chemical occupational exposures were rarely controlled for. The only study that evaluated AML (*i.e.*, Poynter *et al*., 2017) did control for smoking. None of the studies controlled for family history of leukemia, genetics, or other known leukemia risk factors (*e.g.*, history of blood disorders, chemotherapy treatment, or certain viral infections). Approximately half of the studies did not provide information on the degree or impact of missing covariate data. ATSDR (2018b) reported missing data for smoking and other occupational exposures for >5% of participants.

9.1.1.5 Temporality

All cohort and case-control studies assessed or considered exposures that occurred prior to leukemia diagnosis, but many (Smulevich *et al*., 1988; Ward *et al*., 2001; Fedeli *et al*., 2019) did not ensure an appropriate period of time between exposure and diagnosis, either in the design or the analysis (*i.e*., ≥0.5 years for leukemia [CDC, 2015]). Many studies appeared to include cases in the analysis that could have occurred <0.5 years after the exposure began, undermining the ability to properly assess an exposure-response relationship.

9.1.2 Study Results

Overall, cohort and case-control studies reported a wide range of risk estimates for leukemia (overall), AML, and MDS, ranging from 0.26-6.67,[21] but most were close to 1 and not statistically significant. Below, I discuss results for leukemia (overall) and then for AML and MDS.

9.1.2.1 Leukemia

Five cohort studies reported no increased risk of leukemia overall in workers in the vinyl chloride, PVC or the chemical industry and reported risk estimates ranging from 0.59-1.15 (Thériault and Allard, 1981; Ward *et al*., 2001; Carreón *et al*., 2014; Mundt *et al*., 2017; Fedeli *et al*., 2019). Carreón *et al*. (2014) was the only study that examined risk by duration of employment and reported no leukemia deaths in those employed < 90 days, and no increased risk of leukemia death in those employed ≥90 days (SMR = 0.82, 95% CI: 0.17-2.41). One cohort study reported a statistically significant increased risk of all leukemias in workers at a vinyl chloride and PVC plant compared to risk in the general population of the city where the plant was located (SMR = 5.00, 95% CI: not reported) (Smulevich *et al*., 1988), but the results were no longer significant when stratified by sex. Limitations of Smulevich *et al*. (1988) include a small number of exposed cases (n = 5), an unknown loss to follow-up, indirect exposure measurements, and lack of control for age or other chemical exposures.

Bove *et al*. (2014b) reported no increased risk of leukemia mortality with any level of exposure in civilian employees working at Camp Lejeune compared to Marines and Navy personnel at Camp Pendleton or when compared to Marines and Navy personnel at Camp Lejeune with low exposure. Similarly, Bove *et al*. (2014a), reported no increased risk of leukemia mortality with any level of exposure in Marines and Navy personnel stationed at Camp Lejeune. ATSDR (2018b) reported a decreased risk of leukemia in Marines and Navy personnel with the highest exposure levels compared to Marines and Navy personnel at Camp Pendelton (OR = 0.28, 95% CI: 0.09-0.83) and Marines and Navy personnel with low exposures at Camp Lejeune (OR = 0.26, 95% CI: 0.09-0.72). They reported no association with lower levels of exposure.

9.1.2.2 AML

One case-control study examined vinyl chloride exposure and AML incidence and reported an increased risk among participants with <5 years exposure (OR = 2.81, 95% CI: 1.14-6.92), but no association among those with ≥5 years of exposure, compared to those with no vinyl chloride or plastic exposure (OR = 1.03, 95% CI: 0.57-1.86) (Poynter *et al*., 2017). They reported no increased risk with increasing exposure duration (p_{trend} = 0.08). This study had several limitations, including low participation rates in cases and controls, indirect chemical exposure, and the potential for recall bias.

[21] This is excluding an SMR of 0 reported by Carreón *et al*. (2014).

9.1.2.3 MDS

One case-control study evaluated vinyl chloride and MDS (Poynter *et al*., 2017) reported an increased incidence of MDS among participants with ≥5 years of exposure (OR = 2.05, 95% CI: 1.15-3.63), but no association among those with <5 years of exposure (OR not calculated). This study had several limitations, including low participation rates and the potential for recall bias.

9.1.3 Meta-Analysis

Boffetta *et al*. (2003) conducted a meta-analysis of two multi-center cohort studies (Ward *et al*., 2001; Mundt *et al*., 2017) that evaluated risk of leukemia among workers in the vinyl chloride or PVC industry. They reported no increased risk of leukemia mortality (SMR = 0.91, 95% CI: 0.69-1.21, $p_{heterogeneity}$ = 0.8). Although a third study was available (Smulevich *et al*., 1988), the *p* value for heterogeneity among all three studies was 0.005, so the authors did not meta-analyze the three studies together.

9.1.4 Conclusions

Most analyses do not provide evidence of associations between vinyl chloride exposure and leukemia in epidemiology studies. Risk estimates were both above and below 1, but most were not statistically significant. None of the studies that evaluated leukemia risk by level of vinyl chloride exposure reported trends of increasing risk with increasing exposure.

One study evaluated AML and MDS. This study had major limitations, including low participation rates and the potential for recall bias and in isolation does not provide compelling evidence for a causal association between vinyl chloride and AML or MDS.

Given the lack of a consistent or strong association between vinyl chloride exposure and leukemia, AML, and MDS and the methodological limitations of most epidemiology studies, particularly the high likelihood of exposure measurement error, I conclude that the epidemiology evidence does not support a causal association between vinyl chloride exposure and leukemia, AML, or MDS.

9.2 Toxicology

9.2.1 Animal Carcinogenicity Studies

I identified 3 oral, 1 intraperitoneal, and 11 inhalation chronic bioassays that stated they evaluated vinyl chloride and the hematopoietic system. The results of these studies are reported in Attachment K, Tables K.1-K.3; an overview of study quality is described in Attachment K, Table K.4, and individual chronic study quality is shown systematically in Attachment K, Table K.5. Experimental evidence is integrated with epidemiology evidence in Section 9.3.

The two chronic oral vinyl chloride bioassays in rats that examined the hematopoietic system do not provide evidence that vinyl chloride caused leukemia. Feron *et al*. (1981) reported several incidences of leukemia in male and female Wistar rats dosed with up to 14.1 mg/kg-d of vinyl chloride *via* diet or 300 mg/kg-d *via* gavage, but the incidences were not treatment-related. In addition, the exposure duration was inappropriate, as it was based on the point at which 75% of the control rats spontaneously died. Maltoni and Lefemine (1975) and Maltoni *et al*. (1981, 1984) reported sporadic incidences of leukemia in male and female

Sprague-Dawley rats gavaged with up to 50 mg/kg-d of vinyl chloride for 52 weeks, but the incidences were not treatment related.

Among the 11 inhalation chronic bioassays in rats and mice that evaluated the hematopoietic system, only Maltoni and Lefemine (1975), Maltoni *et al*. (1981, 1984), and Maltoni and Cotti (1988) reported leukemias. Maltoni and Lefemine (1975) and Maltoni *et al*. (1981, 1984) reported sporadic incidences of leukemia in five bioassays conducted in Sprague-Dawley rats and two bioassays conducted in Wistar rats exposed to up to 10,000 ppm vinyl chloride for 52 weeks. The leukemias were not dose related or due to treatment. Maltoni and Cotti (1988) exposed adult Sprague-Dawley rats (breeders) to 0 or 2,500 ppm vinyl chloride for 76 weeks. Offspring were exposed to identical concentrations of vinyl chloride from gestational day (GD) 12 by the transplacental route and then by inhalation for 76 weeks. Leukemia was not significantly elevated in either treated breeders or offspring. This bioassay evaluated only one high dose of vinyl chloride, and the observation period was inappropriate. None of the remaining chronic inhalation vinyl chloride bioassays reported incidences of lymphoma, and all exposed animals for 52 weeks.

Maltoni and Lefemine (1975) and Maltoni *et al*. (1981, 1984) described a chronic intraperitoneal injection vinyl chloride bioassay in which sporadic incidences of leukemia were reported in male and female Sprague-Dawley rats, but the incidences were not treatment related.

Overall, treatment-related leukemias were not reported in any chronic vinyl chloride bioassay, though all were of low study quality.

9.2.2 Mechanistic Studies

There is limited information regarding any specific mechanisms or overall MoA by which vinyl chloride could cause leukemia. In animals and humans, vinyl chloride is metabolized in the liver to a highly reactive, short-lived epoxide intermediate (2-chloroethylene oxide) that can directly bind to DNA and cause base-pair transitions (*e.g*., G→A and A→T), ultimately resulting in the potential development of liver angiosarcoma, an extremely rare type of liver cancer in humans (ATSDR, 2024b; US EPA, 2000a; IARC, 2012b).

Although this genotoxic MoA resulting from metabolic activation is well characterized for the development of liver angiosarcoma, it has not been demonstrated for etiologically distinct cancers in other organs and tissues, including hematologic cancers such as leukemia. Because the primary mechanism involves the direct interaction of the intermediate with DNA in the liver, this MoA is likely specific to the liver where the reactive intermediate is formed. Owing to the high reactivity and short-lived nature of the 2-chloroethylene oxide intermediate, migration to other tissues, including the bone marrow, is unlikely to occur and there is no evidence that 2-chloroethylene oxide is found in the bone marrow (US EPA, 2000a). Overall, there is no consistent or compelling evidence to support a biologically plausible mechanism by which vinyl chloride could cause leukemia.

9.3 Evidence Integration

A small number of epidemiology and toxicity studies have evaluated vinyl chloride exposure and leukemia (see Sections 9.1 and 9.2). Most epidemiology studies had higher-quality outcome assessments (*e.g*., confirmed cases), but the changing classification of leukemia subtypes over time makes it difficult to directly compare results of studies using classification schemes from different eras (*e.g*., some studies included CLL in analyses of all leukemias or all myeloid leukemias, while others classified CLL as a type of NHL). Appropriate consideration of temporality, latency period, and control for potential confounders

varied across studies, but none sufficiently controlled for all important potential confounders. Most importantly, none of the studies adequately assessed vinyl chloride exposures, calling into question the validity of reported risk estimates. In addition to being limited in number and quality, animal studies do not provide evidence for causation. Keeping these study strengths and limitations in mind, I evaluated the available evidence in the context of Bradford Hill's considerations, in Table 9.1. I conclude that the evidence does not support a causal association between vinyl chloride exposure and leukemia.

Table 9.1 Bradford Hill Assessment of Vinyl Chloride and Leukemia

Aspect	Analysis
Strength of Association	Epidemiology evidence does not support a strong association between vinyl chloride exposure and leukemia or leukemia subtypes.
Consistency	Risk estimates for leukemia and leukemia subtypes were not consistently elevated.
Specificity	There is no evidence to suggest that there is a specific relationship between vinyl chloride and leukemia in animals or humans.
Temporality	Temporality was adequately addressed in all epidemiology studies, but many did not ensure an appropriate latency period between exposure and diagnosis (*i.e.*, ≥0.5 years).
Dose-Response	The epidemiology evidence does not support a dose-response relationship between vinyl chloride exposure and leukemia, AML, or MDS.
Biological Plausibility	The evidence does not support a biologically plausible MoA by which vinyl chloride can cause leukemia.
Coherence	Collectively, the evidence does not support a causal association between vinyl chloride exposure and leukemia. Risk estimates were not consistent across epidemiology studies and there was no evidence of a dose-response relationship in any study. There is no evidence for a biologically plausible MoA for leukemia, and vinyl chloride did not cause leukemia in animal bioassays.
Experiment	There is no available experimental evidence in humans.
Analogy	I am not aware of any analogous compound to vinyl chloride that causes leukemia

Notes:
HR = Hazard Ratio; JEM = Job Exposure Matrix; MoA = Mode of Action; OR = Odds Ratio; PVC = Polyvinyl Chloride; SMR = Standardized Mortality Ratio; T = Thymine.

9.4 Agency Reviews

Several government and scientific agencies, including ATSDR, NASEM, US EPA, IARC, and NTP, conduct chemical carcinogenicity evaluations. IARC, US EPA, and NTP all classify agents according to whether they are likely to cause cancer in humans, each using a unique framework, as described in Section 3.5.1 and Table 3.5. ATSDR, NASEM, US EPA, and NTP evaluate cancer risks, while IARC classifies cancer hazards (IARC, 2019). That is, IARC only considers whether agents have a potential, no matter how remote, to be carcinogenic, and not the likelihood of agents being carcinogenic under real-world exposure conditions. IARC's framework for evaluating independent realms of evidence (human, animal and mechanistic) is shown in Tables 3.6 and 3.7.

Despite the goal of being systematic and objective, all of these reviews involve some degree of subjectivity. In many instances, the reviews do not fully take study quality into account and conclude that the strength of the evidence is stronger than it truly is. Also, IARC, US EPA, and NTP carcinogenicity categories all include ones called "possibly carcinogenic to humans" or "reasonably anticipated to be a human carcinogen." The requirements for including an agent in these categories are such that the evidence may not be sufficient to make a scientifically informed judgment regarding the agent's carcinogenicity. For example, there may be no human data for the agent at all, or the preponderance of epidemiology studies of the agent may not show evidence of an association at all or may only show evidence of an association that can readily be explained by plausible noncausal alternatives (*e.g.*, chance, bias, or confounding). The

review process for ATSDR (2017a) had even more methodological issues than those discussed above (see Section 3.5.2 and Table 3.8). This report did not evaluate the evidence in a systematic, objective manner. It used non-traditional methods and a biased framework to make determinations regarding causation.

Most government and scientific agency reports have concluded that the scientific evidence is insufficient or does not support an association between vinyl chloride and leukemia (ATSDR, 2017a; IOM, 2003; IARC, 2008b, 2012b; NTP, 2021d) and others did not address leukemia in relation to vinyl chloride (ATSDR, 2006b, 2024b; NRC, 2009; IOM, 2015; US EPA, 2000a). All of these agency assessments of vinyl chloride carcinogenicity are described below.

9.4.1 ATSDR

In its "Toxicological Profile for Vinyl Chloride," ATSDR (2006b) concluded that the strongest human evidence with respect to cancer comes from "the cluster of reports of greater than expected incidences of liver angiosarcoma" and that that liver angiosarcoma had been observed in several animal species. ATSDR (2006b) noted that cancer has also been observed in other tissues (*i.e.*, respiratory tract, lymphatic/hematopoietic system, and the brain and central nervous system) in vinyl chloride workers, but also noted the uncertainties in these associations and did not make a conclusion regarding leukemia. ATSDR (2006b) discussed one epidemiology study in women employed in vinyl chloride production reporting a significant increase in the chance of developing leukemias or lymphomas (Smulevich *et al*., 1988). In addition, ATSDR (2006b) discussed one animal bioassay (Maltoni *et al*., 1981, 1984) that reported leukemias in hamsters exposed to 50-10,000 ppm vinyl chloride *via* inhalation, but the study only used a sub-chronic (30-week) exposure duration. In the subsequent "Addendum to the Toxicological Profile for Vinyl Chloride," ATSDR (2016) did not make additional conclusions regarding cancer.

In its most recent "Toxicological Profile for Vinyl Chloride," ATSDR (2024b) maintained the conclusions of its 2006 evaluation, concluding that the strongest human evidence with respect to cancer is for liver angiosarcoma, which is a rare tumor type, with sufficient evidence from experimental animal studies. While ATSDR (2024b) noted that tumors have also been observed in the mammary gland, lung, and adipose tissue, the agency concluded there is little consistency in the findings across species. Similar to the 2006 evaluation, ATSDR (2024b) did not make a determination regarding leukemia. ATSDR (2024b) again discussed Smulevich *et al*. (1988), but indicated that epidemiology studies evaluating vinyl chloride and cancers of the lymphatic and hematopoietic system (including leukemias) predominantly show no association. In addition, ATSDR (2024b) discussed one animal bioassay (Maltoni *et al*., 1981, 1984) that reported leukemias in hamsters exposed to 50-10,000 ppm vinyl chloride *via* inhalation, but the study only used a sub-chronic (30-week) exposure duration.

In its review of drinking water contaminants at Camp Lejeune, ATSDR (2017a) concluded there was "below equipoise evidence for causation for vinyl chloride and leukemias," based on conflicting findings reported in a meta-analysis and a study of PVC workers with high exposures.

9.4.2 NASEM

In its 2003 review, an IOM (2003) committee concluded "there is inadequate/insufficient evidence to determine whether an association exists between chronic exposure to specific organic solvents under review, other than benzene, and adult leukemia."

IOM (2003) did not discuss any animal or mechanistic data specific to vinyl chloride. NRC (2009) noted that some studies have reported an association between vinyl chloride and cancers of the lymphatic-hematopoietic system, but the findings have been inconsistent. The agency did not discuss any specific

epidemiology, animal, or mechanistic studies regarding vinyl chloride and leukemia. IOM (2015) did not include any discussion of leukemia and vinyl chloride specifically.

9.4.3 US EPA

US EPA (2000a) concluded that vinyl chloride is a known human carcinogen by the inhalation and oral routes of exposure, and highly likely to be carcinogenic by the dermal route, based upon sufficient evidence for liver carcinogenicity in humans, consistent evidence of liver carcinogenicity in experimental animals, and supportive mechanistic evidence. US EPA (2000a) noted one study that reported elevated risk of leukemias in workers highly exposed to vinyl chloride (Smulevich *et al*., 1988). The agency did not discuss any animal or mechanistic evidence, and did not draw a conclusion regarding vinyl chloride and leukemia.

9.4.4 IARC

IARC (2008b) classified vinyl chloride as a Group 1 carcinogen. The agency concluded, "There is sufficient evidence in humans for the carcinogenicity of vinyl chloride. Vinyl chloride causes angiosarcoma of the liver, and hepatocellular carcinoma" (IARC, 2008b). IARC (2008b) also noted that "[t]here is sufficient evidence in experimental animals for the carcinogenicity of vinyl chloride." With respect to leukemia, IARC "did not find strong evidence for associations of exposure to vinyl chloride with cancers of the…lymphatic and haematopoeitic tissues" in humans (IARC, 2008b). The agency did not present any animal or mechanistic evidence for vinyl chloride and leukemias.

In an updated evaluation, IARC (2012b) maintained the same conclusions, discussing sufficient evidence for carcinogenicity of vinyl chloride based on angiosarcoma of the liver and hepatocellular carcinoma in humans and sufficient evidence from experimental animal studies. Similar to its 2008 evaluation, IARC (2012b) did not find strong evidence for associations of exposure to vinyl chloride with hematopoietic or lymphatic cancers. IARC (2012b) did not present any animal or mechanistic evidence for vinyl chloride and leukemias.

9.4.5 NTP

NTP (2021d) concluded "vinyl chloride is known to be a human carcinogen based on sufficient evidence from carcinogenicity studies in humans." NTP (2021d) noted that the strongest evidence was from epidemiology studies and case reports showing associations with hepatic angiosarcoma, a rare tumor type in humans.

NTP (2021d) noted that some studies have reported an association between exposure to vinyl chloride and cancer of the lymphatic and hematopoietic systems, but did not cite any specific studies. The agency also said that recent epidemiology studies of vinyl chloride and leukemia had conflicting results, though did not specify any particular studies. NTP (2021d) further stated that "vinyl chloride caused tumors in three rodent species, at several different tissue sites, and by several different routes of exposure." However, NTP (2021d) did not discuss any animal or mechanistic studies of vinyl chloride and leukemia.

9.4.6 Conclusions

Most government and scientific agency reports have concluded that the scientific evidence is insufficient or does not support an association between vinyl chloride and leukemia (ATSDR, 2017a; IOM, 2003;

IARC, 2008b, 2012b; NTP, 2021d); others did not address leukemia in relation to vinyl chloride (ATSDR, 2006b, 2024b; NRC, 2009; IOM, 2015; US EPA, 2000a).

9.5 Conclusions

Most government and scientific agency reports have concluded that the scientific evidence is insufficient or does not support an association between vinyl chloride and leukemia (ATSDR, 2017a; IOM, 2003; IARC, 2008b, 2012b; NTP, 2021d) and others did not address leukemia in relation to vinyl chloride (ATSDR, 2006b, 2024b; NRC, 2009; IOM, 2015; US EPA, 2000a). Overall, treatment-related leukemias were not reported in any chronic vinyl chloride bioassay. Most epidemiology studies reported risk estimates that were not statistically significant and close to 1, and there were no reported dose-response relationships. All epidemiology studies had several methodological limitations, including a high likelihood of exposure misclassification.

Because (1) the epidemiology studies are not of high quality and most analyses do not provide evidence of associations, (2) animal studies do not provide evidence of causation in humans, and (3) there is no MoA with sufficient scientific support, I conclude that, as a whole, evidence does not support a causal association between vinyl chloride exposure and leukemia.

10 *trans*-1,2-DCE

In this section, I discuss studies that assessed *trans*-1,2-DCE exposure and leukemia, and a government agency review of this evidence. I conclude that the scientific evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE exposure and leukemia.

I did not identify any epidemiology studies that investigated *trans*-1,2-DCE exposure and the risk of leukemia. I identified several studies of Marines and Navy personnel or civilian employees at Camp Lejeune that investigated risks associated with being stationed at or working on base, or with estimated exposures to TVOCs combined on base, but none specifically evaluated risks associated with *trans*-1,2-DCE (see Section 5). As such, they do not provide information with respect to *trans*-1,2-DCE.

I did not identify any chronic *trans*-1,2-DCE animal carcinogenicity studies. NTP (2002) exposed F344/N rats and B6C3F1 mice to *trans*-1,2-DCE in feed for 14 weeks at doses ranging from 3,125 to 50,000 ppm. NTP (2002) did not identify any tumors in rats or mice. In other studies cited by NTP, *trans*-1,2-DCE was determined not to be genotoxic when evaluated by *in vitro* and *in vivo* methods (Greim *et al*., 1975; Sawada *et al*., 1987; Mortelmans *et al*., 1986; Černá and Kypěnová, 1977, all as cited in NTP, 2002). NTP (2002) stated, "No information was found in a search of the literature regarding the carcinogenicity of cis-, *trans*-, or *cis, trans*-1,2-dichloroethylene in animals or humans."

To my knowledge, ATSDR's draft "Toxicological Profile for 1,2-Dichloroethene" is the only agency review of *trans*-1,2-DCE. ATSDR (2023) stated, "No studies evaluating potential carcinogenic effects of inhalation, oral, or dermal exposure of laboratory animals to trans-1,2-dichloroethene…were located."

The currently available scientific evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE exposure and leukemia.

11 Mixtures

People are typically exposed to complex mixtures of chemicals from various sources, including food, drinking water, air, and consumer products, on a daily basis (Feron and Groten, 2002). While people are not adversely affected by these near-constant exposures to chemical mixtures in the environment, in some cases, simultaneous exposures to several chemicals at sufficient concentrations may result in chemical interactions that alter the toxicity of individual chemicals. The nature of these interactions depends on the specific chemicals, their concentrations, their respective MoAs (*i.e.*, the type of mechanism that can lead to toxicity in the body), and the frequency, duration, and route of exposure to each (ATSDR, 2004).

In general, chemicals' joint toxic actions may be either additive (the toxic effects produced by exposure to several chemicals at once is equal to the sum of their individual effects), synergistic (the toxic effects produced by exposure to several chemicals is equal to greater than the sum of their individual effects because interactions enhance the toxicity of each chemical), or antagonistic (the toxic effects produced by exposure to several chemicals is equal to less than the sum of their individual effects because interactions diminish the toxicity of each chemical) (ATSDR, 2004). Chemicals' joint toxic actions at relatively low exposure concentrations, such as those encountered in the ambient environment, usually result in effects that are additive or less than additive (Cassee *et al.*, 1998; Borgert *et al.*, 2004). For additive joint toxic actions to occur, the chemicals in a mixture must act independently and not amplify each other's toxicity.

To determine whether the components of a chemical mixture are additive, one must evaluate each individual component's MoA, movement throughout the body (called pharmacokinetics), and toxicity in specific tissues of the body (US EPA, 2007). In the absence of information regarding potential interactions, US EPA guidance for chemical mixture risk assessment assumes additive joint toxic actions for constituents of a mixture that have the same or a similar MoA and/or tissue where they can exert effects (US EPA, 1989, 2000b, 2007). This is a conservative approach, because assuming additivity can result in an overestimate of the risk of health effects for the chemical mixture (Cassee *et al.*, 1998).

Regarding the potential for additive effects, Bloch *et al.* (2023) explained, "The probability of additive effects of substances in a mixture will decrease with the number of different molecular targets they act upon and with the number of different cell types and tissues that are affected due to differences in toxicokinetics." Similarly, regarding the potential for synergistic effects, Kortenkamp *et al.* (2009) stated, "Deviations from predicted additivity, indicative of synergisms or antagonisms, are comparatively rare, relatively small and largely confined to mixtures with only a few compounds. Any synergistic interaction between the mixture components can be expected to be highly scenario specific, depending on the number and nature of the involved components, the exposed organisms and analyzed endpoint."

The exposure concentrations of each component in a mixture are also the key drivers for potential synergistic effects. The available literature suggests that there is little to no likelihood of synergistic interactions between chemicals present in a mixture at low concentrations (*i.e.*, at or below their individual toxicity thresholds) typical of environmental exposures (Charles *et al.*, 2007; Crofton *et al.*, 2005; Feron *et al.*, 1995). Cedergreen (2014) reviewed the scientific literature on potential interactions among environmental chemical exposures to evaluate whether any groups of substances tend to elicit synergistic interactions and concluded that "true synergistic interactions between chemicals are rare and often occur at high concentrations."

Without a direct evaluation of the chemicals and their concentrations in a particular mixture, it is not possible to know for certain if chemical interactions will occur, and to what extent. Because of this, as well as the general understanding that synergistic interactions are rare and do not typically occur at low levels of exposure, there is no evidence to indicate that there would be additive or synergistic effects on toxicity from exposure to a mixture of the chemicals of concern simply because they are present in the ambient air or water as a chemical mixture.

Finally, while combined exposures to multiple chemicals may be additive or synergistic in experimental animals, this does not provide any indication of whether combined effects would occur in animals of other species, in animals of other strains of the same species, or in subjects of different ages (Mauderly and Samet, 2009). Interspecies, interstrain, and age-related differences exist in susceptibility and sensitivity to adverse effects. It is also possible that synergisms occurring at an intermediate step in an MoA may not manifest at clinical and public health scales in human populations (Mauderly and Samet, 2009).

Although there is sufficient evidence that benzene can cause AML and MDS, scientific evidence does not demonstrate that benzene can cause other kinds of leukemia or that TCE, PCE, vinyl chloride, or *trans*-1,2-DCE can cause leukemia or leukemia subtypes (discussed in Sections 6-9). Each of these chemicals has a distinct MoA, targeting different cell types and operating through separate molecular pathways. Thus, evidence does not support the hypothesis that exposure to a mixture of these chemicals could act in an additive or synergistic manner with respect to leukemia causation.

12 Conclusions

Many epidemiology studies have evaluated TCE, PCE, benzene, or vinyl chloride and leukemia risks (none have evaluated *trans*-1,2-DCE and leukemia). These studies were heterogeneous with respect to how leukemia or leukemia subtypes (*e.g.*, ALL, AML, CML, and MDS) were classified and the accuracy of leukemia diagnosis has likely improved over time (IARC, 2018). Also, the manner in which exposures were estimated varied considerably across studies. For example, several cohort studies used quantitative or semi-quantitative approaches to assess the magnitude or cumulative exposures and, although still subject to inaccuracies and bias, these estimates are more reliable than studies that use solely qualitative measures. Similarly, animal studies varied considerably in quality, particularly with respect to the exposure and observation period.

Five studies evaluated leukemia risks among Marines and Navy personnel stationed at Camp Lejeune or civilian workers on base who may have been exposed to contaminated water. There was variation among studies with respect to the methods used to recruit or assemble the study populations, characterize exposures, and address confounding. Overall, there was no evidence of an association between either working or living at Camp Lejeune or TCE, PCE, benzene, or vinyl chloride exposures on base and leukemia or any leukemia subtype. Although all studies had a high likelihood of exposure misclassification and other limitations and some studies reported a few statistically significant risk estimates, they were not consistent across analyses of the Camp Lejeune population, and several were <1. Collectively, these studies do not provide evidence for an association between working or living at Camp Lejeune or exposure to TCE, PCE, benzene, or vinyl chloride on base and leukemia.

Most analyses do not provide evidence of associations between or exposure-response trends for TCE and leukemia, AML, or CML in cohort or case-control studies. Animal evidence does not indicate that TCE can cause leukemia, and there are no proposed MoAs with sufficient scientific support. Most government and scientific agency reviews either concluded that the scientific evidence is insufficient to make a determination regarding TCE and leukemia causation (IOM, 2003; NRC, 2009; US EPA, 2011, 2020b) or did not draw any conclusions (ATSDR, 2019b; IARC, 2014a; IOM, 2015; NTP, 2015).

Most analyses do not provide evidence of associations between PCE and leukemia or leukemia subtypes in epidemiology studies. None of the epidemiology studies reported a dose-response relationship between PCE and leukemia. There is no animal evidence indicating PCE can cause leukemia in humans, or any proposed MoA with sufficient scientific support. Government and scientific agencies either concluded that the scientific evidence is insufficient to make a determination regarding PCE and leukemia causation in humans (ATSDR, 2017a, 2019a; IOM, 2003; NRC, 2009; US EPA, 2012), or did not draw any conclusions (US EPA, 2020c; IARC, 2014b; IOM, 2015; NTP, 2021b).

Epidemiology evidence supports an association between benzene exposure and AML at cumulative exposures of at least 40 to 75 ppm-years. The evidence for this association is strongest for exposures occurring within 10 to 15 years of diagnosis. Epidemiology evidence does not support an association between benzene and ALL or CML. Although animal bioassay data are not consistent, mechanistic evidence suggests benzene indirectly induces genotoxicity through a threshold-mediated MoA in which exposures below the threshold do not result in genetic toxicity (North *et al.*, 2020). Government and scientific agencies concluded that evidence supports a causal association between benzene and AML. IOM (2003) and NRC (2009) concluded there is limited evidence for other leukemia subtypes; only ATSDR

(2017a), but not ATSDR (2024a), concluded there is equipoise or above evidence of causation for all leukemia subtypes, including ALL, AML, and CML.

The epidemiology evidence does not support an association between vinyl chloride and leukemia. Most analyses in epidemiology studies do not provide evidence of associations, and there were no reported dose-response relationships. Treatment-related leukemias were not reported in any chronic vinyl chloride bioassays or any MoA with sufficient scientific support. Most government and scientific agencies have concluded that the scientific evidence is insufficient or does not support an association between vinyl chloride and leukemia (ATSDR, 2017a; IOM, 2003; IARC, 2008b, 2012b; NTP, 2021d) and others did not address leukemia in relation to vinyl chloride (ATSDR, 2006b, 2024b; NRC, 2009; IOM, 2015; US EPA, 2000a).

The currently available scientific evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE and leukemia. ATSDR (2023) stated, "No studies evaluating potential carcinogenic effects of inhalation, oral, or dermal exposure of laboratory animals to trans-1,2-dichloroethene…were located."

I conclude that many epidemiology studies are not of high quality and, apart from benzene exposure and AML and MDS, most analyses did not provide evidence of associations between TCE, PCE, benzene, or vinyl chloride and leukemia or leukemia subtypes. Animal and mechanistic studies do not provide evidence of causation. As such, I conclude that, as a whole, the scientific evidence does not support a causal association between benzene exposure and ALL or CML, or between TCE, PCE, or vinyl chloride exposure and leukemia or leukemia subtypes. Evidence is too limited to address whether there is a causal association between *trans*-1,2-DCE and leukemia. While evidence supports an association between benzene exposure and AML and MDS in humans at high exposures, I am not aware of any evidence demonstrating that exposures to benzene at Camp Lejeune were sufficient to cause AML or MDS.

Based on the currently available evidence, I conclude, to a reasonable degree of scientific certainty, that TCE, PCE, benzene, vinyl chloride, and *trans*-1,2-DCE in Camp Lejeune drinking water did not cause leukemia. I reserve the right to update or amend the opinions contained herein based on new or additional evidence not currently available.

References

Adami, HO; Berry, SC; Breckenridge, C; Smith, L; Swenberg, J; Trichopoulos, D; Weiss, NS; Pastoor, T. 2011. "Toxicology and epidemiology: Improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference." *Toxicol. Sci.* 122(2):223-234.

Adegoke, OJ; Blair, A; Shu, XO; Sanderson, M; Jin, F; Dosemeci, M; Addy, CL; Zheng, W. 2003. "Occupational history and exposure and the risk of adult leukemia in Shanghai." *Ann. Epidemiol*. 13:1-10.

Agency for Toxic Substances and Disease Registry (ATSDR). 1997. "Toxicological profile for benzene (Update)." 423p., September.

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. "Toxicological Profile for Ionizing Radiation." 438p. Accessed at http://www.atsdr.cdc.gov/toxprofiles/tp149.pdf.

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. "Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures." 106p., May. http://www.atsdr.cdc.gov/interactionprofiles/IP-ga/ipga.pdf.

Agency for Toxic Substances and Disease Registry (ATSDR). 2006a. "Health Consultation, Endicott Area Investigation, Health Statistics Review: Cancer and Birth Outcome Analysis, Endicott Area, Town of Union, Broome County, New York." 86p., May 26.

Agency for Toxic Substances and Disease Registry (ATSDR). 2006b. "Toxicological Profile for Vinyl Chloride (Final)." NTIS PB2007-100671. 329p., July.

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

Agency for Toxic Substances and Disease Registry (ATSDR). 2007b. "Toxicological Profile for Benzene." 438p., August.

Agency for Toxic Substances and Disease Registry (ATSDR). 2008. "Public Health Assessment for Marine Corps Base (MCB) Camp Pendleton, Camp Pendleton, San Diego County, California (EPA Facility ID: CA2170023533)." 145p., September 2. Accessed at https://www.atsdr.cdc.gov/hac/pha/CampPendleton MarineCorpsBase/MCB%20Camp%20Pendleton%20PHAFinal090208.pdf.

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

Agency for Toxic Substances and Disease Registry (ATSDR). 2015. "Addendum to the Toxicological Profile for Benzene." 59p., June.

Agency for Toxic Substances and Disease Registry (ATSDR). 2016. "Addendum to the Toxicological Profile for Vinyl Chloride." 27p. Accessed at http://www.atsdr.cdc.gov/toxprofiles/VinylChloride_addendum_508.pdf.

Agency for Toxic Substances and Disease Registry (ATSDR). 2017a. "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases." 152p., January 13.

Agency for Toxic Substances and Disease Registry (ATSDR). 2017b. "Public Health Assessment for Camp Lejeune Drinking Water, U.S. Marine Corps Base Camp Lejeune, North Carolina." 202p., January 20.

Agency for Toxic Substances and Disease Registry (ATSDR). 2018a. "Minimal Risk Levels (MRLs) - For Professionals."

Agency for Toxic Substances and Disease Registry (ATSDR). 2018b. "Morbidity Study of Former Marines, Employees, and Dependents Potentially Exposed to Contaminated Drinking Water at U.S. Marine Corps Base Camp Lejeune." 127p., April.

Agency for Toxic Substances and Disease Registry (ATSDR). 2019a. "Toxicological Profile for Tetrachloroethylene." 435p. Accessed at https://www.atsdr.cdc.gov/ToxProfiles/tp18.pdf.

Agency for Toxic Substances and Disease Registry (ATSDR). 2019b. "Toxicological Profile for Trichloroethylene." 511p. Accessed at https://www.atsdr.cdc.gov/ToxProfiles/tp19.pdf.

Agency for Toxic Substances and Disease Registry (ATSDR). 2023. "Toxicological Profile for 1,2-Dichloroethene (Draft for Public Comment)." 222p., August.

Agency for Toxic Substances and Disease Registry (ATSDR). 2024a. "Toxicological Profile for Benzene (Draft for Public Comment)." 399p., October.

Agency for Toxic Substances and Disease Registry (ATSDR). 2024b. "Toxicological Profile for Vinyl Chloride (Final)." 312p., January. Accessed at https://www.atsdr.cdc.gov/toxprofiles/tp20.pdf.

Ahlbom, A. 1993. *Biostatistics for Epidemiologists*. Lewis Publishers, Boca Raton, FL, 214p.

Aickin, M; Chapin, CA; Flood, TJ; Englender, SJ; Caldwell, GG. 1992. "Assessment of the spatial occurrence of childhood leukaemia mortality using standardized rate ratios with a simple linear Poisson model." *Int. J. Epidemiol*. 21(4):649-655. doi: 10.1093/ije/21.4.649.

Aksoy, M; Erdem, S; DinCol, G. 1974. "Leukemia in shoe-workers exposed chronically to benzene." *Blood* 44(6):837-841.

Albin, M; Bjork, J; Welinder, H; Tinnerberg, H; Mauritzson, N; Billstrom, R; Stromberg, U; Mikoczy, Z; Johansson, B; Ahlgren, T; Nilsson, PG; Mitelman, F; Hagmar, L. 2003. "Cytogenetic and morphologic subgroups of myelodysplastic syndromes in relation to occupational and hobby exposures." *Scand. J. Work Environ. Health* 29(5):378-387. doi: 10.5271/sjweh.744.

Albin, M; Björk, J; Welinder, H; Tinnerberg, H; Mauritzson, N; Johansson, B; Billström, R; Strömberg, U; Mikoczy, Z; Ahlgren, T; Nilsson, PG; Mitelman, F; Hagmar, L. 2000. "Acute myeloid leukemia and clonal chromosome aberrations in relation to past exposure to organic solvents." *Scand. J. Work Environ. Health* 26(6):482-491.

Aleksunes, LM; Eaton, DL. 2019. "Principles of toxicology." In *Casarett and Doull's Toxicology: The Basic Science of Poisons (Ninth Edition)*. Ed.: Klaassen, CD. McGraw-Hill Education, New York, NY. p25-64.

Alexander, DD; Mink, PJ; Mandel, JH; Kelsh, MA. 2006. "A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukaemia." *Occup. Med*. 56(7):485-493. doi: 10.1093/occmed/kql083.

American Cancer Society (ACS). 2018a. "Risk factors for chronic myeloid leukemia." June 19. Accessed at https://www.cancer.org/cancer/types/chronic-myeloid-leukemia/causes-risks-prevention/risk-factors.html.

American Cancer Society (ACS). 2018b. "Risk factors for acute myeloid leukemia (AML)." August 21. Accessed at https://www.cancer.org/cancer/types/acute-myeloid-leukemia/causes-risks-prevention/risk-factors.html.

American Cancer Society (ACS). 2018c. "Risk factors for acute lymphocytic leukemia (ALL)." October 17. Accessed at https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/causes-risks-prevention/risk-factors.html.

American Cancer Society (ACS). 2018d. "Risk factors for myelodysplastic syndromes." January 22. Accessed at https://www.cancer.org/cancer/types/myelodysplastic-syndrome/causes-risks-prevention/risk-factors.html.

American Cancer Society (ACS). 2018e. "Acute Myeloid Leukemia (AML) subtypes and prognostic factors." August 21. Accessed at https://www.cancer.org/cancer/types/acute-myeloid-leukemia/detection-diagnosis-staging/how-classified.html.

American Cancer Society (ACS). 2018f. "Acute Lymphocytic Leukemia (ALL) subtypes and prognostic factors." October 17. Accessed at https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/detection-diagnosis-staging/how-classified.html.

American Cancer Society (ACS). 2018g. "Types of myelodysplastic syndromes." January 22. Accessed at https://www.cancer.org/cancer/types/myelodysplastic-syndrome/about/mds-types.html.

American Cancer Society (ACS). 2019a. "Cancer Clusters." Accessed at https://www.cancer.org/cancer/cancer-causes/general-info/cancer-clusters.html.

American Cancer Society (ACS). 2019b. "Determining if something is a carcinogen." Accessed at https://www.cancer.org/cancer/cancer-causes/general-info/determining-if-something-is-a-carcinogen.html.

American Cancer Society (ACS). 2019c. "Prostate cancer risk factors." Accessed at http://www.cancer.org/cancer/prostate-cancer/causes-risks-prevention/risk-factors.html.

American Cancer Society (ACS). 2019d. "Leukemia." Accessed at https://www.cancer.org/cancer/leukemia.html.

American Cancer Society (ACS). 2024. "Key statistics for Acute Lymphocytic Leukemia (ALL)" January 17. Accessed at https://www.cancer.org/cancer/types/acute-lymphocytic-leukemia/about/key-statistics.html.

American Lung Association. 2024. "10 of the worst diseases smoking causes." June 7. Accessed at https://www.lung.org/research/sotc/by-the-numbers/10-worst-diseases-smoking-causes.

American Statistical Association. 2016. "American Statistical Association Releases Statement on Statistical Significance and P-Values: Provides Principles to Improve the Conduct and Interpretation of Quantitative Science." 3p.

Andersen, A; Barlow, L; Engeland, A; Kjaerheim, K; Lynge, E; Pukkala, E. 1999. "Work-related cancer in the Nordic countries." *Scand. J. Work Environ. Health* 25(Suppl 2):1-116.

Andersson, EM; Barregard, L; Akerstrom, M; Sallsten, G; Jarvholm, B; Nilsson, RI. 2024. "Cancer incidence in Swedish oil refinery workers exposed to benzene." *Int. J. Hyg. Environ. Health* 261:114420. doi: 10.1016/j.ijheh.2024.114420.

Anttila, A; Pukkala, E; Sallmen, M; Hernberg, S; Hemminki, K. 1995. "Cancer incidence among Finnish workers exposed to halogenated hydrocarbons." *J. Occup. Environ. Med.* 37(7):797-806. doi: 10.1097/00043764-199507000-00008.

Anwar, N; Arshad, A; Fatima, N; Shaheen, S; Bukhari, S; Shamsi, T. 2022. "Environmental and occupational determinants of myelodysplastic syndrome: A case-control study from Pakistan." *Cancer Rep. (Hoboken)* 5(10):e1580. doi: 10.1002/cnr2.1580.

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

Arizona Dept. of Health Services (ADHS). 1990. "Incidence Study of Childhood Cancer in Maricopa County: 1965-1986 (Final)." 111p., April 11.

Arizona Dept. of Health Services (ADHS). 1995. "Update of the Incidence of Childhood Cancers and Testicular Cancer in Southwest Tucson, 1987-1991." 33p., June 6.

Arnold, SM; Price, PS; Dryzga, MD. 2010. "Defining the contribution of non-benzene sources of benzene metabolites in urine: Implications for biomonitoring and risk assessment." *Chem. Biol. Interact.* 184:299-301.

Aschengrau, A; Ozonoff, D; Paulu, C; Coogan, P; Vezina, R; Heeren, T; Zhang, Y. 1993. "Cancer risk and tetrachloroethylene contaminated drinking water in Massachusetts." *Arch. Environ. Health* 48(5):284-292.

Bahr, DE; Aldrich, TE; Seidu, D; Brion, GM; Tollerud, DJ; Paducah Gaseous Diffusion Plant Project Team; Muldoon, S; Reinhart, N; Youseefagha, A; McKinney, P; Hughes, T; Chan, C; Rice, C; Brewer, DE; Freyberg, RW; Mohlenkamp, M; Hahn, K; Hornung, R; Ho, M; Dastidar, A; Freitas, S; Saman, D; Ravdal, H; Scutchfield, D; Contractors; Eger, KJ; Minor, S. 2011. "Occupational exposure to trichloroethylene and cancer risk for workers at the Paducah Gaseous Diffusion Plant." *Int. J. Occup. Med. Environ. Health* 24(1):67-77.

Bassig, BA; Friesen, MC; Vermeulen, R; Shu, XO; Purdue, MP; Stewart, PA; Xiang, YB; Chow, WH; Zheng, T; Ji, BT; Yang, G; Linet, MS; Hu, W; Zhang, H; Zheng, W; Gao, YT; Rothman, N; Lan, Q. 2015. "Occupational exposure to benzene and non-Hodgkin lymphoma in a population-based cohort: The Shanghai Women's Health Study." *Environ. Health Perspect*. 123(10):971-977. doi: 10.1289/ehp.1408307.

Bassig, BA; Shu, XO; Friesen, MC; Vermeulen, R; Purdue, MP; Ji, BT; Yang, G; Wong, JYY; Appel, N; Hu, W; Gao, YT; Zheng, W; Rothman, N; Lan, Q. 2024. "Occupational exposure to benzene and risk of non-Hodgkin lymphoma in an extended follow-up of two population-based prospective cohorts of Chinese men and women." *Int. J. Cancer* 155(12):2159-2168. doi: 10.1002/ijc.35095.

Bassig, BA; Zhang, L; Vermeulen, R; Tang, X; Li, G; Hu, W; Guo, W; Purdue, MP; Yin, S; Rappaport, SM; Shen, M; Ji, Z; Qiu, C; Ge, Y; Hosgood, HD; Reiss, B; Wu, B; Xie, Y; Li, L; Yue, F; Freeman, LE; Blair, A; Hayes, RB; Huang, H; Smith, MT; Rothman, N; Lan, Q. 2016. "Comparison of hematological alterations and markers of B-cell activation in workers exposed to benzene, formaldehyde and trichloroethylene." *Carcinogenesis* 37(7):692-700. doi: 10.1093/carcin/bgw053.

Batke, M; Corsini, E; Fitzgerald, R; Scanziani, E; Schroeder, H; Steffensen, IL; Ulbrich, BC; van Loveren, H; Waalkens-Berendsen, D; Woelfle, D; Gundert-Remy, U. 2023. "Quality of reporting animal studies." *Arch. Toxicol*. 97(8):2285-2286. doi: 10.1007/s00204-023-03537-w.

Becker, RA; Dreier, DA; Manibusan, MK; Cox, LAT; Simon, TW; Bus, JS. 2017. "How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data?" *Regul. Toxicol. Pharmacol.* 90:185-196. doi: 10.1016/j.yrtph.2017.08.021.

Bernard, SM; Cartwright, RA; Bird, CC; Richards, ID; Lauder, I; Roberts, BE. 1984. "Aetiologic factors in lymphoid malignancies: A case-control epidemiological study." *Leuk. Res*. 8(4):681-689. doi: 10.1016/0145-2126(84)90016-x.

Bertazzi, PA; Pesatori, AC; Zocchetti, C; Latocca, R. 1989. "Mortality study of cancer risk among oil refinery workers." *Int. Arch. Occup. Environ. Health* 61(4):261-270.

Berwick, M; Armstrong, BK; Ben-Porat, L; Fine, J; Kricker, A; Eberle, C; Barnhill, R. 2005. "Sun exposure and mortality from melanoma." *J. Natl. Cancer Inst.* 97:195-199.

Bilello, KS; Murin, S; Matthay, RA. 2002. "Epidemiology, etiology, and prevention of lung cancer." *Clin. Chest Med.* 23(1):1-25. doi: 10.1016/S0272-5231(03)00057-1.

Bird, SB. 2024. "General Causation Expert Report of Steven B. Bird, MD: Hematopoietic Cancers: Leukemia and Non-Hodgkin's Lymphoma." 101p., December 9.

Bjork, J; Albin, M; Welinder, H; Tinnerberg, H; Mauritzson, N; Kauppinen, T; Stromberg, U; Johansson, B; Billstrom, R; Mikoczy, Z; Ahlgren, T; Nilsson, PG; Mitelman, F; Hagmar, L. 2001. "Are occupational, hobby, or lifestyle exposures associated with Philadelphia chromosome positive chronic myeloid leukaemia?" *Occup. Environ. Med*. 58(11):722-727.

Blair, A; Haas, T; Prosser, R; Morrissette, M; Blackman, K; Grauman, D; van Dusen, P; Moran, F. 1989. "Mortality among United States Coast Guard marine inspectors." *Arch. Environ. Health* 44(3):150-156.

Blair, A; Hartge, P; Stewart, PA; McAdams, M; Lubin, J. 1998. "Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: Extended follow up." *Occup. Environ. Med.* 55:161-171.

Blair, A; Petralia, SA; Stewart, PA. 2003. "Extended mortality follow-up of a cohort of dry cleaners." *Ann. Epidemiol.* 13(1):50-56.

Blair, A; Stewart, PA; Tolbert, PE; Grauman, D; Moran, FX; Vaught, J; Rayner, J. 1990. "Cancer and other causes of death among a cohort of dry cleaners." *Br. J. Ind. Med.* 47:162-168.

Blair, A; Zheng, T; Linos, A; Stewart, PA; Zhang, YW; Cantor, KP. 2001. "Occupation and leukemia: A population-based case-control study in Iowa and Minnesota." *Am. J. Ind. Med*. 40:3-14.

Blettner, M; Sauerbrei, W; Schlehofer, B; Scheuchenpflug, T; Friedenreich, C. 1999. "Traditional reviews, meta-analyses and pooled analyses in epidemiology." *Int. J. Epidemiol.* 28(1):1-9. doi: 10.1093/ije/28.1.1.

Bloch, D; Diel, P; Epe, B; Hellwig, M; Lampen, A; Mally, A; Marko, D; Villar Fernandez, MA; Guth, S; Roth, A; Marchan, R; Ghallab, A; Cadenas, C; Nell, P; Vartak, N; van Thriel, C; Luch, A; Schmeisser, S; Herzler, M; Landsiedel, R; Leist, M; Marx-Stoelting, P; Tralau, T; Hengstler, JG. 2023. "Basic concepts of mixture toxicity and relevance for risk evaluation and regulation (Editorial)." *Arch. Toxicol*. 97(11):3005-3017. doi: 10.1007/s00204-023-03565-6.

Bloemen, LJ; Youk, A; Bradley, TD; Bodner, KM; Marsh, G. 2004. "Lymphohaematopoietic cancer risk among chemical workers exposed to benzene." *Occup. Environ. Med.* 61:270-274.

Boffetta, P; Matisane, L; Mundt, KA; Dell, LD. 2003. "Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality." *Scand. J. Work Environ. Health* 29(3):220-229.

Boice, JD; Marano, DE; Cohen, SS; Mumma, MT; Blot, WJ; Brill, AB; Fryzek, JP; Henderson, BE; McLaughlin, JK. 2006. "Mortality among Rocketdyne workers who tested rocket engines, 1948-1999." *J. Occup. Environ. Med.* 48(10):1070-1092. doi: 10.1097/01.jom.0000240661.33413.b5.

Boice, JD; Marano, DE; Fryzek, JP; Sadler, CJ; McLaughlin, JK. 1999. "Mortality among aircraft manufacturing workers." *Occup. Environ. Med.* 56:581-597.

Bond, GG; McLaren, EA; Baldwin, CL; Cook, RR. 1986. "An update of mortality among chemical workers exposed to benzene." *Br. J. Med.* 43:685-691.

Borgert, CJ; Quill, TF; McCarty, LS; Mason, AM. 2004. "Can mode of action predict mixture toxicity for risk assessment?" *Toxicol. Appl. Pharmacol*. 201:85-96.

Bove, FJ. [Agency for Toxic Substances and Disease Registry (ATSDR)]. 2024a. "Videotaped & videoconferenced deposition of Dr. Frank J. Bove [re: Camp Lejeune Water Litigation re: All cases]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-897. 455p., October 17, 18.

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

Bove, F. 2024c. "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* doi: 10.1101/2024.01.27.24301873.

Bove, FJ; Greek A; Gatiba, R; Kohler, B; Sherman, R; Shin, GT; Bernstein, A. 2024a. "Cancer incidence among Marines and Navy personnel and civilian workers exposed to industrial solvents in drinking water at US Marine Corps Base Camp Lejeune: A cohort study." *Environ. Health Perspect*. 132(10):107008. doi: 10.1289/EHP14966.

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

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

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

Brigham, JL. [Morgan, Angel, Brigham and Associates, LLC]. 2024. "Expert Report of Jay L. Brigham, Ph.D., In the United States District Court for the Eastern District of North Carolina, Southern Division, Case No. 7:23-CV-897, Camp Lejeune Water Litigation." Report to US Dept. of Justice (US DOJ). 126p., December 9.

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

Bruckner, JV; Anand, SS; Warren, DA. 2013. "Toxic effects of solvents and vapors." In *Casarett and Doull's Toxicology: The Basic Science of Poisons (Eighth Edition)*. (Ed: Klaassen, CD), McGraw-Hill Education, New York, NY. p1031-1112.

Bulbulyan, MA; Ilychova, SA; Zahm, SH; Astashevsky, SV; Zaridze, DG. 1999. "Cancer mortality among women in the Russian printing industry." *Am. J. Ind. Med.* 36(1):166-171. doi: 10.1002/(SICI)1097-0274(199907)36:1<166::AID-AJIM24>3.0.CO;2-P.

Caldwell, DJ. 1999. "Review of mononuclear cell leukemia in F-344 rat bioassays and its significance to human cancer risk: A case study using alkyl phthalates." *Regul. Toxicol. Pharmacol*. 30(1):45-53.

Callahan, CL; Stewart, PA; Blair, A; Purdue, MP. 2019. "Extended mortality follow-up of a cohort of dry cleaners." *Epidemiology* 30(2):285-290. doi: 10.1097/EDE.0000000000000951.

Carreón, T; Hein, MJ; Hanley, KW; Viet, SM; Ruder, AM. 2014. "Coronary artery disease and cancer mortality in a cohort of workers exposed to vinyl chloride, carbon disulfide, rotating shift work, and o-toluidine at a chemical manufacturing plant." *Am. J. Ind. Med.* 57(4):398-411. doi: 10.1002/ajim.22299.

Cassee, FR; Groten, JP; van Bladeren, PJ; Feron, VJ. 1998. "Toxicological evaluation and risk assessment of chemical mixtures." *Crit. Rev. Toxicol.* 28(1):73-101.

Cedergreen, N. 2014. "Quantifying synergy: A systematic review of mixture toxicity studies within environmental toxicology." *PLoS ONE* 9(5):e96580. doi: 10.1371/journal.pone.0096580.

Centers for Disease Control and Prevention (CDC). 2014. "Minimum Latency & Types or Categories of Cancer." World Trade Center (WTC) Health Program. 11p. Accessed at https://www.cdc.gov/wtc/pdfs/policies/wtchpminlatcancer2014-11-07-508.pdf.

Centers for Disease Control and Prevention (CDC). 2015. "Minimum Latency & Types or Categories of Cancer (Revised)." World Trade Center Health Program. 12p., January 6.

Centers for Disease Control and Prevention (CDC). 2017. "Biomonitoring Summary: Benzene (CAS No. 71-43-2)." National Biomonitoring Program.

Chang, YM; Tai, CF; Yang, SC; Chen, CJ; Shih, TS; Lin, RS; Liou, SH. 2003. "A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan." *Ann. Epidemiol*. 13(9):652-660. doi: 10.1016/S1047-2797(03)00038-3.

Charles, GD; Gennings, C; Tornesi, B; Kan, HL; Zacharewski, TR; Bhaskar Gollapudi, B; Carney, EW. 2007. "Analysis of the interaction of phytoestrogens and synthetic chemicals: An in vitro/in vivo comparison." *Toxicol. Appl. Pharmacol*. 218(3):280-288.

Chiu, WA; Ginsberg, GL. 2011. "Development and evaluation of a harmonized physiologically based pharmacokinetic (PBPK) model for perchloroethylene toxicokinetics in mice, rats, and humans." *Toxicol. Appl. Pharmacol.* 253(3):203-234.

Chiu, WA; Okino, MS; Evans, MV. 2009. "Characterizing uncertainty and population variability in the toxicokinetics of trichloroethylene and metabolites in mice, rats, and humans using an updated database, physiologically based pharmacokinetic (PBPK) model, and Bayesian approach." *Toxicol. Appl. Pharmacol.* 241(1):36-60. doi: 10.1016/j.taap.2009.07.032.

Ciccone, G; Mirabelli, D; Levis, A; Gavarotti, P; Rege-Cambrin, G; Davico, L; Vineis, P. 1993. "Myeloid leukemias and myelodysplastic syndromes: Chemical exposure, histologic subtype and cytogenetics in a case-control study." *Cancer Genet. Cytogenet*. 68:135-139.

Cichocki, JA; Guyton, KZ; Guha, N; Chiu, WA; Rusyn, I; Lash, LH. 2016. "Target organ metabolism, toxicity, and mechanisms of trichloroethylene and perchloroethylene: Key similarities, differences, and data gaps." *J. Pharmacol. Exp. Ther.* 359(1):110-123. doi: 10.1124/jpet.116.232629.

Clewell, RA; Thompson, CM; Clewell, HJ III. 2019. "Dose-dependence of chemical carcinogenicity: Biological mechanisms for thresholds and implications for risk assessment." *Chem. Biol. Interact*. 301:112-127. doi: 10.1016/j.cbi.2019.01.025.

Cocco, P; Vermeulen, R; Flore, V; Nonne, T; Campagna, M; Purdue, M; Blair, A; Monnereau, A; Orsi, L; Clavel, J; Becker, N; de Sanjose, S; Foretova, L; Staines, A; Maynadie, M; Nieters, A; Miligi, L; 't Mannetje, A; Kricker, A; Brennan, P; Boffetta, P; Lan, Q; Rothman, N. 2013. "Occupational exposure to trichloroethylene and risk of non-Hodgkin lymphoma and its major subtypes: A pooled IinterLlymph [*sic*] analysis." *Occup. Environ. Med*. 70(11):795-802. doi: 10.1136/oemed-2013-101551.

Cohn, P; Klotz, J; Bove, F; Berkowitz, M; Fagliano, J. 1994. "Drinking water contamination and the incidence of leukemia and non-Hodgkin's lymphoma." *Environ. Health Perspect*. 102(6/7):556-561.

Collingwood, KW; Raabe, GK; Wong, O. 1996. "An updated cohort mortality study of workers at a northeastern United States petroleum refinery." *Int. Arch. Occup. Environ. Health* 68:277-288.

Collins, JJ; Anteau, SE; Swaen, GM; Bodner, KM; Bodnar, CM. 2015. "Lymphatic and hematopoietic cancers among benzene-exposed workers." *J. Occup. Environ. Med.* 57(2):159-163. doi: 10.1097/JOM.0000000000000324.

Collins, JJ; Ireland, B; Buckley, CF; Shepperly, D. 2003. "Lymphohaematopoeitic cancer mortality among workers with benzene exposure." *Occup. Environ. Med*. 60(9):676-679. doi: 10.1136/oem.60.9.676.

Consonni, D; Pesatori, AC; Tironi, A; Bernucci, I; Zocchetti, C; Bertazzi, PA. 1999. "Mortality study in an Italian oil refinery: Extension of the follow-up." *Am. J. Ind. Med*. 35(3):287-294.

Cooper, WC. 1981. "Epidemiologic study of vinyl chloride workers: Mortality through December 31, 1972." *Environ. Health Perspect*. 41:101-106.

Copley, GB; Schnatter, AR; Armstrong, TW; Irons, RD; Chen, M; Wang, XQ; Kerzic, P. 2017. "Hospital-based case-control study of MDS subtypes and benzene exposure in Shanghai." *J. Occup. Environ. Med*. 59(4):349-355. doi: 10.1097/JOM.0000000000000952.

Costantini, AS; Benvenuti, A; Vineis, P; Kriebel, D; Tumino, R; Ramazzotti, V; Rodella, S; Stagnaro, E; Crosignani, P; Amadori, D; Mirabelli, D; Sommani, L; Belletti, I; Troschel, L; Romeo, L; Miceli, G; Tozzi, GA; Mendico, I; Maltoni, SA; Miligi, L. 2008. "Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: Evidence from the Italian Multicenter Case-control study." *Am. J. Ind. Med*. 51(11):803-811. doi: 10.1002/ajim.20592.

Costantini, AS; Miligi, L; Kriebel, D; Ramazzotti, V; Rodella, S; Scarpi, E; Stagnaro, E; Tumino, R; Fontana, A; Masala, G; Vigano, C; Vindigni, C; Crosignani, P; Benvenuti, A; Vineis, P. 2001. "A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation." *Epidemiology* 12(1):78-87.

Costantini, AS; Quinn, M; Consonni, D; Zappa, M. 2003. "Exposure to benzene and risk of leukemia among factory shoe workers." *Scand. J. Work Environ. Health* 29(1):51-59.

Costas, K; Knorr, RS; Condon, SK. 2002. "A case-control study of childhood leukemia in Woburn, Massachusetts: The relationship between leukemia incidence and exposure to public drinking water." *Sci. Total Environ*. 300(1-3):23-35.

Crofton, KM; Craft, ES; Hedge, JM; Gennings, C; Simmons, JE; Carchman, RA; Carter, WH; DeVito, MJ. 2005. "Thyroid-hormone-disruption chemicals: Evidence for dose-dependent additivity or synergism." *Environ. Health Perspect*. 113(11):1549-1554.

Cronkite, EP. 1986. "Benzene hematotoxicity and leukemogenesis." *Blood Cells* 12(1):129-137.

Cronkite, EP; Bullis, J; Inoue, T; Drew, RT. 1984. "Benzene inhalation produces leukemia in mice." *Toxicol. Appl. Pharmacol.* 75(2):358-361. doi: 10.1016/0041-008X(84)90219-9.

Cronkite, EP; Drew, RT; Inoue, T; Bullis, JE. 1985. "Benzene hematotoxicity and leukemogenesis." *Am. J. Ind. Med.* 7(5-6):447-456. doi: 10.1002/ajim.4700070509.

Cronkite, EP; Drew, RT; Inoue, T; Hirabayashi, Y; Bullis, JE. 1989. "Hematotoxicity and carcinogenicity of inhaled benzene." *Environ. Health Perspect.* 82:97-108. doi: 10.1289/ehp.898297.

Crump, KS. 1994. "Risk of benzene-induced leukemia: A sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates." *J. Toxicol. Environ. Health* 42:219-242.

Dagg, TG; Satin, KP; Bailey, WJ; Wong, O; Harmon, LL; Swencicki, RE. 1992. "An updated cause specific mortality study of petroleum refinery workers." *Br. J. Ind. Med.* 49(3):203-212. doi: 10.1136/oem.49.3.203.

DeMoulin, D; Cai, H; Vermeulen, R; Zheng, W; Lipworth, L; Shu, XO. 2024. "Occupational benzene exposure and cancer risk among Chinese men: A report from the Shanghai Men's Health Study." *Cancer Epidemiol. Biomarkers Prev*. doi: 10.1158/1055-9965.EPI-24-0325.

Divine, BJ; Barron, V. 1986. "Texaco Mortality Study: II. Patterns of mortality among white males by specific job groups." *Am. J. Ind. Med*. 10(4):371-381. doi: 10.1002/ajim.4700100405.

Divine, BJ; Barron, V; Kaplan, SD. 1985. "Texaco Mortality Study. I. Mortality among refinery, petrochemical, and research workers." *J. Occup. Med*. 27(6):445-447.

Divine, BJ; Hartman, CM; Wendt, JK. 1999a. "Update of the Texaco Mortality Study 1947-93: Part I. Analysis of overall patterns of mortality among refining, research, and petrochemical workers." *Occup. Environ. Med*. 56(3):167-173. doi: 10.1136/oem.56.3.167.

Divine, BJ; Hartman, CM; Wendt, JK. 1999b. "Update of the Texaco Mortality Study 1947-93: Part II. Analyses of specific causes of death for white men employed in refining, research, and petrochemicals." *Occup. Environ. Med*. 56(3):174-180. doi: 10.1136/oem.56.3.174.

Dobrzynski, L; Fornalski, KW; Feinendegen, LE. 2015. "The human cancer in high natural background radiation areas." *Int. J. Low Radiat.* 10(2):143-154. doi: 10.1504/IJLR.2015.074413.

Dosemeci, M; Wacholder, S; Lubin, JH. 1990. "Does nondifferential misclassification of exposure always bias a true effect toward the null value?" *Am. J. Epidemiol.* 132(4):746-748.

Eastmond, DA; Keshava, N; Sonawane, B. 2014. "Lymphohematopoietic cancers induced by chemicals and other agents and their implications for risk evaluation: An overview." *Mutat. Res*. doi: 10.1016/j.mrrev.2014.04.001.

Egger, M; Smith, GD; Altman, D. 2001. *Systematic Reviews in Health Care: Meta-Analysis in Context (Second Edition)*. BMJ Publishing Group. 475p.

Ellenhorn, MJ; Barceloux, DG. 1988. "Salicylates." "In *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*." (Eds.: Ellenhorn, MJ; Barceloux, DG), Elsevier, New York. 3p.

Environmental Health Associates, Inc. 1984. "An Epidemiologic Analysis of the Mortality Experience of Mobil Corporation Employees at the Beaumont, Texas, Refinery." 70p., April 10.

Environmental Health Associates, Inc. 1985. "An Epidemiologic Analysis of the Mortality Experience of Mobil Corporation Employees at the Paulsboro, New Jersey, Refinery (Final)." January 31.

Farris, GM; Everitt, JI; Irons, RD; Popp, JA. 1993. "Carcinogenicity of inhaled benzene in CBA mice." *Fundam. Appl. Toxicol.* 20(4):503-507. doi: 10.1093/toxsci/20.4.503.

Fartasch, M; Diepgen, TL; Schmitt, J; Drexler, H. 2012. "The relationship between occupational sun exposure and non-melanoma skin cancer: Clinical basics, epidemiology, occupational disease evaluation, and prevention." *Dtsch. Arztebl. Int.* 109(43):715-720. doi: 10.3238/arztebl.2012.0715.

Faustman, EM. 2019. "Risk assessment." In *Casarett and Doull's Toxicology: The Basic Science of Poisons (Ninth Edition)*. (Ed.: Klaassen, CD), McGraw-Hill Education, New York, NY, p127-155.

Fedeli, U; Girardi, P; Gardiman, G; Zara, D; Scoizzato, L; Ballarin, MN; Baccini, M; Pirastu, R; Comba, P; Mastrangelo, G. 2019. "Mortality from liver angiosarcoma, hepatocellular carcinoma, and cirrhosis among vinyl chloride workers." *Am. J. Ind. Med.* 62(1):14-20. doi: 10.1002/ajim.22922.

Felsher, DW. [Stanford University]. 2024. "General Causation Expert Report of Dean W. Felsher, M.D., Ph.D.: Leukemia and Non-Hodgkin Lymphoma." 116p., December 9.

Feron, VJ; Groten, JP. 2002. "Toxicological evaluation of chemical mixtures." *Food Chem. Toxicol.* 40(6):825-839.

Feron, VJ; Groten, JP; van Zorge, JA; Cassee, FR; Jonker, D; van Bladeren, PJ. 1995. "Toxicity studies in rats of simple mixtures of chemicals with the same or different target organs." *Toxicol. Lett.* 82-83:505-512.

Feron, VJ; Hendriksen, CFM; Speek, AJ; Til, HP; Spit, BJ. 1981. "Lifespan oral toxicity study of vinyl chloride in rats." *Food Cosmet. Toxicol.* 19:317-333.

Finkelstein, MM. 2000. "Leukemia after exposure to benzene: Temporal trends and implications for standards." *Am. J. Ind. Med.* 38(1):1-7. doi: 10.1002/1097-0274(200007)38:1<1::aid-ajim1>3.0.co;2-9.

Flegal, KM; Keyl, PM; Nieto, FJ. 1991. "Differential misclassification arising from nondifferential errors in exposure measurement." *Am. J. Epidemiol.* 134(10):1233-1244.

Forsell, K; Bjor, O; Jarvholm, B; Nilsson, R; Andersson, E. 2020. "Hematologic malignancy in tanker crewmembers: A case-referent study among male Swedish seafarers." *Am. J. Ind. Med.* 63(8):685-692. doi: 10.1002/ajim.23122.

French, JE; Saulnier, M. 2000. "Benzene leukemogenesis: An environmental carcinogen-induced tissue-specific model of neoplasia using genetically altered mouse models." *J. Toxicol. Environ. Health A* 61(5-6):377-379. doi: 10.1080/00984100050166389.

Fu, H; Demers, PA; Constantini, AS; Winter, P; Colin, D; Kogevinas, M; Boffetta, P. 1996. "Cancer mortality among shoe manufacturing workers: An analysis of two cohorts." Occup. Environ. Med. 53(6):394-398.

Fukuda, K; Takemoto, K; Tsurata, H. 1983. "Inhalation carcinogenicty of trichloroethylene in mice and rats." *Ind. Health* 21:243-254. doi: 10.2486/indhealth.21.243.

Gamble, JF; Lewis, RJ; Jorgensen, G. 2000. "Mortality among three refinery/petrochemical plant cohorts. II. Retirees." *J. Occup. Environ. Med.* 42(7):730-736.

Garabrant, DH. 2000. "Epidemiologic principles in the evaluation of suspected neurotoxic disorders." *Neurol. Clin.* 18(3):631-648. doi: 10.1016/S0733-8619(05)70215-2.

Garabrant, DH; Held, J; Langholz, B; Bernstein, L. 1988. "Mortality and aircraft manufacturing workers in southern California." *Am. J. Ind. Med.* 13:683-693. doi: 10.1002/ajim.4700130607.

Ghahri, A; Dehghan, MH; Seydi, P; Mashayekhi, S; Naderi, Y; Seydi, E. 2022. "The perchloroethylene-induced toxicity in dry cleaning workers lymphocytes through induction of oxidative stress." *J. Biochem. Mol. Toxicol*. 36(4):e23000. doi: 10.1002/jbt.23000.

Gift, JS; Caldwell, JC; Jinot, J; Evans, MV; Cote, I; Vandenberg, JJ. 2013. "Scientific considerations for evaluating cancer bioassays conducted by the Ramazzini Institute." *Environ. Health Perspect.* 121(11-12):1253-1263. doi: 10.1289/ehp.1306661.

Gilbert, KM. 2024. "General Causation Expert Report of Kathleen M. Gilbert, PHD: TCE, Non-Hodgkin Lymphoma, and Leukemia." 73p., December 9.

Glass, DC; Gray, CN; Jolley, DJ; Gibbons, C; Sim, MR; Fritschi, L; Adams, GG; Bisby, JA; Manuell, R. 2003. "Leukemia risk associated with low-level benzene exposure." *Epidemiology* 14(5):569-577. doi: 10.1097/01.ede.0000082001.05563.e0.

Glass, DC; Schnatter, AR; Tang, G; Irons, RD; Rushton, L. 2014. "Risk of myeloproliferative disease and chronic myeloid leukaemia following exposure to low-level benzene in a nested case-control study of petroleum workers." *Occup. Environ. Med*. 71(4):266-274. doi: 10.1136/oemed-2013-101664.

Glass, DC; Sim, MR; Fritschi, L; Gray, CN; Jolley, DJ; Gibbons, C. 2004. "Leukemia risk and relevant benzene exposure period-Re: follow-up time on risk estimates, *Am J Ind Med 42:481-489, 2002* (Letter)." *Am. J. Ind. Med*. 45(2):222-223. doi: 10.1002/ajim.10327.

Goldstein, BD; Snyder, CA; Laskin, S; Bromberg, I; Albert, RE; Nelson, N. 1982. "Myelogenous leukemia in rodents inhaling benzene." *Toxicol. Lett.* 13(3-4):169-173. doi: 10.1016/0378-4274(82)90206-5.

Gondek, L. [Johns Hopkins University]. 2024. "General Causation Expert Report of Lukasz Gondek, MD, PhD: Leukemia." 55p., December 9.

Goodman, J; Lynch, H. 2017. "Improving the International Agency for Research on Cancer's consideration of mechanistic evidence." *Toxicol. Appl. Pharmacol.* 319:39-46. doi: 10.1016/j.taap.2017.01.020.

Goodman, JE; Lynch, HN; Rhomberg, LR. 2018. "Letter to the editor re: Guyton *et al.* (2018), 'Application of the key characteristics of carcinogens in cancer hazard identification'." *Carcinogenesis* 39(8):1089-1090. doi: 10.1093/carcin/bgy066.

Goodman, JE; Prueitt, RL; Harbison, RD; Johnson, GT. 2020. "Systematically evaluating and integrating evidence in National Ambient Air Quality Standards (NAAQS) reviews." *Glob. Epidemiol.* 2:1000019. doi: 10.1016/j.gloepi.2020.100019.

Gordis, L. 2014. *Epidemiology (Fifth Edition)*. Saunders Elsevier, Philadelphia, PA. 416p.

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

Grosser, T; Smyth, E; FitzGerald, GA. 2011. "Anti-inflammatory, antipyretic, and analgesic agents; Pharmacotherapy of gout." In *Goodman and Gilman's The Pharmacological Basis of Therapeutics (Twelfth Edition)*. (Eds.: Brunton, LL; Chabner, BA; Knollman, BC), McGraw-Hill, New York, NY. p959-1004.

Guenel, P; Imbernon, E; Chevalier, A; Crinquand-Calastreng, A; Goldberg, M. 2002. "Leukemia in relation to occupational exposures to benzene and other agents: A case-control study nested in a cohort of gas and electric utility workers." *Am. J. Ind. Med*. 42(2):87-97.

Hanis, NM; Shallenberger, LG; Donaleski, DL; Sales, EA. 1985a. "A retrospective mortality study of workers in three major U.S. refineries and chemical plants. Part 1: Comparisons with U.S. population." *J. Occup. Med.* 27(4):283-292.

Hanis, NM; Shallenberger, LG; Donaleski, DL; Sales, EA. 1985b. "A retrospective mortality study of workers in three major U.S. refineries and chemical plants. Part II: Internal comparisons by geographic site, occupation and smoking history." *J. Occup. Med*. 27(5):361-369.

Hansen, J; Raaschou-Nielsen, O; Christensen, JM; Johansen, I; McLaughlin, JK; Lipworth, L; Blot, WJ; Olsen, JH. 2001. "Cancer incidence among Danish workers exposed to trichloroethylene." *J. Occup. Environ. Med.* 43(2):133-139. doi: 10.1097/00043764-200102000-00012.

Hansen, J; Sallmen, M; Selden, AI; Anttila, A; Pukkala, E; Andersson, K; Bryngelsson, I; Raaschou-Nielsen, O; Olsen, JH; McLaughlin, JK. 2013. "Risk of cancer among workers exposed to trichloroethylene: Analysis of three Nordic cohort studies." *J. Natl. Cancer Inst*. 105(12):869-877. doi: 10.1093/jnci/djt107.

Haseman, JK. 1984. "Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies." *Environ. Health Perspect.* 58:385-392.

Hayes, AW; Kobets, T; eds. 2023. *Hayes' Principles and Methods of Toxicology (Seventh Edition). Volumes I-II*. CRC Press, Boca Raton, FL. 2143p.

Hayes, RB; Yin, S; Rothman, N; Dosemeci, M; Li, G; Travis, LT; Smith, MT; Linet, MS. 2000. "Benzene and lymphohematopoietic malignancies in China." *J. Toxicol. Environ. Health A* 61(5-6):419-432.

Hayes, RB; Yin, SN; Dosemeci, M; Li, GL; Travis, LB; Li, CY; Rothman, N; Hoover, RN; Linet, MS. 1997. "Benzene and the dose-related incidence of hematologic neoplasms in China." *J. Natl. Cancer Inst*. 89(14):1065-1071.

Health Physics Society (HPS). 2020. "Position statement of the Health Physics Society PS010-4: Radiation risk in perspective." *Health Phys.* 118(1):79-80. doi: 10.1097/HP.0000000000001157.

Hennekens, CH; Buring, JE. 1987. "Case reports and case series." In *Epidemiology in Medicine*. Little, Brown and Co., Boston. p106-107.

Hennet, RJC. [S.S. Papadopulos & Associates, Inc.]. 2024. "Expert Report of Remy J.-C. Hennet, In the United States District Court, Eastern District of North Carolina, No. 7:23-cv-897, In Re: Camp Lejeune Water Litigation." Report to US Dept. of Justice (US DOJ). 221p., December 9.

Henschler, D; Elsasser, H; Romen, W; Eder, E. 1984. "Carcinogenicity study of trichloroethylene, with and without epoxide stabilizers, in mice." *J. Cancer Res. Clin. Oncol.* 107:149-156. doi: 10.1007/BF01032599.

Hill, AB. 1965. "The environment and disease: Association or causation?" *Proc. R. Soc. Med.* 58(5):295-300.

Holmberg, B; Kronevi, T; Winell, M. 1976. "The pathology of vinyl chloride exposed mice." *Acta Vet. Scand.* 17(3):328-342. doi: 10.1186/BF03547913.

Honda, Y; Delzell, E; Cole, P. 1995. "An updated study of mortality among workers at a petroleum manufacturing plant." *J. Occup. Environ. Med*. 37(2):194-200.

Hosgood, HD; Rahman, ML; Blansky, D; Hu, W; Davitt, M; Wen, C; Huang, Y; Tang, X; Li, L; Smith, MT; Zhang, L; Vermeulen, R; Rothman, N; Bassig, BA; Lan, Q. 2022. "Targeted proteomic scan identifies alteration of serum proteins among workers occupationally exposed to low levels of trichloroethylene." *Environ. Mol. Mutagen*. 63(8-9):423-428. doi: 10.1002/em.22518.

Huebner, WW; Wojcik, NC; Rosamilia, K; Jorgensen, G; Milano, CA. 2004. "Mortality updates (1970-1997) of two refinery/petrochemical plant cohorts at Baton Rouge, Louisiana, and Baytown, Texas." *J. Occup. Environ. Med*. 46(12):1229-1245.

Huff, JE; Haseman, JK; DeMarini, DM; Eustis, S; Maronpot, RR; Peters, AC; Persing, RL; Chrisp, CE; Jacobs, AC. 1989. "Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F1 mice." *Environ. Health Perspect.* 82:125-163. doi: 10.1289/ehp.8982125.

Infante, PF; Wagoner, JK; Rinsky, RA; Young, RJ. 1977. "Leukaemia in benzene workers." *Lancet* p76-78.

Institute of Medicine (IOM). 2003. "Gulf War and Health - Volume 2: Insecticides and Solvents." Committee on Gulf War and Health, Literature Review of Selected Environmental Particulates, Pollutants, and Synthetic Chemical Compounds. National Academies Press, Washington, DC. 617p. Accessed at https://nap.nationalacademies.org/catalog/10628/gulf-war-and-health-volume-2-insecticides-and-solvents.

Institute of Medicine (IOM). 2008. *Improving the Presumptive Disability Decision-Making Process for Veterans*. Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans, Board on Military and Veterans Health. (Samet, JM; Bodurow, CC; eds.), National Academies Press, Washington, DC, 781p.

Institute of Medicine (IOM). 2015. "Review of VA Clinical Guidance for the Health Conditions Identified by the Camp Lejeune Legislation." National Academies Press, Washington, DC, 120p. Accessed at https://www.ncbi.nlm.nih.gov/books/NBK284972/pdf/Bookshelf_NBK284972.pdf.

International Agency for Research on Cancer (IARC). 1982. "IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man: Some Industrial Chemicals and Dyestuffs. Volume 29." IARC Monograph No. 29. World Health Organization (WHO). 417p. http://monographs.iarc.fr/ENG/Monographs/vol1-42/index.php.

International Agency for Research on Cancer (IARC). 1987. "Benzene (Group 1): Summary of Data Reported and Evaluation (CAS No. 71-43-2)." In "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Supplement 7." World Health Organization (WHO). p120.

International Agency for Research on Cancer (IARC). 2008a. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Fourth Edition)*. 439p.

International Agency for Research on Cancer (IARC). 2008b. "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)." IARC Monograph No. 97. International Agency for Research on Cancer; World Health Organization (WHO). 525p.

International Agency for Research on Cancer (IARC). 2012a. "Benzene." In "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100F: A Review of Human Carcinogens. Part F: Chemical Agents and Related Occupations." International Agency for Research on Cancer (IARC), World Health Organization (WHO). 46p.

International Agency for Research on Cancer (IARC). 2012b. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100: A Review of Human Carcinogens. Part F: Chemical Agents and Related Occupations." International Agency for Research on Cancer (IARC); World Health Organization (WHO). IARC Monograph No. 100F. 628p.

International Agency for Research on Cancer (IARC). 2014a. "Trichloroethylene." IARC Monograph No. 106. In IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 106: Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. International Agency for Research on Cancer (IARC), World Health Organization (WHO). p35-218. Accessed at http://monographs.iarc.fr/ENG/Monographs/vol106/mono106-001.pdf.

International Agency for Research on Cancer (IARC). 2014b. "Tetrachloroethylene." In "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 106: Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents." IARC Monograph No. 106. International Agency for Research on Cancer (IARC), World Health Organization (WHO). p219-352. Accessed at http://monographs.iarc.fr/ENG/Monographs/vol106/mono106-002.pdf.

International Agency for Research on Cancer (IARC). 2018. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 120: Benzene." IARC Monograph No. 120. International Agency for Research on Cancer (IARC); World Health Organization (WHO). 307p.

International Agency for Research on Cancer (IARC). 2019. "IARC Monographs on the Identification of Carcinogenic Hazards to Humans: Preamble." World Health Organization (WHO). 44p., January.

Ireland, B; Collins, JJ; Buckley, CF; Riordan, SG. 1997. "Cancer mortality among workers with benzene exposure." *Epidemiology* 8(3):318-320.

Irons, RD; Gross, SA; Le, A; Wang, XQ; Chen, Y; Ryder, J; Schnatter, AR. 2010. "Integrating WHO 2001-2008 criteria for the diagnosis of Myelodysplastic Syndrome (MDS): a case-case analysis of benzene exposure." *Chem. Biol. Interact.* 184(1-2):30-38. doi: 10.1016/j.cbi.2009.11.016.

Ishmael, J; Dugard, PH. 2006. "A review of perchloroethylene and rat mononuclear cell leukemia." *Regul. Toxicol. Pharmacol.* 45(2):178-184.

Jakobsen, JC; Gluud, C; Wetterslev, J; Winkel, P. 2017. "When and how should multiple imputation be used for handling missing data in randomised clinical trials - A practical guide with flowcharts." *BMC Med. Res. Methodol.* 17(1):162. doi: 10.1186/s12874-017-0442-1.

Japan Industrial Safety Association (JISA). 1993. "Carcinogenicity Study of Tetrachloroethylene by Inhalation in Rats and Mice: Data No. 3-1." Japan Bioassay Research Center. 53p., March 31.

Ji, J; Hemminki, K. 2005. "Occurrences of leukemia subtypes by socioeconomic and occupational groups in Sweden." *J. Occup. Environ. Med*. 47:1131-1140.

Ji, J; Hemminki, K. 2006. "Socioeconomic/occupational risk factors for lymphoproliferative diseases in Sweden." *Ann. Epidemiol*. 16(5):370-376.

Johns Hopkins Medicine. 2019. "Heart tumors." Accessed at https://www.hopkinsmedicine.org/heart_vascular_institute/conditions_treatments/conditions/heart_tumors.html.

Jones, NL; Davis, RJ. 2024. "Expert Report of Norman L. Jones and R. Jeffery Davis. October 25.

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

Karami, S; Bassig, B; Stewart, PA; Lee, KM; Rothman, N; Moore, LE; Lan, Q. 2013. "Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: A meta-analysis." *Occup. Environ. Med*. 70(8):591-599. doi: 10.1136/oemed-2012-101212.

Kaufman, DW; Anderson, TE; Issaragrisil, S. 2009. "Risk factors for leukemia in Thailand." *Ann. Hematol*. 88(11):1079-1088.

Kawasaki, Y; Hirabayashi, Y; Kaneko, T; Kanno, J; Kodama, Y; Matsushima, Y; Ogawa, Y; Saitoh, M; Sekita, K; Uchida, O; Umemura, T; Yoon, BI; Inoue, T. 2009. "Benzene-induced hematopoietic neoplasms including myeloid leukemia in Trp53-deficient C57BL/6 and C3H/He mice." *Toxicol. Sci*. 110(2):293-306. doi: 10.1093/toxsci/kfp107.

Kelman, A. 2025. "Expert Report of Ari Kelman." February 7.

Khalade, A; Jaakkola, MS; Pukkala, E; Jaakkola, JJ. 2010. "Exposure to benzene at work and the risk of leukemia: A systematic review and meta-analysis." *Environ. Health* 9:31. doi: 10.1186/1476-069X-9-31.

Kirkeleit, J; Riise, T; Bratveit, M; Moen, BE. 2008. "Increased risk of acute myelogenous leukemia and multiple myeloma in a historical cohort of upstream petroleum workers exposed to crude oil." *Cancer Causes Control* 19(1):13-23.

Koh, DH; Chung, EK; Jang, JK; Lee, HE; Ryu, HW; Yoo, KM; Kim, EA; Kim, KS. 2014. "Cancer incidence and mortality among temporary maintenance workers in a refinery/petrochemical complex in Korea." *Int. J. Occup. Environ. Health* 20(2):141-145. doi: 10.1179/2049396714Y.0000000059.

Koh, DH; Kim, TW; Yoon, YH; Shin, KS; Yoo, SW. 2011. "Lymphohematopoietic cancer mortality and morbidity of workers in a refinery/petrochemical complex in Korea." *Saf. Health Work* 2(1):26-33. doi: 10.5491/SHAW.2011.2.1.26.

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

Kortenkamp, A; Backhaus, T; Faust, M. 2009. "State of the Art Report on Mixture Toxicity (Final Report)." Report to European Commission, DG Environment. 070307/2007/485103/ETU/D.1, 391p., December 22.

Kristman, V; Manno, M; Cote, P. 2004. "Loss to follow-up in cohort studies: How much is too much?" *Eur. J. Epidemiol.* 19(8):751-760. doi: 10.1023/b:ejep.0000036568.02655.f8.

Krnic Martinic, M; Pieper, D; Glatt, A; Puljak, L. 2019. "Definition of a systematic review used in overviews of systematic reviews, meta-epidemiological studies and textbooks." *BMC Med. Res. Methodol.* 19(1):203. doi: 10.1186/s12874-019-0855-0.

Kumar, V; Abbas, AK; Aster, JC; Turner, JR; eds. 2021. *Robbins and Cotran Pathologic Basis of Disease (Tenth Edition)*. Elsevier, Philadelphia, PA. 1378p.

Künzli, N; Tager, IB. 1997. "The semi-individual study in air pollution epidemiology: A valid design as compared to ecologic studies." *Environ. Health Perspect.* 105(10):1078-1083. doi: 10.1289/ehp.105-1470382.

Lamm, SH; Engel, A; Joshi, KP; Byrd, DM III; Chen, R. 2009. "Chronic myelogenous leukemia and benzene exposure: A systematic review and meta-analysis of the case-control literature." *Chem. Biol. Interact.* 182(2-3):93-97. doi: 10.1016/j.cbi.2009.08.010.

Lash, LH. 2024. "Trichloroethylene: An update on an environmental contaminant with multiple health effects." *Annu. Rev. Pharmacol. Toxicol*. doi: 10.1146/annurev-pharmtox-022724-120525.

Lash, TL; Fox, MP; Fink, AK. 2009. "*Applying Quantitative Bias Analysis to Epidemiologic Data*." Springer, New York, NY. 192p.

Lash, TL; Vanderweele, TJ; Haneuse, S; Rothman, KJ. 2021. *Modern Epidemiology (Fourth Edition)*. Wolters Kluwe, Philadelphia, PA, 1174p.

Lee, CC; Bhandari, JC; Winston, JM; House, WB; Dixon, RL; Woods, JS. 1978. "Carcinogenicity of vinyl chloride and vinylidene chloride." *J. Toxicol. Environ. Health* 4(1):15-30. doi: 10.1080/15287397809529640.

Lee, KM; Zhang, L; Vermeulen, R; Hu, W; Bassig, BA; Wong, JJ; Qiu, C; Purdue, M; Wen, C; Walker, DI; Jones, DP; Li, L; Huang, Y; Rothman, N; Smith, MT; Lan, Q. 2019a. "Alterations in immune and renal biomarkers among workers occupationally exposed to low levels of trichloroethylene below current regulatory standards." *Occup. Environ. Med*. 76(6):376-381. doi: 10.1136/oemed-2018-105583.

Lee, KM; Bassig, BA; Zhang, L; Vermeulen, RC; Hu, W; Wong, JYY; Qiu, C; Wen, C; Huang, Y; Purdue, MP; Ji, BT; Li, L; Tang, X; Rothman, N; Smith, MT; Lan, Q. 2019b. "Association between occupational exposure to trichloroethylene and serum levels of microRNAs: A cross-sectional molecular epidemiology study in China." *Int. Arch. Occup. Environ. Health* 92(8):1077-1085. doi: 10.1007/s00420-019-01448-x.

Leukemia & Lymphoma Society. 2024. "Facts 2023-2024: Updated Data on Blood Cancers." 40p. Accessed at https://www.lls.org/sites/default/files/2024-09/PS80_FactsBook_2024.pdf.

Lewis, RJ; Gamble, JF; Jorgensen, G. 2000a. "Mortality among three refinery/petrochemical plant cohorts. I. 1970 to 1982 active/terminated workers." *J. Occup. Environ. Med*. 42(7):721-729.

Lewis, RJ; Schnatter, AR; Katz. AM; Thompson, FS; Murray, N; Jorgensen, G; Theriault, G. 2000b. "Updated mortality among diverse operating segments of a petroleum company." *Occup. Environ. Med*. 57:595-604.

Lewis, RJ; Schnatter, AR; Drummond, I; Murray, N; Thompson, FS; Katz, AM; Jorgensen, G; Nicolich, MJ; Dahlman, D; Theriault, G. 2003. "Mortality and cancer morbidity in a cohort of Canadian petroleum workers." *Occup. Environ. Med*. 60(12):918-928. doi: 10.1136/oem.60.12.918.

Li, C; Li, CX; Zhang, Z. 2024. "Oxidative stress and pro-inflammatory cytokines following perchloroethylene exposure in young female dry-cleaning workers." *Work* 77(3):975-979. doi: 10.3233/WOR-230080.

Li, GX; Hirabayashi, Y; Yoon, BI; Kawasaki, Y; Tsuboi, I; Kodama, Y; Kurokawa, Y; Yodoi, J; Kanno, J; Inoue, T. 2006. "Thioredoxin overexpression in mice, model of attenuation of oxidative stress, prevents benzene-induced hemato-lymphoid toxicity and thymic lymphoma." *Exp. Hematol.* 34(12):1687-1697. doi: 10.1016/j.exphem.2006.08.005.

Lightfoot, T; Smith, A; Roman, E. 2008. "Leukemia." In *International Encyclopedia of Public Health*. (Ed.: Hennenhougen, K), Elsevier. p74-83.

Linet, MS; Gilbert, ES; Vermeulen, R; Dores, GM; Yin, SN; Portengen, L; Hayes, RB; Ji, BT; Lan, Q; Li, GL; Chinese Center for Disease Control; Prevention-US National Cancer Institute Benzene Study Group. 2019. "Benzene exposure response and risk of myeloid neoplasms in Chinese workers: A multicenter case-cohort study." *J. Natl. Cancer Inst*. 111(5):465-474. doi: 10.1093/jnci/djy143.

Linet, MS; Gilbert, ES; Vermeulen, R; Dores, GM; Yin, SN; Portengen, L; Hayes, RB; Ji, BT; Lan, Q; Li, GL; Rothman, N. 2020. "Benzene exposure-response and risk of lymphoid neoplasms in Chinese workers: A multicenter case-cohort study." *Am. J. Ind. Med*. 63(9):741-754. doi: 10.1002/ajim.23142.

Linet, MS; Yin, SN; Gilbert, ES; Dores, GM; Hayes, RB; Vermeulen, R; Tian, HY; Lan, Q; Portengen, L; Ji, BT; Li, GL; Rothman, N; Chinese Center for Disease Control and Prevention-U.S. National Cancer Institute Benzene Study Group. 2015. "A retrospective cohort study of cause-specific mortality and incidence of hematopoietic malignancies in Chinese benzene-exposed workers." *Int. J. Cancer* 137(9):2184-2197. doi: 10.1002/ijc.29591.

Lipscomb, JC. 2025. "Expert Report of John C. Lipscomb." February 7.

Lipworth, L; Sonderman, JS; Mumma, MT; Tarone, RE; Marano, DE; Boice, JD Jr.; McLaughlin, JK. 2011. "Cancer mortality among aircraft manufacturing workers: An extended follow-up." *J. Occup. Environ. Med.* 53(9):992-1007. doi: 10.1097/JOM.0b013e31822e0940.

Longley, K. 2024. "Expert Report of Kyle Longley." December 5.

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

Loscalzo, J; Fauci, AS; Kasper, DL; Hauser, SL; Longo, DL; Jameson, JL; eds. 2022. *Harrison's Principles of Internal Medicine (21st Edition)*. McGraw-Hill Medical, New York, NY. 4384p.

Lowengart, RA; Peters, JM; Cicioni, C; Buckley, J; Bernstein, L; Preston-Martin, S; Rappaport, E. 1987. "Childhood leukemia and parents' occupational and home exposures." *J. Natl. Cancer Inst*. 79(1):39-46.

Lv, L; Lin, G; Gao, X; Wu, C; Dai, J; Yang, Y; Zou, H; Sun, H; Gu, M; Chen, X; Fu, H; Bao, L. 2011. "Case-control study of risk factors of myelodysplastic syndromes according to World Health Organization classification in a Chinese population." *Am. J. Hematol*. 86(2):163-169.

Lynch, HN; Goodman, JE; Tabony, JA; Rhomberg, LR. 2016. "Systematic comparison of study quality criteria." *Regul. Toxicol. Pharmacol.* 76:187-198. doi: 10.1016/j.yrtph.2015.12.017.

Lynge, E; Andersen, A; Nilsson, R; Barlow, L; Pukkala, E; Nordlinder, R; Boffetta, P; Grandjean, P; Heikkila, P; Horte, LG; Jakobsson, R; Lundberg, I; Moen, B; Partanene, T; Riise, T. 1997. "Risk of cancer and exposure to gasoline vapors." *Am. J. Epidemiol*. 145(5):449-458.

Lynge, E; Thygesen, L. 1990. "Primary liver cancer among women in laundry and dry-cleaning work in Denmark." *Scand. J. Work Environ. Health* 16:108-112.

Mallon, TM. [Uniformed Services University]. 2024. "General Causation Expert Report of Timothy M. Mallon, M.D., M.P.H., MS.: Leukemia." 66p., December 9.

Maltoni, C; Ciliberti, A; Cotti, G; Conti, B; Belpoggi, F. 1989. "Benzene, an experimental multipotential carcinogen: Results of the long-term bioassays performed at the Bologna Institute of Oncology." *Environ. Health Perspect*. 82:109-124.

Maltoni, C; Conti, B; Cotti, G. 1983. "Benzene: A multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology." *Am. J. Ind. Med.* 4(5):589-630.

Maltoni, C; Conti, B; Cotti, G; Belpoggi, F. 1985. "Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: Current results and ongoing research." *Am. J. Ind. Med.* 7(5-6):415-446. doi: 10.1002/ajim.4700070508.

Maltoni, C; Cotti, G. 1988. "Carcinogenicity of vinyl chloride in Sprague-Dawley rats after prenatal and postnatal exposure." *Ann. NY Acad. Sci.* 534:145-159. doi: 10.1111/j.1749-6632.1988.tb30108.x.

Maltoni, C; Cotti, G; Valgimigli, L; Mandrioli, A. 1982. "Hepatocarcinomas in Sprague-Dawley rats, following exposure to benzene by inhalation. First experimental demonstration." *Med. Lav*. 73(4):446-450.

Maltoni, C; Lefemine, G. 1975. "Carcinogenicity bioassays of vinyl chloride. Current results." *Ann. NY Acad. Sci.* 246:195-218. doi: 10.1111/j.1749-6632.1975.tb51094.x.

Maltoni, C; Lefemine, G; Ciliberti, A; Cotti, G; Carretti, D. 1981. "Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis." *Environ. Health Perspect.* 41:3-29. doi: 10.1289/ehp.81413.

Maltoni, C; Lefemine, G; Ciliberti, A; Cotti, G; Carretti, D. 1984. "*Experimental Research on Vinyl Chloride Carcinogenesis*" [Archives of Research on Industrial Carcinogenesis: Volume 2]. Princeton Scientific Publishing, Co., Princeton, NJ. 533p.

Maltoni, C; Lefemine, G; Cotti, G. 1986a. "Part 2: Experimental carcinogenicity studies performed at the Bentivoglio Laboratories of the Bologna Institute of Oncology (BT Project) (Excerpt)." In *Experimental Research on Trichloroethylene Carcinogenesis*. Princeton Scientific Publishing Co., Inc., Princeton, NJ. p45-81.

Maltoni, C; Lefemine, G; Cotti, G. 1986b. *Experimental Research on Trichloroethylene Carcinogenesis* [Archives of Research on Industrial Carcinogenesis: Volume 5]. Princeton Scientific Publishing Co., Inc., Princeton, NJ. 393p.

Maltoni, C; Lefemine, G; Cotti, G; Perino, G. 1988a. "Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice." *Ann. NY Acad. Sci.* 534:316-342. doi: 10.1111/j.1749-6632.1988.tb30120.x.

Maltoni, C; Conti, B; Perino, G; Di Maio, V. 1988b. "Further evidence of benzene carcinogenicity. Results on Wistar rats and Swiss mice treated by ingestion." *Ann. NY Acad. Sci*. 534(1):412-426. doi: 10.1111/j.1749-6632.1988.tb30131.x.

Maltoni, C; Scarnato, C. 1979. "First experimental demonstration of the carcinogenic effects of benzene: Long-term bioassays on Sprague-Dawley rats by oral administration." *Med. Lav*. 70(5):352-357.

Maronpot, RR; Nyska, A; Foreman, JE; Ramot, Y. 2016. "The legacy of the F344 rat as a cancer bioassay model (a retrospective summary of three common F344 rat neoplasms)." *Crit. Rev. Toxicol*. 46(8):641-675. doi: 10.1080/10408444.2016.1174669.

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

Maslia, ML. 2024a. "Expert Report of Morris L. Maslia." October 25.

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

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

Mauderly, JL; Samet, JM. 2009. "Is there evidence for synergy among air pollutants in causing health effects?" *Environ. Health Perspect*. 117(1):1-6. doi: 10.1289/ehp.11654.

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

McCraw, DS; Joyner, RE; Cole, P. 1985. "Excess leukemia in a refinery population." *J. Occup. Med*. 27(3):220-222.

McGivern, L; Shulman, L; Carney, JK; Shapiro, S; Bundock, E. 2017. "Death certification errors and the effect on mortality statistics." *Public Health Rep.* 132(6):669-675. doi: 10.1177/0033354917736514.

McGuinn, LA; Ghazarian, AA; Ellison, GL; Harvey, CE; Kaefer, CM; Reid, BC. 2012. "Cancer and environment: Definitions and misconceptions." *Environ. Res.* 112:230-234. doi: 10.1016/j.envres.2011.10.009.

McKinney, PA; Alexander, FE; Cartwright, RA; Parker, L. 1991. "Parental occupations of children with leukaemia in West Cumbria, North Humberside, and Gateshead." *Br. Med. J*. 302(6778):681-687.

McLean, D; Mannetje, A; Dryson, E; Walls, C; McKenzie, F; Maule, M; Cheng, S; Cunningham, C; Kromhout, H; Boffetta, P; Blair, A; Pearce, N. 2009. "Leukaemia and occupation: A New Zealand Cancer Registry-based case-control study." *Int. J. Epidemiol.* 38(2):594-606.

Meek, ME; Boobis, A; Cote, I; Dellarco, V; Fotakis, G; Munn, S; Seed, J; Vickers, C. 2014. "New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis." *J. Appl. Toxicol.* 34(1):1-18. doi: 10.1002/jat.2949.

Miligi, L; Seniori Costantini, A; Crosignani, P; Fontana, A; Masala, G; Nanni, O; Ramazzotti, V; Rodella, S; Stagnaro, E; Tumino, R; Vigano, C; Vindigni, C; Vineis, P. 1999. "Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women." *Am. J. Ind. Med.* 36(1):60-69.

Molander, L; Agerstrand, M; Beronius, A; Hanberg, A; Ruden, C. 2014. "Science in Risk Assessment and Policy (SciRAP): An online resource for evaluating and reporting *in vivo* (eco)toxicity studies." *Hum. Ecol. Risk Assess.* 21(3):753-762. doi: 10.1080/10807039.2014.928104.

Morgan, JW; Cassady, RE. 2002. "Community cancer assessment in response to long-term exposure to perchlorate and trichloroethylene in drinking water." *J. Occup. Environ. Med.* 44(7):616-621. doi: 10.1097/00043764-200207000-00005.

Morgan, RW; Kelsh, MA; Zhao, K; Heringer, S. 1998. "Mortality of aerospace workers exposed to trichloroethylene." *Epidemiology* 9(4):424-431.

Mundt, KA; Dell, LD; Austin, RP; Luippold, RS; Noess, R; Bigelow, C. 2000. "Historical cohort studies of 10109 men in the North American vinyl chloride industry, 1942-1972: Update of cancer mortality to 31 December 1995." *Occup. Environ. Med.* 57(11):774-781.

Mundt, KA; Dell, LD; Boffetta, P; Beckett, EM; Lynch, HN; Desai, VJ; Lin, CK; Thompson, WJ. 2021. "The importance of evaluating specific myeloid malignancies in epidemiological studies of environmental carcinogens." *BMC Cancer* 21(1):227. doi: 10.1186/s12885-021-07908-3.

Mundt, KA; Dell, LD; Crawford, L; Gallagher, AE. 2017. "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.* 74(10):709-716. doi: 10.1136/oemed-2016-104051.

Naimi, AI; Whitcomb, BW. 2020. "Can confidence intervals be interpreted?" *Am. J. Epidemiol.* 189(7):631-633. doi: 10.1093/aje/kwaa004.

National Cancer Institute (NCI). 1976. "Carcinogenesis bioassay of trichloroethylene (CAS No. 79-01-6)." National Technical Information Service (NTIS). NTIS PB-264122; NCI-CG-TR-2. 197p.

National Cancer Institute (NCI). 1977. "Bioassay of tetrachloroethylene for possible carcinogenicity." US Public Health Service, National Institutes of Health (Bethesda, MD). NCI-CG-TR-13; DHEW Publication No. (NIH) 77-813.

National Cancer Institute (NCI). 2015 "Risk Factors for Cancer." Accessed at https://www.cancer.gov/about-cancer/causes-prevention/risk.

National Cancer Institute (NCI). 2017. "The Genetics of Cancer: Hereditary Cancer Syndromes." Accessed at https://www.cancer.gov/about-cancer/causes-prevention/genetics#syndromes.

National Cancer Institute (NCI). 2023a. "Cancer Stat Facts: Leukemia." Accessed at https://seer.cancer.gov/statfacts/html/leuks.html.

National Cancer Institute (NCI). 2023b. "Cancer Stat Facts: Leukemia - Acute Myeloid Leukemia (AML)." Accessed at https://seer.cancer.gov/statfacts/html/amyl.html.

National Cancer Institute (NCI). 2023c. "Cancer Stat Facts: Leukemia - Acute Lymphocytic Leukemia (ALL)." Accessed at https://seer.cancer.gov/statfacts/html/alyl.html.

National Cancer Institute (NCI). 2023d. "Cancer Stat Facts: Leukemia - Chronic Myeloid Leukemia (CML)." Accessed at https://seer.cancer.gov/statfacts/html/cmyl.html.

National Cancer Institute (NCI). 2023e. "Myelodysplastic syndromes (MDS): SEER 5-Year Age-Adjusted Incidence Rates, 2017-2021; All States By Sex, All Races/Ethnicities, All Ages." In SEER*Explorer: An interactive website for SEER cancer statistics. Surveillance, Epidemiology, and End Results Program (SEER). Accessed at https://seer.cancer.gov/statistics-network/explorer/application.html.

National Cancer Institute (NCI). 2024a. "Cancer Stat Facts: Non-Hodgkin Lymphoma." Accessed at https://seer.cancer.gov/statfacts/html/nhl.html.

National Cancer Institute (NCI). 2024b. "Cancer Stat Facts: Leukemia." Accessed at https://seer.cancer.gov/statfacts/html/leuks.html.

National Cancer Institute (NCI). 2024c. "Cancer Stat Facts: Leukemia - Acute Myeloid Leukemia (AML)." Accessed at https://seer.cancer.gov/statfacts/html/amyl.html.

National Cancer Institute (NCI). 2024d. "Cancer Stat Facts: Leukemia - Acute Lymphocytic Leukemia (ALL)." Accessed at https://seer.cancer.gov/statfacts/html/alyl.html.

National Cancer Institute (NCI). 2024e. "Cancer Stat Facts: Leukemia - Chronic Myeloid Leukemia (CML)." Accessed at https://seer.cancer.gov/statfacts/html/cmyl.html.

National Cancer Institute (NCI). 2024f. "Myelodysplastic syndromes (MDS): People Alive with Cancer (U.S. Prevalence) on January 1, 2021; By Age at Prevalence, Both Sexes, All Races / Ethnicities, <= 20 Years Since Diagnosis." Surveillance, Epidemiology, and End Results Program (SEER), In "SEER*Explorer: An interactive website for SEER cancer statistics." Accessed at https://seer.cancer.gov/statistics-network/explorer/application.html?site=409&data_type=5&graph_type=12&compareBy=age_range&chk_age_range_1=1&series=9&sex=1&race=1&prev_duration=2&advopt_precision=1&hdn_view=1&advopt_show_apc=on&advopt_display=2#resultsRegion1.

National Research Council (NRC). 2001. "Arsenic in Drinking Water: 2001 Update." Subcommittee to Update the 1999 Arsenic in Drinking Water Report, National Academy Press, Washington, DC. 225p. http://www.nap.edu/openbook.php?isbn=0309076293.

National Research Council (NRC). 2009. "Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects." Committee on Contaminated Drinking Water at Camp Lejeune National Academies Press, Washington, DC, 318p. Accessed at https://nap.nationalacademies.org/catalog/12618/contaminated-water-supplies-at-camp-lejeune-assessing-potential-health-effects.

National Research Council (NRC). 2014. "Review of EPA's Integrated Risk Information System (IRIS) Process." National Academies Press, Washington, DC, 170p. doi: 10.17226/18764.

National Toxicology Program (NTP). 1986a. "Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in F344/N rats and B6C3F(1) mice (inhalation studies)." Report to US Dept. of Health and Human Services, National Institutes of Health. National Technical Information Service (NTIS). NTIS PB87-147054; NTP TR 311; NIH Publication No. 86-2567. 197p., August.

National Toxicology Program (NTP). 1986b. "Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies)." NTP TR 289, NIH Publication No. 86-2545. 279p.

National Toxicology Program (NTP). 1988. "Toxicology and Carcinogenesis studies of Trichloroethylene (CAS No. 79-01-6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies)." National Technical Information Service (NTIS), NTIS PB88-218896, NTP Technical Report Series No. 273, 300p.

National Toxicology Program (NTP). 1990. "Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies)." National Institutes of Health. NTP TR 243; NIH Publication No. 90-1779. 174p., May.

National Toxicology Program (NTP). 2002. "NTP Technical Report on Toxicity Studies of trans-1,2-Dichloroethylene (CAS No. 156-60-5) Administered in Microcapsules in Feed to F344/N Rats and B6C3F1 Mice." NIH Publication No. 02-4410, NTP TOX-55, 114p., April.

National Toxicology Program (NTP). 2005. "Benzene (CAS No. 71-43-2)." In "Report on Carcinogens (Eleventh Edition)." US Dept. of Health and Human Services, Public Health Service, National Toxicology Program. 2p. Accessed at http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932.

National Toxicology Program (NTP). 2006. "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP)." 218p., October.

National Toxicology Program (NTP). 2007. "NTP Report on the Toxicology and Carcinogenesis Study of Benzene (CAS No. 71-43-2) in Genetically Modified Haploinsufficient p16Ink4a/p19Arf Mice (Gavage Study)." NIH Publication No. 08-4425, NTP GMM 8. 82p., October.

National Toxicology Program (NTP). 2015. "Report on Carcinogens Monograph on Trichloroethylene (Final)." RoC Monograph 05. 359p. Accessed at https://ntp.niehs.nih.gov/ntp/roc/monographs/finaltce_508.pdf.

National Toxicology Program (NTP). 2019. "Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration." Office of Health Assessment and Translation (OHAT). 101p. Accessed at https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookmarch2019_508.pdf.

National Toxicology Program (NTP). 2021a. "Trichloroethylene (CAS No. 79-01-6)." In "Report on Carcinogens (15th Edition)." US Dept. of Health and Human Services, Public Health Service, National Toxicology Program, 8p.

National Toxicology Program (NTP). 2021b. "Tetrachloroethylene (CAS No. 127-18-4)." In "Report on Carcinogens (15th Edition)." US Dept. of Health and Human Services, Public Health Service, National Toxicology Program. 3p.

National Toxicology Program (NTP). 2021c. "Benzene (CAS No. 71-43-2)." In "Report on Carcinogens (15th Edition)." US Dept. of Health and Human Services, Public Health Service, National Toxicology Program, 3p.

National Toxicology Program (NTP). 2021d. "Vinyl Halides (Selected)." In "Report on Carcinogens (15th Edition)." US Dept. of Health and Human Services, Public Health Service, National Toxicology Program, 6p.

National Toxicology Program (NTP). 2023. "Report on Carcinogens process & listing criteria." March 7. Accessed at https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria.

Nilsson, RI; Nordlinder, R; Horte, LG; Jarvholm, B. 1998. "Leukaemia, lymphoma, and multiple myeloma in seamen on tankers." *Occup. Environ. Med*. 55(8):517-521. Accessed at http://oem.bmjjournals.com/cgi/reprint/55/8/517.

North, CM; Rooseboom, M; Kocabas, NA; Schnatter, AR; Faulhammer, F; Williams, SD. 2020. "Modes of action considerations in threshold expectations for health effects of benzene." *Toxicol. Lett*. 334:78-86. doi: 10.1016/j.toxlet.2020.09.005.

Organisation for Economic Co-operation and Development (OECD). 2018. "OECD Guideline for the Testing of Chemicals: Carcinogenicity Studies." OECD/OCDE 451, 15p., June 25.

Organisation for Economic Co-operation and Development (OECD). 2024. "OECD Test Guidelines Programme." Accessed at https://www.oecd.org/chemicalsafety/testing/oecd-guidelines-testing-chemicals-related-documents.htm.

Ott, MG; Townsend, JC; Fishbeck, WA; Langner, RA. 1978. "Mortality among individuals occupationally exposed to benzene." *Arch. Environ. Health* 33(1):3-10.

Paci, E; Buiatti, E; Seniori Costantini, AS; Miligi, L; Pucci, N; Scarpelli, A; Petrioli, G; Simonato, L; Winkelmann, R; Kaldor, JM. 1989. "Aplastic anemia, leukemia and other cancer mortality in a cohort of shoe workers exposed to benzene." *Scand. J. Work Environ. Health* 15(5):313-318.

Paneth, N; Susser, E; Susser, M. 2002. "Origins and early development of the case-control study: Part 1, early evolution." *Soz. Praventivmed.* 47(5):282-288.

Paxton, MB; Chinchilli, VM; Brett, SM; Rodricks, JV. 1994a. "Leukemia risk associated with benzene exposure in the pliofilm cohort: I. Mortality update and exposure distribution." *Risk Anal*. 13(2):147-154.

Paxton, MB; Chinchilli, VM; Brett, SM; Rodricks, JV. 1994b. "Leukemia risk associated with benzene exposure in the pliofilm cohort: II. Risk estimates." *Risk Anal*. 14(2):155-161.

Percie du Sert, N; Ahluwalia, A; Alam, S; Avey, MT; Baker, M; Browne, WJ; Clark, A; Cuthill, IC; Dirnagl, U; Emerson, M; Garner, P; Holgate, ST; Howells, DW; Hurst, V; Karp, NA; Lazic, SE; Lidster, K; MacCallum, CJ; Macleod, M; Pearl, EJ; Petersen, OH; Rawle, F; *et al*. 2020. "Reporting animal research: Explanation and elaboration for the ARRIVE guidelines 2.0." *PLoS Biol*. 18(7):e3000411. doi: 10.1371/journal.pbio.3000411.

Perkins, NJ; Cole, SR; Harel, O; Tchetgen Tchetgen, EJ; Sun, B; Mitchell, EM; Schisterman, EF. 2018. "Principled approaches to missing data in epidemiologic studies." *Am. J. Epidemiol.* 187(3):568-575. doi: 10.1093/aje/kwx348.

Pesch, B; Haerting, J; Ranft, U; Klimpel, A; Oelschlagel, B; Schill, W. 2000. "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.* 29(2):238-247.

Phillips, RV; Rieswijk, L; Hubbard, AE; Vermeulen, R; Zhang, J; Hu, W; Li, L; Bassig, BA; Wong, JYY; Reiss, B; Huang, Y; Wen, C; Purdue, M; Tang, X; Zhang, L; Smith, MT; Rothman, N; Lan, Q. 2019. "Human exposure to trichloroethylene is associated with increased variability of blood DNA methylation that is enriched in genes and pathways related to autoimmune disease and cancer." *Epigenetics* 14(11):1112-1124. doi: 10.1080/15592294.2019.1633866.

Pippard, EC; Acheson, ED. 1985. "The mortality of boot and shoe makers, with special reference to cancer." *Scand. J. Work Environ. Health* 11(4):249-255. doi: 10.5271/sjweh.2223.

Porta, M, ed. 2014. *A Dictionary of Epidemiology (Sixth Edition)*. Oxford University Press, New York, NY, 343p.

Poynter, JN; Richardson, M; Roesler, M; Blair, CK; Hirsch, B; Nguyen, P; Cioc, A; Cerhan, JR; Warlick, E. 2017. "Chemical exposures and risk of acute myeloid leukemia and myelodysplastic syndromes in a population-based study." *Int. J. Cancer* 140(1):23-33. doi: 10.1002/ijc.30420.

Pukkala, E. 1998. "Cancer incidence among Finnish oil refinery workers, 1971-1994." *J. Occup. Environ. Med*. 40(8):675-679.

Pukkala, E; Martinsen, JI; Lynge, E; Gunnarsdottir, H; Sparen, P; Tryggvadottir, L; Weiderpass, E; Kjaerheim, K. [Finnish Cancer Registry, Nordic Occupational Cancer Study (NOCCA)]. 2008. "Occupation and cancer - follow-up of 15 million people in five Nordic countries. Appendix: Result tables by occupation." 113p.

Pukkala, E; Martinsen, JI; Lynge, E; Gunnarsdottir, HK; Sparen, P; Tryggvadottir, L; Weiderpass, E; Kjaerheim, K. 2009. "Occupation and cancer - Follow-up of 15 million people in five Nordic countries." *Acta Oncol.* 48(5):646-790.

Raabe, GK; Wong, O. 1996. "Leukemia mortality by cell type in petroleum workers with potential exposure to benzene." *Environ. Health Perspect*. 104(Suppl. 6):1381-1391.

Raaschou-Nielsen, O; Hansen, J; McLaughlin, JK; Kolstad, H; Christensen, JM; Tarone, RE; Olsen, JH. 2003. "Cancer risk among workers at Danish companies using trichloroethylene: A cohort study." *Am. J. Epidemiol.* 158(12):1182-1192.

Radican, L; Blair, A; Stewart, P; Wartenberg, D. 2008. "Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: Extended follow-up." *J. Occup. Environ. Med.* 50(11):1306-1319. doi: 10.1097/JOM.0b013e3181845f7f.

Rhomberg, LR; Bailey, LA; Goodman, JE; Hamade, A; Mayfield, D. 2011. "Is exposure to formaldehyde in air causally associated with leukemia? - A hypothesis-based weight-of-evidence analysis." *Crit. Rev. Toxicol.* 41(7):555-621. doi: 10.3109/10408444.2011.560140.

Rhomberg, LR; Goodman, JE; Tao, G; Zu, K; Chandalia, J; Williams, PRD; Allen, B. 2016. "Evaluation of acute nonlymphocytic leukemia and its subtypes with updated benzene exposure and mortality estimates: A lifetable analysis of the Pliofilm cohort." *J. Occup. Environ. Med*. 58(4):414-420. doi: 10.1097/JOM.0000000000000689.

Richardson, S; Zittoun, R; Bastuji-Garin, S; Lasserre, V; Guihenneuc, C; Cadiou, M; Viguie, F; Laffont-Faust, I. 1992. "Occupational risk factors for acute leukaemia: A case-control study." *Int. J. Epidemiol*. 21(6):1063-1073.

Rinsky, RA; Hornung, RW; Silver, SR; Tseng, CY. 2002. "Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment." *Am. J. Ind. Med*. 42(6):474-480. doi: 10.1002/ajim.10138.

Rinsky, RA; Smith, AB; Hornung, R; Filloon, TG; Young, RJ; Okun, AH; Landrigan, PJ. 1987. "Benzene and leukemia: An epidemiologic risk assessment." *N. Engl. J. Med*. 316:1044-1050.

Rinsky, RA; Young, RJ; Smith, AB. 1981. "Leukemia in benzene workers." *Am. J. Ind. Med*. 2(3):217-245. doi: 10.1002/ajim.4700020305.

Rosenfeld, PE; Spaeth, KR; McCarthy, SJ; Winter, SC; Wilson, MS; Hagemann, M. 2024a. "Camp Lejeune Marine cancer risk assessment for exposure to contaminated drinking water from 1955 to 1987." *Water Air Soil Pollut*. 235(2):124. doi: 10.1007/s11270-023-06863-y.

Rosenfeld, PE; Spaeth, KR; McCarthy, SJ; Winter, SC; Wilson, MS; Hagemann, M. 2024b. "Data set for Camp Lejeune Marine cancer risk assessment for exposure to contaminated drinking water from 1955 to 1987." [CLJA_RosenfeldSubpoena_0000000001]

Rosenfeld, PE; Spaeth, KR; McCarthy, SJ; Winter, SC; Wilson, MS; Hagemann, M. Undated. "Camp Lejeune Marine cancer risk assessment for exposure to contaminated drinking water from 1955 to 1987 (Preprint)."

Ruckart, PZ; Bove, FJ; Maslia, M. 2013. "Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: A case-control study." *Environ. Health* 12:104. doi: 10.1186/1476-069X-12-104.

Ruder, AM; Ward, EM; Brown, DP. 1994. "Cancer mortality in female and male dry-cleaning workers." *J. Occup. Med.* 36(8):867-874.

Ruder, AM; Ward, EM; Brown, DP. 2001. "Mortality in dry-cleaning workers: An update." *Am. J. Ind. Med.* 39(2):121-132.

Rushton, L; Alderson, MR. 1981. "A case-control study to investigate the association between exposure to benzene and deaths from leukaemia in oil refinery workers." *Br. J. Cancer* 43(1):77-84.

Rushton, L; Romaniuk, H. 1997. "A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom." *Occup. Environ. Med*. 54(3):152-166. doi: 10.1136/oem.54.3.152.

Rushton, L; Schnatter, AR; Tang, G; Glass, DC. 2014. "Acute myeloid and chronic lymphoid leukaemias and exposure to low-level benzene among petroleum workers." *Br. J. Cancer* 110(3):783-787.

Rusyn, I; Chiu, WA; Lash, LH; Kromhout, H; Hansen, J; Guyton, KZ. 2014. "Trichloroethylene: Mechanistic, epidemiologic and other supporting evidence of carcinogenic hazard." *Pharmacol. Ther*. 141(1):55-68. doi: 10.1016/j.pharmthera.2013.08.004.

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

Saberi Hosnijeh, F; Christopher, Y; Peeters, P; Romieu, I; Xun, W; Riboli, E; Raaschou-Nielsen, O; Tjønneland, A; Becker, N; Nieters, A; Trichopoulou, A; Bamia, C; Orfanos, P; Oddone, E; Luján-Barroso, L; Dorronsoro, M; Navarro, C; Barricarte, A; Molina-Montes, E; Wareham, N; Vineis, P; Vermeulen, R. 2013. "Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC)." *Occup. Environ. Med*. 70(7):464-470.

Sackett, DL. 1979. "Bias in analytic research." *J. Chronic Dis.* 32(1-2):51-63. doi: 10.1016/0021-9681(79)90012-2.

Savitz, DA. [Brown University]. 2024. "Deposition and exhibits of David A. Savitz, Ph.D. [re: Camp Lejeune Water Litigation *vs*. United States]." Submitted to US District Court, Eastern District of North Carolina, Southern Division. Case No. 7:23-cv-897. 294p., June 10, July 17.

Savitz, DA; Andrews, KW. 1997. "Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers." *Am. J. Ind. Med*. 31:287-295.

Savitz, DA; Wellenius, GA; Trikalinos, TA. 2019. "The problem with mechanistic risk of bias assessments in evidence synthesis of observational studies and a practical alternative: Assessing the impact of specific sources of potential bias." *Am. J. Epidemiol.* 188(9):1581-1585. doi: 10.1093/aje/kwz131.

Savitz, DA; Wise, LA; Bond, JC; Hatch, EE; Ncube, CN; Wesselink, AK; Willis, MD; Yland, JJ; Rothman, KJ. 2024. "Responding to reviewers and editors about statistical significance testing (Editorial)." *Ann. Intern. Med*. 177(3):385-386. doi: 10.7326/M23-2430.

Schnatter, AR; Armstrong, TW; Nicolich, MJ; Thompson, FS; Katz, AM; Huebner, WW; Pearlman, ED. 1996a. "Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers." *Occup. Environ. Med*. 53(11):773-781.

Schnatter, AR; Armstrong, TW; Thompson, LS; Nicolich, MJ; Katz, AM; Huebner, WW; Pearlman, ED. 1996b. "The relationship between low-level benzene exposure and leukemia in Canadian petroleum distribution workers." *Environ. Health Perspect*. 104(6):1375-1379.

Schnatter, AR; Glass, DC; Tang, G; Irons, RD; Rushton, L. 2012. " Myelodysplastic syndrome and benzene exposure among petroleum workers: an international pooled analysis." *J. Natl. Cancer Inst.* 104(22):1724-1737. doi: 10.1093/jnci/djs411.

Schnatter, AR; Katz, AM; Nicolich, MJ; Theriault, G. 1993. "A retrospective mortality study among Canadian petroleum marketing and distribution workers." *Environ. Health Perspect*. 101(Suppl. 6):85-99.

Schnatter, AR; Theriault, G; Katz, AM; Thompson, FS; Donaleski, D; Murray, N. 1992. "A retrospective mortality study within operating segments of a petroleum company." *Am. J. Ind. Med*. 22:209-229.

Schoenberg, JB; Stemhagen, A; Mogielnicki, AP; Altman, R; Abe, T; Mason, TJ. 1984. "Case-control study of bladder cancer in New Jersey. I. Occupational exposure in white males." *J. Natl. Cancer Inst.* 72:973-981.

Seidler, A; Mohner, M; Berger, J; Mester, B; Deeg, E; Elsner, G; Nieters, A; Becker, N. 2007. "Solvent exposure and malignant lymphoma: a population-based case-control study in Germany." *J. Occup. Med. Toxicol*. 2:2.

Seldén, AI; Ahlborg, G Jr. 2011. "Cancer morbidity in Swedish dry-cleaners and laundry workers: Historically prospective cohort study." *Int. Arch. Occup. Environ. Health* 84(4):435-443.

Shallenberger, LG; Acquavella, JF; Donaleski, D. 1992. "An updated mortality study of workers in three major United States refineries and chemical plants." *Br. J. Ind. Med*. 49:345-354.

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

Shu, XO; Stewart, P; Wen, WQ; Han, D; Potter, JD; Buckley, JD; Heineman, E; Robison, LL. 1999. "Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring." *Cancer Epidemiol. Biomarkers Prev*. 8(9):783-791.

Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ. 2014. "Retrospective cohort study of a microelectronics and business machine facility." *Am. J. Ind. Med.* 57(4):412-424. doi: 10.1002/ajim.22288.

Silver, SR; Rinsky, RA; Cooper, SP; Hornung, RW; Lai, D. 2002. "Effect of follow-up time on risk estimates: A longitudinal examination of the relative risks of leukemia and multiple myeloma in a rubber hydrochloride cohort." *Am. J. Ind. Med*. 42(6):481-489.

Simonato, L; L'Abbe, KA; Andersen, A; Belli, S; Comba, P; Engholm, G; Ferro, G; Hagmar, L; Langard, S; Lundberg, I; Pirastu, R; Thomas, P; Winkelmann, MA; Saracci, R. 1991. "A collaborative study of cancer incidence and mortality among vinyl chloride workers." *Scand. J. Work Environ. Health* 17(3):159-169.

Smith, DD. 2001. "Re: 'Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden' (Letter)." *Am. J. Epidemiol.* 153(10):1028-1029. doi: 10.1093/aje/153.10.1028.

Smith, EM; Miller, ER; Woolson, RF; Brown, CK. 1985. "Bladder cancer risk among laundry workers, dry cleaners, and others in chemically related occupations." *J. Occup. Med.* 27(4):295-297.

Smulevich, VB; Fedotova, IV; Filatova, VS. 1988. "Increasing evidence of the rise of cancer in workers exposed to vinylchloride." *Br. J. Ind. Med.* 45:93-97.

Snyder, CA; Goldstein, BD; Sellakumar, A; Wolman, SR; Bromberg, I; Erlichman, MN; Laskin, S. 1978. "Hematotoxicity of inhaled benzene to Sprague-Dawley rats and AKR mice at 300 ppm." *J. Toxicol. Environ. Health* 4(4):605-618. doi: 10.1080/15287397809529683.

Snyder, CA; Goldstein, BD; Sellakumar, AR; Albert, RE. 1984. "Evidence for hematotoxicity and tumorigenesis in rats exposed to 100 ppm benzene." *Am. J. Ind. Med*. 5(6):429-434. doi: 10.1002/ajim.4700050603.

Snyder, CA; Goldstein, BD; Sellakumar, AR; Bromberg, I; Laskin, S; Albert, RE. 1980. "The inhalation toxicology of benzene: Incidence of hematopoietic neoplasms and hematotoxicity in ARK/J and C57BL/6J mice." *Toxicol. Appl. Pharmacol.* 54(2):323-331. doi: 10.1016/0041-008x(80)90202-1.

Snyder, CA; Sellakumar, AR; James, DJ; Albert, RE. 1988. "The carcinogenicity of discontinuous inhaled benzene exposures in CD-1 and C57Bl/6 mice." *Arch. Toxicol.* 62(5):331-335. doi: 10.1007/BF00293618.

Sorahan, T; Kinlen, LJ; Doll, R. 2005. "Cancer risks in a historical UK cohort of benzene exposed workers." *Occup. Environ. Med.* 62:231-236.

Sorahan, T; Mohammed, N. 2016. "Incidence of myelodysplastic syndrome in UK petroleum distribution and oil refinery workers, 1995-2011." *Int. J. Environ. Res. Public Health* 13(5):474. doi: 10.3390/ijerph13050474.

Spiliotopoulos, A. [S.S. Papadopulos & Associates, Inc.]. 2024. "Expert Report of Alexandros Spiliotopoulos, PhD, In the United States District Court for the Eastern District of North Carolina, No. 7:23-cv-897, In Re: Camp Lejeune Water Litigation." Report to US Dept. of Justice (US DOJ). 138p., December 9.

Spirtas, R; Stewart, PA; Lee, JS; Marano, DE; Forbes, CD; Grauman, DJ; Pettigrew, HM; Blair, A; Hoover, RN; Cohen, JL. 1991. "Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results." *Br. J. Ind. Med.* 48:515-530.

Stang, A; Rothman, KJ. 2011. "That confounded P-value revisited (Letter)." *J. Clin. Epidemiol*. 64(9):1047-1048. doi: 10.1016/j.jclinepi.2011.03.004.

StatsDirect Ltd. 2020. "P values." Accessed at https://www.statsdirect.com/help/basics/p_values.htm.

Stenehjem, JS; Kjaerheim, K; Bratveit, M; Samuelsen, SO; Barone-Adesi, F; Rothman, N; Lan, Q; Grimsrud, TK; UK Inflammatory Breast Cancer Working Group. 2015. "Benzene exposure and risk of lymphohaematopoietic cancers in 25 000 offshore oil industry workers." *Br. J. Cancer* 112(9):1603-1612. doi: 10.1038/bjc.2015.108.

Stoner, GD; Conran, PB; Greisiger, EA; Stober, J; Morgan, M; Pereira, MA. 1986. "Comparison of two routes of chemical administration on the lung adenoma response in strain A/J mice." *Toxicol. Appl. Pharmacol.* 82(1):19-31. doi: 10.1016/0041-008x(86)90433-3.

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

Tabershaw, IR; Gaffey, WR. 1974. "Mortality study of workers in the manufacture of vinyl chloride and its polymers." *J. Occup. Med*. 16(8):509-518.

Talibov, M; Lehtinen-Jacks, S; Martinsen, JI; Kjærheim, K; Lynge, E; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kauppinen, T; Kyyrönen, P; Pukkala, E. 2014. "Occupational exposure to solvents and acute myeloid leukemia: A population-based, case-control study in four Nordic countries." *Scand. J. Work Environ. Health* 40(5):511-517. doi: 10.5271/sjweh.3436.

Teschke, K; Morgan, MS; Checkoway, H; Franklin, G; Spinelli, JJ; van Belle, G; Weiss, NS. 1997. "Surveillance of nasal and bladder cancer to locate sources of exposure to occupational carcinogens." *Occup. Environ. Med.* 54(6):443-451. doi: 10.1136/oem.54.6.443.

Thériault, G; Allard, P. 1981. "Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer." *J. Occup. Med.* 23(10):671-676.

Thomas, J; Haseman, JK; Goodman, JI; Ward, JM; Loughran, TP Jr.; Spencer, PJ. 2007. "A review of large granular lymphocytic leukemia in Fischer 344 rats as an initial step toward evaluating the implication of the endpoint to human cancer risk assessment." *Toxicol. Sci.* 99(1):3-19. doi: 10.1093/toxsci/kfm098.

Tomasetti, C; Vogelstein, B. 2015. "Cancer etiology: Variation in cancer risk among tissues can be explained by the number of stem cell divisions." *Science* 347(6217):78-81.

Travier, N; Gridley, G; De Roos, AJ; Plato, N; Moradi, T; Boffetta, P. 2002. "Cancer incidence of dry cleaning, laundry and ironing workers in Sweden." *Scand. J. Work Environ. Health* 28(5):341-348.

Triebig, G. 2010. "Implications of latency period between benzene exposure and development of leukemia—A synopsis of literature." *Chem. Biol. Interact*. 184(1-2):26-29. doi: 10.1016/j.cbi.2009.12.014.

Tsai, SP; Ahmed, FS; Wendt, JK; Foster, DE; Donnelly, RP; Strawmyer, TR. 2007. "A 56-year mortality follow-up of Texas petroleum refinery and chemical employees, 1948-2003." *J. Occup. Environ. Med*. 49:557-567.

Tsai, SP; Gilstrap, EL; Cowles, SR; Snyder, PJ; Ross, CE. 1993. "A cohort mortality study of two California refinery and petrochemical plants." *J. Occup. Med*. 35(4):415-421.

Tsai, SP; Wendt, JK; Cardarelli, KM; Fraser, AE. 2003. "A mortality and morbidity study of refinery and petrochemical employees in Louisiana." *Occup. Environ. Med*. 60:627-633.

US EPA. 1986. "Guidelines for carcinogen risk assessment." *Fed. Reg.* 51(185):33992(12).

US EPA. 1989. "Risk Assessment Guidance for Superfund (RAGS). Volume I: Human Health Evaluation Manual (Part A) (Interim final)." Office of Emergency and Remedial Response, NTIS PB90-155581, EPA-540/1-89-002, 287p., December.

US EPA. 1998. "Carcinogenic Effects of Benzene: An Update." National Center for Environmental Assessment (NCEA). EPA/600/P-97/001F. 57p., April.

US EPA. 2000a. "Toxicological Review of Vinyl Chloride (CAS No. 75-01-4)." EPA/635/R-00/004. 197p., May.

US EPA. 2000b. "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures." Risk Assessment Forum, EPA/630/R-00/002. 209p., August.

US EPA. 2003. "IRIS Chemical Assessment Summary for Benzene (CAS No. 71-43-2)." 43p., April 17. Accessed at https://www.epa.gov/iris.

US EPA. 2004. "An Examination of EPA Risk Assessment Principles and Practices." Office of the Science Advisor, Risk Assessment Task Force, EPA/100/B-04/001, 193p.

US EPA. 2005. "Guidelines for Carcinogen Risk Assessment." Risk Assessment Forum. EPA/630/P-03/001F, 166p., March.

US EPA. 2007. "Considerations for Developing a Dosimetry-Based Cumulative Risk Assessment Approach for Mixtures of Environmental Contaminants." National Center for Environmental Assessment (NCEA), EPA/600/R-07/064, 77p., September.

US EPA. 2011. "Toxicological Review of Trichloroethylene (CAS No. 79-01-6) in Support of Summary Information on the Integrated Risk Information System (IRIS) (Final)." EPA/635/R-09/011F, 2469p., September.

US EPA. 2012. "Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in Support of Summary Information on the Integrated Risk Information System (IRIS) (Final)." EPA/635/R-08/011F, 1077p., February.

US EPA. 2019. "Technical Memorandum to E. Craig and M. Mannix re: Pyrethroids: Tier II Epidemiology Report." Office of Chemical Safety and Pollution Prevention, Health Effects Division, 134p., April 30. Accessed at https://www.epa.gov/sites/default/files/2019-08/documents/tier-ii-epidemiology-report.pdf.

US EPA. 2020a. "Final Scope of the Risk Evaluation for *trans*-1,2-Dichloroethylene (CASRN 156-60-5)." Office of Chemical Safety and Pollution Prevention (OCSPP), Submitted to US EPA Docket. EPA-740-R-20-007, EPA-HQ-OPPT-2018-0465-0042, 132p., August.

US EPA. 2020b. "Risk Evaluation for Trichloroethylene (CASRN: 79-01-6) (Final)." Office of Chemical Safety and Pollution Prevention. EPA Document # 740R18008. 803p.

US EPA. 2020c. "Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro-) (CASRN: 127-18-4) (Final)." Office of Chemical Safety and Pollution Prevention. EPA Document # 740-R1-8011. 714p.

US EPA. 2022. "ORD Staff Handbook for Developing IRIS Assessments." Office of Research and Development (ORD), Center for Public Health and Environmental Assessment (CPHEA), EPA/600/R-22/268, 243p., December.

US Public Health Service (US PHS). 2004. "The Health Consequences of Smoking: A Report of the Surgeon General." Office of the Surgeon General.

Van Smeden, M; Lash, TL; Groenwold, RHH. 2020. "Reflection on modern methods: Five myths about measurement error in epidemiological research." *Int. J. Epidemiol.* 49(1):338-347. doi: 10.1093/ije/dyz251.

Vlaanderen, J; Lan, Q; Kromhout, H; Rothman, N; Vermeulen, R. 2011. "Occupational benzene exposure and the risk of lymphoma subtypes: A meta-analysis of cohort studies incorporating three study quality dimensions." *Environ. Health Perspect.* 119(2):159-167.

Vlaanderen, J; Lan, Q; Kromhout, H; Rothman, N; Vermeulen, R. 2012. "Occupational benzene exposure and the risk of chronic myeloid leukemia: A meta-analysis of cohort studies incorporating study quality dimensions." *Am. J. Ind. Med.* 55(9):779-785. doi: 10.1002/ajim.22087.

Ward, AC. 2009. "The role of causal criteria in causal inferences: Bradford Hill's 'Aspects of Association.'" *Epidemiol. Perspect. Innov.* 6:2.

Ward, CO; Kuna, RA; Snyder, NK; Alsaker, RD; Coate, WB; Craig, PH. 1985. "Subchronic inhalation toxicity of benzene in rats and mice." *Am. J. Ind. Med.* 7(5-6):457-473. doi: 10.1002/ajim.4700070510.

Ward, E; Boffetta, P; Andersen, A; Colin, D; Comba, P; Deddens, JA; De Santis, M; Engholm, G; Hagmar, L; Langard, S; Lundberg, I; McElvenny, D; Pirastu, R; Sali, D; Simonato, L. 2001. "Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry." *Epidemiology* 12(6):710-718.

Wartenberg, D; Reyner, D; Scott, CS. 2000. "Trichloroethylene and cancer: Epidemiologic evidence." *Environ. Health Perspect.* 108(Suppl. 2):161-176. doi: 10.1289/ehp.00108s2161.

Waspe, J; Bui, T; Dishaw, L; Kraft, A; Luke, A; Beronius, A. 2021. "Evaluating reliability and risk of bias of *in vivo* animal data for risk assessment of chemicals – Exploring the use of the SciRAP tool in a systematic review context." *Environ. Int.* 146:106103. doi: 10.1016/j.envint.2020.106103.

Webster, TF. 2007. "Bias magnification in ecologic studies: A methodological investigation." *Environ. Health* 6:17. Accessed at http://www.ehjournal.net/content/6/1/17.

Weisenburger, DD. 1992. "Pathological classification of non-Hodgkin's lymphoma for epidemiological studies." *Cancer Res.* 52(19 Suppl.):5456S-5464s.

Weiss, W. 1997. "Cigarette smoking and lung cancer trends. A light at the end of the tunnel?" *Chest* 111(5):1414-1416. doi: 10.1378/chest.111.5.1414.

Whiteman, DC; Wilson, LF. 2016. "The fractions of cancer attributable to modifiable factors: A global review." *Cancer Epidemiol.* 44:203-221. doi: 10.1016/j.canep.2016.06.013.

Wilcosky, TC; Checkoway, H; Marshall, EG; Tyroler, HA. 1984. "Cancer mortality and solvent exposures in the rubber industry." *Am. Ind. Hyg. Assoc. J.* 45(12):809-811.

Williams, PRD; Paustenbach, DJ. 2003. "Reconstruction of benzene exposure for the pliofilm cohort (1936-1976) using Monte Carlo techniques." *J. Toxicol. Environ. Health* A 66(8):677-781.

Wolf, DC; Cohen, SM; Boobis, AR; Dellarco, VL; Fenner-Crisp, PA; Moretto, A; Pastoor, TP; Schoeny, RS; Seed, JG; Doe, JE. 2019. "Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge." *Regul. Toxicol. Pharmacol.* 103:86-92. doi: 10.1016/j.yrtph.2019.01.021.

Wong, O. 1987a. "An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results." *Br. J. Ind. Med.* 44:365-381.

Wong, O. 1987b. "An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose response analyses." *Br. J. Ind. Med*. 44:382-395.

Wong, O. 1995. "Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene." *Occup. Environ. Med.* 52(6):380-384.

Wong, O; Harris, F; Armstrong, TW; Hua, F. 2010. "A hospital-based case-control study of acute myeloid leukemia in Shanghai: Analysis of environmental and occupational risk factors by subtypes of the WHO classification." *Chem. Biol. Interact*. 184(1-2):112-128.

Wong, O; Harris, F; Rosamilia, K; Raabe, GK. 2001a. "Updated mortality study of workers at a petroleum refinery in Torrance, California, 1959 to 1997." *J. Occup. Environ. Med*. 43(12):1089-1102.

Wong, O; Harris, F; Rosamilia, K; Raabe, GK. 2001b. "An updated mortality study of workers at a petroleum refinery in Beaumont, Texas, 1945 to 1996." *J. Occup. Environ. Med*. 43(4):384-401.

Wong, O; Harris, F; Smith, TJ. 1993. "Health effects of gasoline exposure. II. Mortality patterns of distribution workers in the United States." *Environ. Health Perspect.* 101(Suppl. 6):63-76.

Wong, O; Morgan, RW; Bailey, WJ; Swencicki, RE; Claxton, K; Kheifets, L. 1986. "An epidemiological study of petroleum refinery employees." *Br. J. Ind. Med*. 43:6-17.

Wong, O; Whorton, D; Follart, DE; Ragland, D. 1991. "An industry-wide epidemiologic study of vinyl chloride workers, 1942-1982." *Am. J. Ind. Med*. 20:317-334.

Wongsrichanalai, C; Delzell, E; Cole, P. 1989. "Mortality from leukemia and other diseases among workers at a petroleum refinery." *J. Occup. Med*. 31(2):106-111.

World Health Organization (WHO). 2018. "Cancer." Accessed at https://www.who.int/news-room/fact-sheets/detail/cancer.

World Health Organization, Special Programme for Research and Training in Tropical Diseases (WHO TDR). 2009. "Handbook: Good Laboratory Practice (GLP): Quality Practices for Regulated Non-Clinical Research and Development (Second Edition)." Report to United Nations Children's Fund (UNICEF); United Nations Development Programme (UNDP); World Bank. 328p.

Wu, S; Powers, S; Zhu, W; Hannun, YA. 2016. "Substantial contribution of extrinsic risk factors to cancer development." *Nature* 529(7584):43-47. doi: 10.1038/nature16166.

Yarosh, R; Roesler, MA; Murray, T; Cioc, A; Hirsch, B; Nguyen, P; Warlick, E; Poynter, JN. 2021. "Risk factors for de novo and therapy-related myelodysplastic syndromes (MDS)." *Cancer Causes Control* 32(3):241-250. doi: 10.1007/s10552-020-01378-x.

Yin, SN; Hayes, RB; Linet, MS; Li, GL; Dosemeci, M; Travis, LB; Li, CY; Zhang, ZN; Lig, DG; Chow, WH; Wacholder, S; Wang, YZ; Jiang, ZL; Dai, TR; Zhang, WY; Chao, XJ; Ye, PZ; Kou, QR; Zhang, XC; Lin, XF; Meng, JF; Ding, CY; Zho, JS; Blot, WJ. 1996a. "A cohort study of cancer among benzene-exposed workers in China: Overall results." *Am. J. Ind. Med*. 29(3):227-235.

Yin, SN; Hayes, RB; Linet, MS; Li, GL; Dosemeci, M; Travis, LB; Zhang, ZN; Li, DG; Chow, WH; Wacholder, S; Blot, WJ. 1996b. "An expanded cohort study of cancer among benzene-exposed workers in China." *Environ. Health Perspect.* 104(Suppl. 6):1339-1341.

Zhao, Y; Krishnadasan, A; Kennedy, N; Morgenstern, H; Ritz, B. 2005. "Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers." *Am. J. Ind. Med.* 48(4):249-258. doi: 10.1002/ajim.20216.

Zhu, L; Jia, X; Xie, H; Zhang, J; Zhu, Q. 2024. "Trichloroethylene exposure, multi-organ injury, and potential mechanisms: A narrative review." *Sci. Total Environ.* 946:174029. doi: 10.1016/j.scitotenv.2024.174029.

Attachment A

Literature Search Methods

A.1 Trichloroethylene and Leukemia

A.1.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated trichloroethylene (TCE) and leukemia for various purposes (US EPA, 2011, 2020b; ATSDR, 2017a, 2019b; NTP, 2021a; IARC, 2014a). I then conducted literature searches using PubMed and Scopus for studies published after agency literature searches were completed. For TCE and leukemia, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published from January 1, 2016-May 23, 2023.

I conducted weekly searches of PubMed and Scopus using the search terms "Trichloroethylene OR Ethinyl Trichloride OR Trichloroethene OR Trilene OR Trielina" to identify any relevant papers published after the last date of my search through the end of 2023.

A.1.2 PubMed Search Terms

A.1.2.1 Epidemiology

((("Trichloroethylene"[Mesh] OR trichloroethylene[tiab] OR TCE[ti] OR "1,1-Dichloro-2-chloroethylene"[tiab] OR "1-Chloro-2,2-dichloroethylene"[tiab] OR 79-01- 6[rn] OR Anamenth[tiab] OR Benzinol[tiab] OR Blacosolv[tiab] OR Cecolene[tiab] OR Chlorilen[tiab] OR Chlorylea[tiab] OR Circosolv[tiab] OR Crawhaspol[tiab] OR Densinfluat[tiab] OR "Dow-Tri"[tiab] OR Dukeron[tiab] OR "Ethene trichloro"[tiab] OR Ethinyl-trichloride[tiab] OR (Ethylene[tiab] AND trichloro[tiab]) OR Ethylene-trichloride[tiab] OR "Fleck-Flip"[tiab] OR Fluate[tiab] OR Lanadin[tiab] OR Lethurin[tiab] OR Narcogen[tiab] OR Narkosoid[tiab] OR Nialk[tiab] OR Petzinol[tiab] OR TCE[ti] OR Triasol[tiab] OR Trichlorethene[tiab] OR Trichloroethene[tiab] OR Trichloroethylene[MeSH] OR Trichloroethylene[tiab] OR Trike[tiab] OR Trilene[tiab] OR "Tri-Plus"[tiab] OR TTE[ti] OR Vestrol[tiab] OR Vitran[tiab] OR Trichlororan[tiab]) AND ("Humans"[Mesh] OR human[Title/Abstract] OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR "Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Case-Control"[tiab:~0] OR "Retrospective Study"[tiab:~0] OR "Retrospective Studies"[tiab:~0] OR "Longitudinal Study"[tiab:~0] OR "Longitudinal Studies"[tiab:~0] OR "Cross-Sectional"[tiab:~0] OR "observational study"[tiab:~0] OR "observational studies"[tiab:~0] OR "observational study"[tiab:~0] OR "observational studies"[tiab:~0] OR "epidemiology" [Subheading] OR "Child"[Mesh] OR "Adult Children"[Mesh] OR "Infant"[Mesh] OR "Men"[Mesh] OR "Women"[Mesh] OR "Female"[Mesh] OR "Adult"[Mesh] OR "Young Adult"[Mesh] OR "Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Population Groups"[Mesh] OR "Persons"[Mesh] OR "Occupational Groups"[Mesh] OR "Prospective Studies"[Mesh]) AND ("Leukemia"[Mesh] OR leukemia[Title/Abstract])))

A.1.2.2 Animal Carcinogenicity and Mode of Action Search Terms

((("Trichloroethylene"[Mesh] OR trichloroethylene[tiab] OR TCE[ti] OR "1,1-Dichloro-2-chloroethylene"[tiab] OR "1-Chloro-2,2-dichloroethylene"[tiab] OR 79-01- 6[rn] OR Anamenth[tiab] OR Benzinol[tiab] OR Blacosolv[tiab] OR Cecolene[tiab] OR Chlorilen[tiab] OR Chlorylea[tiab] OR

Circosolv[tiab] OR Crawhaspol[tiab] OR Densinfluat[tiab] OR "Dow-Tri"[tiab] OR Dukeron[tiab] OR "Ethene trichloro"[tiab] OR Ethinyl-trichloride[tiab] OR (Ethylene[tiab] AND trichloro[tiab]) OR Ethylene-trichloride[tiab] OR "Fleck-Flip"[tiab] OR Fluate[tiab] OR Lanadin[tiab] OR Lethurin[tiab] OR Narcogen[tiab] OR Narkosoid[tiab] OR Nialk[tiab] OR Petzinol[tiab] OR TCE[ti] OR Triasol[tiab] OR Trichlorethene[tiab] OR Trichloroethene[tiab] OR Trichloroethylene[MeSH] OR Trichloroethylene[tiab] OR Trike[tiab] OR Trilene[tiab] OR "Tri-Plus"[tiab] OR TTE[ti] OR Vestrol[tiab] OR Vitran[tiab] OR Trichlororan[tiab]) AND (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR Toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR Teratogenicity OR Terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Lethal dose" OR PBPK OR Pharmacokinetics OR "dose response " OR "reference dose" OR Poison* OR poisoning OR Mutagen* OR "Lethal Dose 50"[Mesh] OR "Poisons"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Threshold of Toxicological Concern"[Title/Abstract] OR "Toxicological Concern"[Title/Abstract] OR "toxicity" [Subheading] OR "No-Observed-Adverse-Effect Level"[Mesh] OR NOAEL OR " Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Cardiotoxicity"[Mesh] OR "pharmacokinetics" [Subheading] OR "Toxicokinetics"[Mesh] OR "Teratogens"[Mesh] OR "Mutagenesis"[Mesh] OR "Genes, Suppressor"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Cardiovascular Diseases/chemically induced"[Mesh] OR "Digestive System Diseases/chemically induced"[Mesh] OR "Endocrine System Diseases/chemically induced"[Mesh] OR "Pregnancy Complications/chemically induced"[Mesh] OR "Eye Diseases/chemically induced"[Mesh] OR "Hemic and Lymphatic Diseases/chemically induced"[Mesh] OR "Immune System Diseases/chemically induced"[Mesh] OR "LC50"[Title/Abstract] OR "Neoplasms/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Skin and Connective Tissue Diseases/chemically induced"[Mesh] OR terata* OR Teratogenesis OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "Toxicol*"[Journal] OR "Reproductive and Urinary Physiological Phenomena/drug effects"[Mesh] OR mechanistic* OR mechanism* OR "mode of action") AND ("Leukemia"[Mesh] OR leukemia[Title/Abstract])))

A.1.3 Scopus Search Terms

A.1.3.1 Epidemiology

(TITLE-ABS-KEY (human OR humans OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR "population group" OR "demographic group" OR epidemiolog* OR occupation* OR worker* OR cohort OR "case-control stud*" OR "case report" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR "human stud*" OR persons)) AND (((TITLE-ABS-KEY (trichloroethylene OR trichloroethylene) OR TITLE (tce) OR CASREGNUMBER (79-01-6)) OR TITLE-ABS-KEY ({1,1-Dichloro-2-chloroethylene} OR {1-Chloro-2,2-dichloroethylene} OR anamenth OR benzinol OR blacosolv OR cecolene OR chlorilen OR chlorylea OR circosolv OR crawhaspo OR densinfluat OR {Dow-Tri} OR dukeron OR "ethylene trichloro" OR {Ethylene-trichloride} OR {Fleck-Flip} OR fluate OR lanadin OR lethurin OR narcogen OR narkosoid OR nialk OR petzinol OR triaso OR tric OR trichlorethene OR trichloroethene OR trichloroethylene OR trike OR trilene OR {Tri-Plus} OR vestrol OR vitran OR trichlororan))) AND ((TITLE-ABS-KEY ("adult leukemia" OR {adult leukemia})) OR (adult PRE/5 leukemia))

A.1.3.2 Animal Carcinogenicity and Mode of Action Search Terms

((TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis OR mechanistic* OR mechanism* OR "mode of action") OR SRCTITLE (toxciol*))) AND (((TITLE-ABS-KEY (trichloroethylene OR trichloroethylene) OR TITLE (tce) OR CASREGNUMBER (79-01-6)) OR TITLE-ABS-KEY ({1,1-Dichloro-2-chloroethylene} OR {1-Chloro-2,2-dichloroethylene} OR anamenth OR benzinol OR blacosolv OR cecolene OR chlorilen OR chlorylea OR circosolv OR crawhaspo OR densinfluat OR {Dow-Tri} OR dukeron OR "ethylene trichloro" OR {Ethylene-trichloride} OR {Fleck-Flip} OR fluate OR lanadin OR lethurin OR narcogen OR narkosoid OR nialk OR petzinol OR triaso OR tric OR trichlorethene OR trichloroethene OR trichloroethylene OR trike OR trilene OR {Tri-Plus} OR vestrol OR vitran OR trichlororan))) AND ((TITLE-ABS-KEY ("adult leukemia" OR {adult leukemia})) OR (adult PRE/5 leukemia))

A.2 Perchloroethylene and Leukemia

A.2.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated perchloroethylene (PCE) and leukemia for various purposes (US EPA, 2012, 2020c; ATSDR, 2017a, 2019a; IARC, 2014b). I then conducted literature searches using PubMed and Scopus for studies published after agency literature searches were completed. For PCE and leukemia, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published from January 1, 2016-May 23, 2023.

I conducted weekly searches of PubMed and Scopus using the search terms "Perchlorethylene OR Tetrachlorethylene OR Tetrachloroethylene OR Perchloroethylene OR Tetrachloroethene" to identify any relevant papers published after the last date of my search through the end of 2023.

A.2.2 PubMed Search Terms

A.2.2.1 Epidemiology

((("Tetrachloroethylene"[Mesh] OR Tetrachloroethylene OR Perchloroethylene OR PCE[Title] OR PerSec OR Tetravec OR Tetrachloroethene OR Tetrachlorethylene OR Perchlorethylene OR Perchloroethylene OR "Ethylene tetrachloride" OR PERC OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene"[Text Word]) OR 127-18-4[EC/RN Number]) OR (Ankilostin OR Antisal[Title/Abstract] OR "Dee-Solve" OR "Didakene" OR "Dow-per" OR "Fedal-Un" OR Perclene OR Percosolv OR Perklone OR "PerSec" OR Tetlen OR Tetracap OR Tetraleno OR Tetravec OR Tetroguer OR Tetropil OR Perawin OR Tetralex OR "Dowclene EC"[tiab:~0]) AND ("Humans"[Mesh] OR human[Title/Abstract] OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR"Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Case-Control"[tiab:~0] OR "Retrospective Study"[tiab:~0] OR "Retrospective Studies"[tiab:~0] OR "Longitudinal Study"[tiab:~0] OR "Longitudinal Studies"[tiab:~0] OR "Cross-Sectional"[tiab:~0] OR "observational study"[tiab:~0] OR "observational studies"[tiab:~0] OR "observational study"[tiab:~0] OR "observational studies"[tiab:~0] OR "epidemiology" [Subheading] OR "Child"[Mesh] OR "Adult Children"[Mesh] OR "Infant"[Mesh] OR "Men"[Mesh] OR "Women"[Mesh] OR "Female"[Mesh] OR "Adult"[Mesh] OR "Young Adult"[Mesh] OR "Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Population Groups"[Mesh] OR "Persons"[Mesh] OR "Occupational Groups"[Mesh] OR "Prospective Studies"[Mesh]) AND ("Leukemia"[Mesh] OR leukemia[Title/Abstract])))

A.2.2.2 Animal Carcinogenicity and Mode of Action

((("Tetrachloroethylene"[Mesh] OR Tetrachloroethylene OR Perchloroethylene OR PCE[Title] OR PerSec OR Tetravec OR Tetrachloroethene OR Tetrachlorethylene OR Perchlorethylene OR Perchloroethylene OR "Ethylene tetrachloride" OR PERC OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene"[Text Word]) OR 127-18-4[EC/RN Number]) OR (Ankilostin OR Antisal[Title/Abstract] OR "Dee-Solve" OR "Didakene" OR "Dow-per" OR "Fedal-Un" OR Perclene OR Percosolv OR Perklone OR "PerSec" OR Tetlen OR Tetracap OR Tetraleno OR Tetravec OR Tetroguer

OR Tetropil OR Perawin OR Tetralex OR "Dowclene EC"[tiab:~0]) AND (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR Toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR Teratogenicity OR Terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Lethal dose" OR PBPK OR Pharmacokinetics OR "dose response " OR "reference dose" OR Poison* OR poisoning OR Mutagen* OR "Lethal Dose 50"[Mesh] OR "Poisons"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Threshold of Toxicological Concern"[Title/Abstract] OR "Toxicological Concern"[Title/Abstract] OR "toxicity" [Subheading] OR "No-Observed-Adverse-Effect Level"[Mesh] OR NOAEL OR " Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Cardiotoxicity"[Mesh] OR "pharmacokinetics" [Subheading] OR "Toxicokinetics"[Mesh] OR "Teratogens"[Mesh] OR "Mutagenesis"[Mesh] OR "Genes, Suppressor"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Cardiovascular Diseases/chemically induced"[Mesh] OR "Digestive System Diseases/chemically induced"[Mesh] OR "Endocrine System Diseases/chemically induced"[Mesh] OR "Pregnancy Complications/chemically induced"[Mesh] OR "Eye Diseases/chemically induced"[Mesh] OR "Hemic and Lymphatic Diseases/chemically induced"[Mesh] OR "Immune System Diseases/chemically induced"[Mesh] OR "LC50"[Title/Abstract] OR "Neoplasms/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Skin and Connective Tissue Diseases/chemically induced"[Mesh] OR terata* OR Teratogenesis OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "Toxicol*"[Journal] OR "Reproductive and Urinary Physiological Phenomena/drug effects"[Mesh] OR mechanistic* OR mechanism* OR "mode of action") AND ("Leukemia"[Mesh] OR leukemia[Title/Abstract])))

A.2.3 Scopus Search Terms

A.2.3.1 Epidemiology

(TITLE-ABS-KEY ("Tetrachloroethylene" OR tetrachloroethylene OR perchloroethylene OR tetravec OR tetrachloroethene OR tetrachlorethylene OR perchlorethylene OR perchloroethylene OR "Ethylene tetrachloride" OR "perchloror" OR perchloroethylene OR {1,1,2,2-tetrachloroethylene}) OR TITLE-ABS-KEY (ankilostin OR {Antisal 1} OR {Dee-Solve} OR {Didakene} OR {Dow-per} OR {Fedal-Un} OR perclene OR percosolv OR perklone OR {PerSec} OR tetlen OR tetracap OR tetraleno OR tetravec OR tetroguer OR tetropil OR perawin OR tetralex OR {Dowclene EC}) OR CASREGNUMBER (127-18-4)) AND (TITLE-ABS-KEY (human OR humans OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR "population group" OR "demographic group" OR epidemiolog* OR occupation* OR worker* OR cohort OR "case-control stud*" OR "case report" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR "human stud*" OR persons)) AND ((TITLE-ABS-KEY ("adult leukemia" OR {adult leukemia})) OR (adult PRE/5 leukemia))

A.2.3.2 Animal Carcinogenicity and Mode of Action

(TITLE-ABS-KEY ("Tetrachloroethylene" OR tetrachloroethylene OR perchloroethylene OR tetravec OR tetrachloroethene OR tetrachlorethylene OR perchlorethylene OR perchloroethylene OR "Ethylene tetrachloride" OR "perchloror" OR perchloroethylene OR {1,1,2,2-tetrachloroethylene}) OR TITLE-ABS-KEY (ankilostin OR {Antisal 1} OR {Dee-Solve} OR {Didakene} OR {Dow-per} OR {Fedal-Un} OR perclene OR percosolv OR perklone OR {PerSec} OR tetlen OR tetracap OR tetraleno

OR tetravec OR tetroguer OR tetropil OR perawin OR tetralex OR {Dowclene EC}) OR CASREGNUMBER (127-18-4)) AND ((TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis OR mechanistic* OR mechanism* OR "mode of action") OR SRCTITLE (toxciol*))) AND ((TITLE-ABS-KEY ("adult leukemia" OR {adult leukemia})) OR (adult PRE/5 leukemia))

A.3 Benzene and Leukemia

A.3.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated benzene and leukemia for various purposes (US EPA, 2003; ATSDR, 2007b, 2015, 2017a; IARC, 2018). I then conducted literature searches using PubMed and Scopus. For benzene and leukemia, the searches identified all epidemiology, animal carcinogenicity, and mode-of-action studies published from January 1, 2016-May 21, 2023.

I conducted weekly searches of PubMed and Scopus using the search terms "benzene OR BTEX" to identify any relevant papers published after the last date of my search through the end of 2023.

A.3.2 PubMed Search Terms

A.3.2.1 Epidemiology

(((71-43-2[EC/RN Number] OR "Benzene"[Mesh] OR "benzene"[Title/Abstract]) AND ("Humans"[Mesh] OR human[Title/Abstract] OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR"Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Case-Control"[tiab:~0] OR "Retrospective Study"[tiab:~0] OR "Retrospective Studies"[tiab:~0] OR "Longitudinal Study"[tiab:~0] OR "Longitudinal Studies"[tiab:~0] OR "Cross-Sectional"[tiab:~0] OR "observational study"[tiab:~0] OR "observational studies"[tiab:~0] OR "observational study"[tiab:~0] OR "observational studies"[tiab:~0] OR "epidemiology" [Subheading] OR "Child"[Mesh] OR "Adult Children"[Mesh] OR "Infant"[Mesh] OR "Men"[Mesh] OR "Women"[Mesh] OR "Female"[Mesh] OR "Adult"[Mesh] OR "Young Adult"[Mesh] OR "Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Population Groups"[Mesh] OR "Persons"[Mesh] OR "Occupational Groups"[Mesh] OR "Prospective Studies"[Mesh]) AND ("Leukemia"[Mesh] OR leukemia[Title/Abstract])))

A.3.2.2 Animal Carcinogenicity and Mode of Action

((71-43-2[EC/RN Number] OR "Benzene"[Mesh] OR "benzene"[Title/Abstract]) AND (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR Toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR Teratogenicity OR Terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Lethal dose" OR PBPK OR Pharmacokinetics OR "dose response " OR "reference dose" OR Poison* OR poisoning OR Mutagen* OR "Lethal Dose 50"[Mesh] OR "Poisons"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Threshold of Toxicological Concern"[Title/Abstract] OR "Toxicological Concern"[Title/Abstract] OR "toxicity" [Subheading] OR "No-Observed-Adverse-Effect Level"[Mesh] OR NOAEL OR " Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[Mesh] OR "Maximum Tolerated Dose"[Mesh] OR "Cardiotoxicity"[Mesh] OR "pharmacokinetics" [Subheading] OR "Toxicokinetics"[Mesh] OR "Teratogens"[Mesh] OR "Mutagenesis"[Mesh] OR "Genes, Suppressor"[Mesh] OR "Chromosome Aberrations"[Mesh] OR "Birth Weight/drug effects"[Mesh] OR "Cardiovascular Diseases/chemically induced"[Mesh] OR "Digestive System Diseases/chemically

induced"[Mesh] OR "Endocrine System Diseases/chemically induced"[Mesh] OR "Pregnancy Complications/chemically induced"[Mesh] OR "Eye Diseases/chemically induced"[Mesh] OR "Hemic and Lymphatic Diseases/chemically induced"[Mesh] OR "Immune System Diseases/chemically induced"[Mesh] OR "LC50"[Title/Abstract] OR "Neoplasms/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Nervous System Diseases/chemically induced"[Mesh] OR "Skin and Connective Tissue Diseases/chemically induced"[Mesh] OR terata* OR Teratogenesis OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "Toxicol*"[Journal] OR "Reproductive and Urinary Physiological Phenomena/drug effects"[Mesh] OR mechanistic* OR mechanism* OR "mode of action") AND ("Leukemia"[Mesh] OR leukemia[Title/Abstract])))

A.3.3 Scopus Search Terms

A.3.3.1 Epidemiology

(TITLE-ABS-KEY (benzene OR {Benzene} OR benzol OR cyclohexatriene OR annulene OR "benzole" OR {phenyl hydride} OR pyrobenzol OR "phene") OR CASREGNUMBER (71-43-2)) AND ((TITLE-ABS-KEY ("adult leukemia" OR {adult leukemia})) OR (adult PRE/5 leukemia)) AND (TITLE-ABS-KEY (human OR humans OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR "population group" OR "demographic group" OR epidemiolog* OR occupation* OR worker* OR cohort OR "case-control stud*" OR "case report" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR "human stud*" OR persons))

A.3.3.2 Animal Carcinogenicity and Mode of Action

(TITLE-ABS-KEY (benzene OR {Benzene} OR benzol OR cyclohexatriene OR annulene OR "benzole" OR {phenyl hydride} OR pyrobenzol OR "phene") OR CASREGNUMBER (71-43-2)) AND ((TITLE-ABS-KEY ("adult leukemia" OR {adult leukemia})) OR (adult PRE/5 leukemia)) AND (TITLE-ABS-KEY (mechanistic* OR mechanism* OR "mode of action"))

(TITLE-ABS-KEY (benzene OR {Benzene} OR benzol OR cyclohexatriene OR annulene OR "benzole" OR {phenyl hydride} OR pyrobenzol OR "phene") OR CASREGNUMBER (71-43-2)) AND ((TITLE-ABS-KEY ("adult leukemia" OR {adult leukemia})) OR (adult PRE/5 leukemia)) AND ((TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis) OR SRCTITLE (toxciol*)))

A.4 Vinyl Chloride and Leukemia

A.4.1 Publication Date Range

I first identified scientific studies from government and other agency reports that evaluated vinyl chloride and leukemia for various purposes (US EPA, 2000a; ATSDR, 2006b, 2016, 2017a; IARC, 2012b). I then conducted literature searches using PubMed and Scopus. For vinyl chloride and leukemia, the searches identified epidemiology, animal carcinogenicity, and mode-of-action studies published through July 1, 2024.

I conducted weekly searches of PubMed and Scopus using the search terms "vinyl chloride" to identify any relevant papers published after the last date of my search through the end of 2023.

A.4.2 PubMed Search Terms

A.4.2.1 Epidemiology

("vinyl chloride"[MeSH Terms] OR "vinyl chloride"[All Fields] OR ("chloroethenes"[All Fields] OR "vinyl chloride"[MeSH Terms] OR ("vinyl"[All Fields] AND "chloride"[All Fields]) OR "vinyl chloride"[All Fields] OR "chloroethene"[All Fields]) OR ("chloroethylenes"[All Fields] OR "vinyl chloride"[MeSH Terms] OR ("vinyl"[All Fields] AND "chloride"[All Fields]) OR "vinyl chloride"[All Fields] OR "chloroethylene"[All Fields]) OR "1-chloroethylene"[Title/Abstract:~0] OR (("ethylen"[All Fields] OR "ethylene"[Supplementary Concept] OR "ethylene"[All Fields] OR "ethylenes"[MeSH Terms] OR "ethylenes"[All Fields] OR "ethylene s"[All Fields] OR "ethylenic"[All Fields]) AND ("monochloride"[All Fields] OR "monochlorides"[All Fields])) OR ("monovinyl"[All Fields] AND ("chlorid"[All Fields] OR "chlorides"[MeSH Terms] OR "chlorides"[All Fields] OR "chloride"[All Fields])) OR "monochloroethene"[All Fields] OR "monochloroethylene"[All Fields] OR "Trovidur"[All Fields] OR "75-01-4"[EC/RN Number]) AND ("Humans"[MeSH Terms] OR "human"[Title/Abstract] OR "child*"[All Fields] OR "infant*"[All Fields] OR ("Men"[MeSH Terms] OR "Men"[All Fields] OR "boy"[All Fields]) OR ("Women"[MeSH Terms] OR "Women"[All Fields] OR "girl"[All Fields]) OR "adolescent*"[All Fields] OR "teenager*"[All Fields] OR ("Men"[MeSH Terms] OR "Men"[All Fields]) OR ("womans"[All Fields] OR "Women"[MeSH Terms] OR "Women"[All Fields] OR "woman"[All Fields] OR "women s"[All Fields] OR "womens"[All Fields]) OR ("femal"[All Fields] OR "Female"[MeSH Terms] OR "Female"[All Fields] OR "females"[All Fields] OR "female s"[All Fields] OR "femals"[All Fields]) OR ("male"[MeSH Terms] OR "male"[All Fields]) OR "adult*"[All Fields] OR ("Aged"[MeSH Terms] OR "Aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("populate"[All Fields] OR "populated"[All Fields] OR "populates"[All Fields] OR "populating"[All Fields] OR "population"[MeSH Terms] OR "population"[All Fields] OR "Population Groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "Population Groups"[All Fields] OR "populations"[All Fields] OR "population s"[All Fields] OR "populational"[All Fields] OR "populous"[All Fields]) OR "epidemiolog*"[All Fields] OR "occupation*"[All Fields] OR "worker*"[All Fields] OR ("cohort"[All Fields] OR "cohort s"[All Fields] OR "cohorte"[All Fields] OR "cohorts"[All Fields]) OR "Cohort Studies"[MeSH Terms] OR "Case-Control Studies"[MeSH Terms] OR "Case Reports"[Publication Type] OR "Retrospective Studies"[MeSH Terms] OR "Longitudinal Studies"[MeSH Terms] OR "Observational Study"[Publication Type] OR "Cross-Sectional Studies"[MeSH Terms] OR "Epidemiologic Studies"[MeSH Terms] OR "Case-Control"[Title/Abstract:~0] OR "Retrospective Study"[Title/Abstract:~0] OR "Retrospective Studies"[Title/Abstract:~0] OR "Longitudinal Study"[Title/Abstract:~0] OR "Longitudinal

Studies"[Title/Abstract:~0] OR "Cross-Sectional"[Title/Abstract:~0] OR "Observational Study"[Title/Abstract:~0] OR "observational studies"[Title/Abstract:~0] OR "Observational Study"[Title/Abstract:~0] OR "observational studies"[Title/Abstract:~0] OR "epidemiology"[MeSH Subheading] OR "Child"[MeSH Terms] OR "Adult Children"[MeSH Terms] OR "Infant"[MeSH Terms] OR "Men"[MeSH Terms] OR "Women"[MeSH Terms] OR "Female"[MeSH Terms] OR "Adult"[MeSH Terms] OR "Young Adult"[MeSH Terms] OR "Aged"[MeSH Terms] OR "Middle Aged"[MeSH Terms] OR "Population Groups"[MeSH Terms] OR "Persons"[MeSH Terms] OR "Occupational Groups"[MeSH Terms] OR "Prospective Studies"[MeSH Terms]) AND ("Leukemia"[MeSH Terms] OR "Leukemia"[Title/Abstract])

A.4.2.2 Animal Carcinogenicity and Mode of Action

("vinyl chloride"[MeSH Terms] OR "vinyl chloride"[All Fields] OR ("chloroethenes"[All Fields] OR "vinyl chloride"[MeSH Terms] OR ("vinyl"[All Fields] AND "chloride"[All Fields]) OR "vinyl chloride"[All Fields] OR "chloroethene"[All Fields]) OR ("chloroethylenes"[All Fields] OR "vinyl chloride"[MeSH Terms] OR ("vinyl"[All Fields] AND "chloride"[All Fields]) OR "vinyl chloride"[All Fields] OR "chloroethylene"[All Fields]) OR "1-chloroethylene"[Title/Abstract:~0] OR (("ethylen"[All Fields] OR "ethylene"[Supplementary Concept] OR "ethylene"[All Fields] OR "ethylenes"[MeSH Terms] OR "ethylenes"[All Fields] OR "ethylene s"[All Fields] OR "ethylenic"[All Fields]) AND ("monochloride"[All Fields] OR "monochlorides"[All Fields])) OR ("monovinyl"[All Fields] AND ("chlorid"[All Fields] OR "chlorides"[MeSH Terms] OR "chlorides"[All Fields] OR "chloride"[All Fields])) OR "monochloroethene"[All Fields] OR "monochloroethylene"[All Fields] OR "Trovidur"[All Fields] OR "75-01-4"[EC/RN Number]) AND ("toxic"[All Fields] OR "toxical"[All Fields] OR "toxically"[All Fields] OR "toxicant"[All Fields] OR "toxicant s"[All Fields] OR "toxicants"[All Fields] OR "toxicated"[All Fields] OR "toxication"[All Fields] OR "toxicities"[All Fields] OR "toxicity"[MeSH Subheading] OR "toxicity"[All Fields] OR "toxicity s"[All Fields] OR "toxics"[All Fields] OR "toxicolog*"[All Fields] OR ("toxic"[All Fields] OR "toxical"[All Fields] OR "toxically"[All Fields] OR "toxicant"[All Fields] OR "toxicant s"[All Fields] OR "toxicants"[All Fields] OR "toxicated"[All Fields] OR "toxication"[All Fields] OR "toxicities"[All Fields] OR "toxicity"[MeSH Subheading] OR "toxicity"[All Fields] OR "toxicity s"[All Fields] OR "toxics"[All Fields]) OR ("toxic"[All Fields] OR "toxical"[All Fields] OR "toxically"[All Fields] OR "toxicant"[All Fields] OR "toxicant s"[All Fields] OR "toxicants"[All Fields] OR "toxicated"[All Fields] OR "toxication"[All Fields] OR "toxicities"[All Fields] OR "toxicity"[MeSH Subheading] OR "toxicity"[All Fields] OR "toxicity s"[All Fields] OR "toxics"[All Fields]) OR "carcinogen*"[All Fields] OR ("carcinogenesis"[MeSH Terms] OR "carcinogenesis"[All Fields] OR "carcinogeneses"[All Fields]) OR "cardiotox*"[All Fields] OR ("Pharmacokinetics"[MeSH Terms] OR "Pharmacokinetics"[All Fields] OR "toxicokinetic"[All Fields] OR "Pharmacokinetics"[MeSH Subheading] OR "Toxicokinetics"[All Fields] OR "Toxicokinetics"[MeSH Terms]) OR ("carcinogen s"[All Fields] OR "carcinogenes"[All Fields] OR "carcinogenic"[All Fields] OR "carcinogenically"[All Fields] OR "carcinogenicities"[All Fields] OR "carcinogenicity"[All Fields] OR "carcinogenity"[All Fields] OR "carcinogenous"[All Fields] OR "carcinogens"[Pharmacological Action] OR "carcinogens"[MeSH Terms] OR "carcinogens"[All Fields] OR "carcinogen"[All Fields]) OR ("embryolethal"[All Fields] OR "embryolethality"[All Fields]) OR "embryotox*"[All Fields] OR ("teratogenesis"[MeSH Terms] OR "teratogenesis"[All Fields] OR "teratogenicity"[All Fields] OR "teratogenic"[All Fields] OR "teratogenically"[All Fields] OR "teratogenity"[All Fields] OR "teratogenous"[All Fields] OR "Teratogens"[Pharmacological Action] OR "Teratogens"[MeSH Terms] OR "Teratogens"[All Fields] OR "teratogen"[All Fields]) OR "terato*"[All Fields] OR ("Mutagenesis"[MeSH Terms] OR "Mutagenesis"[All Fields] OR "mutageneses"[All Fields]) OR "Gene mutation"[All Fields] OR "Chromosome aberration"[All Fields] OR ("aneuploidy"[MeSH Terms] OR "aneuploidy"[All Fields] OR "aneuploidies"[All Fields]) OR ("polyploidy"[MeSH Terms] OR "polyploidy"[All Fields] OR "polyploidies"[All Fields]) OR "neurotox*"[All Fields] OR "nephrotox*"[All Fields] OR

"immunotox*"[All Fields] OR "hepatotox*"[All Fields] OR "epigenetic*"[All Fields] OR "genotox*"[All Fields] OR "cytotox*"[All Fields] OR "Lethal dose"[All Fields] OR "PBPK"[All Fields] OR ("pharmacokinetic"[All Fields] OR "pharmacokinetical"[All Fields] OR "pharmacokinetically"[All Fields] OR "Pharmacokinetics"[MeSH Subheading] OR "Pharmacokinetics"[All Fields] OR "Pharmacokinetics"[MeSH Terms]) OR "dose response"[All Fields] OR "reference dose"[All Fields] OR "poison*"[All Fields] OR ("poisoned"[All Fields] OR "poisoning"[MeSH Terms] OR "poisoning"[All Fields] OR "poisonings"[All Fields] OR "poisoning"[MeSH Subheading] OR "poisonous"[All Fields] OR "Poisons"[Pharmacological Action] OR "Poisons"[MeSH Terms] OR "Poisons"[All Fields] OR "poison"[All Fields]) OR "mutagen*"[All Fields] OR "Lethal Dose 50"[MeSH Terms] OR "Poisons"[MeSH Terms] OR "Pharmacokinetics"[MeSH Terms] OR "Threshold of Toxicological Concern"[Title/Abstract] OR "Toxicological Concern"[Title/Abstract] OR "toxicity"[MeSH Subheading] OR "No-Observed-Adverse-Effect Level"[MeSH Terms] OR ("No-Observed-Adverse-Effect Level"[MeSH Terms] OR ("no observed adverse effect"[All Fields] AND "level"[All Fields]) OR "No-Observed-Adverse-Effect Level"[All Fields] OR "noael"[All Fields] OR "noaels"[All Fields]) OR "Tolerable Daily Intake"[Title/Abstract] OR "Toxicological Phenomena"[MeSH Terms] OR "Maximum Tolerated Dose"[MeSH Terms] OR "Cardiotoxicity"[MeSH Terms] OR "Pharmacokinetics"[MeSH Subheading] OR "Toxicokinetics"[MeSH Terms] OR "Teratogens"[MeSH Terms] OR "Mutagenesis"[MeSH Terms] OR "genes, suppressor"[MeSH Terms] OR "Chromosome Aberrations"[MeSH Terms] OR "birth weight/drug effects"[MeSH Terms] OR "cardiovascular diseases/chemically induced"[MeSH Terms] OR "digestive system diseases/chemically induced"[MeSH Terms] OR "endocrine system diseases/chemically induced"[MeSH Terms] OR "pregnancy complications/chemically induced"[MeSH Terms] OR "eye diseases/chemically induced"[MeSH Terms] OR "hemic and lymphatic diseases/chemically induced"[MeSH Terms] OR "immune system diseases/chemically induced"[MeSH Terms] OR "LC50"[Title/Abstract] OR "neoplasms/chemically induced"[MeSH Terms] OR "nervous system diseases/chemically induced"[MeSH Terms] OR "nervous system diseases/chemically induced"[MeSH Terms] OR "skin and connective tissue diseases/chemically induced"[MeSH Terms] OR "terata*"[All Fields] OR ("teratogenesis"[MeSH Terms] OR "teratogenesis"[All Fields]) OR "Regul Toxicol Pharmacol"[Journal] OR "Toxicol Appl Pharmacol"[Journal] OR "toxicol*"[Journal] OR "reproductive and urinary physiological phenomena/drug effects"[MeSH Terms] OR "mechanistic*"[All Fields] OR "mechanism*"[All Fields] OR "mode of action"[All Fields]) AND ("Leukemia"[MeSH Terms] OR "Leukemia"[Title/Abstract])

A.4.3 Scopus Search Terms

A.4.3.1 Epidemiology

(TITLE-ABS-KEY ("Vinyl chloride" OR {Vinyl chloride} OR chloroethene OR chloroethylene OR {1-chloroethylene} OR {ethylene monochloride} OR {monovinyl chloride} OR monochloroethene OR monochloroethylene OR trovidur) OR CASREGNUMBER (75-01-4)) AND (TITLE-ABS-KEY (human OR humans OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR "population group" OR "demographic group" OR epidemiolog* OR occupation* OR worker* OR cohort OR "case-control stud*" OR "case report" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR "human stud*" OR persons)) AND (TITLE-ABS (leukemia))

A.4.3.2 Animal Carcinogenicity and Mode of Action

(TITLE-ABS-KEY ("Vinyl chloride" OR {Vinyl chloride} OR chloroethene OR chloroethylene OR {1-chloroethylene} OR {ethylene monochloride} OR {monovinyl chloride} OR monochloroethene OR

monochloroethylene OR trovidur) OR CASREGNUMBER (75-01-4)) AND (TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis OR mechanistic* OR mechanism* OR "mode of action") OR SRCTITLE (toxciol*)) AND (TITLE-ABS-KEY (leukemia))

A.5 Trichloroethylene, Perchloroethylene, Benzene, Vinyl Chloride, and Myelodysplastic Syndrome

A.5.1 Publication Date Range

I conducted literature searches that evaluated TCE, PCE, benzene, vinyl chloride, and myelodysplastic syndrome using PubMed and Scopus for epidemiology studies published through March 15, 2024.

A.5.2 PubMed Search Terms

A.5.2.1 Epidemiology

((((("Tetrachloroethylene"[Mesh] OR "Tetrachloroethylene" OR Perchloroethylene OR PCE[Title] OR PerSec OR Tetravec OR Tetrachloroethene OR Tetrachlorethylene OR Perchlorethylene OR Perchloroethylene OR "Ethylene tetrachloride" OR PERC OR "perchloror" OR perchloroethylene OR "1,1,2,2-tetrachloroethylene"[Text Word]) OR 127-18-4[EC/RN Number]) OR (Ankilostin OR Antisal[Title/Abstract] OR "Dee-Solve" OR "Didakene" OR "Dow-per" OR "Fedal-Un" OR Perclene OR Percosolv OR Perklone OR "PerSec" OR Tetlen OR Tetracap OR Tetraleno OR Tetravec OR Tetroguer OR Tetropil OR Perawin OR Tetralex OR "Dowclene EC"[tiab:~0])) OR (("Trichloroethylene"[Mesh] OR trichloroethylene OR TCE[ti]) OR (79-01-06[EC/RN Number]) OR (1,1-Dichloro-2-chloroethylene[tiab] OR 1-Chloro-2,2-dichloroethylene[tiab] OR 79-01- 6[rn] OR Anamenth[tiab] OR Benzinol[tiab] OR Blacosolv[tiab] OR Cecolene[tiab] OR Chlorilen[tiab] OR Chlorylea[tiab] OR Circosolv[tiab] OR Crawhaspol[tiab] OR Densinfluat[tiab] OR Dow-Tri[tiab] OR Dukeron[tiab] OR (Ethene[tiab] AND trichloro[tiab]) OR Ethinyl-trichloride[tiab] OR (Ethylene[tiab] AND trichloro[tiab]) OR Ethylene-trichloride[tiab] OR Fleck-Flip[tiab] OR Fluate[tiab] OR Lanadin[tiab] OR Lethurin[tiab] OR Narcogen[tiab] OR Narkosoid[tiab] OR Nialk[tiab] OR Petzinol[tiab] OR TCE[ti] OR Triasol[tiab] OR TRIC[tiab] OR Trichlorethene[tiab] OR Trichloroethene[tiab] OR Trichloroethylene[MeSH] OR Trichloroethylene[tiab] OR Trike[tiab] OR Trilene[tiab] OR Tri-Plus[tiab] OR TTE[ti] OR Vestrol[tiab] OR Vitran[tiab] OR Trichlororan[tiab])) OR (("Benzene"[Mesh] OR "benzene"[Title/Abstract])) OR (("Vinyl Chloride"[Mesh] OR "Vinyl chloride" OR Chloroethene OR chloroethylene OR "1-chloroethylene"[tiab:~0] OR "ethylene monochloride" OR "monovinyl chloride" OR monochloroethene OR monochloroethylene OR Trovidur) OR 75-01-4[EC/RN Number]))) AND ("Myelodysplastic Syndromes"[Mesh] OR "myelodysplastic syndrome") AND ((("Humans"[Mesh] OR human[Title/Abstract] OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR group OR epidemiolog* OR occupation* OR worker* OR cohort OR"Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Case-Control Study"[tiab:~3] OR "Case Control Studies"[tiab:~3] OR "Retrospective Study"[tiab:~2] OR "Retrospective Studies"[tiab:~2] OR "Longitudinal Study"[tiab:~2] OR "Longitudinal Studies"[tiab:~2] OR "Cross-Sectional Study"[tiab:~3] OR "Cross-Sectional Studies"[tiab:~3] OR "observational study"[tiab:~2] OR "observational studies"[tiab:~2] OR "observational study"[tiab:~2] OR "observational studies"[tiab:~2] OR "epidemiology" [Subheading] OR "Child"[Mesh] OR "Adult Children"[Mesh] OR "Infant"[Mesh] OR "Men"[Mesh] OR "Women"[Mesh] OR "Female"[Mesh] OR "Adult"[Mesh] OR "Young Adult"[Mesh] OR "Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Population Groups"[Mesh] OR "Persons"[Mesh] OR "Occupational Groups"[Mesh] OR "Prospective Studies"[Mesh])))

A.5.3 Scopus Search Terms

A.5.3.1 Epidemiology

(((TITLE-ABS-KEY ("Tetrachloroethylene" OR tetrachloroethylene OR perchloroethylene OR tetravec OR tetrachloroethene OR tetrachlorethylene OR perchlorethylene OR perchloroethylene OR "Ethylene tetrachloride" OR "perchloror" OR perchloroethylene OR {1,1,2,2-tetrachloroethylene}) OR TITLE-ABS-KEY (ankilostin OR {Antisal 1} OR {Dee-Solve} OR {Didakene} OR {Dow-per} OR {Fedal-Un} OR perclene OR percosolv OR perklone OR {PerSec} OR tetlen OR tetracap OR tetraleno OR tetravec OR tetroguer OR tetropil OR perawin OR tetralex OR {Dowclene EC}) OR CASREGNUMBER (127-18-4)) OR (TITLE-ABS-KEY (trichloroethylene OR trichloroethylene) OR TITLE (tce AND ot AND tte) OR CASREGNUMBER (79-01-6) OR TITLE-ABS-KEY ({1,1-Dichloro-2-chloroethylene} OR {1-Chloro-2,2-dichloroethylene} OR anamenth OR benzinol OR blacosolv OR cecolene OR chlorilen OR chlorylea OR circosolv OR crawhaspo OR densinfluat OR {Dow-Tri} OR dukeron OR (ethene AND trichloro) OR {Ethinyl-trichloride} OR (ethylene AND trichloro) OR {Ethylene-trichloride} OR {Fleck-Flip} OR fluate OR lanadin OR lethurin OR narcogen OR narkosoid OR nialk OR petzinol OR triaso OR tric OR trichlorethene OR trichloroethene OR trichloroethylene OR trike OR trilene OR {Tri-Plus} OR vestrol OR vitran OR trichlororan)) OR (TITLE-ABS-KEY (benzene OR {Benzene} OR benzol OR cyclohexatriene OR annulene OR "benzole" OR {phenyl hydride} OR pyrobenzol OR "phene") OR CASREGNUMBER (71-43-2)) OR (TITLE-ABS-KEY ("Vinyl chloride" OR {Vinyl chloride} OR chloroethene OR chloroethylene OR {1-chloroethylene} OR {ethylene monochloride} OR {monovinyl chloride} OR monochloroethene OR monochloroethylene OR trovidur) OR CASREGNUMBER (75-01-4))) AND (TITLE-ABS-KEY (human OR humans OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR "population group" OR "demographic group" OR epidemiolog* OR occupation* OR worker* OR cohort OR "case-control stud*" OR "case report" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR "human stud*" OR persons))) AND (TITLE-ABS-KEY ("myelodysplastic syndrome"))

A.6 *trans*-1,2-Dichloroethylene and Leukemia

A.6.1 Publication Date Range

I conducted literature searches using PubMed and Scopus for epidemiology, animal carcinogenicity, and mode-of-action studies published through May 6, 2024.

A.6.2 PubMed Search Terms

A.6.2.1 Epidemiology

("trans-1,2-Dichloroethene"[tiab:~0] OR "(E)-1,2-Dichloroethene"[tiab:~0] OR "(E)-1,2-Dichloroethylene"[tiab:~0] OR "trans-Acetylene dichloride"[tiab:~0] OR "trans-1,2-Dichloroethylene"[tiab:~0] OR "trans-Dichloroethylene"[tiab:~0] OR 156-60-5[EC/RN Number])

("Humans"[Mesh] OR human[Title/Abstract] OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR "Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Case Reports" [Publication Type] OR "Retrospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Cross-Sectional Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Case-Control Study"[tiab:~2] OR "Case Control Studies"[tiab:~2] OR "Retrospective Study"[tiab:~2] OR "Retrospective Studies"[tiab:~2] OR "Longitudinal Study"[tiab:~2] OR "Longitudinal Studies"[tiab:~2] OR "Cross-Sectional Study"[tiab:~3] OR "Cross-Sectional Studies"[tiab:~3] OR "observational study"[tiab:~2] OR "observational studies"[tiab:~2] OR "observational study"[tiab:~2] OR "observational studies"[tiab:~2] OR "epidemiology" [Subheading] OR "Child"[Mesh] OR "Adult Children"[Mesh] OR "Infant"[Mesh] OR "Men"[Mesh] OR "Women"[Mesh] OR "Female"[Mesh] OR "Adult"[Mesh] OR "Young Adult"[Mesh] OR "Aged"[Mesh] OR "Middle Aged"[Mesh] OR "Population Groups"[Mesh] OR "Occupational Groups"[Mesh] OR "Prospective Studies"[Mesh])

"Kidney Neoplasms"[Mesh] OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "Carcinoma, Renal Cell"[Mesh] OR "Renal Cell Carcinoma"[tiab:~3] OR "Nephroma, Mesoblastic"[Mesh] OR "Wilms Tumor"[Mesh]

"Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]

("Leukemia"[Mesh] OR leukemia[Title/Abstract])

"Lymphoma, Non-Hodgkin"[Mesh] OR "Non-Hodgkin's Lymphoma"[tiab:~0] OR "Non-Hodgkin Lymphoma"[tiab:~0]

A.6.2.2 Animal Carcinogenicity and Mode of Action

("trans-1,2-Dichloroethene"[tiab:~0] OR "(E)-1,2-Dichloroethene"[tiab:~0] OR "(E)-1,2-Dichloroethylene"[tiab:~0] OR "trans-Acetylene dichloride"[tiab:~0] OR "trans-1,2-Dichloroethylene"[tiab:~0] OR "trans-Dichloroethylene"[tiab:~0] OR 156-60-5[EC/RN Number])

(toxicity OR toxicolog* OR toxicology OR toxic* OR "Toxicology"[Mesh] OR carcinogen* OR Carcinogenesis OR "Carcinogenesis"[Mesh] OR cancer*[Title/Abstract] OR "Neoplasms"[Mesh] OR neoplasm* OR tumor* OR cardiotox* OR "Cardiotoxins"[Mesh] OR Cardiotoxicity OR "Cardiotoxicity"[Mesh] OR Toxicokinetics OR "Pharmacokinetics"[Mesh] OR carcinogenicity OR embryolethality OR embryotoxicity OR Teratogenicity OR "Teratogenesis"[Mesh] OR Terato* OR mutagenesis OR "Mutagenesis"[Mesh] OR "Gene mutation" OR "Chromosome aberration" OR "Chromosome Aberrations"[Mesh] OR Aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR Epigenetic* OR genotox* OR Cytotox* OR "Reproductive Health"[Mesh] OR DNA OR mutagen* OR mechanistic* OR mechanism* OR "mode of action" OR "oxidative stress" OR inflammat*)

"Kidney Neoplasms"[Mesh] OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "Carcinoma, Renal Cell"[Mesh] OR "Renal Cell Carcinoma"[tiab:~3] OR "Nephroma, Mesoblastic"[Mesh] OR "Wilms Tumor"[Mesh]

"Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer*" OR "bladder tumor*" OR "bladder cancer"[Title/Abstract:~2]

("Leukemia"[Mesh] OR leukemia[Title/Abstract])

"Lymphoma, Non-Hodgkin"[Mesh] OR "Non-Hodgkin's Lymphoma"[tiab:~0] OR "Non-Hodgkin Lymphoma"[tiab:~0]

A.6.3 Scopus Search Terms

A.6.3.1 Epidemiology

TITLE-ABS-KEY ({trans-1,2-Dichloroethene} OR {(E)-1,2-Dichloroethene} OR {(E)-1,2-Dichloroethylene} OR {trans-Acetylene dichloride} OR {trans-1,2-Dichloroethylene} OR {trans-Dichloroethylene}) OR CASREGNUMBER (156-60-5)

TITLE-ABS-KEY (human OR child* OR infant* OR boy OR girl OR adolescent* OR teenager* OR men OR women OR female OR male OR adult* OR elderly OR population OR epidemiolog* OR occupation* OR worker* OR cohort OR "cohort stud*" OR "case-control stud*" OR "retrospective stud*" OR "longitudinal stud*" OR "observational stud*" OR "cross-sectional stud*" OR resident*)

TITLE-ABS-KEY ("Kidney Neoplasms" OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "Renal Cell Carcinoma" OR "Nephroma, Mesoblastic" OR "Wilms Tumor")

TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})

TITLE-ABS-KEY (Leukemia)

TITLE-ABS-KEY ("Non-Hodgkin's Lymphoma*" OR "Non-Hodgkin Lymphoma*" OR "Lymphoma, Non-Hodgkin" OR "Lymphoma, Non-Hodgkin's" OR {Non-Hodgkin's} OR {Non Hodgkin's} OR {Non-Hodgkin} OR {Non Hodgkin})

A.6.3.2 Animal Carcinogenicity and Mode of Action Search Terms

TITLE-ABS-KEY ({trans-1,2-Dichloroethene} OR {(E)-1,2-Dichloroethene} OR {(E)-1,2-Dichloroethylene} OR {trans-Acetylene dichloride} OR {trans-1,2-Dichloroethylene} OR {trans-Dichloroethylene}) OR CASREGNUMBER (156-60-5)

(TITLE-ABS-KEY (toxicity OR toxicolog* OR toxic OR toxicant OR carcinogen* OR carcinogenesis OR cardiotox* OR toxicokinetics OR carcinogenicity OR embryolethality OR embryotox* OR teratogenicity OR terato* OR mutagenesis OR "Gene mutation" OR "Chromosome aberration" OR aneuploidy OR polyploidy OR neurotox* OR nephrotox* OR immunotox* OR hepatotox* OR epigenetic* OR genotox* OR cytotox* OR "Lethal dose" OR pbpk OR pharmacokinetics OR "dose response " OR "reference dose" OR poison* OR poisoning OR mutagen* OR "LD50" OR pharmacokinetics OR "Threshold of Toxicological Concern" OR "Toxicological Concern" OR "No Observed Adverse Effect Level" OR noael OR "Tolerable Daily Intake" OR "Maximum Tolerated Dose" OR teratogens OR mutagenesis OR "Chromosome Aberrations" OR terata* OR teratogenesis OR mechanistic* OR mechanism* OR "mode of action" OR "oxidative stress" OR inflammat*) OR SRCTITLE (toxciol*)

TITLE-ABS-KEY ("Kidney Neoplasms" OR "kidney cancer" OR "renal cancer" OR "kidney neoplasm" OR "renal neoplasms" OR "kidney tumor" OR "renal tumor" OR "Renal Cell Carcinoma" OR "Nephroma, Mesoblastic" OR "Wilms Tumor")

TITLE-ABS-KEY ("Bladder Neoplasms" OR "bladder cancer*" OR "bladder tumor*" OR {bladder cancer})

TITLE-ABS-KEY (Leukemia)

TITLE-ABS-KEY ("Non-Hodgkin's Lymphoma*" OR "Non-Hodgkin Lymphoma*" OR "Lymphoma, Non-Hodgkin" OR "Lymphoma, Non-Hodgkin's" OR {Non-Hodgkin's} OR {Non Hodgkin's} OR {Non-Hodgkin} OR {Non Hodgkin})

Attachment B

Camp Lejeune Epidemiology Studies

List of Tables

Table B.1	Camp Lejeune Cohort Study Characteristics
Table B.2	Employment/Assignment at Camp Lejeune and Leukemia Risk
Table B.3	Employment/Assignment at Camp Lejeune and Acute Lymphocytic Leukemia Risk
Table B.4	Employment/Assignment at Camp Lejeune and Acute Myeloid Leukemia Risk
Table B.5	Employment/Assignment at Camp Lejeune and Chronic Myeloid Leukemia Risk
Table B.6	Employment/Assignment at Camp Lejeune and Myelodysplastic Syndrome Risk
Table B.7	TCE Exposure at Camp Lejeune and Leukemia Risk
Table B.8	PCE Exposure at Camp Lejeune and Leukemia Risk
Table B.9	Benzene Exposure at Camp Lejeune and Leukemia Risk
Table B.10	Vinyl Chloride Exposure at Camp Lejeune and Leukemia Risk

Table B.1 Camp Lejeune Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Bove *et al.* (2014a)	US	Marines and Navy personnel at CL and CP	B	CL and CP: 20-49[a]	CL: 154,932 CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[a] CP: 34-60[a]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia; ANLL	SSA and NDI	1979-2008
ATSDR (2018b)	US	Marines & Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54 Civilian Employees CL: 60-64 CP: ≥65	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168 CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines and Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Leukemia	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-up Period
Bove *et al.* (2024a)	US	Marines & Navy personnel and civilian employees at CL and CP	B	**Marines & Navy Personnel** All 1975-1985 CL: $\bar{x}$ = 37.3 CP: $\bar{x}$ = 37.8 Began Active Duty 1975-1985 CL: $\bar{x}$ = 35.0 CP: $\bar{x}$ = 35.2 **Civilian Employees** CL: $\bar{x}$ = 52.9 CP: $\bar{x}$ = 55.1	**Marines & Navy Personnel** All 1975-1985 CL: 208,063 CP: 225,999 Began Active Duty 1975-1985 CL: 154,821 CP: 163,484 **Civilian Employees** CL: 6,494 CP: 5,797	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Assignment/ employment at base	Inc	Leukemia; ALL; AML; CML	SSA Data for Epidemiological Researchers, NDI, and cancer registries (state, territory, DOD, and VA)	1996-2017
Bove *et al.* (2024b)	US	Marines & Navy personnel and civilian employees at CL and CP	B	**Marines & Navy Personnel** All 1975-1985 CL: $\bar{x}$ = 22.1 CP: $\bar{x}$ = 22.4 Began Active Duty 1975-1985 CL: $\bar{x}$ = 20.2 CP: $\bar{x}$ = 20.5 **Civilian Employees** CL: $\bar{x}$ = 39.1 CP: $\bar{x}$ = 41.2	**Marines & Navy Personnel** All 1975-1985 CL: 219,988 CP: 232,026 Began Active Duty 1975-1985[b] CL: 159,128 CP: 168,406 **Civilian Employees** CL: 7,332 CP: 6,677	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Assignment/ employment at base	Mort	Leukemia; ALL; AML; CML; MDS	SSA Data for Epidemiological Researchers and NDI	1979-2018

Notes:

ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; ANLL = Acute Nonlymphocytic Leukemia; B = Both Males and Females; CL = Camp Lejeune; CML = Chronic Myeloid Leukemia; CP = Camp Pendleton; DOD = Department of Defense; Inc = Incidence; MDS = Myelodysplastic Syndromes; Mort = Mortality; NDI = National Death Index; SSA = Social Security Administration; US = United States; VA = Veterans Affairs; Yrs = Years.

$\bar{x}$ = Mean.

(a) Median age from start to end of follow-up (Bove *et al*., 2014a,b).

(b) Bove *et al*. (2024b) reported that this subgroup consisted of 154,821 Camp Lejeune and 163,484 Camp Pendleton Marines and Navy personnel in the methods section. However, the abstract and tables report 159,128 Camp Lejeune and 168,406 Camp Pendleton Marines and Navy personnel.

Table B.2 Employment/Assignment at Camp Lejeune and Leukemia Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Bove *et al.* (2014a)	US general population	Mort	SMR	**CL Marines & Navy Personnel**					
				All	66	84.43	**0.78 (0.60-0.99)**	–	Age, sex, race, and calendar period
	CP Marines & Navy personnel		HR	All (10 yr lag)	66	–	1.11 (0.75-1.62)		Age, sex, race, rank, and education
Bove *et al.* (2014b)	US general population	Mort	SMR	**CL Civilian Employees**					
				All	12	7.73	1.55 (0.80-2.71)	–	Age, sex, race, and calendar period
	CP civilian employees		HR	All (10 yr lag)	12	–	1.59 (0.66-3.84)		Age, sex, race, blue- or white-collar occupation, and education
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					
				All	125	–	0.97 (0.61-1.52)	–	Age
	CP civilian employees			**CL Civilian Employees**					
				All	8	–	1.10 (0.36-3.38)	–	Age
Bove *et al.* (2024a)	CP Marines & Navy personnel	Inc	HR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	314	–	1.07 (0.91-1.25)	–	Age, sex, race, rank, and education level
				All	566		1.05 (0.93-1.18)		
				Personnel who began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-6)	189	–	1.11 (0.92-1.33)	–	Age, sex, race, rank, and education level
				Medium (7-10)	60		0.91 (0.69-1.21)		
				High (>10)	65		1.15 (0.86-1.55)		
	CP civilian employees			**CL Civilian Employees**					
				All	36	–	0.86 (0.54-1.36)	–	Age, sex, race, blue collar work, and education level
				Duration of employment (quarter yrs)					
				Low/medium (1-21)	17	–	0.65 (0.36-1.18)	–	Age, sex, race, blue collar work, and education level
				High (>21)	19		1.43 (0.72-2.86)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Bove *et al.* (2024b)[b]	US general population	Mort	SMR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	142	–	0.87 (0.73-1.02)	–	Age, sex, race, and calendar period
				All	284		0.92 (0.82-1.04)		
	CP Marines & Navy personnel		RR	Began active duty between 1975-1985	142		1.13 (0.89-1.43)		Age, sex, and race
				All	284		1.13 (0.95-1.33)		
			HR	Began active duty between 1975-1985	142		1.10 (0.87-1.40)		Age, sex, race, rank, and education level
				All	284		1.10 (0.93-1.30)		
				Personnel who began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-2)	–	–	1.17 (0.84-1.64)	–	Age, sex, race, rank, and education level
				Medium (>2-7)			1.19 (0.86-1.64)		
				High (>7)			0.95 (0.67-1.35)		
	US general population		SMR	**CL Civilian Employees**					
				All	31	–	0.98 (0.67-1.39)	–	Age, sex, race, and calendar period
	CP civilian employees		RR		31		1.00 (0.61-1.64)		Age, sex, and race
			HR		31		1.00 (0.61-1.64)		Age, sex, race, blue collar work, and education level
				Duration of employment (quarter yrs)					
				Low (1-5)	–	–	0.67 (0.26-1.72)	–	Age, sex, race, blue collar work, and education level
				Medium (6-22)			0.94 (0.45-2.00)		
				High (23-53)			1.23 (0.67-2.26)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; OR = Odds Ratio; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; US = United States; Yr(s) = Year(s).
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Bove *et al.* (2024b) also ran analyses based on contributing causes, which I do not report here.

Table B.3 Employment/Assignment at Camp Lejeune and Acute Lymphocytic Leukemia Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Bove *et al.* (2024a)	CP Marines & Navy personnel	Inc	HR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	23	–	0.94 (0.53-1.67)	–	Age, sex, race, rank, and education level
				All	33		1.03 (0.64-1.67)		
				Personnel who began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-6)	14	–	0.96 (0.49-1.89)	–	Age, sex, race, rank, and education level
				Medium (7-10)	5		0.93 (0.35-2.45)		
				High (>10)	4		0.79 (0.25-2.49)		
	CP civilian employees			**CL Civilian Employees**					
				All	1	–	0.27 (0.03-2.63)	–	–
Bove *et al.* (2024b)[b]	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	20	–	0.85 (0.47-1.53)	–	Age, sex, race, rank, and education level
				All	35		1.07 (0.67-1.71)		
				Personnel who began active duty between 1975-1985, by duration of employment (quarter yrs)					
				Low (1-2)	–	–	0.96 (0.41-2.23)	–	Age, sex, race, rank, and education level
				Medium (>2-7)			1.05 (0.47-2.34)		
				High (>7)			0.66 (0.25-1.74)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; RR = Relative Risk; SIR = Standardized Incidence Ratio; US = United States; yrs = Years.
– = Not Reported.
(a) Observed cases and expected cases for SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Bove *et al.* (2024b) also ran analyses based on contributing causes, which I do not report here.

Table B.4 Employment/Assignment at Camp Lejeune and Acute Myeloid Leukemia Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Bove *et al.* (2014b)	CP civilian employees	Mort	HR	**ANLL**					
				CL civilian employees (10 yr lag)	6	–	2.13 (0.57-7.95)	–	Sex, race, blue- or white-collar occupation, and education
Bove *et al.* (2024a)	CP Marines & Navy personnel	Inc	HR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	104	–	**1.38 (1.03-1.85)**	–	Age, sex, race, rank, and education level
				All	174		**1.34 (1.07-1.67)**		
				Personnel who began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-6)	62	–	1.36 (0.97-1.90)	–	Age, sex, race, rank, and education level
				Medium (7-10)	18		1.11 (0.66-1.87)		
				High (>10)	24		**1.90 (1.12-3.21)**		
	CP civilian employees			**CL Civilian Employees**					
				All	14	–	1.35 (0.59-3.09)	–	Age, sex, race, blue collar work, and education level
				Duration of employment (quarter yrs)					
				Low/medium (1-21)	6	–	0.92 (0.32-2.67)	–	Age, sex, race, blue collar work, and education level
				High (>21)	8		2.53 (0.76-8.37)		
Bove *et al.* (2024b)[b]	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	62	–	1.11 (0.78-1.59)	–	Age, sex, race, rank, and education level
				All	125		1.21 (0.94-1.56)		
				Personnel who began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-2)	–	–	1.18 (0.72-1.94)	–	Age, sex, race, rank, and education level
				Medium (>2-7)			0.83 (0.48-1.44)		
				High (>7)			1.13 (0.69-1.84)		
	CP civilian employees			**CL Civilian Employees**					
				All	15	–	0.97 (0.47-2.02)	–	Age, sex, race, blue collar work, and education level

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				Duration of employment (quarter yrs)					
				Low (1-5)	–	–	0.55 (0.12-2.42)	–	Age, sex, race, blue collar work, and education level
				Medium (6-22)			0.79 (0.26-2.42)		
				High (23-53)			1.32 (0.56-3.12)		

Notes:
ANLL = Acute Nonlymphocytic Leukemia; CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; SIR = Standardized Incidence Ratio; Yr(s) = Year(s).
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Bove *et al.* (2024b) also ran analyses based on contributing causes, which I do not report here.

Table B.5 Employment/Assignment at Camp Lejeune and Chronic Myeloid Leukemia Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Variables Adjusted For
Bove *et al.* (2024a)	CP Marines & Navy personnel	Inc	HR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	39	–	0.74 (0.49-1.12)	–	Age, sex, race, rank, and education level
				All	70		0.87 (0.64-1.20)		
				Personnel who began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-6)	22	–	0.74 (0.44-1.22)	–	Age, sex, race, rank, and education level
				Medium (7-10)	8		0.68 (0.32-1.43)		
				High (>10)	9		0.82 (0.38-1.78)		
	CP civilian employees			**CL Civilian Employees**					
				All	6	–	0.69 (0.24-2.01)	–	Age, sex, race, blue collar work, and education level
				Duration of employment (quarter yrs)					
				Low/medium (1-4)	3	–	0.46 (0.12-1.78)	–	Age, sex, race, blue collar work, and education level
				High (22-53)	3		1.61 (0.29-8.91)		
Bove *et al.* (2024b)[b]	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	11	–	0.65 (0.30-1.40)	–	Age, sex, race, rank, and education level
				All	23		0.73 (0.43-1.25)		
				Personnel who began active duty between 1975-1985, by duration of assignment (quarter yrs)					
				Low (1-2)	–	–	0.19 (0.03-1.44)	–	Age, sex, race, rank, and education level
				Medium (>2-7)			1.63 (0.72-3.69)		
				High (>7)			0.18 (0.02-1.37)		
	CP civilian employees			**CL Civilian Employees**					
				All	8	–	1.26 (0.29-5.48)	–	Age, sex, race, blue collar work, and education level
				Duration of employment (quarter yrs)					
				Low (1-5)	–	–	1.32 (0.14-12.27)	–	Age, sex, race, blue collar work, and education level
				Medium (6-22)			0.00 (–)		
				High (23-53)			1.81 (0.34-9.77)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; Yrs = Years.
– = Not Reported.

Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Bove *et al*. (2024b) also ran analyses based on contributing causes, which I do not report here.

Table B.6 Employment/Assignment at Camp Lejeune and Myelodysplastic Syndrome Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Variables Adjusted For
Bove *et al.* (2024b)[b]	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					
				Began active duty between 1975-1985	11	–	2.26 (0.83-6.17)	–	Age, sex, race, rank, and education level
				All	32		1.36 (0.81-2.28)		
				Personnel who began active duty between 1975-1985, by duration of assignment (quarter yrs)[c]					
				Low (1-2)	–	–	1.77 (0.44-7.11)	–	Age, sex, race, rank, and education level
				Medium (>2-7)			2.37 (0.66-8.49)		
				High (>7)			3.11 (0.86-11.20)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Mort = Mortality; Yrs = Years.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Bove *et al.* (2024b) also ran analyses based on contributing causes, which I do not report here.
(c) Bove *et al.* (2024b) reported that "a monotonic trend was observed…with the adjusted HR ranging from 1.77 (95% CI: 0.44-7.11) in the low duration to 3.11 (95% CI: 0.86-11.20) in the high duration strata." This trend was not evaluated for statistical significance.

Table B.7 TCE Exposure at Camp Lejeune and Leukemia Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					
				Cumulative exposure level (µg/L-mos) with 10 yr lag					
				No/low (0-3,100)[a]	42	–	0.76 (0.47-1.21)	–	Age, sex, race, rank, and education
				Medium/high (>3,100-8,585)[a]	24		1.40 (0.93-2.12)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[b]			Low (>1-3,100)	16		2.00 (1.00-4.00)		
				Medium (>3,100-7,700)	11		1.54 (0.71-3.36)		
				High (>7,700-39,745)	13		1.81 (0.85-3.85)		
Bove *et al.* (2014b)	CL civilian employees with no/low exposure[b]	Mort	HR	**CL Civilian Employees**					
				Cumulative exposure level with 10 yr lag					
				Medium	2	–	0.94 (0.13-6.97)	–	Age, sex, race, blue- or white-collar occupation, and education
				High	8		1.65 (0.32-8.49)		
	CL civilian employees with < median exposure			≥Median	–		1.36 (0.35-5.30)		
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					
				Cumulative exposure level (µg/L-mos)[c,d]					
				Low (<110)	80	–	1.08 (0.66-1.78)	–	Age and sex
				Medium (110-<11,030)	41		0.76 (0.44-1.30)		
				High (≥11,030)	4		**0.28 (0.09-0.83)**		
	CL Marines & Navy personnel with low exposure (<110 µg/L-mos)			Medium (110-<11,030)	41		0.70 (0.47-1.03)		
				High (≥11,030)	4		**0.26 (0.09-0.72)**		
	CP civilian employees			**CL Civilian Employees**					
				Cumulative exposure level (µg/L-mos)[c,e]					
				Low (<10,868)	3	–	0.84 (0.20-3.52)	–	None
				Medium (10,868-<50,563)	4		1.41 (0.38-5.28)		
				High (>50,563)	1		1.32 (0.15-11.40)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
	CL civilian employees with low exposure (<10,868 µg/L-mos)			Medium (10,868-<50,563)	4		1.69 (0.38-7.57)		
				High (>50,563)	1		1.58 (0.16-15.30)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Mort = Mortality; Mos = Months; µg/L = Microgram per Liter; OR = Odds Ratio; TCE = Trichloroethylene; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al.*, 2014a). I report the values consistent with the text definition.
(b) To evaluate exposure-response relationships, the authors evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were not statistically significant. (Bove *et al.*, 2014a,b).
(c) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th (3,948 µg/L-mos) and 90th (7,863 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos (ATSDR, 2018b).
(d) There was complete correlation (gamma coefficient >0.99) between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs; the authors only reported results based on TCE analyses ATSDR (2018b).
(e) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).

Table B.8 PCE Exposure at Camp Lejeune and Leukemia Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-mos) with 10 yr lag					
				No/low (0-155)[a]	44	–	0.80 (0.51-1.26)	–	
				Medium/high (>155-8,585)[a]	22		1.37 (0.90-2.08)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[b]			Low (>1-155)	16		1.95 (0.99-3.85)		
				Medium (>155-380)	11		1.42 (0.66-3.07)		
				High (>380-8,585)	11		1.36 (0.62-2.95)		
Bove *et al.* (2014b)	CL civilian employees with no/low exposure[b,c]	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Cumulative exposure level with 10 yr lag					
				Medium	2	–	1.00 (0.14-7.39)	–	
				High	8		1.82 (0.36-9.32)		
	CL civilian employees with <median exposure			≥Median	–		1.30 (0.33-5.05)		
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					Age and sex
				Cumulative exposure level (µg/L-mos)[d]					
				Low (0-<36)	72	–	0.96 (0.58-1.59)	–	
				Medium (36-<711)	39		0.73 (0.42-1.27)		
				High (≥711)	14		0.98 (0.48-1.98)		
	CL Marines & Navy personnel with low exposure (>0-<36 µg/L-mos)			Medium (36-<711)	39		0.76 (0.51-1.15)		
				High (≥711)	14		0.98 (0.54-1.79)		
	CP civilian employees			**CL Civilian Employees**					None
				Cumulative exposure level (µg/L-mos)[d,e]					
				Low (<457)	3	–	0.84 (0.20-3.52)	–	
				Medium (457-<2,118)	4		1.41 (0.38-5.28)		
				High (≥2,118)	1		1.32 (0.15-11.40)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
	CL civilian employees with low exposure (<457 µg/L-mos)			Medium (457-<2,118)	4		1.69 (0.38-7.57)		
				High (≥2,118)	1		1.58 (0.16-15.30)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; µg/L = Microgram per Liter; Mo = Month; Mort = Mortality; OR = Odds Ratio; PCE = Perchloroethylene; TCE = Trichloroethylene; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al*., 2014a). I report the values consistent with the text definition.
(b) To evaluate exposure-response relationships, the authors evaluated continuous and log10 continuous cumulative exposures (µg/L-year). The beta coefficients were not statistically significant (Bove *et al*., 2014a,b).
(c) Bove *et al*. (2014b) report a positive monotonic exposure response relationship. This trend was not evaluated for statistical significance.
(d) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th (167 µg/L-mos) and 90th (441 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos (ATSDR, 2018b).
(e) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).

Table B.9 Benzene Exposure at Camp Lejeune and Leukemia Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-months) with 10 yr lag					
				No/low (0-45)[a]	43	–	0.73 (0.46-1.16)	–	
				Medium/high (>45-601)[a]	23		1.47 (0.97-2.23)		
	CL Marines & Navy personnel with exposure <2 µg/L-months[b]			Low (2-45)	17		**2.54 (1.27-5.08)**		
				Medium (>45-110)	11		1.46 (0.66-3.20)		
				High (>110-601)	12		1.69 (0.77-3.67)		
Bove *et al.* (2014b)	CL civilian employees with no/low exposure[b]	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Cumulative exposure level with 10 yr lag					
				Medium	1	–	0.36 (0.04-3.52)	–	
				High	8		1.25 (0.31-5.10)		
	CL civilian employees with < median exposure			≥Median	–		1.38 (0.35-5.43)		
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy personnel**					Age and sex
				Cumulative exposure level[c,d]					
				Low	80	–	1.08 (0.66-1.78)	–	
				Medium	41		0.76 (0.44-1.30)		
				High	4		**0.28 (0.09-0.83)**		
	CL Marines & Navy personnel with low exposure			Medium	41		0.70 (0.47-1.03)		
				High	4		**0.26 (0.09-0.72)**		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; µg/L = Microgram per Liter; Mos = Months; Mort = Mortality; OR = Odds Ratio; TCE = Trichloroethylene; Yr = Year.

– = Not Reported.
Bolded values indicate statistical significance.
(a) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al*., 2014a). I report the values consistent with the text definition.
(b) To evaluate exposure-response relationships, the authors evaluated continuous and log10 continuous cumulative exposures (µg/L-yr). The beta coefficients were not statistically significant, however, the log10 transformed beta coefficient was statistically significant (p = 0.05) for Marines and Navy personnel (Bove *et al*., 2014a,b).
(c) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018b).
(d) There was complete correlation (gamma coefficient >0.99) between the categorical variable for TCE and the categorical variable for benzene; the authors only reported results based on TCE analyses (ATSDR, 2018b).

Table B.10 Vinyl Chloride Exposure at Camp Lejeune and Leukemia Risk

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-Cases	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-months) with 10 yr lag					
				No/low (0-205)[a]	43	–	0.80 (0.51-1.26)	–	
				Medium/high (>205-2,800)[a]	23		1.37 (0.90-2.08)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-months[b]			Low (>1-205)	15		1.85 (0.93-3.68)		
				Medium (>205-500)	10		1.27 (0.58-2.80)		
				High (>500-2,800)	13		1.63 (0.78-3.43)		
Bove *et al.* (2014b)	CL civilian employees with no/low exposure[b,c]	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Cumulative exposure level with 10 yr lag					
				Medium	2	–	1.01 (0.14-7.45)	–	
				High	8		1.72 (0.33-8.83)		
	CL civilian employees with < median exposure			≥Median	–		1.44 (0.37-5.63)		
	CL civilian employees with no/low exposure[b]			*Average exposure level with 10 yr lag*					
				Medium	–	–	1.64 (0.31-8.73)	–	
				High	–	–	1.95 (0.37-10.43)	–	
ATSDR (2018b)	CP Marines and Navy personnel	Inc	OR	**CL Marines & Navy personnel**					Age and sex
				Cumulative exposure level[d,e]					
				Low	80	–	1.08 (0.66-1.78)	–	
				Medium	41		0.76 (0.44-1.30)		
				High	4		**0.28 (0.09-0.83)**		
	CL Marines and Navy personnel with low exposure			Medium	41		0.70 (0.47-1.03)		
				High	4		**0.26 (0.09-0.72)**		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; µg/L = Microgram per Liter; Mort = Mortality; OR = Odds Ratio; TCE = Trichloroethylene; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.

(a) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al*., 2014a). I report the values consistent with the text definition.
(b) To evaluate exposure-response relationships, the authors evaluated continuous and log10 continuous cumulative exposures (µg/L-yr). The beta coefficients were non-significant (Bove *et al*., 2014a,b).
(c) Bove *et al*. (2014b) report a positive monotonic exposure response relationship. This trend was not evaluated for statistical significance.
(d) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018b).
(e) There was complete correlation (gamma coefficient >0.99) between the categorical variable for TCE and the categorical variable for vinyl chloride; the authors only reported results based on TCE analyses (ATSDR, 2018b).

Attachment C

Epidemiology Study Quality Assessment

List of Tables

Table C.1 Leukemia Study Quality Assessment

Table C.1 Leukemia Study Quality Assessment

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Cohort Studies										
Aksoy *et al.* (1974)	Shoe, slipper, and handbag industry workers			B		Strengths • Appropriate study and comparison groups • No exclusions Weaknesses • Total worker population is an imprecise estimate based on city records • Unknown loss to follow-up	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, city employment records) • Qualitative exposure estimate (*i.e.*, ever employment in leather industry) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Cases identified using a reliable source (*i.e.*, hospital admission records) • Assessed disease incidence • 7 yrs of follow-up Weaknesses • Assessed aggregated leukemia types	Strengths • No major strengths Weaknesses • Did not control for or consider: age, sex, race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Thériault and Allard (1981)	Vinyl chloride plant and industrial complex production workers				V	Strengths • Appropriate study and comparison groups • <3% loss to follow-up Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, union lists, company payrolls, and interviews with worker/next of kin/ co-workers) • Qualitative exposure estimate (*i.e.*, ever employment at vinyl chloride plant) • Did not assess time-varying nature of exposure	Strengths • Deaths identified and validated using reliable sources (*i.e.*, death certificates and validated by nosologist) • 30 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure measured or documented before outcome • Appropriate consideration of latency (*i.e.*, required minimum of 5 yrs of exposure) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Wong (1987a,b)	Male chemical workers			B		Strengths • Appropriate study and comparison groups • 2.3% loss to follow-up Weaknesses • Unknown number of exclusions (*i.e.*, company participation and missing records)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered frequency, duration, and intensity) • No missing data • Assessed time-varying nature of exposure Weaknesses • Indirect chemical exposure measurement (*i.e.*, work location/ type of work, and uniform task approach)	Strengths • Deaths identified using reliable sources (*i.e.*, company records, SSA, DMV, and death certificates) • 32 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types • 2.2% of all deaths without death certificate (1.1% in continuously exposed group, 1.3% in intermittently exposed group, and 4.3% in unexposed group)	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • About 8% missing race data (assumed white)	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, exclusion of cases occurring ≤0.5 yrs after exposure; 10-19 or 20 year latency analyses) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Garabrant *et al.* (1988)	Aircraft manufacturing workers	T				Strengths • Appropriate study and comparison groups • 4.7% loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history) • Qualitative exposure estimate (*i.e.*, ever employment at facility) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, DMV, and credit records, death certificates, and California Death Tapes) • 25 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Race missing for unspecified number of subjects; assumed white	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, minimum 4 yrs employment at company) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Smulevich *et al.* (1988)	Vinyl chloride and PVC plant workers				V	Strengths • Appropriate study and comparison groups Weaknesses • Unknown loss to follow-up • Unknown number of exclusions	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, plant administrative registers, attendance journals, and lists of shops) • Qualitative exposure estimate (*i.e.*, ever employment at vinyl chloride or PVC plant) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, death certificates, medical histories, and necropsy protocols) • 39 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: sex Weaknesses • Did not control for or consider: age, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Blair *et al.* (1989)	Coast Guard officers and personnel	T	P	B		Strengths • Appropriate study and comparison groups • 4% loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity) • No missing data Weaknesses • Indirect chemical exposure measurements (*i.e.*, job title) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, Coast Guard, VA, SSA, credit, and DMV records, and death certificates) • 39 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types • ~8.5% of deaths had no death certificate; unclear how this was addressed	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • 8% missing race data; assumed white	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Dagg *et al.* (1992)	Employees at oil refineries, US			B		Strengths • Appropriate study and comparison groups • 4.8% loss to follow-up • <1% excluded from individual refinery analyses (*i.e.*, worked at both refineries under study) Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, company records, NDI, SSA, California death index, and Equifax) • 37 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for or considered: age, sex, and race • No missing data Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*e.g.*, analyses based on 10-19, 20-29, and ≥30 yrs since hire) Weaknesses • No major weaknesses
Schnatter *et al.* (1993)	Male Petroleum marketing/ distribution workers			B		Strengths • Appropriate study and comparison groups Weaknesses • Unknown loss to follow-up	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history) • Qualitative exposure estimate (*e.g.*, ever employment in petroleum industry) • Did not assess time-varying nature of exposure • Unknown amount of missing data	Strengths • Deaths identified using reliable source (*i.e.*, company records, Statistics Canada, and NDI) • 20 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Did not include relevant covariates in a time-varying manner	Strengths • Exposure documented before outcome • Appropriate consideration of disease latency (*i.e.*, 10 and 20 yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Tsai *et al.* (1993)	Male refinery/ petrochemical workers, US			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job history) • Qualitative exposure estimate- based on (*i.e.*, ever employment in a refinery/ petrochemical plant) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable source (*i.e.*, company records, NDI, SSA) • 17 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for or considered: age, sex, and race/ethnicity Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, workers had to have worked ≥6 mos for inclusion in cohort) Weaknesses • No major weaknesses
Wong *et al.* (1993)	Petroleum marketing/ distribution workers (land and marine)			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • Unknown number of subjects excluded	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration, frequency, and intensity) • Assessed time-varying nature of exposure • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history and JEM)	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, DMF, NDI, company records, and state vital statistics departments) • Assessed leukemia types • 44 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • 40% missing race data; assumed white	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses based on time since first exposure and at least 1 yr of exposure required) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Ruder *et al.* (1994)	Dry-cleaning workers		P			Strengths • Appropriate study and comparison groups Weaknesses • Unknown loss to follow-up	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, dry-cleaning union records) • Qualitative exposure estimate (*i.e.*, ever employment in the dry-cleaning industry) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Deaths identified using a reliable source (*i.e.*, NDI) • 51 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, follow-up period begun after >1 yr of employment) Weaknesses • No major weaknesses
Anttila *et al.* (1995)	Occupationally exposed workers	T				Strengths • Appropriate study and comparison groups • Excluded 7% of samples (not matched to subject) • No loss to follow-up Weaknesses • No major weaknesses	Strengths • Direct chemical exposure measurement (*i.e.*, U-TCA) • Quantitative exposure estimate (*i.e.*, mean personal U-TCA) • No missing data Weaknesses • Sampling was not standardized and infrequent (average 2.5 samples/participant) • Did not assess time-varying nature of exposure	Strengths • Cases identified using reliable sources (*i.e.*, Population Register Center, Finnish Cancer Registry, and Central Statistical Office of Finland) • Assessed disease incidence • 26 yrs of follow-up Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 10 and 20 yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Honda *et al.* (1995)	White male workers at a petroleum manufacturing plant, US			B		Strengths • Appropriate study and comparison groups • 3% loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment at the plant) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, state and company records) • Assessed leukemia types • 48 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race/ethnicity • No missing data Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, duration of employment ≥0.5 yrs) Weaknesses • No major weaknesses
Collingwood *et al.* (1996)	Workers at an oil refinery, US			B		Strengths • Appropriate study and comparison groups • 2% loss to follow-up • No exclusions Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, company's personnel database, PBI, NDI, SSA, and death certificates) • Assessed leukemia types • 41 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race • About 3.5% missing race data; classified as white Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses of 20-29 and 30+ yrs since first employment) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Fu *et al.* (1996)	Shoe manufacturing workers			B		Strengths • Appropriate study and comparison groups • 1% loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered intensity) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history and job titles) • Did not assess time-varying nature of exposure	Strengths • 53 yrs of follow-up Weaknesses • Assessed mortality • Unclear how deaths were identified (other than "mortality records") • Assessed aggregated leukemia	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Hayes *et al.* (1997) [Hayes *et al.*, 2000; Linet *et al.*, 2019]	NCI-CAPM cohort			B		Strengths • Appropriate study and comparison groups • <1% loss to follow-up Weaknesses • Notable weakness in study population (*i.e.*, 60% of person-yrs at risk contributed by subjects <30 yrs of age at entry) • Unknown number of exclusions	Strengths • Direct chemical exposure measurement (*i.e.*, air measurements and benzene use data) • Semi-quantitative exposure estimate (*i.e.*, considered duration and intensity) • No missing data • Assessed time-varying nature of exposure Weaknesses • No major weaknesses	Strengths • Cases identified using a reliable source (*i.e.*, occupational and medical records) • Assessed leukemia types • Assessed disease incidence • 16 yrs of follow-up Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, and chemotherapy treatment	Strengths • Exposure measured or documented before outcome • Appropriate consideration of latency (*i.e.*, 1.5 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Lynge *et al.* (1997)	Service station workers in Denmark, Finland, Norway, and Sweden			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement- based on (*i.e.*, job at time of census) • Qualitative exposure estimate (*i.e.*, employment at service station) • Did not assess time-varying nature of exposure	Strengths • Cases identified using reliable sources (*i.e.*, national cancer registries) • Assessed leukemia types • Assessed disease incidence • ≥5 yrs follow-up (Denmark: 18 yrs; Finland: 16 yrs; Norway: 21 yrs; Sweden: 20 yrs) Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures family history, genetics, smoking, blood disorders and chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Morgan *et al.* (1998)	Aircraft manufacturing workers	T				Strengths • Appropriate study and comparison groups • <0.01% excluded (missing information) Weaknesses • Unknown loss to follow-up	Strengths • No missing data • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity and peaks) Weaknesses • Indirect chemical exposure measurement (*i.e.*, job classification and JEM) • Did not consider time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, SSA or NDI and death certificates) Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race • No missing data Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Pukkala (1998)	Employees of an oil and chemical enterprise			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job categories) • Did not assess time-varying nature of exposure	Strengths • Cases identified using a reliable source (*i.e.*, Finnish Cancer Registry) • Assessed disease incidence • 24 yrs of follow-up Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, results for employees with at least 5 yrs of employment) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bulbulyan *et al.* (1999)	Female Russian printing plant employees			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job type) • Qualitative exposure estimate (*i.e.*, job title) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using a reliable source (*i.e.*, Moscow Vital Statistics Department) • 15 yrs follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Did not include relevant covariates in a time-varying manner	Strengths • Exposure measured or documented before outcome • Appropriate consideration of latency (*i.e.*, ≥2 yrs of employment at baseline) Weaknesses • No major weaknesses
Consonni *et al.* (1999)	Italian oil refinery workers			B		Strengths • Appropriate study and comparison groups • ~4.3% loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect exposure measurement (*i.e.*, job histories) • Did not assess time-varying nature of exposure • Amount of missing data unknown	Strengths • Deaths identified using reliable sources (*i.e.*, Population Statistics Offices and death certificates) • 43 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 10 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Divine *et al.* (1999a)	Employees at refineries, petrochemical facilities and research laboratories, US			B		Strengths • Appropriate study and comparison groups • 2.5% loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • Semiquantitative exposure measurement (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history and job title) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, company records, NDI, SSA, HCFA, and death certificates) • 47 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race • 1% missing data on sex or race, assumed to be male and/or white Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, had to be employed ≥5 yrs) Weaknesses • No major weaknesses
Divine *et al.* (1999b)	White male employees at refineries, petrochemical facilities and research laboratories, US			B		Strengths • Appropriate study and comparison groups • 2.5% loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • Semiquantitative exposure measurement (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history and job title) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, company records, NDI, SSA, HCFA, and death certificates) • Assessed leukemia types • 47 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, had to be employed ≥5 yrs) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Lewis *et al.* (2000a)	Active and terminated workers at 3 oil refineries and petrochemical facilities			B		Strengths • Appropriate study and comparison groups Weaknesses • Unknown loss to follow-up • Unknown number of exclusions	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, company records and work histories) • Qualitative exposure estimate (*i.e.*, employment at plant) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, benefit records, NDI, SSA, and death certificates) • 23 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia	Strengths • Controlled for: age, sex, and race • No missing data Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Hansen *et al.* (2001)	TCE-exposed workers	T				Strengths • Appropriate sample and comparison groups Weaknesses • Unable to identify individual for 36% and 48% of urine and air samples, respectively	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment history) • Qualitative exposure estimate (*i.e.*, ever exposed) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Cases identified using a reliable source (*i.e.*, Danish Cancer Registry) • Assessed disease incidence • 29 yrs follow-up Weaknesses • Assessed aggregated leukemia	Strengths • Considered age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency in sensitivity analyses (*i.e.*, 10 and 20 yr lags) Weaknesses • No major weaknesses
Ward *et al.* (2001)	Workers in the vinyl chloride industry				V	Strengths • Appropriate study and comparison groups • ≤3% loss to follow-up Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, facility records and JEM) • Qualitative exposure measurement (*i.e.*, employment in vinyl chloride industry) • Did not assess time-varying nature of exposure	Strengths • Deaths identified from using reliable sources (*i.e.*, death certificates, cancer registry records, and medical records) • Assessed disease incidence • 43 yrs follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not consider or control for: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Wong *et al.* (2001a)	Employees at oil refinery, US			B		Strengths • Appropriate study and comparison groups • 1.1% loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • Semiquantitative exposure measurement (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, SSA and NDI) • Assessed leukemia types • 39 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race/ethnicity Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • >5% were assumed white (Hispanics and unknown race) • Did not include relevant covariates in a time-varying manner	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses based on 20-39 and 40+ yrs since first exposure; 10-29 and 30+ yrs of employment) Weaknesses • No major weaknesses
Wong *et al.* (2001b)	Employees at oil refinery, US			B		Strengths • Appropriate study and comparison groups • 1.7% loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure measurement (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, SSA and NDI) • 51 yrs of follow-up • Assessed leukemia types Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race/ethnicity • No missing data Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, ≥1 yr of employment at baseline) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Rinsky *et al.* (2002)	Pliofilm manufacturing workers			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure measurement (*i.e.*, considered duration and intensity) • No missing data • Assessed time-varying nature of exposure Weaknesses • Indirect chemical exposure measurement (*i.e.*, job histories, job titles, industrial hygiene data, some air sampling data, and JEM)	Strengths • Deaths identified and validated using reliable sources (*i.e.*, SSA, DMV, death certificates, and NDI) • 47 yrs of follow-up • Assessed leukemia types Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing race data unknown	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, reported a result for cumulative exposure based on 2.5 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Travier *et al.* (2002)	Dry-cleaning workers		P			Strengths • Appropriate study and comparison groups Weaknesses • Amount lost to follow-up or excluded unknown	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported employment and industrial codes from censuses) • Qualitative exposure estimate (*i.e.*, employment in dry-cleaning industry) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Cases and deaths identified using a reliable source (*i.e.*, CERIII; a linkage of the 1960 and 1970 censuses, Swedish National Cancer Register and national register of causes of death) • Assessed leukemia types • Assessed disease incidence • 18 yrs of follow-up Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infection	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Chang *et al.* (2003)	Electronics factory workers	T	P			Strengths • Appropriate study and comparison groups • No exclusions • No loss to follow-up Weaknesses • Relatively young subjects (mean age 39 yrs at end of follow-up)	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment status at factory) • Qualitative exposure estimate (*i.e.*, ever employment at factory) • Did not assess time-varying nature of exposure	Strengths • Deaths were identified using a reliable source (*i.e.*, National Mortality Database) • 13 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 0.5, 1, and 5 yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Collins *et al.* (2003)	Benzene-exposed workers			B		Strengths • Appropriate study and comparison groups • ~2% lost to follow-up Weaknesses • Unknown number of exclusions	Strengths • Direct chemical exposure measurement (*i.e.*, area sampling and individual air exposure levels) • Quantitative exposure estimate (*i.e.*, considered duration x intensity and peak) • No missing data • Assessed time-varying nature of exposure Weaknesses • No major weaknesses	Strengths • Deaths identified using a reliable source (*i.e.*, death certificates) • Assessed leukemia types • 58 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age • No missing data Weaknesses • Did not control for or consider: sex, race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Costantini *et al.* (2003)	Shoe factory workers			B		Strengths • Appropriate study and comparison groups • No loss to follow-up • 16% excluded Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity, and peak) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, JEM constructed from factory records, photographs, interviews, and seven Dräger tube measurements) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, official register of municipality of residence, regional mortality, and official municipal registers) • 50 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not consider or control for: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Lewis *et al.* (2003)	Canadian refinery/ petrochemical workers			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • Young study population at cohort inception ($\bar{x}$ = 29.1 [M]; $\bar{x}$ = 27.5 [F])	Strengths • Semiquantitative exposure measurement (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, location, department, function, date and expert review) • Did not assess time-varying nature of exposure	Strengths • Cases and deaths identified using reliable sources (*i.e.*, Canadian Cancer Data Base and Canadian Mortality Data Base) • Assessed leukemia types • Assessed disease incidence • 31 yrs of follow-up Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure or documented before outcome • Appropriate consideration of latency (*i.e.*, employees all had ≥1 yr of employment at baseline) Weaknesses • No major weaknesses
Raaschou-Nielsen *et al.* (2003)	Blue-collar workers at TCE using companies	T				Strengths • Appropriate study and comparison groups Weaknesses • Excluded large companies that reported TCE use (200+ employees; 24% of TCE-using companies)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment history and job title/blue-collar status at companies) • ~37% of workers with unknown blue- or white-collar status (this group was assessed in sensitivity analyses) • Did not assess time-varying nature of exposure	Strengths • Cases identified using a reliable source (*i.e.*, Danish Cancer Registry) • Assessed disease incidence • 30 yrs follow-up Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, result based on at least 1 yr of employment) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Tsai *et al.* (2003)	Male chemical/ refinery workers US			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job history) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, company records, NDI, SSA) • 27 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for or considered: age, sex, and race/ethnicity Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure documented before outcome • Appropriate consideration of latency (results for employees with minimum 10 yrs of employment) Weaknesses • No major weaknesses
Bloemen *et al.* (2004)	Employees in benzene exposed jobs, US			B		Strengths • Appropriate study and comparison groups Weaknesses • Amount lost to follow-up unknown	Strengths • Direct chemical exposure measurement (*i.e.*, industrial hygiene air measurements) • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) • No missing data Weaknesses • No direct chemical exposure measurement in individuals (*i.e.*, no personal air monitors) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, company records and state registers) • Assessed leukemia types • 57 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for or considered: age, sex, and race/ethnicity • No missing data Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure measured before outcome • Appropriate consideration of latency (*i.e.*, 15 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Huebner *et al.* (2004)	Employees at 2 oil refineries and petrochemical facilities, US			B		Strengths • Appropriate study and comparison groups • ≤2% loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • ≤1% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, company records and work histories) • Did not assess time-varying nature of exposure	Strengths • Cases/deaths identified using reliable sources (*i.e.*, benefit records, NDI, and SSA) • Assessed leukemia types • 28 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for or considered: age, sex, and race/ethnicity • No missing data Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, results for employees with minimum 15 yrs of employment) Weaknesses • No major weaknesses
Sorahan *et al.* (2005)	Benzene-exposed workers			B		Strengths • Appropriate study and comparison group • 5.7% loss to follow-up Weaknesses • Unknown number of exclusions • Unclear if follow-up ended with first cancer incidence	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, personnel officer reports at firms or plants using benzene) • Qualitative exposure estimate (*i.e.*, employment in job with benzene exposure) • Did not assess time-varying nature of exposure	Strengths • Cases and deaths identified using reliable sources (*i.e.*, ONS and DHSS) • Assessed disease incidence • Assessed leukemia types • 35 yrs of follow-up Weaknesses • Cancer unconfirmed for 22 cases	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetic, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Boice *et al.* (2006)	Test stand mechanics at aerospace field laboratory	T				Strengths • Appropriate study and comparison groups • <1% loss to follow-up • <1% excluded for insufficient identifying information Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job title, personnel listings, structured worker discussions, and expert opinion) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, California death tapes, California death index, NDI, Pension Benefit Information files, SSA files, HCFA files, employment work history cards, pension records, and retirement records, and death certificates coded by trained nosologist) • 52 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race • Appropriately addressed missing data (*i.e.*, 16% missing race, used weighted approximation based on known racial proportions) Weaknesses • Did not consider or control for: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses based on 5+ yrs of employment) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Sung *et al.* (2007)	Female Taiwanese electronics factory workers	T				Strengths • Appropriate study and comparison groups • No major exclusions Weaknesses • Unknown loss to follow-up	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment status at factory from Bureau of Labor Insurance) • Qualitative exposure estimate (*i.e.*, ever employment at factory) • Number of subjects with missing employment data unknown • Did not assess time-varying nature of exposure	Strengths • Cases identified using a reliable source (*i.e.*, Taiwan National Cancer Registry) • Assessed disease incidence • 23 yrs of follow-up Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 5 yr lag) Weaknesses • No major weaknesses
Tsai *et al.* (2007)	Male petroleum refinery and chemical workers, US			B		Strengths • Appropriate study and comparison groups • 0.87% loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job history) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, company records, NDI, and SSA) • 56 yrs of follow-up • Assessed leukemia types Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race/ethnicity, Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses of employees with at least 10 yrs of employment) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Kirkeleit *et al.* (2008)	Upstream petroleum industry workers in Norway			B		Strengths • Appropriate study and comparison groups Weaknesses • Unknown loss to follow-up	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job codes) • Qualitative exposure estimate (*i.e.*, job category) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable source (*i.e.*, Cancer Registry of Norway) • Assessed leukemia types • Assessed disease incidence • 23 yrs of follow-up Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Radican *et al.* (2008)	Aircraft maintenance employees	T				Strengths • Appropriate study and comparison groups Weaknesses • Unknown number of subjects lost to follow-up or excluded	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity and frequency of peak exposure) Weaknesses • Indirect chemical exposure measurement (*i.e.*, facility files, walk through surveys and interviews of long-term employees) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Deaths identified and validated using reliable sources (*i.e.*, NDI and NDI Plus) • 22 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • About 11% had unknown race; assumed white	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Pukkala *et al.* (2009)	General population in Denmark, Finland, Iceland, Norway and Sweden	T	P			Strengths • Appropriate study and comparison groups • No loss to follow-up or exclusions • Very large dataset (~14.9 million subjects) Weaknesses • No major weaknesses	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupation in censuses) • Qualitative exposure (*i.e.*, job title) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Cases identified using reliable sources (*i.e.*, Central Population Register and national cancer registries) • Assessed leukemia types • Assessed disease incidence • ≥5 yrs of follow-up: Denmark (33 yrs), Finland (35 yrs), Iceland (23 yrs), Norway (43 yrs), Sweden (45 yrs) Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency
Bahr *et al.* (2011)	Paducah Gaseous Diffusion Plant workers	T				Strengths • Appropriate study and comparison groups • <7% excluded for unusable data, female Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure assessment (*i.e.*, level of likelihood of exposure) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment at facility and JEM) • Did not assess time-varying nature of exposure	Strengths • Cases identified using reliable sources (*i.e.*, KY Cancer Registry and death certificates) • 52 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Koh *et al.* (2011)	Male South Korean workers in a refinery and petrochemical complex			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work department) • Qualitative exposure estimate (*i.e.*, job title) • Did not assess time-varying nature of exposure	Strengths • Cases and deaths identified using reliable sources (*i.e.*, Korea National Statistics Office and Korea National Cancer Registry) • Assessed disease incidence • ≥5 yrs follow-up (mortality: 16 yrs; incidence: 9 yrs) Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders and chemotherapy treatment, and certain viral infections	Strengths • Exposure measured or documented before outcome Weaknesses • No consideration of latency
Lipworth *et al.* (2011)	Aircraft manufacturing workers	T	P			Strengths • Appropriate sample and comparison groups • <2% loss to follow-up • <2% excluded for incomplete work information Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job codes/titles, facility files, walk-through visits, and interviews with employees) • Qualitative exposure estimate (*i.e.*, all exposed workers) • Did not consider time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, California Death Statistical Master File, NDI, SSA Death Master File, pension, and other records, SSA Service to Epidemiologic Researchers, and LexisNexis records) • 49 yrs of follow-up Weaknesses • Only assessed mortality • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Seldén and Ahlborg (2011)	Dry-cleaning workers		P			Strengths • Appropriate study and comparison groups • ~2.6% of subjects excluded for missing data or "other" reasons Weaknesses • Unknown loss to follow-up; excluded 62.1% of "washing establishments" due to non-response	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, employer reported job history from questionnaire) • Qualitative exposure estimate (*i.e.*, ever employment in a dry-cleaning establishment) • Did not assess time-varying nature of exposure	Strengths • Cases identified using a reliable source (*i.e.*, national cancer registry) • Assessed disease incidence • 20 yrs follow-up Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure measured or documented before outcome • Appropriate consideration of latency (*i.e.*, built-in latency of 1-12 yrs) Weaknesses • No major weaknesses
Saberi Hosnijeh *et al.* (2013)	EPIC project subjects	T		B		Strengths • Appropriate study and comparison groups • <1% lost to follow-up Weaknesses • >50% excluded for missing information	Strengths • Semiquantitative exposure estimate (*i.e.*, considered exposure levels: high, low, and no exposure) • No missing data Weaknesses • Indirect chemical exposure assessment (*i.e.*, occupational history from questionnaire and JEM) • Did not assess time-varying nature of exposure	Strengths • Assessed leukemia types • Assessed disease incidence • ≥5 yrs follow-up (11-19 yrs, depending on cohort) Weaknesses • Some cases were self- or proxy-reported without validation	Strengths • Controlled for: age, sex, and smoking status • <2% missing data for smoking status Weaknesses • Did not consider or control for: race/ethnicity, other chemical exposures, family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections • Did not include relevant covariates (*i.e.*, smoking) in a time-varying manner	Strengths • Exposure was documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bove *et al.* (2014a)	Marines and Navy Personnel at CL	T	P	B	V	Strengths • Appropriate study and comparison groups • 2% loss to follow-up Weaknesses • Unclear if any participants were excluded	Strengths • Direct chemical exposure measurement (*i.e.*, measured in groundwater) • Semiquantitative exposure estimate (*i.e.*, considered duration × intensity) • No missing data • Assessed time-varying nature of exposure Weaknesses • No direct chemical exposure measurement in individuals (*e.g.*, no water consumption information)	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, commercial tracing service, and NDI) • 30 yrs follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race • Considered smoking using negative control diseases Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure measured before outcome • Appropriate consideration of latency (*i.e.*, 10 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bove *et al.* (2014b)	Civilian employees at CL and CP	T	P	B	V	Strengths • Appropriate study and comparison groups • ≤2% loss to follow-up Weaknesses • Unclear whether any participants were excluded	Strengths • Direct chemical exposure measurement (*i.e.*, measured in groundwater) • Semiquantitative exposure estimate (*i.e.*, duration x intensity) • No missing data • Assessed time-varying nature of exposure Weaknesses • No direct chemical exposure measurement in individuals (*e.g.*, no water consumption information)	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, a commercial tracing service, NDI, and NDI Plus) • Assessed leukemia types • 30 yrs follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for or considered: age, sex, race, and occupation (blue *vs.* white collar as a proxy for other potential occupational/ chemical exposures) • Considered smoking using negative control diseases Weaknesses • Did not control for or consider: family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections • Did not include relevant covariates in a time-varying manner • Amount of missing data is unknown	Strengths • Exposure measured before outcome • Appropriate consideration of latency (*i.e.*, 10 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Carreón *et al.* (2014)	Workers at a chemical manufacturing plant				V	Strengths • Appropriate study and comparison groups • 2% loss to follow-up • <1% excluded Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment at facility) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, NDI, NDI Plus, and Florida Department of Health) • 48 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race/ethnicity Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • 54.2% missing race/ethnicity; assumed white	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Koh *et al.* (2014)	Korean petrochemical plant maintenance workers			B		Strengths • Appropriate study and comparison groups • No loss to follow up Weakness • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, union membership) • Qualitative exposure estimate (*i.e.*, job title) • Did not assess time-varying nature of exposure	Strengths • Cases and deaths identified using reliable source (*i.e.*, Korea National Statistics Office and Korea National Cancer Registry) • Assessed disease incidence Weaknesses • Assessed aggregated leukemia types • 0-3 yrs of follow-up for incidence; 0-6 yrs of follow-up for mortality	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • No major strengths Weaknesses • No consideration of latency • Exposure not documented before outcome

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Silver *et al.* (2014)	Microelectronics facility workers	T	P			Strengths • Appropriate study and comparison groups Weaknesses • Number of subjects excluded and lost to follow-up unknown • Relatively young cohort ($\bar{x}$ = at hire was mid-20s, average follow-up 25.7 yrs)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) Weaknesses • Indirect chemical exposure measurement (*i.e.*, employment at facility and department-exposure matrix) • Amount of missing/ incomplete/conflicting data regarding work dates, facility location, department, and position (particularly for early yrs) unknown • Did not assess time-varying nature of exposure	Strengths • Cases identified using reliable sources (*i.e.*, SSA, NDI, and IRS records, and death certificates) • 40 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 2 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bassig *et al.* (2015)	Women living in urban Shanghai, China			B		Strengths • Appropriate study and comparison groups • 92.7% of eligible women participated Weaknesses • Unknown loss to follow-up	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity) Weaknesses • Indirect chemical exposure measurement (*i.e.*, lifetime occupational history from interviews/ questionnaires and JEMs) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Cases identified using reliable sources (*i.e.*, local cancer and vital statistics registries and medical charts from hospitals) • Assessed disease incidence • 13 yrs of follow-up Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and smoking • Only 1 subject missing smoking data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections • Did not include relevant covariates in a time-varying manner	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency (though all cases occurred 18+ yrs after first exposure)
Collins *et al.* (2015)	Benzene-exposed chemical workers			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • Direct chemical exposure measurement (*i.e.*, occupational air measurements) • Semiquantitative exposure estimate (*i.e.*, considered duration × intensity) • No missing data Weaknesses • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, HR records, NDI, and state vital statistics bureaus) • Assessed leukemia types • 70 yrs follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data is unknown	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 15 and 30 yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Linet *et al.* (2015)	NCI-CAPM cohort			B		Strengths • Appropriate study and comparison groups • <2% loss to follow-up Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, factory records and job title) • Qualitative exposure estimate (*i.e.*, ever exposed) • Did not assess time-varying nature of exposure	Strengths • Cases identified and validated using reliable sources (*i.e.*, facility and medical records, death certificates, and expert validation) • Assessed disease incidence • Assessed leukemia types • 28 yrs of follow-up Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 2 yr lag) Weaknesses • No major weaknesses
Stenehjem *et al.* (2015)	Male offshore oil workers in Norway			B		Strengths • Appropriate study and comparison groups • ≤1% loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration, intensity, and peak exposure) • ≤5% missing data • Assessed time-varying nature of exposure Weaknesses • Indirect chemical exposure measurement (*i.e.*, JEM)	Strengths • Cases identified using reliable source (*i.e.*, registry) • Assessed disease incidence • Assessed leukemia types • 12 yrs of follow-up Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, smoking, or other potential chemical/ occupational exposures • ≤5% missing data Weaknesses • Did not control for or consider: race/ ethnicity, family history, genetics, blood disorders, chemotherapy treatment and certain viral infections	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, analyses based on 5.5+ yrs of exposure) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Rhomberg *et al.* (2016)	Pliofilm manufacturing workers			B		Strengths • Appropriate study and comparison groups • No loss to follow-up Weaknesses • Unknown number of exclusions	Strengths • Direct chemical exposure measurement (*i.e.*, some air measurements in facility) • Quantitative exposure estimate (*i.e.*, considered duration x intensity) • Assessed the time-varying nature of exposure • No missing data Weaknesses • No direct chemical exposure measurement in individuals (*e.g.*, no individual air measurements)	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, DMV, and death certificates coded by a certified nosologist) • Assessed specific leukemia types • 57 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, and race • No missing data Weaknesses • Did not consider or control for: other chemical exposures, family history, genetics, smoking, blood disorders, and chemotherapy treatment	Strengths • Exposure measured/ documented before outcome • Appropriate consideration of latency (*i.e.*, analyses with 5, 10, 15, and 20 yr latency intervals) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Mundt *et al.* (2017)	Vinyl chloride or PVC resin manufacturing workers				V	Strengths • Appropriate study and comparison groups • <3% loss to follow-up • <2% excluded Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure assessment (*i.e.*, employment at factory >1 yr) • Qualitative exposure estimate (*e.g.*, ever employment in manufacturing plant) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, SSA, NDI, and death certificates) • 72 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not consider or control for: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, and chemotherapy treatment, and certain viral infections • Used rates for white men though 3.2% of subjects were non-white	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, all workers required to have at least 1 yr of employment) Weaknesses • No major weaknesses
Sorahan and Mohammed (2016)	Male UK petroleum distribution and oil refinery workers			B		Strengths • Appropriate study and comparison groups • 3% loss to follow-up Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, job history) • Amount of missing data unknown • Did not assess time-varying nature of exposure	Strengths • Cases identified using a reliable source (*i.e.*, registries) • Assessed disease incidence • Assessed leukemia types • 17 yrs of follow-up Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age and sex Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, and chemotherapy treatment	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, subjects had to have worked ≥1 yr for inclusion into study) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
ATSDR (2018b)	Marines & Navy personnel and civilian employees at CL and CP	T	P	B	V	Strengths • Appropriate study and comparison groups Weaknesses • 70% of CL Marines, 72% CP Marines, 55% CL civilians and 62% CP civilians did not enroll • 10% of those who reported an outcome excluded for not completing HIPAA form	Strengths • Direct chemical exposure measurement (*i.e.*, measured in groundwater) • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity) • No missing data • Assessed time-varying nature of exposure Weaknesses • No direct chemical exposure measurement in individuals (*e.g.*, no water consumption information)	Strengths • Deaths validated using reliable sources (*i.e.*, medical records and death certificates) • Assessed disease incidence • 41 yrs follow-up Weaknesses • Initial case identification relied on self-report • Assessed aggregated leukemia types	Strengths • Controlled for or considered: age, sex, race, other chemical exposures, and smoking Weaknesses • Did not control for or consider: family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections • Did not include relevant covariates in a time-varying manner • Smoking and other occupational exposures missing for >5% of participants	Strengths • Exposure measured before outcome • Appropriate consideration of latency (*i.e.*, "virtually all" participants developed cancer ≥10 yrs after being stationed or employed at CL) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Callahan *et al.* (2019)	Dry-cleaning workers		P			Strengths • Appropriate study and comparison groups Weaknesses • Unknown loss to follow-up and exclusions	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) Weaknesses • Indirect chemical exposure measurement (*i.e.*, job titles from union records, and expert opinion) • ~9% missing data that are not addressed • Did not assess time-varying nature of exposure	Strengths • Deaths identified using reliable sources (*i.e.*, death certificates, NDI, and SSA DMF) • 67 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, 10 and 20 yr lags) Weaknesses • No major weaknesses
Fedeli *et al.* (2019)	Vinyl chloride production and polymerization facility workers				V	Strengths • Appropriate study and comparison groups • <1% lost to follow-up Weaknesses • Unknown number of exclusions	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, JEM and work histories) • Qualitative exposure estimate (*i.e.*, ever employed in a vinyl chloride production and polymerization facility) • Did not assess time-varying nature of exposure	Strengths • Deaths identified using a reliable source (*i.e.*, regional mortality register) • 45 yrs of follow-up Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age • No missing data Weaknesses • Did not consider or control for: sex, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bove *et al.* (2024a)	Marines & Navy personnel and civilian workers at CL and CP	T	P	B	V	Strengths • Appropriate study and comparison groups • <2% excluded Weaknesses • Unknown loss to follow-up	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, assignment or employment at base) • Did not assess time-varying nature of exposure	Strengths • Cases identified and validated using reliable sources (*i.e.*, SSA Data for Epidemiological Researchers, NDI, and cancer registries) • Assessed leukemia types • Assessed disease incidence • 22 yrs of follow-up Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, race, and (for civilians) blue-collar work as a proxy for other occupational exposures Weaknesses • Did not control for or consider: family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • 5.2% of CP Marines & Navy personnel and 14.7% of CP civilians had other/unknown race	Strengths • Exposure documented before outcome • Appropriate consideration of latency (*i.e.*, follow-up began 10 yrs after last exposure of interest) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bove *et al.* (2024b)	Marines & Navy personnel and civilian workers at CL and CP	T	P	B	V	Strengths • Appropriate study and comparison groups • <1% loss to follow-up • No exclusions Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, assignment or employment at base) • Did not assess time-varying nature of exposure	Strengths • Cases identified and validated using reliable sources (*i.e.*, SSA Data for Epidemiological Researchers and NDI) • Assessed leukemia types • 40 yrs of follow-up Weaknesses • Assessed mortality only	Strengths • Controlled for: age, sex, race, and (for civilians) occupation (blue *vs.* white collar as a proxy for other potential occupational exposures) Weaknesses • Did not control for or consider: family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • 5.2% of CP Marines/ Navy personnel and 14.7% of CP civilians had other/unknown race	Strengths • Exposure documented before outcome Weaknesses • No consideration of latency (though, 75% of the deaths occurred >10 yrs after the water contamination ended)

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Case-Control Studies										
Bernard *et al.* (1984)	Male patients from the Yorkshire Health Region, UK			B		Strengths • Appropriate case selection Weaknesses • Unknown participation/ enrollment rates in controls or cases • Inappropriate control selection (*i.e.*, hospital-based)	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported exposure from questionnaire and interview) • Qualitative exposure estimate (*i.e.*, ever occupational benzene exposure) • Amount of missing data unknown • Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis)	Strengths • Cases identified confirmed using reliable sources (*i.e.*, registry, hospital records and histologically confirmed) • Assessed leukemia types • Assessed disease incidence Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, and certain viral infections • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency
Wilcosky *et al.* (1984)	White male rubber workers in OH	T	P	B		Strengths • Appropriate case and control selection • 100% participation rates in cases and controls (nested case-control study) • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history records linked to solvent usage) • Qualitative exposure estimate (*i.e.*, ever worked in process area with chemical exposure)	Strengths • Deaths confirmed using a reliable source (*i.e.*, company records) Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and race • No missing data Weaknesses • Did not control for or consider: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Aschengrau *et al.* (1993)	Residents of five Upper Cape towns, MA		P			Strengths • Appropriate case and control selection • Characteristics of participants and non-participants were similar • Nondifferential (≤15%) participation rates Weaknesses • ~24% of eligible controls did not participate; 20.5% of cases did not participate	Strengths • Direct chemical exposure measurement (*i.e.*, modeled contaminated drinking water wells) • Semiquantitative exposure estimate (*i.e.*, considered intensity) Weaknesses • No direct chemical exposure measurement in individuals (*e.g.*, no water consumption information) • Amount of missing data unknown	Strengths • Cases identified and validated using a reliable source (*i.e.*, MA Cancer Registry; confirmed by medical professional) • Assessed disease incidence Weaknesses • Assessed aggregated leukemia subtypes	Strengths • Controlled for: age, sex, other chemical exposures, smoking, and medical treatment with irradiation Weaknesses • Did not control for or consider: race/ ethnicity (>96% white), family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 5 yr lag) Weaknesses • No major weaknesses
Ciccone *et al.* (1993)	MDS cases in Torino, Italy			B		Strengths • Appropriate case selection • 91% participation among cases, and 99 and 82% participation rates for hospital and population-based controls, respectively • Nondifferential (≤15%) participation rates Weaknesses • Inappropriate control selection (*i.e.*, hospital-based)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered exposure likelihood) Weaknesses • Indirect chemical exposure measurement (*i.e.*, job history) • Amount of missing data unknown • Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis)	Strengths • Cases identified using reliable source (*i.e.*, hospital records) • Assessed disease incidence • Assessed leukemia types Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age, sex, genetics, and smoking Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, blood disorders, and chemotherapy treatment • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis. Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Greenland *et al.* (1994)	Workers at a transformer-assembly facility	T		B		Strengths • Appropriate case and control selection Weaknesses • About 40% excluded for various reasons (*e.g.*, ~36% for missing job history) • Unknown participation rates	Strengths • <2% of person-yrs of employment had exposure level assigned by imputation Weaknesses • Indirect chemical exposure measurement (*i.e.*, work history records and JEM) • Qualitative exposure estimate (*i.e.*, ever employment at facility and direct *vs.* indirect exposure)	Strengths • Deaths identified using reliable sources (*i.e.*, company pension office; validated by medical professional) Weaknesses • Assessed mortality only • Assessed aggregated leukemia types • Not all cancer diagnoses were validated by medical professional	Strengths • Controlled for: age, sex, and race Weaknesses • Did not consider or control for: other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 2 yr lag) Weaknesses • No major weaknesses
Schnatter *et al.* (1996a)	Male Canadian petroleum workers			B		Strengths • Appropriate case and control selection • 100% participation rate among cases Weaknesses • Unknown participation/ enrollment rates in controls	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity, duration x intensity) • Appropriately addressed missing data *via* sensitivity analysis Weaknesses • Indirect chemical exposure measurement (*i.e.*, industrial hygienists' opinion)	Strengths • Deaths identified using a reliable source (*i.e.*, Statistics Canada) Weaknesses • Assessed mortality only • Assessed aggregated leukemia types	Strengths • Controlled for or considered: age, sex, other chemical exposures, and family history Weaknesses • Did not control for or consider: race/ ethnicity, genetics, smoking, blood disorders, and chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 5 yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Nilsson *et al.* (1998)	Seamen from Sweden			B		Strengths • Appropriate case and control selection • 100% participation rates in cases and controls • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, occupational categories) • Qualitative exposure estimate (*i.e.*, job title) • Amount of missing data unknown	Strengths • Cases confirmed using a reliable source (*i.e.*, Swedish National Cancer registry) • Assessed disease incidence Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age and sex Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis Weaknesses • Insufficient consideration of latency (only >1 mo of exposure for inclusion)
Miligi *et al.* (1999)	Female residents of Italy		P			Strengths • Appropriate case and control selection • 90.6% participation rate among cases and 80.2% participation rate among controls • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • ≤5% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history) • Qualitative exposure estimate (*i.e.*, ever exposure) • Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis)	Strengths • Cases identified using reliable sources (*i.e.*, registry and hospital records) • Assessed disease incidence Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for or considered: age, sex, and smoking • ≤5% missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (excluded cases <5 yrs after exposure) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Bjork *et al.* (2001)	Residents of southern Sweden			B		Strengths • Appropriate case and control selection • 89% participation rates among cases Weaknesses • 72% participation rate among controls • Case and control participation rates differed by 17%	Strengths • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, occupational history and JEM) • Qualitative exposure estimate (*i.e.*, any exposure)	Strengths • Cases were identified/ validated using a reliable source (*i.e.*, hospital records) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex Weaknesses • Did not consider or control for: race/ ethnicity and other chemical exposures	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 20 yr lag) Weaknesses • No major weaknesses
Blair *et al.* (2001)	Residents of IA and MN			B		Strengths • Appropriate case and control selection • 86% participation rate among cases • Nondifferential (≤15%) participation rates Weaknesses • <80% participation rate among controls	Strengths • Semiquantitative exposure estimate (*i.e.*, considered intensity) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and JEM) • Potential for recall bias (*i.e.*, self-reported occupational history after diagnosis)	Strengths • Cases identified using reliable sources (*i.e.*, Cancer Registry of IA and a surveillance network of hospitals in MN; all cases were confirmed by pathology review) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, family history, and smoking Weaknesses • Did not control for or consider: other chemical exposures, genetics, blood disorders, chemotherapy treatments, or certain viral infections • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Costantini *et al.* (2001)	Male residents of 12 regions of Italy	T	P			Strengths • Appropriate case and control selection • 88% participation rate among cases, and 81% participation rate among controls • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • ≤5% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported work histories) • Qualitative exposure estimate (*i.e.*, occupational history) • Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis)	Strengths • Cases identified using reliable sources (*i.e.*, hospital records and cancer registry) • Assessed disease incidence Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for or considered: age and sex • ≤5% missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (only subjects with 5 yrs of employment before diagnosis were considered) Weaknesses • No major weaknesses
Guenel *et al.* (2002)	Gas and electric utility workers in France			B		Strengths • Appropriate case and control selection • 100% participation rate among cases and 99% participation rate among controls • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, occupational records and JEM)	Strengths • Cases identified using reliable source (*i.e.*, company cancer register) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, and other chemical exposures • No missing data Weaknesses • Did not control for or consider: race/ethnicity, family history, genetics, smoking, blood disorders and chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 2, 5, and 10 yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Adegoke *et al.* (2003)	Residents of Shanghai, China			B		Strengths • Appropriate selection of cases and controls • 91.4% participation rate among cases and 94% participation rate among controls • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • Semi-quantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported benzene exposure and JEM) • Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis) • Amount of missing data unknown	Strengths • Cases identified using a reliable source (*i.e.*, Shanghai Cancer Registry) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, prior chemotherapy treatment, or certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, analyses based on ≥15 yrs of exposure) Weaknesses • No major weaknesses
Albin *et al.* (2003)	General population of Southern Sweden			B		Strengths • Appropriate case and control selection • 85% participation rate among cases Weaknesses • 60% participation rate among controls • Case and control participation rates differed by 25%	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, self or proxy - reported exposure) • Qualitative exposure estimate (*i.e.*, ever exposure) • Amount of missing data unknown • Potential for recall bias (*i.e.*, self-reported exposure history reported after diagnosis)	Strengths • Cases identified using a reliable source (Department of Clinical Genetics, Lund University Hospital) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age and sex Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, at least 1 yr of exposure during 20 yrs prior to diagnosis) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Glass *et al.* (2003)	Australian males from the Health Watch cohort study			B		Strengths • Appropriate case and control selection • 100% participation rate in cases and controls (nested case-control) • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration, intensity) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, task-based algorithm)	Strengths • Cases identified using reliable sources (*i.e.*, registry, pathology reports, hospital records, or death certificates) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age and sex • ≤5% missing data • Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, analyses based on ≥11 yrs of employment) Weaknesses • No major weaknesses
Costantini *et al.* (2008)	Residents of eight areas in Italy	T	P	B		Strengths • Appropriate case and control selection • 85.4% participation rate among cases • Nondifferential (≤15%) participation rates Weaknesses • 71.2% participation among controls	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational history and JEM) • Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis) • Amount of missing data unknown	Strengths • Cases identified using reliable sources (*i.e.*, hospital records and Varese Cancer Registry; all cases were histologically confirmed) • Assessed disease incidence • Assessed leukemia types Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • No missing data Weaknesses • Did not control for or consider: race/ ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Kaufman *et al.* (2009)	Residents of Bangkok, Thailand			B		Strengths • Appropriate case selection • 100% participation rates in cases and controls • Nondifferential (≤15%) participation rates Weaknesses • Inappropriate control selection (*i.e.*, hospital-based)	Strengths • ≤5% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational exposure) • Qualitative exposure estimate (*i.e.*, ever exposed) • Potential for recall bias (*i.e.*, self-reported occupational exposure reported after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, hospital records) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age, sex, other chemical exposures, family history, smoking, and chemotherapy treatment Weaknesses • Did not control for or consider: race/ethnicity, genetics, or blood disorders • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency
McLean *et al.* (2009)	Residents of New Zealand		P			Strengths • Appropriate case and control selection • Nondifferential (≤15%) participation rates Weaknesses • 57% participation rate among cases and 48% participation rate among controls	Strengths • ≤5% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational histories) • Qualitative exposure estimate (*i.e.*, ever employed in textile, dyeing industry or as a machine operator) • Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, New Zealand Cancer Registry) • Assessed disease incidence Weaknesses • Assessed aggregated leukemia types	Strengths • Controlled for: age, sex, and smoking • ≤5% missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Irons *et al.* (2010)	MDS cases in Shanghai, China			B		Strengths • Appropriate case selection Weaknesses • Unknown participation rates in cases and controls • Inappropriate control selection (*i.e.*, cases treated as controls; hospital-based)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration and intensity) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job history, surrogate measurements, literature assessments, proximal measurements, and simulations) • Potential for recall bias (*i.e.*, self-reported exposure history reported after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, hospital records) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, and chemotherapy treatment	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, ≥0.5 yrs) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Lv *et al.* (2011)	MDS cases in Shanghai, China			B		Strengths • Appropriate case selection Weaknesses • Unknown participation rates in controls and cases • Inappropriate control selection (*i.e.*, hospital-based)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration, frequency, and intensity) • <2% missing data Weaknesses • Indirect chemical exposure measurement (job history and self-reported exposure) • Potential for recall bias (*i.e.*, self-reported exposure history reported after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, hospital records) • Assessed disease incidence • Assessed leukemia types Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age, sex, other chemical exposures, and smoking • <2% missing data Weaknesses • Did not control for or consider: race/ethnicity, family history, genetics, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency Weaknesses • No major weaknesses
Wong *et al.* (2010)	Residents of Shanghai, China			B		Strengths • Appropriate case selection • 97% participation rate among cases Weaknesses • Unknown participation rates in controls • Inappropriate control selection (*i.e.*, hospital-based)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, occupational self-report and expert assessment) • Potential for recall bias (*i.e.*, self-reported exposure reported after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, hospital records) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, and other chemical exposures • ≤5% missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 10 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Talibov *et al.* (2014)	NOCCA cohort	T	P	B		Strengths • Appropriate case and control selection • 97.7% participation rate among cases and 97.2% participation rate among controls • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered exposure levels) • Occupational history reported before diagnosis • ≤5% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, census occupational histories and NOCCA-JEM)	Strengths • Cases identified using reliable sources (*i.e.*, national registries) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Considered or controlled for: age, sex, and other chemical exposures • ≤5% missing data Weaknesses • Did not control for or consider: race/ethnicity, genetics, family history, prior chemotherapy treatment, smoking, and some blood disorders	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 3, 5, 7, 10, and 20 yr lags) Weaknesses • No major weaknesses
Poynter *et al.* (2017)	MN general population				V	Strengths • Appropriate case and control selection • Nondifferential (≤15%) participation rates Weaknesses • 42% participation rate among cases and 36% participation rate among controls	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported occupational exposure) • Amount of missing data unknown • Potential for recall bias (*i.e.*, self-reported exposure after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, MN Cancer Surveillance System) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age, sex, and smoking Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, blood disorders, chemotherapy treatment, and other viral infections • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, analysis of subjects with ≥5 yrs of exposure) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Copley *et al.* (2017)	MDS cases in Shanghai, China			B		Strengths • Appropriate case selection • 99.7% participation rate among controls and >99% for controls • Nondifferential (≤15%) participation rates Weaknesses • Inappropriate control selection (*i.e.*, hospital-based)	Strengths • Semiquantitative exposure estimate (*i.e.*, considered intensity) • No missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, job history and self-reported exposure) • Potential for recall bias (*i.e.*, self-reported occupational history reported after diagnosis)	Strengths • Cases identified using reliable sources (*i.e.*, hospital records) • Assessed disease incidence • Assessed leukemia types Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age, sex, other chemical exposures, smoking, and blood disorders Weaknesses • Did not control for or consider: race/ethnicity, family history, genetics, chemotherapy treatment, and certain viral infections • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency
Linet *et al.* (2019)	NCI-CAPM cohort			B		Strengths • Appropriate case and control selection • 100% participation rates in cases and controls (case-cohort) • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity) • ≤5% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, JEM)	Strengths • Cases confirmed using reliable sources (*i.e.*, medical records and death reports) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age, sex, and other chemical exposures • ≤5% missing data Weaknesses • Did not control for or consider: race/ethnicity, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 2 to 10 yr lags) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Forsell *et al.* (2020)	Male seafarers from Sweden			B		Strengths • Appropriate case and control selection • 100% participation rates in cases and controls • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration) • ≤5% missing data Weaknesses • Indirect chemical exposure measurement (*i.e.*, ever employment as a seafarer)	Strengths • Cases identified using a reliable source (*i.e.*, cancer registry) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for: age and sex • ≤5% missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, lag of ≤15, 15-19, and ≥20 yrs) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Linet *et al.* (2020)	NCI-CAPM cohort			B		Strengths • Appropriate case and control selection • 100% participation rates in cases and controls (case-cohort) • Nondifferential (≤15%) participation rates Weaknesses • No major weaknesses	Strengths • Semiquantitative exposure estimate (*i.e.*, considered duration x intensity) • No missing data Weaknesses • Indirect exposure measurement (*i.e.*, modeled exposure data from monitoring data and occupation records)	Strengths • Cases were identified using reliable sources (*i.e.*, medical records, pathology reports, and death reports) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age and sex • No missing data Weaknesses • Did not control for or consider: race/ethnicity, other chemical exposures, family history, genetics, smoking, blood disorders, chemotherapy treatment, and certain viral infections	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, considered lags of 2, 2-10, and ≥10 yrs) Weaknesses • No major weaknesses
Yarosh *et al.* (2021)	MDS patients in MN			B		Strengths • Appropriate case and control selection • Nondifferential (≤15%) participation rates Weaknesses • 64% participation rate among cases and 49% participation rate among controls	Strengths • ≤4% of cases missing exposure data Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported exposure) • Qualitative exposure estimate (*i.e.*, ever exposure) • Potential for recall bias (*i.e.*, self-reported exposure history reported after diagnosis)	Strengths • Cases identified using a reliable source (*i.e.*, MN Cancer Reporting System) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age, sex, other chemical exposures, family history, smoking, and chemotherapy treatment • <4% missing data Weaknesses • Did not control for or consider: race/ethnicity, genetics, and blood disorders	Strengths • Exposure considered prior to diagnosis • Appropriate consideration of latency (*i.e.*, 2 yr lag) Weaknesses • No major weaknesses

Study	Population	Chemical				Study Quality Factors				
		T	P	B	V	Study Population	Exposure Assessment	Outcome Assessment	Covariates Considered	Temporality
Anwar *et al.* (2022)	Patients from a hospital in Pakistan			B		Strengths • Appropriate case selection • 100% enrollment rates in cases and controls • Nondifferential (≤15%) participation rates Weaknesses • Inappropriate control selection (*i.e.*, hospital based)	Strengths • No major strengths Weaknesses • Indirect chemical exposure measurement (*i.e.*, self-reported exposure) • Qualitative exposure estimate (*i.e.*, ever exposure) • Amount of missing data unknown • Potential for recall bias (*i.e.*, self-reported exposure history)	Strengths • Cases identified using a reliable source (*i.e.*, hospital records) • Assessed leukemia types • Assessed disease incidence Weaknesses • No major weaknesses	Strengths • Controlled for or considered: age, sex, other chemical exposures, smoking, and chemotherapy treatment Weaknesses • Did not control for or consider: race/ethnicity, family history, genetics, and blood disorders • Amount of missing data unknown	Strengths • Exposure considered prior to diagnosis Weaknesses • No consideration of latency

Notes:
B = Benzene; CERIII = Cancer Environment Registry III; CL = Camp Lejeune; CP = Camp Pendleton; DHSS = Department of Health and Social Services; DMF = Death Master File; DMV = Department of Motor Vehicles; EPIC = European Prospective Investigation into Cancer and Nutrition; F = Females; HCFA = Health Care Financing Administration; HR = Human Resources; IA = Iowa; IRS = Internal Revenue Service; JEM = Job-Exposure Matrix; KY = Kentucky; M = Males; MA = Massachusetts; MDS = Myelodysplastic Syndromes; MN = Minnesota; Mo = Month; NCI-CAPM = National Cancer Institute-Chinese Academy of Preventive Medicine; NDI = National Death Index; NOCCA = Nordic Occupational Cancer Studies; NOCCA-JEM = Nordic Occupational Cancer Studies Job-Exposure Matrix; OH = Ohio; ONS = Office for National Statistics; P = Perchloroethylene; PBI = Pension Benefits Information; PVC = Polyvinyl Chloride; SSA = Social Security Administration; T/TCE = Trichloroethylene; UK = United Kingdom; US = United States; U-TCA = Urinary Trichloroacetic Acid; V = Vinyl Chloride; VA = Veterans Administration; Yr = Year.
$\bar{x}$ = Mean.

Attachment D

TCE Epidemiology Studies

List of Tables

Table D.1 TCE and Leukemia Cohort Study Characteristics

Table D.2 TCE and Leukemia Cohort Study Results

Table D.3 TCE and Acute Myeloid Leukemia Cohort Study Results

Table D.4 TCE and Chronic Myeloid Leukemia Cohort Study Results

Table D.5 TCE and Leukemia Case-Control Study Characteristics

Table D.6 TCE and Leukemia Case-Control Study Results

Table D.7 TCE and Acute Myeloid Leukemia Case-Control Study Results

Table D.8 TCE and Leukemia Meta-Analyses and Pooled Study Results

Table D.1 TCE and Leukemia Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Garabrant *et al.* (1988)	US	Aircraft manufacturing workers	B	–	14,067	1958-1982	Company employment records, termination reports, and benefits records	Mort	Leukemia & aleukemia	SSA, DMV, and credit records, death certificates, and California Death Tapes	1958-1982
Blair *et al.* (1989)	US	Coast Guard officers and personnel	M	–	3,681	1942-1970	Job titles	Mort	Leukemia	Coast guard records, VA records, SSA, credit bureaus, DMVs, and death certificates	1942-1980
Anttila *et al.* (1995)	Finland	Occupationally exposed workers	B	$\bar{x}$ = M: 32.8 F: 37.7[a]	Total: 3,089 M: 1,698 F: 1,391	1965-1982	U-TCA	Inc	Leukemia	Finnish Cancer Registry	1967-1992
Morgan *et al.* (1998)	US	Aircraft manufacturing workers	B	–	20,508 (TCE-exposed subcohort: 4,733)	1952-1977	JEM	Mort	Leukemia & aleukemia	SSA and NDI	1950-1993
Hansen *et al.* (2001)	Demark	TCE exposed workers	B	–	803	1947-1989	Employment history, and U-TCA and air-TCE	Inc	Leukemia	Danish Cancer Registry	1968-1996
Chang *et al.* (2003)	Taiwan	Electronics factory workers	B	39.25[b]	86,868	1973-1992	Employment in the factory	Mort	Leukemia	National Mortality Database	1985-1997
Raaschou-Nielsen *et al.* (2003)	Denmark	Blue-collar workers at TCE-using companies	B	–	40,049	1964-1997	Employment history (particularly at TCE-using companies) and job title	Inc	Leukemia	Danish Cancer Registry	1968-1997
Zhao *et al.* (2005)	US	Aerospace workers	M	Mort: 68.7[b] Inc: 68.6[b]	Mort: 6,044 Inc: 5,049	1950-1993	JEM	Mort & Inc	Leukemia	SSA, vital statistics, NDI, and state cancer registries	1950-2001 (mortality); 1988-2000 (incidence)
Boice *et al.* (2006)	US	Test stand mechanics at aerospace field laboratory	M	–	1,642	1948-1999	Job title, personnel listings, structured worker discussions, and expert opinion	Mort	Leukemia & aleukemia; leukemias other than CLL	California death tapes, NDI, and death certificates	1948-1999
Sung *et al.* (2007)	Taiwan	Electronics factory workers	F		63,982	1973-1992	Employment at factory	Inc	Leukemia	Taiwan National Cancer Registry	1979-2001

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Radican *et al.* (2008) [Spirtas *et al.*, 1991; Blair *et al.*, 1998]	US	Aircraft maintenance employees	B	$\bar{x}$ = 75[c]	14,455	1952-1956	Facility files, walk through surveys and interviews of long-term employees	Mort	Leukemia	NDI Plus	1979-2000
Pukkala *et al.* (2009) [Andersen *et al.*, 1999]	Denmark, Finland, Iceland, Norway, and Sweden	General population	B	30-64[d]	~14.9 million	1960-1990	Occupation based on first census at age 30-64: Denmark: 1970 Sweden: 1960, 1970, 1980, 1990 Norway: 1960, 1970, 1980 Finland: 1970, 1980, 1990 Iceland: 1981	Inc	Leukemia AML	National cancer registries	Denmark: 1971-2003 Sweden: 1961-2005 Norway: 1961-2003 Finland: 1971-2005 Iceland: 1982-2004
Bahr *et al.* (2011)	US	Paducah Gaseous Diffusion Plant workers	M	–	5,535	1952-2004	JEM	Mort	Leukemia & aleukemia	KY Cancer Registry and death certificates	1952-2004
Lipworth *et al.* (2011) [Boice *et al.*, 1999]	US	Aircraft manufacturing workers	B	–	5,443	1960-1996	Job codes/titles and activities linked to records on chemical use, environmental monitoring, employee interviews, and IH records	Mort	Leukemia; aleukemia; leukemias other than CLL	CA Death Statistical Master File, NDI, SSA, Comserv, Inc.,[e] company pension and records	1960-2008
Saberi Hosnijeh *et al.* (2013)	Europe	EPIC cohorts[f]	B	$\bar{x}$ = 53.01 (range: 35-70)	241,465	–	Occupational history obtained from questionnaire at recruitment, and JEM	Inc	Myeloid leukemia; lymphoid leukemia; AML; CML	Population cancer registries, health insurance records, pathology registries, and contact with subject or next of kin	1992-2010

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Bove *et al.* (2014a)	US	Marines and Navy personnel at CL and CP	B	CL and CP: 20-49[g]	CL: 154,932 CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[g] CP: 34-60[g]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008
Silver *et al.* (2014)	US	Microelectronics facility workers	B	$\bar{x}$ = 25.7-28.7[h]	34,494	1969-2001	Department-exposure matrix and work history	Mort	Non-CLL leukemia	SSA, NDI, IRS, and death certificates	1969-2009
ATSDR (2018b)[i]	US	Marines & Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[j] Civilian Employees CL: 60-64[j] CP: ≥65[j]	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168 CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines and Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Leukemia	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Notes:

AML = Acute Myeloid Leukemia; ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CA = California; CL = Camp Lejeune; CLL = Chronic Lymphocytic Leukemia; CML = Chronic Myeloid Leukemia; CP = Camp Pendleton; DMV = Department of Motor Vehicles; EPIC = European Prospective Investigation into Cancer and Nutrition; F = Females; IH = Industrial Hygiene; Inc = Incidence; IRS = Internal Revenue Service; JEM = Job-Exposure Matrix; KY = Kentucky; M = Males; Mort = Mortality; NDI = National Death Index; SSA = Social Security Administration; TCE = Trichloroethylene; UK = United Kingdom; US = United States; U-TCA = Urinary Trichloroacetic Acid; VA = Veterans Affairs; Yr = Year.

$\bar{x}$ = Mean; – = Not Reported.

When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.

(a) Mean age at first sampling for total cohort (Anttila *et al.*, 1995).

(b) Mean age at end of follow-up (Chang *et al.*, 2003; Zhao *et al.*, 2005).

(c) Mean age of subjects still alive at the end of follow-up (Radican *et al.*, 2008).

(d) Age at initial census (Pukkala *et al.*, 2009).

(e) Comserv, Inc. is "a computer services firm specializing in locating death records (www.comserv-inc.com)" (Lipworth *et al.*, 2011).

(f) At the time, the EPIC project consisted of 23 cohorts from centers in 10 European countries (Denmark, France, Greece, Germany, Italy, The Netherlands, Norway, Spain, Sweden, and the UK) (Saberi Hosnijeh *et al*., 2013).
(g) Median age from start to end of follow-up (Bove *et al*., 2014a,b).
(h) Mean age at hire (Silver *et al*., 2014).
(i) Ages and population sizes are reflective of Marines, Navy personnel, and civilian respondents to the 2011-2012 morbidity survey and do not include the 5,263 Marines, Navy personnel, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis (ATSDR, 2018b).
(j) Median age range at survey or death (ATSDR, 2018b).

Table D.2 TCE and Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Garabrant *et al.* (1988)	US national population	Mort	SMR	Overall	16	19.35	0.82 (0.47-1.34)	–	Age, sex, race, and calendar yr
Blair *et al.* (1989)	US national population	Mort	SMR	Marine inspectors	7	5	1.55 (0.62-3.19)	–	Age, sex, race, and calendar time
				Non-inspectors	3	5	0.66 (0.14-1.94)		
				Nonspecific Chemical Exposure Levels (by Working Level x Mos)[b]					
				Non-exposed	4	5	0.8	1.46[b]	Age, sex, race, and calendar time
				130	2	2	1.05		
				≥130	4	2	1.84		
Anttila *et al.* (1995)	Finland general population	Inc	SIR	**Yrs Since First Measurement**					
				0-9	3	–	1.76 (0.36-5.16)	–	Age, sex, and calendar yr
				10-19	0	2.18	– (0-1.69)		
				20+	2	–	2.72 (0.33-9.83)		
				Over entire period	5		1.08 (0.35-2.53)		
				Mean Personal U-TCA Level (µmol/L)					
				<100	1	–	0.39 (0.01-2.19)	–	Age, sex, and calendar yr
				100+	4		2.65 (0.72-6.78)		
Morgan *et al.* (1998)	US national population	Mort	SMR	**Leukemia and Aleukemia**					
				Overall cohort	42	42.8	0.98 (0.72-1.33)	–	–
				TCE-exposed subcohort	10	9.5	1.05 (0.50-1.93)		
				Low cumulative exposure	3	3.55	0.85 (0.17-2.47)		
				High cumulative exposure	7	5.98	1.17 (0.47-2.41)		
	Low and no exposure		RR	Low and no exposure	–	–	Ref		Age at hire and gender
				Peak: Medium and high exposure	7		1.10 (0.49-2.49)		
				Cumulative (low)	3		0.69 (0.21-2.32)		
				Cumulative (high)	7		1.14 (0.50-2.60)		
Hansen *et al.* (2001)	Danish general population	Inc	SIR	Men	5	2.7	1.9 (0.6-4.4)	–	Age, sex, and calendar yr
				Women	1	0.3	3.1 (0.04-18)		
				Group 2:[c] 1960 and 1970 census	15	–	1.84 (1.11-3.06)		
Chang *et al.* (2003)	Taiwanese general population	Mort	SMR	Males	2	4.55	0.44 (0.05-1.59)	–	Age, sex, and calendar yr
				Females	8	14.71	0.54 (0.23-1.07)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Raaschou-Nielsen *et al.* (2003)	Danish general population	Inc	SIR	Men	69	63.8	1.1 (0.84-1.37)	–	Age, sex, and calendar yr
				Women	13	7.8	1.7 (0.89-2.86)		
				All workers in subcohort with expected higher exposure levels[d]	–	–	0.96 (0.69-1.30)		
Boice *et al.* (2006)	California general population	Mort	SMR	**Leukemia and Aleukemia**					
				Any exposure	5	4.6	1.08 (0.35-2.53)	–	Age, sex, race, and calendar yr
				Duration of employment as a test stand mechanic					
				<5 yrs	6	4.3	1.40 (0.52-3.05)	–	Age, sex, race, and calendar yr
				≥5 yrs	2	2.3	0.86 (0.10-3.10)		
				Leukemias Other than CLL					
				Any exposure	4	3.8	1.05 (0.29-2.69)	–	Age, sex, race, and calendar yr
				Duration of employment as a test stand mechanic					
				<5 yrs	5	3.5	1.41 (0.46-3.29)	–	Age, sex, race, and calendar yr
				≥5 yrs	2	1.9	1.06 (0.13-3.82)		
Sung *et al.* (2007)	Taiwan general population	Inc	SIR	Female electronics factory workers (5 yr lag)	23	29.5	0.78 (0.49-1.17)	–	Age, sex, and calendar yr
Radican *et al.* (2008)	Unexposed workers	Mort	HR	**Male Workers**					
				Tertile of cumulative exposure score					
				0-5 unit yrs	11	–	0.86 (0.36-2.02)	–	Age, sex, and race
				5-25 unit yrs	4		0.51 (0.16-1.63)		
				>25-unit yrs	9		0.87 (0.35-2.14)		
				Category of exposure[e]					
				Low, intermittent	20	–	0.89 (0.42-1.91)	–	Age, sex, and race
				Low, continuous	16		1.11 (0.50-2.45)		
				Peak, infrequent	3		0.63 (0.17-2.30)		
				Peak frequent	9		0.69 (0.28-1.69)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				Female Workers					
				Tertile of cumulative exposure score					
				0-5 unit yrs	1	–	0.35 (0.05-2.72)	–	Age, sex, and race
				5-25 unit yrs	0		–		
				>25 unit yrs	2		0.48 (0.10-2.19)		
				Category of exposure[e]					
				Low, intermittent	1	–	0.27 (0.03-2.09)	–	Age, sex, and race
				Low, continuous	0		–		
				Peak, infrequent	0		–		
				Peak frequent	2		0.38 (0.08-1.75)		
Pukkala *et al.* (2008, 2009)	Denmark, Finland, Iceland, Norway, and Sweden general populations	Inc	SIR	**Men**					
				Mechanics, ironware workers, and metalware workers	2,350	–	0.97 (0.94-1.02)	–	Country, sex, age, and 5 yr calendar period
				Electrical workers	876	–	1.02 (0.96-1.09)	–	Country, sex, age, and 5 yr calendar period
				Printers and related workers	267	–	0.96 (0.85-1.08)	–	Country, sex, age, and 5 yr calendar period
				Painters and wallpaper hangers	475	–	0.97 (0.88-1.06)	–	Country, sex, age, and 5 yr calendar period
				Women					
				Mechanics, ironware workers, and metalware workers	110	–	0.96 (0.79-1.15)	–	Country, sex, age, and 5 yr calendar period
				Electrical workers	99	–	1.13 (0.92-1.37)	–	Country, sex, age, and 5 yr calendar period

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
				Printers and related workers	61	–	0.88 (0.67-1.13)	–	Country, sex, age, and 5 yr calendar period
				Painters and wallpaper hangers	6	–	0.67 (0.25-1.46)	–	Country, sex, age, and 5 yr calendar period
Bahr *et al.* (2011)	US general population	Mort	SMR	**Exposure Level Group[f]**					
				All workers	24	–	1.15 (0.74-1.72)	–	Age, sex, and race
				0	0		0.00 (0.00-9.12)		
				0-1	4		0.90 (0.24-2.30)		
				2-3	5		0.72 (0.23-1.69)		
				0-3	9		0.79 (0.36-1.50)		
				4-5	15		1.47 (0.82-2.43)		
	Exposure level category 1		SRR	**Exposure Level Category[f]**					
				2	–	–	0.73 (0.15-3.45)	–	Age, sex, and race
				3			1.89 (0.61-5.86)		
				Total			1.40 (0.46-4.24)		
Lipworth *et al.* (2011)	California general population (white workers), US general population (non-white workers)	Mort	SMR	**Leukemia and Aleukemia**					
				Exposed factory workers	35	39.7	0.88 (0.61–1.23)	–	Race, age, calendar yr, and sex
				Leukemia Other than CLL					
				Exposed factory workers	27	31.1	0.87 (0.57-1.26)	–	Race, age, calendar yr, and sex

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Saberi Hosnijeh *et al.* (2013)	Unexposed subjects	Inc	HR	**Myeloid Leukemias**					
				Low exposure	70	75,975	1.02 (0.74-1.39)	0.58	Age, sex, smoking status, alcohol intake, and country
				High exposure	5	7,865	0.60 (0.24-1.51)		
				Lymphoid Leukemias					
				Low exposure	85	75,975	0.91 (0.68-1.20)	0.36	Age, sex, smoking status, alcohol intake, and country
				High exposure	8	7,865	0.76 (0.37-1.59)		
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					
				Cumulative exposure level (µg/L-mos) with 10 yr lag					
				No/low (0-3,100)[g]	42	–	0.76 (0.47-1.21)	–	Age, sex, race, rank, and education
				Medium/high (>3,100-8,585)[g]	24		1.40 (0.93-2.12)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[h]			Low (>1-3,100)	16		2.00 (1.00-4.00)		
				Medium (>3,100-7,700)	11		1.54 (0.71-3.36)		
				High (>7,700-39,745)	13		1.81 (0.85-3.85)		
Bove *et al.* (2014b)	CL civilian employees with no/low exposure[h]	Mort	HR	**CL Civilian Employees**					
				Cumulative exposure level with 10 yr lag					
				Medium	2	–	0.94 (0.13-6.97)	–	Age, sex, race, blue- or white-collar occupation, and education
				High	8		1.65 (0.32-8.49)		
	CL civilian employees with < median exposure			≥Median	–		1.36 (0.35-5.30)		
Silver *et al.* (2014)	Unexposed workers	Mort	HR	5 modified exposure-yrs[i]	–	–	1.31 (0.98-1.75)	–	Age, sex, and pay code

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					
				Cumulative exposure level (µg/L-mos)[j,k]					
				Low (<110)	80	–	1.08 (0.66-1.78)	–	Age and sex
				Medium (110 to <11,030)	41		0.76 (0.44-1.30)		
				High (≥11,030)	4		**0.28 (0.09-0.83)**		
	CL Marines & Navy personnel with low exposure (<110 µg/L-mos)			Medium (110 to <11,030)	41		0.70 (0.47-1.03)		
				High (≥11,030)	4		**0.26 (0.09-0.72)**		
	CP civilian employees			**CL Civilian Employees**					
				Cumulative exposure level (µg/L-mos)[j,l]					
				Low (<10,868)	3	–	0.84 (0.20-3.52)	–	None
				Medium (10,868 to <50,563)	4		1.41 (0.38-5.28)		
				High (>50,563)	1		1.32 (0.15-11.40)		
	CL civilian employees with low exposure (<10,868 µg/L-mos)			Medium (10,868 to <50,563)	4		1.69 (0.38-7.57)		
				High (>50,563)	1		1.58 (0.16-15.30)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CLL = Chronic Lymphocytic Leukemia; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mo = Month; Mort = Mortality; OR = Odds Ratio; Ref = Reference; RR = Relative Risk; SIR = Standard Incidence Ratio; SMR = Standardized Mortality Ratio; SRR = Standardized Rate Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; US = United States; U-TCA = Urinary Trichloroacetic Acid; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Derived using 4-point exposure rating scale (no exposure: administrative positions; low exposure: staff with duties that occasionally required vessel inspections; moderate exposure: staff with inspection duties that did not regularly include hull structures and regular inspection of hull structures in geographic areas where chemicals were not major cargo items; high exposure: persons who performed hull inspections at ports where vessels transported chemicals) and duration of months on the job. The trend value is χ^2 (Blair *et al.*, 1989).
(c) Persons classified with either a relevant occupational code or the relevant industrial code at the time of both censuses (Hansen *et al.*, 2001).
(d) This subcohort with expected higher exposure levels consisted of those with at least 1 yr duration of employment and yr of first employment before 1980 (Raaschou-Nielsen *et al.*, 2003).

(e) Intermittent: subjects who used TCE infrequently; continuous: subjects who used TCE regularly; low exposure: subjects who used TCE for bench top work (to clean small parts); peak exposure: subjects who worked with vapor degreasers (Radican *et al*., 2008).
(f) The job-exposure matrix specified exposure levels 0 (*i.e*., no possibility of exposure) through 5 (*i.e*., highest probability of exposure) for the workers. The authors specified five exposure groups: 0 consisted of exposure level 0; 1 consisted of exposure levels 0 and 1; 2 consisted of levels 2 and 3; 3 consisted of levels 0-3; 4 consisted of levels 4 and 5. The authors also specified four exposure categories: 0 consisted of exposure level 0; 1 consisted of level 1; 2 consisted of levels 2 and 3; 3 consisted of levels 4 and 5 (Bahr *et al*., 2011).
(g) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al*., 2014a). I report the values consistent with the text definition.
(h) To evaluate exposure-response relationships, the authors evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were not statistically significant. (Bove *et al*., 2014a,b).
(i) Modified exposure-yrs were based on the duration of employment in a department using a chemical or chemical class, modified by the extent of general chemical use based on department factors and by position factor for the worker's position title (Silver *et al*., 2014).
(j) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th (3,948 µg/L-mos) and 90th (7,863 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos (ATSDR, 2018b).
(k) There was complete correlation (gamma coefficient >0.99) between the categorical variables for TCE, benzene, vinyl chloride, and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018b).
(l) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).

Table D.3 TCE and Acute Myeloid Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Pukkala *et al.* (2008, 2009)	Denmark, Finland, Iceland, Norway, and Sweden general populations	Inc	SIR	**Men**					
				Mechanics, ironware workers, and metalware workers	626	–	0.98 (0.90-1.06)	–	Country, sex, age, and 5 yr calendar period
				Electrical workers	246	–	1.06 (0.93-1.20)	–	Country, sex, age, and 5 yr calendar period
				Printers and related workers	58	–	0.77 (0.59-1.00)	–	Country, sex, age, and 5 yr calendar period
				Painters and wallpaper hangers	126	–	0.98 (0.82-1.16)	–	Country, sex, age, and 5 yr calendar period
				Women					
				Mechanics, ironware workers, and metalware workers	32	–	0.84 (0.57-1.19)	–	Country, sex, age, and 5 yr calendar period
				Electrical workers	26	–	0.86 (0.56-1.26)	–	Country, sex, age, and 5 yr calendar period
				Printers and related workers	21	–	0.89 (0.55-1.37)	–	Country, sex, age, and 5 yr calendar period
				Painters and wallpaper hangers	2	–	0.66 (0.08-2.37)	–	Country, sex, age, and 5 yr calendar period

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Saberi Hosnijeh *et al*. (2013)	Unexposed subjects	Inc	HR	Low exposure	–	–	1.00 (0.66-1.51)	0.77	Age, sex, smoking status, alcohol intake, and country
				High exposure			0.73 (0.22-2.38)		

Notes:
CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; SIR = Standardized Incidence Ratio; TCE = Trichloroethylene; Yr = Year.
– = Not Reported.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.

Table D.4 TCE and Chronic Myeloid Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-cases	Risk Estimate (95% CI)	p_{trend}	Variables Adjusted For
Saberi Hosnijeh *et al.* (2013)	Unexposed subjects	Inc	HR	Low exposure	–	–	0.98 (0.51-1.87)	0.80	Age, sex, smoking status, alcohol intake, and country
				High exposure	–	–	0.77 (0.18-3.42)		

Notes:
CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; TCE = Trichloroethylene.
– = Not Reported.

Table D.5 TCE and Leukemia Case-Control Study Characteristics

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Wilcosky *et al.* (1984)	OH (US)	Mor	Lymphatic leukemia	1964-1974	M	40-84	10	Cohort of male rubber workers	1,336	Cohort of male rubber workers	Work history records linked to data on all authorized solvent usage in the plant by process area and yr
Greenland *et al.* (1994)	US	Mort	Leukemia	1969-1984	M[a]	21-90[b]	22	Employee pension records (subset validated)	1,202	Workers at same transformer-manufacturing facility[c]	JEM from job history records[d]
Costantini *et al.* (2001)	Italy	Inc	Leukemia	1991-1993	M	20-74	383	Local and major city hospitals, regional cancer institutes, and Cancer Registries	918	Random sample of general population from municipal demographic and National Health Service files	Self-reported occupational history from in-person interviews
Costantini *et al.* (2008)	Italy	Inc	Leukemia and AML	1991-1993	B	20-74	586	Local and major city hospitals, regional cancer institutes, and the Varese Cancer Registry[e]	1,278	Demographic files of municipalities	Occupational history from in-person interview/ questionnaire and JEM
Talibov *et al.* (2014)	Finland, Iceland, Norway, and Sweden	Inc	AML	Sweden & Norway: 1961-2005 Finland: 1971-2005 Iceland: 1982-2004	B	≥20	14,982	NOCCA cohort	74,505	NOCCA cohort	NOCCA-JEM, occupational information from census records

Notes:
AML = Acute Myeloid Leukemia; B = Both Males and Females; CLL = Chronic Lymphocytic Leukemia; Inc = Incidence; JEM = Job-Exposure Matrix; M = Males; Mort = Mortality; NOCCA = Nordic Occupational Cancer Studies; NOCCA-JEM = Nordic Occupational Cancer Studies Job-Exposure Matrix; OH = Ohio; TCE = Trichloroethylene; US = United States; Yr = Year.
– = Not Reported.
(a) Participants restricted to white males (Greenland *et al.*, 1994).
(b) Age at death (Greenland *et al.*, 1994).
(c) Controls consisted "of workers who died of causes thought to be unrelated to the exposures under study" (Greenland *et al.*, 1994).
(d) TCE was used at the company between 1930 and 1977 as a degreaser (Greenland *et al.*, 1994).
(e) Based on information from Costantini *et al.* (2001, 2008).

Table D.6 TCE and Leukemia Case-Control Study Results

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{trend}	Covariate Adjustment
Wilcosky *et al.* (1984)	Mort	OR	**Lymphatic Leukemia**					
			Unexposed	–	–	Ref	–	Age, sex, and race
			Cumulative exposure >1 yr	2		0.81 (–)		
Greenland *et al.* (1994)	Mort	OR	No exposure	–	–	Ref	–	Age and yr of death
			Any exposure			1.10 (0.46-2.66)		
Costantini *et al.* (2001)	Inc	OR	Not employed as machinery fitters, assemblers, and precision instrument makers	–	–	Ref	–	Age
			Machinery fitters, assemblers, and precision instrument makers	24		1.0 (0.6-1.7)		
			Not employed as a painter	–		Ref		
			Painters	10		1.7 (0.8-3.8)		
Costantini *et al.* (2008)	Inc	OR	**Leukemia by Level of Exposure**					
			Unexposed	355	811	Ref	–	Age, gender, education, and study area
			Very low/low	17	34	1.0 (0.5-1.8)		
			Medium/high	11	29	0.7 (0.4-1.5)		

Notes:
CI = Confidence Interval; Inc = Incidence; Mort = Mortality; OR = Odds Ratio; Ref = Reference; TCE = Trichloroethylene; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.

Table D.7 TCE and Acute Myeloid Leukemia Case-Control Study Results

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{trend}	Covariate Adjustment
Costantini *et al.* (2008)	Inc	OR	**Exposure Level**					
			Unexposed	133	811	Ref	–	Age, gender, education, and study area
			Very low/low	6	34	1.0 (0.4-2.5)		
			Medium/high	6	29	1.1 (0.5-2.9)		
Talibov *et al.* (2014)	Inc	HR	**Cumulative Exposure with 10 Yr Lag (ppm-yr)**					Country, sex, year of birth, and exposure to aliphatic and alicyclic hydrocarbons, methylene chloride, other organic solvents, PCE, 1,1,1-TCA, benzene, toluene, formaldehyde, and ionizing radiation
			Occupationally unexposed	–	–	Ref	0.08	
			≤16.2	302	1,760	0.93 (0.79-1.09)		
			16.2-121	275	1,373	1.12 (0.94-1.33)		
			>121	68	345	1.12 (0.83-1.49)		
			Sex-Specific Cumulative Exposure with 10 Yr Lag (ppm-yr)					
			Males					
			Occupationally unexposed	–	–	Ref	0.08	
			≤16.2	239	1,400	0.92 (0.77-1.09)		
			16.2-121	225	1,117	1.09 (0.91-1.32)		
			>121	49	242	1.10 (0.79-1.54)		
			Females					
			Occupationally unexposed	–	–	Ref	0.61	
			≤16.2	63	360	1.15 (0.71-1.85)		
			16.2-121	50	258	1.41 (0.85-2.36)		
			>121	19	101	1.52 (0.71-3.26)		
			Age-Specific Cumulative Exposure with 10 Yr Lag (ppm-yr)					
			<50 yrs					
			Occupationally unexposed	–	–	Ref	0.40	
			≤5.62	38	229	0.84 (0.53-1.35)		
			5.62-24.9	35	178	1.03 (0.65-1.64)		
			>24.9	11	43	1.28 (0.62-2.63)		

Study	Statistical Analysis							
	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{trend}	Covariate Adjustment
			≥50 yrs					
			Occupationally unexposed	–	–	Ref	0.13	
			≤5.62	88	562	0.87 (0.66-1.14)		
			5.62-24.9	194	1,043	1.07 (0.87-1.31)		
			>24.9	279	1,423	1.08 (0.90-1.29)		

Notes:
1,1,1-TCA = 1,1,1-Trichloroethane; CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; OR = Odds Ratio; PCE = Perchloroethylene; ppm = Parts Per Million; Ref = Reference; TCE = Trichloroethylene; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.

Table D.8 TCE and Leukemia Meta-Analyses and Pooled Study Results

Study	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Included Study Designs	Statistical Model	Group	Risk Estimate	Risk Estimate (95% CI)
Wartenberg *et al.* (2000)	Meta-analysis	Inc	Leukemia	2	Cohort	Inverse-variance weighting	Tier I[a]	SIR	1.0 (0.5-2.1)
		Mort		4			Tier I[a]	SMR	1.0 (0.7-1.3)
		Mort		4			Tier II[b]	SMR	0.9 (0.7-1.2)
		Inc		1			Tier III[c]	SIR	0.7 (0.4-1.5)
		Mort		3			Tier IV[d]	SMR	0.8 (0.5-1.3)
Alexander *et al.* (2006)	Meta-analysis	Inc and Mort	Leukemia	7	Cohort and case-control	Random effects	Overall	SRRE	1.11 (0.93-1.32)
Hansen *et al.* (2013)	Pooled	Inc	Leukemia	3	Cohort	Poisson	Men and women	SIR	1.06 (0.67-1.60)
Karami *et al.* (2013)	Meta-analysis	Inc and Mort	Leukemia	10	Cohort and case-control	Random effects	All occupational TCE exposure studies	RR	1.10 (0.94-1.28)
				9	Cohort				1.10 (0.94-1.29)

Notes:
CI = Confidence Interval; Inc = Incidence; Mort = Mortality; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; SRRE = Summary Relative Risk Estimate; TCE = Trichloroethylene.
– = Not Reported.
Bolded values indicate statistical significance.
(a) "Tier I studies are those which TCE exposure has been inferred for individual study subjects and best characterized - such as biomarkers and JEMs and studies that conducted other worksite exposure evaluations such as walkthroughs" (Wartenberg *et al.*, 2000).
(b) "Tier II studies are those in which there is putative TCE exposure, but individuals are not identified as uniquely exposed to TCE" (Wartenberg *et al.*, 2000).
(c) "Tier III studies are studies of dry cleaner and laundry workers in which subjects are exposed to a variety of solvents including TCE" (Wartenberg *et al.*, 2000).
(d) Wartenberg *et al.* (2000) lists this result in Table 9 under "Tier IV cohort" studies, but Tier IV is not described in the text and the included studies are listed as Tier III studies in Table 3.

Attachment E

TCE Animal Carcinogenicity Studies

List of Tables

Table E.1 TCE and Leukemia Chronic Oral Study Results

Table E.2 TCE and Leukemia Chronic Inhalation Study Results

Table E.3 TCE and Leukemia Chronic Toxicity Study Quality Overview

Table E.4 TCE and Leukemia Chronic Toxicity Study Quality Assessment

Table E.1 TCE and Leukemia Chronic Oral Study Results

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-d)	Leukemia Outcome				
						Leukemia	Lymphocytic Leukemia	Monocytic Leukemia	Myelomonocytic Leukemia	Lymphoma or Leukemia
NCI (1976)[a]	Osborne-Mendel rat	78	110 wks	20 M	0	0/20	NR	NR	NR	NR
				50 M	549	0/50	NR	NR	NR	NR
					1,097	0/50	NR	NR	NR	NR
				20 F	0	0/20	NR	NR	NR	NR
				50 F	549	0/48	NR	NR	NR	NR
					1,097	0/50	NR	NR	NR	NR
	$B6C3F_1$ mouse		90 wks	20 M	0	0/20	NR	NR	NR	NR
				50 M	1,169	0/50	NR	NR	NR	NR
					2,339	0/48	NR	NR	NR	NR
				20 F	0	0/20	NR	NR	NR	NR
				50 F	869	0/50	NR	NR	NR	NR
					1,739	0/47	NR	NR	NR	NR
Henschler *et al.* (1984)[b]	Swiss (ICR/HA) mouse	72	106 wks	50 M	0	NR	NR	NR	NR	NR
					2,400 (TCE industrial)	NR	NR	NR	NR	NR
					2,400 (TCE pure)	NR	NR	NR	NR	NR
					2,400 (TCE + EB)	NR	NR	NR	NR	NR
					2,400 (TCE + EPC)	NR	NR	NR	NR	NR
					2,400 (TCE + EB + EPC)	NR	NR	NR	NR	NR
				50 F	0	NR	NR	NR	NR	NR
					1,800 (TCE industrial)	NR	NR	NR	NR	NR
					1,800 (TCE pure)	NR	NR	NR	NR	NR
					1,800 (TCE + EB)	NR	NR	NR	NR	NR
					1,800 (TCE + EPC)	NR	NR	NR	NR	NR
					1,800 (TCE + EB + EPC)	NR	NR	NR	NR	NR

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-d)	Leukemia Outcome				
						Leukemia	Lymphocytic Leukemia	Monocytic Leukemia	Myelomonocytic Leukemia	Lymphoma or Leukemia
Maltoni *et al.* (1986a, 1988a)[c]	Sprague-Dawley rat	52	Until natural death	30 M	0	0/30	NR	NR	NR	NR
					50	2/30	NR	NR	NR	NR
					250	3/30	NR	NR	NR	NR
				30 F	0	1/30	NR	NR	NR	NR
					50	0/30	NR	NR	NR	NR
					250	0/30	NR	NR	NR	NR
NTP (1988)[d,e]	ACI rat	103	103 wks	50 M	0	1/50	0/50	2/50	NR	NR
					500	0/50	0/50	0/50	NR	NR
					1,000	0/46	0/46	0/46	NR	NR
				50 F	0	0/50	0/50	0/50	NR	NR
					500	0/50	0/50	0/50	NR	NR
					1,000	1/46	0/46	0/46	NR	NR
	August rat			50 M	0	0/50	0/50	1/50	NR	NR
					500	0/50	0/50	0/50	NR	NR
					1,000	0/49	0/49	0/49	NR	NR
				50 F	0	1/50	0/50	0/50	NR	NR
					500	0/50	0/50	0/50	NR	NR
					1,000	3/50[†]	0/50	2/50[†]	NR	NR
	Marshall rat			50 M	0	0/50	0/50	0/50	NR	NR
					500	0/50	0/50	0/50	NR	NR
					1,000	0/50	0/50	0/50	NR	NR
				50 F	0	0/50	1/50	0/50	NR	NR
					500	0/50	0/50	0/50	NR	NR
					1,000	0/48	0/48	0/48	NR	NR
	Osborne-Mendel rat			50 M	0	0/50	0/50	1/50	NR	NR
					500	0/50	0/50	0/50	NR	NR
					1,000	1/50	0/50	1/50	NR	NR
				50 F	0	0/50	0/50	0/50	NR	NR
					500	1/50	0/50	2/50	NR	NR
					1,000	0/50	0/50	0/50	NR	NR

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-d)	Leukemia Outcome				
						Leukemia	Lymphocytic Leukemia	Monocytic Leukemia	Myelomonocytic Leukemia	Lymphoma or Leukemia
NTP (1990)[f]	F344/N rat	103	103 wks	50 M	0	5/50	NR	0/50	0/50	6/50
					500	5/50	NR	0/50	0/50	5/50
					1,000	1/49	NR	0/49	0/49	1/49
				50 F	0	14/50	NR	0/50	0/50	NR
					500	4/50**,‡	NR	0/50	0/50	NR
					1,000	9/50	NR	0/50	0/50	NR
	$B6C3F_1$ mouse			50 M	0	0/50	NR	0/50	0/50	NR
					1,000	0/50	NR	0/50	0/50	NR
				50 F	0	0/48	NR	0/48	0/48	7/48
					1,000	0/49	NR	0/49	1/49	14/49‡

Notes:
EB = Epoxybutane; EPC = Epichlorohydrin; F = Females; M = Males; mg-kg-d = Milligram per Kilogram per Day; NCI = National Cancer Institute; NOS = Not Otherwise Specified; NR = Not Reported; NTP = National Toxicology Program; TCE = Trichloroethylene; US EPA = United States Environmental Protection Agency; Wk = Week.
*$p < 0.05$; **$p < 0.01$; †$p_{trend} < 0.05$; ‡Life Table-$p < 0.05$
(a) I used the number of animals examined when the denominators for incidences were not specified. NCI (1976) concluded that the results in rats were inconclusive due to significant early mortality. The technical-grade TCE used in this study contained two stabilizer compounds that are known carcinogens (epichlorohydrin and 1,2-epoxybutane).
(b) The exposure duration of 72 wks is based on US EPA (2011). Henschler *et al.* (1984) exposed mice to a TCE alone or with triethanolamine and/or 1,2-epoxybutane (stabilizers). The stabilizer compound 1,2-epoxybutane is a known carcinogen. US EPA (2011) stated, "Background incidence of tumors was high in all groups." Due to overt toxicity attributable to gavage protocol, the exposures were noncontinuous (stopped for all groups during wks 35-40, 65, and 69-78) and doses were reduced by a factor of 2 from wk 40 onward. Overall, the authors concluded that "this study does not support the suggestion that trichloroethylene itself is carcinogenic under realistic exposure conditions" (Henschler *et al.*, 1984).
(c) I calculated these incidences from percentages provided in Maltoni *et al.* (1986a). Maltoni *et al.* (1986a, 1988a) reported, "A borderline higher frequency of leukemias was observed in treated males (NS) [not significant], mainly due to lymphoblastic lymphosarcomas, but not in females." Maltoni *et al.* (1986a, 1988a) also noted, "For all the TCE dependent tumors in rats and mice, a concentration/daily dose relationship has been observed, with the sole exception of immunoblastic lymphosarcomas in rats."
(d) I used the number of animals necropsied when the denominators for incidences were not specified. US EPA (2011) said the TCE was stabilized with diisopropylamine. Due to the high dose, NTP (1988) concluded that "the studies are considered inadequate for either comparing or assessing trichloroethylene-induced carcinogenesis in these strains of rats."
(e) NTP (1988) reported a significant p_{trend} for combined "NOS" and "monocytic" incidences (5/50), not separately.
(f) I used the number of animals necropsied when the denominators for incidences were not specified. NTP (1990) concluded that the results in male F344/N rats were "equivocal for detecting a carcinogenic response because both groups receiving TCE showed significantly reduced survival compared to vehicle controls (35/50, 70%; 20/50, 40%; 16/50, 32%) and because 20% of the animals in the high dose group were killed accidently by gavage error." NTP (1990) also noted that "[t]he increased incidence of dosed female mice with malignant lymphoma ($p < 0.05$) and lymphoma or leukemia ($p < 0.05$) are not considered to be related to the administration of TCE. The incidence in the concurrent control group was somewhat lower than that in the historical controls, and the incidences in dosed females were within the ranges of historical incidences." Regarding rats, a decreased trend in the group of "lymphoma or leukemia" incidences was reported for males; however, the trend was not statistically significant.

Table E.2 TCE and Leukemia Chronic Inhalation Study Results

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Leukemia
Fukuda *et al.* (1983)[a]	Crj:CD (Sprague-Dawley) rat	104	107 wks	49-51 F	0	NR
					50	NR
					150	NR
					450	NR
	Crj:CD-1 (ICR) mouse			49-50 F	0	NR
					50	NR
					150	NR
					450	NR
Maltoni *et al.* (1986a, 1988a)[b]	$B6C3F_1$ mouse	78	Until natural death	90 M	0	6/90
					100	1/90
					300	0/90
					600	1/90
				90 F	0	33/90
					100	33/90
					300	36/90
					600	38/90
	Swiss mouse			90 M	0	3/90
					100	4/90
					300	1/90
					600	5/90
				90 F	0	21/90
					100	15/90
					300	15/90
					600	25/90
	Sprague-Dawley rat	104		40 M	0	3/40
					100	3/40
					300	3/40
					600	6/40
				40 F	0	0/40
					100	3/40
					300	2/40
					600	4/40
				90-95 M	0	6/95
					100	10/90
					300	11/90
					600	9/90
				90-105 F	0	7/105
					100	6/90
					300	0/90
					600	7/90

Notes:
F = Females; IARC = International Agency for Research on Cancer; M = Males; NR = Not Reported; ppm = Parts Per Million; TCE = Trichloroethylene; Wk = Week.
(a) Fukuda *et al.* (1983) did not differentiate between lymphoma and leukemia. The TCE contained a stabilizer compound that is a known carcinogen (epichlorohydrin). In addition, Fukuda *et al.* (1983) noted that "a few [animals]...were killed accidentally, severely autolyzed or cannibalized, and died before the first appearance of tumors among the groups." Finally, as noted by IARC (2014a), there was incomplete reporting of tumor incidences, *i.e.*, "Only malignant tumours were counted when both malignant and benign tumours were observed in the same organ."

(b) I calculated these incidences from percentages provided in Maltoni *et al*. (1986a, 1988a). Maltoni *et al*. (1986a) reported that TCE "possibly increases [in] the incidence (no dose-correlated) of leukemias (mainly immunoblastic lymphosarcomas) in rats" when TCE was administered by inhalation.

Table E.3 TCE and Leukemia Chronic Toxicity Study Quality Overview

Parameter	Summary
Reporting	Most studies reported sufficient information on the species, test article name, experimental design, exposure conditions, and outcome assessment methods, with the exception of NTP (1988) and Fukuda *et al*. (1983). Fukuda *et al*. (1983) reported tumor incidences incompletely (only malignant tumors were reported when both malignant and benign tumors were observed in the same organ). NTP (1988) stated, "There was insufficient documentation of animal breeding, clinical observations, environmental conditions, and analytical chemistry data. Also, individual animal identification was not always verifiable." All the bioassays for which it was stated that the hematopoietic system was examined reported leukemia findings, with the exception of Fukuda *et al*. (1983) and Henschler *et al*. (1984).
Allocation	Animals were randomly allocated to dose groups in the majority of chronic studies with the exception of Fukuda *et al*. (1983).
Bias	Two chronic oral gavage studies conducted by NTP (1988, 1990) were concluded by the agency to be insufficient to evaluate the potential carcinogenicity of TCE due, in part, to reduced survival in the high-dose group from accidental gavage error. Furthermore, the tested doses were too high, resulting in early mortality in both of these studies (NTP, 1988, 1990). Fukuda *et al*. (1983) and Henschler *et al*. (1984) exposed mice to TCE that contained stabilizer compounds known to be carcinogenic (epichlorohydrin and 1,2-epoxybutane, respectively). Fukuda *et al*. (1983) also indicated that "a few [animals] that were killed accidentally, severely autolyzed or cannibalized, and died before the first appearance of tumors among the groups," suggesting inadequate animal husbandry. NCI (1976) also exposed mice to TCE that contained two stabilizer compounds (epichlorohydrin and 1,2-epoxybutane) known to be carcinogenic; high early mortality was observed due to the testing of high doses. No other studies had indications that there were differences across treatment groups that could bias results.
Sample	Chronic bioassays had adequate sample sizes, with the exception of NCI (1976) (for controls) and Maltoni *et al*. (1986a, 1988a) (for oral exposure and experiment BT304 bis).
Chemical Administration and Characterization	All studies provided adequate information on chemical source, purity, and composition, and independently verified chemical purity or took steps to ensure reported exposure levels were accurate, with the exception of NCI (1976), in which exposure levels were not verified.
Exposure Conditions	The exposure duration was too short for assessing carcinogenicity in rats in five chronic oral studies (NCI, 1976; Maltoni *et al*., 1986a, 1988a; NTP, 1988, 1990): rats were exposed for 78 wks in NCI (1976), 52 wks (oral exposure) in Maltoni *et al*. (1986a, 1988a), and 103 wks in NTP (1988, 1990). The exposure period was too short for assessing carcinogenicity (72 wks) in mice in one chronic oral study (Henschler *et al*., 1984). The exposure period for mice in NTP (1990) and Fukuda *et al*. (1983) was too long for assessing carcinogenicity (103 and 104 wks, respectively). Therefore, the studies have limited human relevance. In an additional chronic study (Henschler *et al*., 1984), only one dose was tested per sex, and the exposures were noncontinuous due to overt toxicity attributable to gavage protocol (stopped for all groups during wks 35-40, 65, and 69-78), and doses were reduced by a factor of 2 from wk 40 onward.

Parameter	Summary
Outcome Assessment	In some chronic studies, there was a reliable, valid, sensitive, and specific outcome assessment method and an appropriate observation period. However, six studies (Maltoni *et al.*, 1986a, 1988a; NCI, 1976; Fukuda *et al.*, 1983; Henschler *et al.*, 1984; NTP, 1990) had observation periods that were too long. Maltoni *et al.* (1986a, 1988a) examined animals after "spontaneous death." Fukuda *et al.* (1983) examined rats and mice after 107 wks (3 wks post-exposure), and NCI (1976) observed rats and mice until 110 wks (32 wks post-exposure) and 90 wks (12 wks post-exposure). Henschler *et al.* (1984) observed mice for 106 wks (34 wks post-exposure). Finally, NTP (1990) observed mice for 103 wks. In these bioassays, animals were observed either over their entire lifetimes, when moribund, or following spontaneous death, which could have biased results. In addition, Maltoni *et al.* (1986a, 1988a) used statistical methods that did not account for the extended observation period (Gift *et al.*, 2013). In addition, NTP (1990) only observed rats for 103 wks, which is too short for evaluating carcinogenicity.

Notes:
NCI = National Cancer Institute; NTP = National Toxicology Program; TCE = Trichloroethylene; Wk = Week.

Table E.4 TCE and Leukemia Chronic Toxicity Study Quality Assessment

Study	Strengths	Weaknesses	Human Relevance
Chronic – Oral			
NCI (1976)	Reporting Allocation Exposure Conditions (mice)	**Bias:** TCE contained two stabilizer compounds that are carcinogens; high early mortality in rats due to testing high doses **Sample:** Small sample size (controls) **Exposure Conditions:** Exposure duration too short (rats) **Chemical Administration and Characterization:** Did not verify exposure levels **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Henschler *et al.* (1984)	Allocation Sample Chemical Administration and Characterization	**Reporting:** No leukemia data **Exposure Conditions:** Non-continuous exposure; only one dose tested per sex; exposure duration too short **Bias:** TCE contained a stabilizer compound that is carcinogenic **Outcome Assessment:** Exposures were intermittent and doses were reduced due to overt toxicity from initial dosing protocols; observation period too long	**None:** No leukemia data
Maltoni *et al.* (1986a, 1988a)	Reporting Allocation Bias Chemical Administration and Characterization	**Sample:** Small sample size **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too long; improper statistics	**Limited:** Low study quality
NTP (1988)	Allocation Sample Chemical Administration and Characterization	**Reporting:** Insufficient documentation of animal breeding, clinical observations, environmental conditions, and analytical chemistry data **Bias:** Reduced survival in high dose groups due to gavage error and high doses **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too short	**Limited:** Low study quality

Study	Strengths	Weaknesses	Human Relevance
NTP (1990)	Reporting Allocation Sample Chemical Administration and Characterization	**Bias:** Reduced survival in high dose group due to gavage error; tested doses were too high, resulting in mortality **Exposure Conditions:** Exposure duration too short (rats); too long (mice) **Outcome Assessment:** Observation period too short (rats); too long (mice)	**Limited:** Low study quality
Chronic – Inhalation			
Fukuda *et al.* (1983)	Sample Chemical Administration and Characterization Exposure Conditions (rats)	**Reporting:** Incomplete reporting of tumor incidences; no leukemia data. **Bias:** TCE contained stabilizer compounds that are carcinogenic; animal husbandry inadequate **Allocation:** Did not specify whether random **Exposure Conditions:** Exposure duration too long (mice) **Outcome Assessment:** Observation period too long	**None:** No leukemia data.
Maltoni *et al.* (1986a, 1988a)	Reporting Allocation Bias Sample Chemical Administration and Characterization Exposure Conditions	**Outcome Assessment:** Observation period too long; improper statistics	**Limited:** Low study quality

Note:
TCE = Trichloroethylene.

Attachment F

PCE Epidemiology Studies

List of Tables

Table F.1 PCE and Leukemia Cohort Study Characteristics

Table F.2 PCE and Leukemia Cohort Study Results

Table F.3 PCE and Acute Lymphocytic Leukemia Cohort Study Results

Table F.4 PCE and Acute Myeloid Leukemia Cohort Study Results

Table F.5 PCE and Chronic Myeloid Leukemia Cohort Study Results

Table F.6 PCE and Leukemia Case-Control Study Characteristics

Table F.7 PCE and Leukemia Case-Control Study Results

Table F.8 PCE and Acute Myeloid Leukemia Case-Control Study Results

Table F.1 PCE and Leukemia Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Blair *et al.* (1989)	US	Coast Guard officers and personnel	M	–	3,681	1942-1970	Job titles	Mort	Leukemia	Coast guard, VA, SSA, credit bureau, and DMV records, and death certificates	1942-1980
Ruder *et al.* (1994)	US	Dry-cleaning workers	B	$\bar{x}$ = 34.6[a]	1,708	1940-1990	Membership of dry-cleaning union based on union records	Mort	Leukemia & aleukemia combined	NDI	1940-1990
Travier *et al.* (2002)	Sweden	Dry-cleaning workers	B	–	–	1960 and 1970 censuses	Census job codes	Inc	Leukemia, ALL, ANLL, CNLL	CERIII	1971-1989
Chang *et al.* (2003)	Taiwan	Electronics factory workers	B	39.25[b]	86,868	1973-1992	Employment in the factory	Mort	Leukemia	National Mortality Database	1985-1997
Pukkala *et al.* (2009) [Lynge and Thygesen, 1990; Andersen *et al.*, 1999; Ji and Hemminki, 2005, 2006]	Denmark, Finland, Iceland, Norway, and Sweden	General population	B	30-64[c]	~14.9 million	1960-1990	Occupation based on first census at age 30-64: Denmark: 1970 Sweden: 1960, 1970, 1980, 1990 Norway: 1960, 1970, 1980 Finland: 1970, 1980, 1990 Iceland: 1981	Inc	Leukemia, AML	National cancer registries	Denmark: 1971-2003 Sweden: 1961-2005 Norway: 1961-2003 Finland: 1971-2005 Iceland: 1982-2004
Seldén and Ahlborg (2011)	Sweden	Laundry and dry-cleaning workers	B	–	9,440	1973-1983	Questionnaire mailed to all "washing establishments" in Swedish Postal Address Registry	Inc	Lymphoid leukemia, myeloid leukemia	National cancer registry	1985-2006

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Lipworth *et al.* (2011) [Boice *et al.*, 1999]	US	Aircraft manufacturing workers	B	–	5,830	1960-1996	Job codes/titles and activities linked to records on chemical use, environmental monitoring, employee interviews, and IH records	Mort	Leukemia & aleukemia combined, non-CLL leukemia	CA Death Statistical Master File, NDI, SSA, Comserv, Inc.,[d] company pension and records	1960-2008
Bove *et al.* (2014a)	US	Marines and Navy personnel at CL and CP	B	CL and CP: 20-49[e]	CL: 154,932 CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[e] CP: 34-60[e]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008
Silver *et al.* (2014)	US	Microelectronics facility workers	B	$\bar{x}$ = 25.7-28.7[f]	34,494	1969-2001	Department-exposure matrix matched with work history	Mort	Non-CLL leukemia	SSA, NDI, IRS, and death certificates	1969-2009
ATSDR (2018b)[g]	US	Marines & Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[h] Civilian Employees CL: 60-64[h] CP: ≥65[h]	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168 CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines and Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Leukemia	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Callahan *et al.* (2019) [Blair *et al.*, 1990, 2003]	US	Dry-cleaning workers	B	$\bar{x}$ = 36.7	5,369	1948-2014	Solvent exposure scores calculated based on job titles from union records, and expert opinion	Mort	Leukemia	Death certificates, NDI, and SSA Death Master File	1948-2014

Notes:
ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; ANLL = Acute Nonlymphocytic Leukemia; ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CA = California; CERIII = Cancer Environment Registry III; CL = Camp Lejeune; CLL = Chronic Lymphatic Leukemia; CNLL = Chronic Nonlymphocytic Leukemia; CP = Camp Pendleton; DMV = Department of Motor Vehicles; IH = Industrial Hygiene; Inc = Incidence; IRS = Internal Revenue Service; M = Males; Mort = Mortality; NDI = National Death Index; PCE = Perchloroethylene; SSA = Social Security Administration; US = United States; VA = Veterans Affairs; Yr = Year.
$\bar{x}$ = Mean; – = Not Reported.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Age at first employment (Ruder *et al.*, 1994).
(b) Mean age at end of follow-up (Chang *et al.*, 2003).
(c) Age at initial census (Pukkala *et al.*, 2009).
(d) Comserv, Inc. is "a computer services firm specializing in locating death records (www.comserv-inc.com)" (Lipworth *et al.*, 2011).
(e) Median age from start to end of follow-up (Bove *et al.*, 2014a,b).
(f) Mean age at hire (Silver *et al.*, 2014).
(g) Ages and population sizes are reflective of Marines, Navy personnel, and civilian respondents to the 2011-2012 morbidity survey and do not include the 5,263 Marines, Navy personnel, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis (ATSDR, 2018b).
(h) Median age range at survey or death (ATSDR, 2018b).

Table F.2 PCE and Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Blair *et al.* (1989)	US general population	Mort	SMR	Marine inspectors	7	5	1.55 (0.62-3.19)	–	Age, sex, race, and calendar time
				Non-inspectors	3	5	0.66 (0.14-1.94)		
				Non-specific Chemical Exposure Levels (by Working Level x Mos)[b]					
				Non-exposed	4	5	0.8	1.46	Age, sex, race, and calendar time
				130	2	2	1.05		
				≥130	4	2	1.84		
Ruder *et al.* (1994)	US general population	Mort	SMR	Entire cohort	2	–	0.40 (0.05-1.44)	–	Age, sex, and race
				Women	2	–	0.76 (0.09-2.74)		
				Men	0	–	–		
Travier *et al.* (2002)	Never employed in relevant occupation or industry	Inc	RR	Group 1:[c] 1960 or 1970 census	86	–	1.06 (0.85-1.31)	–	Age, sex, calendar period, geographic region, and urban setting
				Group 2:[d] 1960 and 1970 census	15		**1.84 (1.11-3.06)**		
				Group 2:[d] Males	3		0.93 (0.30-2.88)		
				Group 2:[d] Females	12		**2.53 (1.44-4.46)**		
Chang *et al.* (2003)	Taiwanese general population	Mort	SMR	Males	2	4.55	0.44 (0.05-1.59)	–	Age, sex, and calendar yr
				Females	8	14.71	0.54 (0.23-1.07)		
Pukkala *et al.* (2009)	Denmark, Finland, Iceland, Norway, and Sweden general populations	Inc	SIR	**Launderers and Dry Cleaners**					
				Men	37	–	**0.71 (0.50-0.99)**	–	Country, sex, age, and 5-yr calendar period
				Women	167		1.03 (0.88-1.19)		
Seldén and Ahlborg (2011)	Swedish national population	Inc	SIR	**Lymphoid Leukemia**					
				All workers	11	–	1.01 (0.51-1.81)	–	Age, sex, and calendar yr
				Females	6		0.86 (0.32-1.87)		
				Males	5		1.29 (0.42-3.01)		
				Myeloid Leukemia					
				All workers	11	–	1.06 (0.53-1.89)	–	Age, sex, and calendar yr
				Females	6		0.82 (0.30-1.77)		
				Males	5		1.64 (0.53-3.83)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Lipworth *et al.* (2011)	California general population (white workers), US general population (non-white workers)	Mort	SMR	**Leukemia and Aleukemia**					
				Exposed factory workers	18	25.5	0.71 (0.42–1.12)	–	Race, age, calendar yr, and sex
				Non-CLL Leukemia					
				Exposed factory workers	14	20.2	0.69 (0.38-1.16)	–	Race, age, calendar yr, and sex
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					
				Cumulative exposure level (µg/L-mos) with 10-yr lag					
				No/low (0-155)[e]	44	–	0.80 (0.51-1.26)	–	Age, sex, race, rank, and education
				Medium/high (>155-8,585)[e]	22		1.37 (0.90-2.08)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[f]			Low (>1-155)	16		1.95 (0.99-3.85)		
				Medium (>155-380)	11		1.42 (0.66-3.07)		
				High (>380-8,585)	11		1.36 (0.62-2.95)		
Bove *et al.* (2014b)	CL civilian employees with no/low exposure[f,g]	Mort	HR	**CL Civilian Employees**					
				Cumulative exposure level with 10-yr lag					
				Medium	2	–	1.00 (0.14-7.39)	–	Age, sex, race, blue- or white-collar occupation, and education
				High	8		1.82 (0.36-9.32)		
	CL civilian employees with <median exposure			≥Median	–		1.30 (0.33-5.05)		
Silver *et al.* (2014)	Unexposed workers	Mort	HR	5 modified exposure-yrs[h]	–	–	1.05 (0.66-1.66)	–	Age, sex, and pay code
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					
				Cumulative exposure level (µg/L-mos)[i]					
				Low (0 to < 36)	72	–	0.96 (0.58-1.59)	–	Age and sex
				Medium (36 to <711)	39		0.73 (0.42-1.27)		
				High (≥711)	14		0.98 (0.48-1.98)		
	CL Marines & Navy personnel			Medium (36 to <711)	39		0.76 (0.51-1.15)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
	with low exposure (>0 to <36 µg/L-mos)			High (≥711)	14		0.98 (0.54-1.79)		
	CP civilian employees			**CL Civilian Employees**					
				Cumulative exposure level (µg/L-mos)[i,j]					
				Low (<457)	3	–	0.84 (0.20-3.52)	–	None
				Medium (457 to <2,118)	4		1.41 (0.38-5.28)		
				High (≥2,118)	1		1.32 (0.15-11.40)		
	CL civilian employees with low exposure (<457 µg/L-mos)			Medium (457 to <2,118)	4		1.69 (0.38-7.57)		
				High (≥2,118)	1		1.58 (0.16-15.30)		
Callahan *et al.* (2019)	US general population	Mort	SMR	**External Comparison**					
				Entire cohort	20	23	0.9 (0.5-1.3)	–	Age, sex, race, and calendar period
				Follow-up through 1992	12	15	0.8 (0.4-1.4)		
				Follow-up from 1993-2014	8	8	1.0 (0.4-1.9)		
				Yr joined the union					
				Before 1960	16	17	0.9 (0.5-1.5)	–	Age, sex, race, and calendar period
				During/after 1960	4	6	0.7 (0.2-1.7)		
	No/low estimated solvent exposure		HR	**Internal Comparison: Levels of Solvent Exposure[k,l]**					
				Medium	5	–	0.5 (0.2-1.7)	0.97	Age, sex, race, and decade of enrollment
				High	1		1.2 (0.1-11.4)		
	Tertile 1 of cumulative estimated solvents exposure			**Internal Comparison: Cumulative Exposure[k,l]**					
				Tertile 2	3	–	0.3 (0.1-1.1)	0.55	Age, sex, race, and decade of enrollment
				Tertile 3	5		0.4 (0.1-1.5)		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CLL = Chronic Lymphatic Leukemia; CP = Camp Pendleton; HR = Hazard Ratio; Inc = Incidence; Mo = Month; Mort = Mortality; OR = Odds Ratio; PCE = Tetrachloroethylene; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; US = United States; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.

(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Derived using 4-point exposure rating scale (no exposure: administrative positions; low exposure: staff with duties that occasionally required vessel inspections; moderate exposure: staff with inspection duties that did not regularly include hull structures and regular inspection of hull structures in geographic areas where chemicals were not major cargo items; high exposure: persons who performed hull inspections at ports where vessels transported chemicals) and number of mos on the job (Blair *et al.*, 1989).
(c) Group 1: Persons classified with either a relevant occupational code or the relevant industrial code at the time of one or both censuses (Travier *et al.*, 2002).
(d) Group 2: Persons classified with either a relevant occupational code or the relevant industrial code at the time of both censuses (Travier *et al.*, 2002).
(e) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al.*, 2014a). I report the values consistent with the text definition.
(f) To evaluate exposure-response relationships, the authors evaluated continuous and log 10 continuous cumulative exposures (µg/L-yr). The beta coefficients were not statistically significant (Bove *et al.*, 2014a,b).
(g) Bove *et al.* (2014b) report a positive monotonic exposure response relationship. This trend was not evaluated for statistical significance.
(h) Modified exposure-yrs were based on the duration of employment in a department using a chemical or chemical class, modified by the extent of general chemical use based on department factors and by position factor for the worker's position title (Silver *et al.*, 2014).
(i) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th (167 µg/L-mos) and 90th (441 µg/L-mos) percentiles because the 50th percentile was 0 µg/L-mos (ATSDR, 2018b).
(j) The correlation between TCE and PCE was approximately 1 (ATSDR, 2018b).
(k) Tertiles based on cumulative exposure score: Exposure Score x Duration of Union Membership (Callahan *et al.*, 2019).
(l) Results incorporating a 10 or 20 year lag were similar to those with no lag (Callahan *et al.*, 2019).

Table F.3 PCE and Acute Lymphocytic Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-cases	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Travier *et al.* (2002)	Never employed in relevant occupation or industry	Inc	RR	Group 1:[a] 1960 or 1970 census	5	–	1.95 (0.80-4.75)	–	Age, sex, calendar period, geographic region, and urban setting
				Group 2:[b] 1960 and 1970 census	0		–		

Notes:
CI = Confidence Interval; Inc = Incidence; PCE = Perchloroethylene; RR = Relative Risk.
– = Not Reported.
(a) Group 1: Persons classified with either a relevant occupational code or the relevant industrial code at the time of one or both censuses (Travier *et al.*, 2002).
(b) Group 2: Persons classified with either a relevant occupational code or the relevant industrial code at the time of both censuses (Travier *et al.*, 2002).

Table F.4 PCE and Acute Myeloid Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Travier *et al.* (2002)	Never employed in relevant occupation or industry	Inc	RR	**ANLL**					
				Group 1:[b] 1960 or 1970 census	23	–	0.95 (0.63-1.44)	–	Age, sex, calendar period, geographic region, and urban setting
				Group 2:[c] 1960 and 1970 census	3		1.25 (0.40-3.89)		
				Group 2:[c] Males	2		2.42 (0.61-9.69)		
				Group 2:[c] Females	1		0.66 (0.09-4.66)		
Pukkala *et al.* (2008, 2009)	Denmark, Finland, Iceland, Norway, and Sweden general populations	Inc	SIR	**Launderers and Dry Cleaners**					
				Men	8	–	0.60 (0.26-1.18)	–	Country, sex, age, and 5-yr calendar period
				Women	47	–	0.89 (0.65-1.18)	–	

Notes:
ANLL = Acute Nonlymphocytic Leukemia; CI = Confidence Interval; Inc = Incidence; PCE = Perchloroethylene; RR = Relative Risk; SIR = Standardized Incidence Ratio; Yr = Year.
– = Not Reported.
(a) Observed cases and expected cases for SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Group 1: Persons classified with either a relevant occupational code or the relevant industrial code at the time of one or both censuses (Travier *et al.*, 2002).
(c) Group 2: Persons classified with either a relevant occupational code or the relevant industrial code at the time of both censuses (Travier *et al.*, 2002).

Table F.5 PCE and Chronic Myeloid Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases	Exposed Non-cases	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Travier *et al.* (2002)	Never employed in relevant occupation or industry	Inc	RR	**CNLL**					
				Group 1:[a] 1960 or 1970 census	13	–	1.15 (0.66-1.98)	–	Age, sex, calendar period, geographic region, and urban setting
				Group 2:[b] 1960 and 1970 census	3		2.77 (0.89-8.61)		
				Group 2:[b] Males	0		–		
				Group 2:[b] Females	3		**4.43 (1.42-13.81)**		

Notes:
CI = Confidence Interval; CNLL = Chronic Non-lymphocytic Leukemia; Inc = Incidence; PCE = Perchloroethylene; RR = Relative Risk.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Group 1: Persons classified with either a relevant occupational code or the relevant industrial code at the time of one or both censuses (Travier *et al.*, 2002).
(b) Group 2: Persons classified with either a relevant occupational code or the relevant industrial code at the time of both censuses (Travier *et al.*, 2002).

Table F.6 PCE and Leukemia Case-Control Study Characteristics

Study	Location	Outcome Type	Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Wilcosky *et al.* (1984)	Male rubber workers in OH	Mort	Lymphatic leukemia	1964-1974	M	40-84	10	Cohort of male rubber workers	1,336	Cohort of male rubber workers	Work history records were linked to data on all authorized solvent usage in the plant by process area and yr
Aschengrau *et al.* (1993)	US	Inc	Leukemia	1983-1986	B	–	34	MCR	737	RDD, HCFA, and death certificates	Estimated from drinking water using an algorithm[a]
Miligi *et al.* (1999)	Italy	Inc	Leukemia	–	F	20-74	260	Hospitals, pathology departments, cancer registries, large cancer institutes	828	Demographic files from local areas and the National Health Service	Occupational history and from in-person interviews
Costantini *et al.* (2001)	Italy	Inc	Leukemia	1991-1993	M	20-74	383	Local and major city hospitals, regional cancer institutes, and Cancer Registries	918	Random sample of general population from municipal demographic and National Health Service files	Self-reported occupational history from in-person interviews
Costantini *et al.* (2008)	Italy	Inc	Leukemia, AML	1991-1993	B	20-74	586	Local and major city hospitals, regional cancer institutes, and the Varese Cancer Registry[b]	1,278	Demographic files of municipalities	Occupational history from in-person interview/ questionnaire, and JEM
McLean *et al.* (2009)	NZ	Inc	Leukemia	2003-2004	B	20-75	225	National Cancer Registry	471	Electoral Roll	Occupational history from in-person interviews coded according to the NZSCO 1999
Talibov *et al.* (2014)	Finland, Iceland, Norway, Denmark, and Sweden	Inc	AML	1961-2005	B	67 (median)	14,982	Nordic Occupational Cancer Study cohort	74,505	Nordic Occupational Cancer Study cohort	JEM, occupational information from census records

Notes:
AML = Acute Myeloid Leukemia; B = Both Females and Males; F = Females; HCFA = Health Care Financing Administration; Inc = Incidence; JEM = Job Exposure Matrix; M = Males; MCR = Massachusetts Cancer Registry; Mort = Mortality; NZ = New Zealand; NZSCO = New Zealand Standard Classification of Occupations; OH = Ohio; PCE = Perchloroethylene; RDD = Random Digit Dialing; US = United States; Yr = Year.
– = Not Reported.
(a) This algorithm was developed by Webler and Brown to calculate the relative delivered dose – "the estimated mass of PCE in milligrams that entered a given house as a solute in drinking water over a specified time period" – and is "based on a model for PCE leaching from vinyl-lined pipe" (Aschengrau *et al.*, 1993).
(b) Based on information from Costantini *et al.* (2001, 2008).

Table F.7 PCE and Leukemia Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Wilcosky *et al.* (1984)	Mort	OR	**Lymphatic Leukemia**					
			Unexposed	–	–	Ref	–	Age, sex and race
			Cumulative exposure >1 yr	1		–		
Aschengrau *et al.* (1993)[a]	Inc	OR	Unexposed	–	–	Ref	–	Sex, age at diagnosis or index yr, vital status at interview, educational level, and occupational exposure to PCE, benzene and other solvents, medical treatment with irradiation
			Any PCE exposure			2.13 (0.88-5.19)		
			Any PCE exposure, mostly baths			**7.02 (1.50-32.79)**		
			Low PCE exposure			–		
			High PCE exposure			**8.33 (1.53-45.29)**		
Miligi *et al.* (1999)	Inc	OR	Never employed as launderer, dry cleaner, or presser	–	–	Ref	–	Age
			Employed for ≥5 yrs as launderer, dry cleaner, or presser[b]	5		1.1 (0.4-3.2)		
Costantini *et al.* (2001)	Inc	OR	Not employed as launderer, dry cleaner, or presser	–	–	Ref	–	Age
			Launderers, dry cleaners, or pressers	2		3.3 (0.3-32.4)		
Costantini *et al.* (2008)	Inc	OR	**Leukemia by Level of Exposure**					
			Unexposed	355	811	Ref	–	Age, gender, education, and study area
			Very low/low	6	17	0.6 (0.2-1.6)		
			Medium/high	7	12	1.0 (0.4-2.7)		
McLean *et al.* (2009)	Inc	OR	**All Participants**					
			Never employed in textile bleaching, dyeing, or as cleaning machine operator	219	461	Ref	–	Age, gender, smoking, and SES

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			Ever employed in textile bleaching, dyeing, or as cleaning machine operator	6	10	2.07 (0.70-6.09)		
			Males					
			Never employed in textile bleaching, dyeing, or as cleaning machine operator	136	221	Ref	–	Age, gender, smoking, and SES
			Ever employed in textile bleaching, dyeing, or as cleaning machine operator	1	0	–		
			Females					
			Never employed in textile bleaching, dyeing, or as cleaning machine operator	83	240	Ref	–	Age, gender, smoking, and SES
			Ever employed in textile bleaching, dyeing, or as cleaning machine operator	5	10	2.20 (0.68-7.08)		

Notes:
CI = Confidence Interval; Inc = Incidence; Mort = Mortality; OR = Odds Ratio; PCE = Perchloroethylene; Ref = Reference; SES = Socioeconomic Status; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Results incorporating a 5-year latency period between exposure and outcome were similar to those without a latency period (Aschengrau *et al.*, 1993).
(b) Unclear if those who accumulated less than 5 yrs as launderers, dry cleaners, and pressers were excluded from the analysis or included in the reference (Miligi *et al.*, 1999).

Table F.8 PCE and Acute Myeloid Leukemia Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Costantini *et al.* (2008)	Inc	OR	**Exposure Level**					
			Unexposed	133	811	Ref	–	Age, gender, education, and study area
			Very low/low	2	17	–		
			Medium/high	2	12	–		
Talibov *et al.* (2014)	Inc	HR	**Cumulative Exposure (ppm-yr) with 10-Yr Lag**					
			Occupationally unexposed	–	–	Ref	0.39	Country, sex, yr of birth, and exposure to aliphatic and alicyclic hydrocarbons, methylene chloride, other organic solvents, TCE, 1,1,1-TCA, benzene, toluene, formaldehyde, and ionizing radiation
			≤12.1	89	472	1.07 (0.83-1.38)		
			12.1-106	67	381	0.83 (0.61-1.12)		
			>106	16	96	0.72 (0.39-1.34)		

Notes:
1,1,1-TCA = 1,1,1-Trichloroethane; CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; OR = Odds Ratio; PCE = Perchloroethylene; ppm = Parts Per Million; Ref = Reference; TCE = Trichloroethylene; Yr = Year.
– = Not Reported.

Attachment G

PCE Animal Carcinogenicity Studies

List of Tables

Table G.1 PCE and Leukemia Chronic Oral Study Results

Table G.2 PCE and Leukemia Chronic Inhalation Study Results

Table G.3 PCE and Leukemia Chronic Toxicity Study Quality Overview

Table G.4 PCE and Leukemia Chronic Toxicity Study Quality Assessment

Table G.1 PCE and Leukemia Chronic Oral Study Results

Study	Strain/Species	Exposure Duration	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Leukemia
NCI (1977)[a]	Osborne-Mendel rat	78 wks	110 wks	20 M	0	0/20
				50 M	471	0/50
				50 M	941	0/50
				20 F	0	0/20
				50 F	474	0/50
				50 F	949	0/50
	$B6C3F_1$ mouse		90 wks	20 M	0	0/20
				50 M	536	0/49
				50 M	1,072	0/47
				20 F	0	0/20
				50 F	386	0/48
				50 F	772	0/48

Notes:
F = Females; M = Males; NCI = National Cancer Institute; PCE = Perchloroethylene; ppm = Parts per Million; Wk = Week.
(a) Following exposure, rats and mice were observed for 32 and 12 wks, respectively. NCI (1977) concluded, "No significant increase in tumor incidence was observed among rats treated with tetrachloroethylene, but because of a high rate of early deaths in treated rats the results of this bioassay do not allow an evaluation of the carcinogenicity of this compound."

Table G.2 PCE and Leukemia Chronic Inhalation Study Results

Study	Strain/Species	Exposure Duration	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Leukemia Outcome
						Malignant MNCL
NTP (1986a)[a]	F344/N rat	104 wks	112-113 wks	50 M	0	28/50‡‡
					200	37/50‡,*
					400	37/50‡‡
				50 F	0	18/50*
					200	30/50‡,*
					400	29/50*
	B6C3F$_1$ mouse			50 M	0	0/49
					100	0/50
					200	0/50
				50 F	0	0/49
					100	0/50
					200	0/50
JISA (1993)[b]	Fischer rat	104 wks	110-111 wks	50 M	0	11/50††
					50	14/50††
					200	22/50††
					600	27/50*,††
				50 F	0	10/50†
					50	17/50†
					200	16/50†
					600	19/50†
	Crj:BDF$_1$ mouse			50 M	0	4/50
					10	3/50
					50	3/50
					250	4/50
				50 F	0	6/50
					10	4/47
					50	13/49
					250	10/50

Notes:
F = Females; JISA = Japan Industrial Safety Association; M = Males; MNCL = Mononuclear Cell Leukemia; NTP = National Toxicology Program; PCE = Perchloroethylene; ppm = Parts Per Million; Wk = Week.
*$p < 0.05$; †$p_{trend} < 0.05$; ††$p_{trend} < 0.01$; ‡ Lifetable-$p < 0.05$; ‡‡ Lifetable-$p < 0.01$.
(a) NTP (1986a) reported reduced survival in male rats at the high dose, but not in female rats at any dose. Survival was also reduced in male mice at both doses, and in female mice at the high dose only. NTP (1986a) determined that many of the early deaths in rats were due to leukemia, and that most of the leukemias were an advanced stage of mononuclear cell leukemia, MNCL (*i.e.*, stage 3 MNCL). Therefore, NTP (1986a) conducted a separate statistical analysis of stage 3 MNCL. A significant increase ($p < 0.05$) in the incidence of stage-3 MNCL was reported in males (control = 20/50; 200 ppm = 24/50; 400 ppm = 27/50) and females (control = 10/50; 200 ppm = 18/50; 400 ppm = 21/50) in the high dose groups only (NTP, 1986a). In addition, there were positive trends for stage 3 MNCL in males ($p = 0.024$) and females ($p = 0.027$). Based on MNCL incidences, the authors concluded there was "clear evidence of carcinogenicity of tetrachloroethylene" for male F344/N rats, and "some evidence of carcinogenicity" in female rats (NTP, 1986a).
(b) JISA (1993) reported, "There was a tendency toward an increase in monocytic leukemia of the spleen among male and female rats administered tetrachloroethylene, with the incidence among males of the 600 ppm group being significantly increased when compared to the control group." In addition, significant positive trends were observed for both sexes (JISA, 1993). The authors concluded, "An increase in the occurrence of monocytic leukemia of the spleen was seen among male and female rats, proving that tetrachloroethylene is carcinogenic in F344/DuCrj (Fischer) rats" (JISA, 1993). Regarding mice, none of the MNCL incidences were statistically significant.

Table G.3 PCE and Leukemia Chronic Toxicity Study Quality Overview

Parameter	Summary
Reporting	Studies reported sufficient information on the species, test article name, experimental design, exposure conditions, and outcome evaluation methods.
Allocation	Animals were randomly allocated to dose groups in two chronic studies; they were not randomly allocated in NCI (1977).
Bias	Potential bias was identified in the chronic studies of PCE. NCI (1977) stated that study animals were housed in the same rooms as other animals exposed to volatile chemicals, and that dose adjustments were made during the study. There was reduced survival in both NTP (1986a) and JISA (1993) chronic inhalation studies attributed to MNCL. NTP (1986a) reported that survival was statistically significantly reduced in treated rats ($p < 0.001$) and mice ($p < 0.001$) of both sexes compared to controls. Also, NTP (1986a) reported that in several instances rats and mice escaped from their cages within the exposure chambers. ATSDR (2019a) noted that this may have resulted in potentially small exposure aberrations. Another limitation of JISA (1993) was a high mortality of rats due to the use of maximum tolerated doses and MNCL, and JISA (1993) did not perform a statistical analysis on survival data.
Sample	Two chronic studies had adequate sample sizes. In NCI (1977), the number of animals in the control groups (n = 20) for rats and mice were significantly less than the number of animals in the exposure groups (n = 50).
Chemical Administration and Characterization	All chronic studies provided adequate information on chemical source, purity, and composition, and independently verified chemical purity and took steps to ensure reported exposure levels were accurate.
Exposure Conditions	Exposure duration was limited to assess carcinogenicity in one chronic study (NCI, 1977). This study used an exposure period that was too short in rats (78 wks). Two chronic studies (NTP, 1986a; JISA, 1993) had exposure periods that were too long for mice (104 wks).
Outcome Assessment	One chronic study was reported to have a limited outcome evaluation. This study, conducted by NCI (1977), was determined to have an observation period that was too long (90 wks in mice, 110 wks in rats), which is not appropriate for carcinogenicity studies (OECD, 2018). Two chronic studies (NTP, 1986a; JISA, 1993) had observation periods that were too long (110-113 wks).

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; JISA = Japan Industrial Safety Association; MNCL = Mononuclear Cell Leukemia; NCI = National Cancer Institute; NTP = National Toxicology Program; PCE = Perchloroethylene; Wk = Week.

Table G.4 PCE and Leukemia Chronic Toxicity Study Quality Assessment

Study	Strengths	Weaknesses	Human Relevance
Chronic - Oral			
NCI (1977)	Reporting Chemical Administration and Characterization Exposure Conditions (mice)	**Allocation:** Did not specify whether random **Bias:** Animal husbandry inadequate; high early mortality in all rats due to testing of maximum tolerated doses **Sample:** Small sample size (controls) **Exposure Conditions:** Exposure duration too short (rats) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Chronic – Inhalation			
NTP (1986a)	Reporting Allocation Sample Chemical Administration and Characterization Exposure Conditions (rats)	**Bias:** Reduced survival (potentially due to MNCL); high MNCL background rate in F344 (Fischer) rats **Exposure Conditions:** Exposure duration too long (mice) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
JISA (1993)	Reporting Allocation Bias Sample Chemical Administration and Characterization Exposure Conditions (rats)	**Bias:** Reduced survival; statistical analysis of survival data not performed; high MNCL background rate in F344 (Fischer) rats **Exposure Conditions:** Exposure duration too long (mice) **Outcome Assessment:** Observation period too long	**Limited:** Low study quality

Notes:
MNCL = Mononuclear Cell Leukemia; PCE = Perchloroethylene.

Attachment H

Benzene Epidemiology Studies

List of Tables

Table H.1 Benzene and Leukemia Cohort Study Characteristics

Table H.2 Benzene and Aggregate Leukemia Cohort Study Results

Table H.3 Benzene and Acute Lymphocytic Leukemia Cohort Study Results

Table H.4 Benzene and Acute Myeloid Leukemia Cohort Study Results

Table H.5 Benzene and Chronic Myeloid Leukemia Cohort Study Results

Table H.6 Benzene and MDS Cohort Study Results

Table H.7 Benzene and Leukemia Case-Control Study Characteristics

Table H.8 Benzene and Leukemia Case-Control Study Results

Table H.9 Benzene and ALL Case-Control Study Results

Table H.10 Benzene and AML Leukemia Case-Control Study Results

Table H.11 Benzene and Chronic Myeloid Leukemia Case-Control Study Results

Table H.12 Benzene and MDS Leukemia Case-Control Study Results

Table H.13 Benzene and Leukemia Meta-Analyses and Pooled Study Results

Table H.1 Benzene and Leukemia Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Aksoy *et al.* (1974)	Turkey	Shoe, slipper, and handbag industry workers	B	Cases $\bar{x}$ = 34.2 (range: 16-58)	~28,500	–	Official records of Istanbul	Inc	Acute leukemia & preleukemia combined	Hospital records	1967-1973
Wong (1987a,b)	US	Chemical workers	M	Median = 25-29	7,676	1946-1975	Job title, location of work, and uniform task approach by industrial hygienist	Mort	Leukemia & aleukemia combined	Company records, SSA, DMV, and death certificates	1946-1977
Blair *et al.* (1989)	US	Coast Guard officers and personnel	M	–	3,681	1942-1970	Job titles	Mort	Leukemia	Coast guard, VA, SSA, credit bureau, and DMV records, and death certificates	1942-1980
Dagg *et al.* (1992) [Wong *et al.*, 1986]	US	Employees at oil refineries	M	$\bar{x}$ = 27.3 (range = 11.8-79)	13,397	1950-1986	Work histories	Mort	Leukemia & aleukemia combined	Company records, NDI, SSA, California Death Index, Equifax,[a] and death certificates	1950-1986
Schnatter *et al.* (1993)	Canada	Petroleum marketing/ distribution workers	M	38[b]	6,672	1960-1983[c]	Work history records	Mort	Leukemia, lymphoid/ myeloid	Internal company databases, US National death indexes, Statistics Canada, certified nosologist	1964-1983

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Tsai *et al.* (1993)	US	Refinery/ petrochemical workers	M	Baseline $\bar{x}$ = 45	4,585	1910-1989	Shell Health Surveillance System and work history data	Mort	Leukemia	Company records, NDI, SSA Master Beneficiary Record file	1973-1989
Wong *et al.* (1993)	US	Petroleum marketing/ distribution workers[d]	B	–	18,135	1946-1985	Work history and JEM	Mort	Leukemia & aleukemia combined, ALL, AML, CML	SSA, DMF, NDI, company records, and state vital statistics departments	1946-1989
Honda *et al.* (1995) [McCraw *et al.*, 1985; Wongsrichanalai *et al.*, 1989]	US	White workers at a petroleum manufacturing plant	M	–	9,796	1940-1989	Work history data files and company's health surveillance system data	Mort	Leukemia	Company records, SSA Death Master file, NDI, state DMV, and death certificates	Salaried: 1940-1989 Hourly: 1942-1989
Collingwood *et al.* (1996) [Environmental Health Associates, Inc., 1985]	US	Workers at an oil refinery	B	Median: 20-39	4,855	1946-1987	Job, job title, and department based on work history data	Mort	Leukemia & aleukemia combined; ALL, AML, CML	Personnel database, PBI, NDI, SSA and death certificates	1947-1987
Fu *et al.* (1996)[e] [Pippard and Acheson, 1985]	England	Shoe manufacturing workers	M	$\bar{x}$ = 50	4,215	–	Work history and job titles	Mort	Leukemia	"Mortality records"	1939-1991

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Hayes *et al.* (1997) [Hayes *et al.*, 2000; Linet *et al.*, 2019]	China	NCI-CAPM cohort	B	–	74,828 benzene exposed and 35,805 benzene unexposed	1949-1987	Company records, work histories, ambient measurements, and detailed production and process information	Inc	Leukemia	Occupational and health records or reported by physician, colleagues, next of kin, or others, and confirmed by medical records	1972-1987
Lynge *et al.* (1997)	Denmark, Finland, Norway, and Sweden	Service station workers	B	–	Denmark: 5,250 Finland: 1,552 Norway: 3,561 Sweden: 8,606	Denmark: 1970-1987 Finland: 1970-1985 Norway: 1971-1991 Sweden: 1970-1989	Denmark: Job registered in 1970 census Job registered in 1970 census Norway: Job registered in 1970 census Sweden: Participated in both 1960 and 1970 census and classified as service station workers in 1970 census	Inc	Leukemia, AML	Denmark: National Cancer Register Finland: Finnish Cancer Register Norway: National Cancer Register Sweden: National Cancer Register	Denmark: 1970-1987 Finland: 1970-1985 Norway: 1971-1991 Sweden: 1970-1989
Pukkala (1998)	Finland	Oil and chemical company workers[f]	B	–	9,454: 7,512(M); 1,942 (F)	1967-1982	By occupational category or department	Inc	Leukemia	Finnish Cancer Registry	1971-1994
Bulbulyan *et al.* (1999)	Russia	Printing plant employees	F	–	3,473	Minimum 2 yrs of employment at baseline: 1979[g]	Personnel records and job group	Mort	Leukemia	Death certificates from Moscow Vital Statistics Department	1979-1993

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Consonni *et al.* (1999) [Bertazzi *et al.*, 1989]	Italy	Oil refinery workers	M	–	1,583	1949-1982	Work history based on personnel records	Mort	Leukemia	Population Statistics Offices and death certificates	1949-1991
Divine *et al.* (1999a) [Divine *et al.*, 1985; Divine and Barron, 1986]	US	Employees at refineries, petrochemical facilities and research laboratories	B	–	28,480: 24,604 white M; 1,783 non-white M; 2,093 W –	1947-1977	Personnel separation rosters and complete work histories	Mort	Leukemia	Company files, NDI, SSA, and HCFA, and death certificates	1947-1993
Divine *et al.* (1999b)[h] [Divine *et al.*, 1985; Divine and Barron, 1986]	US	White male employees at refineries, petrochemical facilities and research laboratories	M	–	24,604	1947-1977	Personnel separation rosters and complete work histories	Mort	Acute unspecified, cell type unspecified, ALL, AML	Company files, NDI, SSA, and HCFA, and death certificates	1947-1993
Lewis *et al.* (2000a) [Hanis *et al.*, 1985a,b; Shallenberger *et al.*, 1992; Gamble *et al.*, 2000]	US	Active and terminated workers at 3 oil refineries and petrochemical facilities	B	Total Cohort: $\bar{x}$ = 25.9 Bayway: $\bar{x}$ = 26.2	Total Cohort: 19,075 M: 17,025 F: 2,050 Bayway: 4,643 M: 4,030 F: 613	1970-1982	Company personnel and payroll records	Mort	Leukemia	Company records, NDI, SSA, and death certificates	1970-1992
Wong *et al.* (2001a)	US	Employees at an oil refinery	B	–	3,328: 2,965 (M); 363 (F)	1959-1997	Personnel records and payroll files	Mort	Leukemia & aleukemia combined, ALL, AML, CML	PBI, SSA Death Master File, NDI/NDI Plus, and death certificates	1960-1997

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Wong *et al.* (2001b) [Environmental Health Associates, Inc., 1984]	US	Employees at an oil refinery	B	Median: 20-39	7,543: 6,832 (M); 711 (F)	1945-1997	Personnel records and payroll files	Mort	Leukemia and aleukemia combined, ALL, AML, CML	PBI, SSA Death Master File, NDI/NDI Plus, and death certificates	1946-1996
Rinsky *et al.* (2002) [Infante *et al.*, 1977; Rinsky *et al.*, 1981, 1987; Crump, 1994; Paxton *et al.*, 1994a,b; Silver *et al.*, 2002)	US	Pliofilm manufacturing workers	B	–	1,291	1940-1976	Work histories, job titles, industrial hygiene data, and available air sampling data used to create a JEM	Mort	Leukemia	SSA, Ohio Bureau of Motor Vehicles, commercial tracing agency, NDI, and death certificates	1950-1996
Costantini *et al.* (2003) [Paci *et al.*, 1989; Fu *et al.*, 1996[e]]	Italy	Shoe factory workers	B	–	1,687	1939-1965	JEM based on factory records, photographs, worker interviews, and seven Dräger tube measurements	Mort	Leukemia	Regional mortality and official municipal registers	1950-1999
Collins *et al.* (2003) [Ireland *et al.*, 1997]	US	Benzene-exposed workers at chemical plant	B	–	4,417	–	Process changes, area sampling levels, individual level exposures, and plant's industrial hygienist's judgment	Mort	Leukemia, ANLL	Death certificates	1940-1997

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Lewis *et al.* (2003) [Lewis *et al.*, 2000b; Schnatter *et al.*, 1992, 1993]	Canada	Refinery/ petrochemical workers	B	M: $\bar{x}$ = 29.1 F: $\bar{x}$ = 27.5	25,292; M: 17,230 F: 8,062	1964-1994	Based on location, department, function, date, and expert review	Inc & Mort	Leukemia, ALL, AML, ANLL, CML	Cases: Canadian Cancer Data Base Deaths: Canadian Mortality Data Base	1964-1994
Tsai *et al.* (2003)	US	Chemical and refinery facility workers	M	Baseline $\bar{x}$ = 34.2 (includes F)	3,579	1973-1999	Shell Health Surveillance System and work history data	Mort	Leukemia & aleukemia combined	Company records, NDI, SSA Master Beneficiary Record file	1973-1999
Bloemen *et al.* (2004)	US	Employees in benzene exposed jobs	B	–	2,226	1938-1970	Industrial hygiene measurements, work histories and expert opinion	Mort	Leukemia & aleukemia combined, ANLL	Company research database *via* NDI, state vital statistic bureaus and other sources	1940-1996
Huebner *et al.* (2004) [Lewis *et al.*, 2000a]	US	Employees at two oil refineries and petrochemical facilities	M	$\bar{x}$ = 27 (includes F)	13,182	1970-1982	Company employee health status and work history register	Mort	Leukemia, ANLL, CML, ALL	Benefit records, NDI, and SSA	1970-1997
Sorahan *et al.* (2005)	UK	Benzene-exposed workers	B	< 85	5,514	–	Personnel reports	Inc & Mort	Leukemia, ALL, AML, AMoL, ANLL, CML, lymphoid, myeloid, monocytic	ONS and DHSS	1968-2002 (mortality); 1971-2001 (incidence)

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Tsai *et al.* (2007)	US	Petroleum refinery and chemical workers	M	–	9,764	1948-2003	Shell Health Surveillance System and work history data	Mort	Leukemia & aleukemia combined, ALL, AML, ANLL, CML, other	Company records, NDI, SSA Master Beneficiary Record file	1948-2003
Kirkeleit *et al.* (2008)	Norway	Upstream petroleum industry workers[i]	B	$\bar{x}$: 33.8 (referent from general working population); 32.6-34.3 Petroleum workers)	27,919	1981-2003	Work histories from the Norwegian Registry of Employers and Employees	Inc	AML, ALL, CML	Cancer Registry of Norway	1981-2003
Koh *et al.* (2011)	South Korea	Workers in a refinery and petrochemical complex	M	20-74	8,866	Early 1960s-2007	Work history and most recent job department	Inc & Mort	Leukemia	Cases: Central Registry of Cancer in Korea Deaths: Korea National Statistical Office	Incidence: 1997-2005 Mortality: 1992-2007
Saberi Hosnijeh *et al.* (2013)	Europe	EPIC[j]	B	$\bar{x}$ = 53.01 (range = 35-70)	241,465	–	Occupational history obtained from questionnaire at recruitment, and JEM	Inc	Myeloid, lymphoid, AML, CML	Population cancer registries, health insurance records, pathology registries, and contact with subject or next of kin	1992-2010

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Bove *et al.* (2014a)	US	Marines and Navy personnel at CL and CP	B	CL and CP: 20-49[k]	CL: 154,932 CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL and CP	B	CL: 31-58[k] CP: 34-60[k]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008
Koh *et al.* (2014)	South Korea	Petrochemical plant maintenance workers	M	39	14,698	2002-2007	Union membership records	Mort Inc	Leukemia	KNSO and KNCCR	2002-2007 2002-2005
Bassig *et al.* (2015)	China	Women living in urban Shanghai	F	$\bar{x}$ = 52 (range: 40-70)	73,087	–	Occupational history interview/ questionnaire, JEMs, and air measurements database	Inc	Myeloid	Local cancer and vital statistics registries; medical charts from hospitals	1996-2009
Collins *et al.* (2015) [Ott *et al.*, 1978; Bond *et al.*, 1986; Bloemen *et al.*, 2004]	US	Benzene-exposed chemical workers	B	–	2,266	1940-2009	Industrial hygiene measurements based on work history	Mort	Leukemia, lymphoid, myeloid, AML, ANLL, MDS	HR records, NDI, state vital statistics bureaus, and death certificates	1940-2009

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Leukemia Type	Ascertainment	Follow-Up Period
Stenehjem *et al.* (2015)	Norway	Offshore oil workers	M	15-67	24,917	1965-1999	JEM scores	Inc	Myeloid,[a] AML	Cancer Registry of Norway and the Norwegian National Population Register	1999-2011
Rhomberg *et al.* (2016) [Crump, 1994; Wong, 1995)	US	Pliofilm manufacturing workers	M	–	1,696	1934-1976	Employment and facility history (including some air measurements), and Monte Carlo techniques	Mort	ANLL, AML	Death certificates	1940-1996
Sorahan and Mohammed (2016)	UK	Male UK petroleum distribution and oil refinery workers	M	15-99	45,021	1946-1974	Employment at UK petroleum distribution centers or oil refineries	Inc	MDS	NHSCR of the HSCIC and the General Register Office for Scotland	1995-2011
ATSDR (2018b)[l]	US	Marines and Navy personnel and civilian employees at CL and CP	B	Marines & Navy Personnel CL and CP: 50-54[m] Civilian Employees CL: 60-64[m] CP: ≥ 65[m]	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168 CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines and Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Leukemia	Self-report, confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012

Notes:
ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; AMoL = Acute Monocytic Leukemia; ANLL = Acute Nonlymphocytic Leukemia; ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CML = Chronic Myeloid Leukemia; CP = Camp Pendleton; DHSS = Department of Health and Social Services; DMF = Death Master File; DMV = Department of Motor Vehicles; EPIC = European Prospective Investigation into Cancer and Nutrition; F = Females; HCFA = Health Care Financing Administration; HR = Human Resources; HSCIC = Health and Social Care Information Centre; Inc = Incidence; JEM = Job-Exposure Matrix; KNCCR = Korea National Central Cancer Registry; KNSO = Korea National Statistics Office; M = Males; MDS = Myelodysplastic Syndrome;

Mort = Mortality; NCI-CAPM = National Cancer Institute-Chinese Academy of Preventive Medicine; NDI = National Death Index; NHSCR = National Health Service Central Register; ONS = Office of National Statistics; PBI = Pension Benefits Information; SSA = Social Security Administration; UK = United Kingdom; US = United States; VA = Veterans Affairs; yr = Year.
$\bar{x}$ = Mean; – = Not Reported.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) An information services company that provided cohort member tracing (Dagg *et al.,* 1992).
(b) Average age at entry into follow up (Schnatter *et al*., 1993).
(c) One year of employment in the marketing/distribution segment was required for inclusion in the cohort (Schnatter *et al*., 1993).
(d) Potential exposure to gasoline for at least 1 year on land terminals or marine vessels (Wong *et al.*, 1993).
(e) Fu *et al*. (1996) reports results for an Italian and English cohort separately. I only include results from the English cohort here. I include results from the Italian cohort reported in Costantini *et al*. (2003), which has a longer period of follow-up.
(f) Includes employees in clerical, technical, and blue collar positions (Pukkala, 1998).
(g) Benzene was used in book binding processes in these plants till 1958 (Bulbulyan *et al*., 1999).
(h) Many of the characteristics of this study (*e.g*., population size, exposure period, exposure/outcome ascertainment) are based on what was reported in Divine *et al*. (1999a,b).
(i) Upstream petroleum workers included the following: upstream operators offshore, drilling and well maintenance workers offshore, catering offshore workers, other offshore workers, and petroleum workers onshore (Kirkeleit *et al.,* 2008).
(j) At the time, the EPIC project consisted of 23 cohorts from centers in 10 European countries (Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the UK) (Saberi Hosnijeh *et al*., 2013).
(k) Median age from start to end of follow-up (Bove *et al*., 2014a,b).
(l) Ages and population sizes are reflective of Marines, Navy personnel, and civilian respondents to the 2011-2012 morbidity survey and do not include the 5,263 Marines, Navy personnel, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis (ATSDR, 2018b).
(m) Median age range at survey or death (ATSDR, 2018b).

Table H.2 Benzene and Aggregate Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Aksoy *et al.* (1974)	Turkish general population	Inc	Obs/ exp	**Acute Leukemia and Preleukemia**					–
				All workers	26	12	**$p > 0.02$[b]**	–	
Wong (1987a,b)[c]	US general population	Mort	SMR	**Leukemia and Aleukemia Among Continuously Exposed Workers**					Age, sex, race, and calendar time
				All	6	4.43	1.35 (0.50-2.95)	–	
				Duration of exposure (yrs)					
				<5	2	–	0.76		
				5-14	3		2.84		
				≥15	4		1.23		
				Cumulative exposure (ppm-mos)					
				<180	2	2.07	0.97 (0.12-3.49)	–	
				180-719	1	1.28	0.78 (0.02-4.34)		
				≥720	3	1.09	2.76 (0.57-8.06)		
	Non-exposed		RR	<180	2	–	Undefined	**0.01**	Age, sex, and race
				180-719	1				
				≥720	3				
Blair *et al.* (1989)	US general population	Mort	SMR	Marine inspectors	7	5	1.55 (0.62-3.19)	–	Age, sex, race, and calendar time
				Non-inspectors	3	5	0.66 (0.14-1.94)		
				Non-specific Chemical Exposure Levels (by Working Level x Mos)[d]					
				Non-exposed	4	5	0.8	–	
				130	2	2	1.05		
				≥ 130	4	2	1.84		
Dagg *et al.* (1992)	US general population	Mort	SMR	**Work Location**					Age, sex, race, and calendar period
				Richmond	21	–	0.98 (0.61-1.50)	–	
				El Segundo	12		0.99 (0.51-1.72)		
				Overall	33		0.98 (0.67-1.37)		
				Duration of Employment (Yrs)					
				Richmond Oil Refinery					
				< 5	0	–	– (0-1.61)	–	
				5-14	2		0.44 (0.05-1.60)		
				15-29	5		0.75 (0.24-1.76)		
				≥ 30	14		1.80 (0.98-3.02)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				El Segundo Oil Refinery					
				< 5	0	–	– (0-2.18)	–	
				5-14	2		0.86 (0.11-3.12)		
				15-29	5		1.25 (0.41-2.91)		
				≥ 30	2		1.20 (0.39-2.80)		
				Time Since Hire (Yrs)					
				Richmond Oil Refinery					
				< 10	0	–	– (0-2.15)	–	
				10-19	1		0.34 (0.01-1.91)		
				20-29	2		0.46 (0.06-1.65)		
				≥ 30	18		1.46 (0.86-2.31)		
				El Segundo Oil Refinery					
				< 10	0	–	– (0-3.71)	–	
				10-19	2		1.25 (0.15-4.51)		
				20-29	2		0.82 (0.10-2.95)		
				≥ 30	8		1.12 (0.48-2.21)		
				Hire Date					
				Richmond Oil Refinery					
				≤ 1948	20	–	1.19 (0.73-1.83)	–	
				> 1948	1		0.22 (0.01-1.24)		
				El Segundo Oil Refinery					
				≤ 1948	11	–	1.17 (0.58-2.09)	–	
				> 1948	1		0.36 (0.01-2.02)		
Schnatter *et al.* (1993)	Canadian general population	Mort	SMR	**Leukemia**					Age and gender
				All distribution workers	14	10.4	1.35 (0.74,2.77)	–	
				Length of employment with 10 yr latency (yrs)					
				< 10	0	–	0	–	
				10-19	2	–	1.44		
				20-29	3	–	1.32		
				30+	1	–	0.50		
				Latent periods (10 and 20 yrs after first exposure)					
				Latency > 10	6	6.1	0.99	–	
				Latency > 20	6	4.9	1.22		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Occupation-specific					
				Tank truck drivers	5	1.5	**3.35 (1.08,7.81)**	–	
			SMR	**Myeloid/Lymphatic Leukemia**					Age and gender
				All distribution workers	7	7.2	0.98 (0.39, 2.02)	–	
				Length of employment with 10 yr latency (yrs)					
				< 10	0	–	0	–	
				10-19	1	–	0.97		
				20-29	2	–	1.56		
				30+	0	–	0		
				Latent periods (10 and 20 yrs after first exposure)					
				Latency > 10	3	4.2	0.72	–	
				Latency > 20	3	3.3	0.90		
				Occupation-specific					
				Tank truck drivers	4	1.0	**3.87 (1.06,9.92)**	–	
Tsai *et al.* (1993)	California general population	Mort	SMR	**By Location**					Age, sex, race, time period
				Martinez location	2	–	0.36 (0.04-1.29)	–	
				Wilmington location	7	–	1.47 (0.59-3.02)	–	
				Locations combined	9	–	0.87 (0.40-1.65)	–	
Wong *et al.* (1993)	US general population	Mort	SMR	**Land-Based Terminal Employees**					Age, sex, race, and calendar period
				All workers	27	–	0.891 (0.594-1.288)	–	
				Length of exposure (yrs)					
				1-4	2	–	0.784	–	
				5-9	2	–	0.748		
				10-19	7	–	1.076		
				20-29	9	–	0.909		
				30+	7	–	0.814		
				Time since first exposure (yrs)					
				< 10	0	–	–	–	
				10-19	4	–	1.048		
				20-29	4	–	0.768		
				30+	19	–	1.002		
				Generic job category					
				Driver only	5	–	0.688	–	

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Operator only	4	–	1.555		
				Other terminal jobs only	2	–	0.875		
				Cumulative exposure (ppm-yrs)					
				< 500	5	–	0.884	–	
				500-1,000	3	–	0.733		
				1,000-2,000	7	–	1.035		
				2,000+	12	–	0.873		
				Cumulative frequency of peak exposure					
				< 100	6	–	1.047	–	
				100-500	5	–	1.478		
				500-3,000	4	–	0.488		
				> 3,000	12	–	0.872		
			SMR	**Marine Employees**					Age, sex, race, and calendar period
				All workers	16		0.700 (0.422, 1.094)	–	
				Length of exposure (yrs)					
				1-4	11	–	0.871	–	
				5-9	3	–	0.587		
				10-19	2	–	0.481		
				20-29	0	–	–		
				30+	0	–	–		
				Time since first exposure (yrs)					
				< 10	0	–	–	–	
				10-19	6	–	1.385		
				20-29	3	–	0.548		
				30+	7	–	0.741		
				Generic job category					
				Deck only	5	–	0.804	–	
				Nondeck only	5	–	0.534		
Honda *et al.* (1995)	US white male population	Mort	SMR	**Total Cohort**[e]					Age, sex, race, and calendar period
				All workers	46	–	1.23 (0.90-1.64)	–	
				Died 1940-1984	44	29	**1.49 (1.08-2.00)**		
				Died < 1980	38	23	**1.68 (1.19-2.30)**		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Died 1980-1989	8	14	0.55 (0.24-1.08)		
				Died 1985-1989	2	7.7	**0.26 (0.03-0.94)**		
				Hourly Workers					
				Ever hourly	35	–	1.09 (0.76-1.52)	–	
				< 45 yrs at time of death	6	2.8	2.11 (0.77-4.60)		
				Died < 1970	20	10.7	**1.88 (1.15-2.90)**		
				Hired < 1940	19	15	1.23 (0.74-1.92)		
				Worked 10+ yrs	27	21.9	1.23 (0.81-1.79)		
				10-39 yrs since hire	28	18.2	**1.54 (1.02-2.22)**		
				Salaried Workers					
				Salaried workers	11	5.1	**2.16 (1.08-3.86)**	–	
				45+ yrs at time of death	11	4.3	**2.56 (1.28-4.59)**		
				Died 1940-1984	9	3.7	**2.42 (1.10-4.60)**		
				Hired < 1950	10	3.7	**2.75 (1.32-5.05)**		
				Worked 10+ yrs	7	2.3	**3.06 (1.23-6.30)**		
				10+ yrs since hire	11	4.7	**2.36 (1.18-4.22)**		
Collingwood *et al.* (1996)	US general population	Mort	SMR	Overall	15	14.9	1.01 (0.56-1.66)	–	Age, sex, race, and calendar period
				White males	14	13.6	1.03 (0.56-1.72)		
				Duration Employment (Yrs): White Males					
				< 20	2	–	0.56 (0.07-2.01)	–	
				20-29	3		0.92 (0.19-2.69)		
				30+	9		1.33 (0.61-2.52)		
				Time Since First Employment (Yrs): White Males					
				< 20	0	–	0 (–)	–	
				20-29	2		0.92 (0.11-3.31)		
				30+	12		1.24 (0.64-2.17)		
				Yr of First Employment: All Males					
				< 1950	15	12.7	1.18 (0.66-1.95)	–	
				1950+	0	1.7	0 (–)		
				Overall	15	14.4	1.04 (0.58-1.71)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Fu *et al.* (1996)[f]	English general population	Mort	SMR	All subjects	16	–	0.89 (0.51-1.45)	–	Age and sex
				Level of Solvent Exposure					
				Probable	4	–	0.68 (0.19-1.75)	–	
				High	0	–	0 (0-7.85)		
				By Job Task					
				Manufacturing of Women's Shoes	–	–	**2.45 (1.06-4.82)**	–	
				Lasting and making	–	–	4.84 (1.00-14.14)		
Hayes *et al.* (1997)	Unexposed workers	Inc	RR	**Leukemia**					Age and sex
				Exposed workers	38	–	**2.5 (1.2-5.1)**	–	
				Average exposure levels (ppm)					
				< 10	15	–	2.0 (0.9-4.5)	**0.02**	
				10-24	13		**3.7 (1.6-8.7)**		
				≥ 25	10		2.3 (0.9-5.7)		
				Constant exposure (ppm)[g]					
				< 10	12	–	1.7 (0.7-4.1)	**0.009**	
				10-24	7		**4.0 (1.5-10.7)**		
				≥ 25	7		2.8 (1.0-7.4)		
				Duration of exposure (yrs)					
				< 5	14	–	**4.0 (1.7-9.6)**	0.98	
				5-9	11		**3.1 (1.3-7.5)**		
				≥ 10	13		1.5 (0.6-3.6)		
				Cumulative Exposure (ppm-yrs)					
				< 40	11	–	1.9 (0.8-4.7)	**0.04**	
				40-99	8		**3.1 (1.2-8.0)**		
				≥ 100	19		**2.7 (1.2-6.0)**		
				Other Leukemia (Non-ANLL or Undefined)					
				Exposed workers	17	–	2.0 (0.7-5.4)	–	
				Average exposure levels (ppm)					
				< 10	8	–	1.9 (0.6-5.9)	0.27	
				10-24	4		2.1 (0.6-7.8)		
				≥ 25	5		2.1 (0.6-7.1)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Constant exposure (ppm)[g]					
				< 10	6	–	1.6 (0.5-5.2)	0.31	
				10-24	3		3.2 (0.8-13.4)		
				≥ 25	2		1.4 (0.3-7.4)		
				Duration of exposure (yrs)					
				< 5	5	–	2.7 (0.7-9.7)	0.83	
				5-9	5		2.7 (0.8-9.3)		
				≥ 10	7		1.4 (0.5-4.6)		
				Cumulative exposure (ppm-yrs)					
				< 40	6	–	2.0 (0.6-6.6)	0.36	
				40-99	3		2.1 (0.5-9.0)		
				≥ 100	8		1.9 (0.6-6.0)		
Lynge *et al.* (1997)	Danish, Finnish, Norwegian, and Swedish general populations	Inc	SIR	**Leukemia**					Age and sex
				Males					
				Demark	5	6.74	0.7	–	
				Norway	9	6.58	1.4		
				Sweden	12	13.69	0.9		
				Finland	0	2.15	–		
				Overall	26	29.16	0.9 (0.6-1.3)		
				Females					
				Demark	2	1.32	1.5	–	
				Norway	0	0.63	–		
				Sweden	0	0.88	–		
				Finland	0	0.16	–		
				Overall	2	2.99	0.7 (0.1-2.4)		
Pukkala (1998)	Finish general population	Inc	SIR	All employees	9	9	1.02 (0.47-1.93)	–	Age, and calendar period
				By Duration of Employment (Yrs)					Age, sex, and calendar period
				< 5	1	2.4	0.41 (0.01-2.28)	–	
				≥ 5	3	2.8	1.09 (0.23-3.19)		
Bulbulyan *et al.* (1999)	Moscow general population[h]	Mort	SMR	All printing plant employees	4	5.1	0.8 (0.2-2.0)	–	Age, sex, and calendar yr
				Compositors	0	0.6	–		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Press operators	0	0.7	–		
				Bookbinders	3	1.9	1.6 (0.3-4.6)		
Consonni *et al.* (1999)	Italian general (1949-1968) and Lombardy Region populations (1969-1991)	Mort	SMR	All workers	8	3.6	2.25 (0.97-4.43)	–	Age, sex, and calendar yr
				Length of Employment (Yrs), Lagged 10 Yrs					
				0-4	2	1.2	1.68 (0.19-6.06)	–	
				5-14	2	1.3	1.53 (0.17-5.51)		
				15+	4	1.1	**3.77 (1.01-9.65)**		
				Time Since First Employment (Yrs)					
				0-9	1	0.6	1.77 (0.02-9.84)	–	
				10-19	3	0.8	3.67 (0.74-10.71)		
				20-29	1	1.1	0.88 (0.01-4.88)		
				≥30	3	1.0	2.89 (0.58-8.45)		
				Yr of First Employment					
				< 1954	4	2.2	1.78 (0.48-4.55)	–	
				1954-1962	1	0.7	1.46 (0.02-8.11)		
				> 1962	3	0.6	4.78 (0.96-13.97)		
Divine *et al.* (1999a)	US general population	Mort	SMR	**Demographic Group**					Age, sex, and race
				White men	93	–	1.01 (0.81-1.23)	–	
				Non-white men	0		0 (0-1.22)		
				Women	4		1.29 (0.35-3.31)		
				Duration of Employment (Yrs): White Males					
				< 10	7	–	0.93 (0.37-1.92)	–	
				10-19	17		1.25 (0.73-2.00)		
				20-29	23		1.01 (0.64-1.52)		
				> 30	46		0.94 (0.69-1.26)		
				Period of Employment: White Males					
				< 1950	84	–	1.13 (0.90-1.40)	–	
				> 1950	9		**0.50 (0.23-0.94)**		
				Job and Process Unit: White Males Employed > 5 Yrs					
				Office; professional; supervisor	23	–	0.79 (0.50-1.18)	–	
				Controlmen; operators	37		0.98 (0.69-1.35)		
				Craft; maintenance	25		0.76 (0.49-1.12)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Laboratory	8		0.85 (0.37-1.67)		
				Fluid catalytic cracking	8		1.42 (0.61-2.80_		
				Pipefitter; boilermaker	14		1.60 (0.88-2.69)		
				Crude stills	3		0.39 (0.08-1.14)		
				Motor oil	4		1.21 (0.33-3.10)		
Divine *et al.* (1999b)	US general population	Mort	SMR	**Acute Unspecified Leukemia**					Age, sex, and race
				All employees	15	5.4	**2.76 (1.54-4.55)**	–	
				Period of employment					
				Employed < 1950	13	4.7	**2.76 (1.47-4.72)**	–	
				Employed ≥ 1950	2	0.7	2.73 (0.30-9.86)		
				Cell Type Unspecified Leukemia					
				All employees	15	6.5	**2.31 (1.29-3.81)**	–	
				Period of employment					
				Employed < 1950	14	5.3	**2.62 (1.43-4.40)**	–	
				Employed ≥ 1950	1	1.1	0.87 (0.01-4.86)		
Lewis *et al.* (2000a)[i]	US male general population	Mort	SMR	Total cohort	56	37.3	**1.50 (1.13-1.95)**	–	Age, sex, race, and calendar yr
	NJ male general population			Bayway, NJ, facility employees	10	7.9	1.26 (0.61-2.33)		
Wong *et al.* (2001a)	US general population	Mort	SMR	**Leukemia and Aleukemia**					Age, sex, race, and calendar period
				Total cohort	5	7.37	0.678 (0.220-1.583)	–	
				Male employees					
				All	5	7.19	0.695 (0.226-1.622)		
				Maintenance workers	2	2.70	0.742 (0.090-2.680)		
				Process workers	2	2.32	0.864 (0.105-3.121)		
				Leukemia					
				Duration of employment (yrs): Male employees					
				< 10	1	–	0.623	–	
				10-29	4		0.966		
				30+	0		0.0		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Time since first employment (yrs): Male employees					
				< 20	2	–	1.663	–	
				20-39	0		0.0		
				40+	3		1.088		
Wong *et al.* (2001b)	US general population	Mor	SMR	**Leukemia and Aleukemia**					Age, sex, race, and calendar period
				Total cohort	39	28.07	1.389 (0.988-1.899)	–	
				Male employees	37	27.10	1.365 (0.961-1.882)		
				Female employees	2	0.97	2.062 (0.250-7.450)		
				Leukemia					
				Duration of employment (yrs): Male employees					
				< 10	6	–	1.521	–	
				10-29	12		1.403		
				30+	19		1.301		
				Time since first employment (yrs): Male employees					
				< 20	2	–	0.568	–	
				20-39	14		1.407		
				40+	21		1.541		
				Duration of employment (yrs): Male maintenance employees					
				< 10	5	–	1.171	> 0.05	
				10-29	7		1.194		
				30+	7		1.659		
				Overall	19		1.324		
				Duration of employment (yrs): Male process employees					
				< 10	2	–	0.584	**< 0.05**	
				10-29	3		0.622		
				30+	6		2.190		
				Overall	11		1.001		
Rinsky *et al.* (2002)	US general population	Mort	SMR	All exposed workers	15	6.08	**2.47 (1.38-4.07)**	–	Age, sex, race, and calendar period
				White male exposed workers	15	5.87	**2.56 (1.43-4.22)**		
				White Males by Exposure Category (ppm-yrs)					
				1-30.99	6	4.13	1.45 (0.53-3.31)	–	
				40-199.99	4	1.25	3.21 (0.86-8.89)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				200-399.99	2	0.36	5.55 (0.62-24.08)		
				> 400	3	0.13	**23.96 (4.82-78.51)**		
	Unexposed workers		RR	**Duration of Exposure**					Age
				Per Yr	–	–	**1.392**	–	
				Average Exposure Rate					
				Per ppm	–	–	**1.076**	–	
				Cumulative Exposure[j]					
				Per ppm-yr	–	–	**1.023**	–	
				Per ppm-yr (2.5 yr lag)			**1.025**		
Collins *et al.* (2003)	Illinois mortality rate	Mort	SMR	**Cumulative Exposure (ppm-yrs)**					Age
				No exposure	10	10.4	1.0 (0.5-1.8)	–	
				< 1	2	2.9	0.7 (0.1-2.5)		
				1-6	4	2.9	1.4 (0.4-3.6)		
				> 6	6	3.5	1.7 (0.6-3.8)		
				Number of Days with Peak Exposure > 100 ppm					
				None	15	15.6	1.0 (0.5-1.6)	–	
				< 7	1	0.8	1.2 (0.0-6.8)		
				7-40	1	1.4	0.7 (0.0-4.0)		
				> 40	5	1.8	2.7 (0.8-6.4)		
Costantini *et al.* (2003)	Italian (1950-1969) and regional (1970-1993) mortality rates	Mort	SMR	**All Leukemia by Cumulative Exposure for Men and Women (ppm-yrs)**					Age, sex, and calendar yr
				< 40	3	2.36	1.3 (0.3-3.7)	–	
				40-99	2	0.49	4.1 (0.5-14.7)		
				100-199	2	0.79	2.5 (0.3-9.1)		
				≥ 200	4	0.79	**5.1 (1.4-13.0)**		
				All Leukemia by Cumulative Exposure for Men (ppm-yrs)					
				< 40	2	1.45	1.4 (0.2-5.0)	–	
				40-99	1	0.27	3.7 (0.1-20.6)		
				100-199	2	0.66	3.0 (0.4-10.9)		
				≥ 200	4	0.57	**7.0 (1.9-18.0)**		
				All Leukemia by Peak Exposure for Men and Women (ppm)					
				< 1	1	1.2	0.8 (0.02-4.7)	–	
				1-29	4	1.5	2.6 (0.7-6.8)		
				≥ 30	6	1.7	**3.5 (1.3-7.6)**		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				All Leukemia by Peak Exposure for Men (ppm)					
				< 1	1	0.8	1.2 (0.03-6.7)	–	
				1-29	2	0.8	2.5 (0.3-9.1)		
				≥ 30	6	1.3	**4.5 (1.1-9.9)**		
	Workers with < 40 ppm-yrs		RR	**All Leukemia by Cumulative Exposure for Men and Women (ppm-yrs)**					
				40-99	1	–	3.0 (0.5-19.6)	–	
				100-199	2	–	2.1 (0.3-13.6)		
				≥ 200	4	–	4.7 (0.9-24.0)		
Lewis *et al.* (2003)	Canadian general population	Inc	SIR	**Leukemia**					Age, sex, and calendar period
				Males	13	13.49	0.96 (0.51-1.65)	–	
				Females	3	4.23	–[k]		
				By duration of employment for male workers (yrs)					
				< 10	4	4.74	–[k]	–	
				≥ 10-< 20	4	3.08	–[k]		
				≥ 20	0	0.90	–[k]		
		Mort	SMR	Males	7	8.18	0.86 (0.34-1.76)	–	
				Females	2	2.63	–[k]		
Tsai *et al.* (2003)	US general population	Mort	SMR	Male employees	4	7.0	0.57 (0.16-1.46)	–	Age, sex, race, calendar time
				At Least 10 Yrs of Employment (by Location)					
				Male employees	3	6.3	0.48	–	
	Louisiana general population				–	6.8	0.44	–	
	Industrial corridor general population				–	7.0	0.43	–	
Bloemen *et al.* (2004)	US general population and local populations	Mort	SMR	**0 Yr Lag**					Age, sex, race, and calendar period
				By duration of exposure (yrs)					
				< 5	5	–	0.70 (0.23-1.63)	–	
				5-9	4		3.09 (0.84-7.90)		
				10+	3		1.44 (0.30-4.20)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				By cumulative exposure (ppm-yrs)					
				< 340	4	–	0.60 (0.16-1.54)	–	
				28.3-79.1	4		2.00 (0.54-5.11)		
				79.1+	4		2.16 (0.59-5.53)		
				By average intensity (ppm)					
				< 5	3	–	0.75 (0.16-2.20)	–	
				5-14	5		1.57 (0.51-3.66)		
				15+	4		1.19 (0.32-3.05)		
				15 Yr Lag					
				By duration of exposure (yrs)					
				< 5	6	–	0.78 (0.29-1.70)	–	
				5-9	3		2.51 (0.52-7.34)		
				10+	3		1.84 (0.38-5.38)		
				By cumulative exposure (ppm-yrs)					
				< 340	5	–	0.69 (0.23-1.62)	–	
				28.3-79.1	3		1.71 (0.35-5.00)		
				79.1+	4		2.55 (0.70-6.54)		
				By average intensity (ppm)					
				< 5	9	–	0.95 (0.44-1.81)	–	
				5-14	3		2.96 (0.61-8.64)		
				15+	0		0.00 (0.00-60.93)		
Huebner *et al.* (2004)[i]	Louisiana and Texas general populations	Mort	SMR	**Leukemia**					Age, sex, race, and calendar period
				Work location					
				Baton Rouge	37	21.92	**1.69 (1.19-2.33)**	–	
				Baytown	27	19.56	1.38 (0.91-2.01)		
				For employees hired < 1950					
				Baton Rouge	34	17.42	**1.95 (1.35-2.73)**	–	
				Baytown	18	15.42	1.17 (0.69-1.84)		
				For employees hired ≥ 1950					
				Baton Rouge	3	4.50	0.67 (1.14-1.95)	–	
				Baytown	9	4.14	2.17 (0.99-4.12)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Duration of employment (yrs) for 20+ yrs of latency					
				Baton Rouge					
				< 15	1	0.49	–	–	
				15-29	9	4.99	1.80 (0.62-3.42)		
				30+	25	14.26	**1.75 (1.13-2.59)**		
				Baytown					
				< 15	1	0.56	–	–	
				15-29	4	4.78	0.64 (0.23-2.14)		
				30+	16	11.92	1.34 (0.77-2.18)		
				By < 1950 hire group: Baton Rouge					
				< 1940	12	4.98	**2.41 (1.24-4.21)**	–	
				1940-1944	17	8.68	**1.96 (1.14-3.14)**		
				1945-1949	5	3.76	1.33 (0.43-3.10)		
Sorahan *et al.* (2005)	England and Wales general population	Mort	SMR	**All Exposed Workers by Leukemia Subtype**					Age, sex, and calendar yr
				All leukemia	22	16.08	1.37 (0.86-2.07)	–	
				Lymphoid leukemia	5	5.05	0.99 (0.32-2.31)		
				Myeloid leukemia	14	9.41	1.49 (0.81-2.50)		
				Monocytic leukemia	0	0.34	0 (–)		
		Inc	SIR	All leukemia	25	20.9	1.20 (0.78-1.77)	–	
Tsai *et al.* (2007)	County general population	Mort	SMR	**By Work Location**					Age, sex, race, time period
				Refinery	23	–	0.95 (0.60-1.42)	–	
				Chemical	18	–	1.10 (0.65-1.73)		
				Total	41	–	1.01 (0.72-1.36)		
				By Period of Hire					
				< 1950	25	–	1.01 (0.65-1.49)	–	
				1950-1959	10	–	0.90 (0.43-1.66)		
				≥ 1960	6	–	1.23 (0.45-2.68)		
				Worked for ≥ 10 Yrs (By Work Location)					
				Refinery	17	–	0.97 (0.57-1.55)	–	
				Chemical	12	–	1.22 (0.63-2.12)		
				Total	29	–	1.06 (0.71-1.52)		
	US general population			**Other Leukemias**					
				Total cohort	14	12.76	1.10 (0.60-1.84)	–	

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				≥ 10 yrs of employment	11	8.76	1.26 (0.63-2.25)		
				≥ 20 yrs of employment	8	6.73	1.19 (0.51-2.34)		
Kirkeleit *et al.* (2008)	Norway's general working population	Inc	RR	**Upstream Operators Offshore**					Age at inclusion into cohort, sex, yr of first exposure, and education
				By period of first exposure					
				1981-1985	10	–	**2.49 (1.30-4.78)**	–	
				1986-2003	1		0.80 (0.11-5.75)		
				Offshore Workers Combined					
				By period of first exposure					
				1981-1985	14	–	**1.84 (1.05-3.22)**	–	
				1986-2003	4		0.50 (0.18-1.37)		
Koh *et al.* (2011)	South Korean general population	Inc	SIR	All workers	3	–	1.05 (0.22-3.06)	–	Age, sex, and calendar period
				Manufacturing workers	3		1.40 (0.29-4.08)		
				Office workers	0		– (0-4.20)		
				By Job Classification					
				Product workers	3	–	2.24 (0.46-6.54)	–	
				Maintenance workers	0		– (0-5.89)		
				Laboratory workers	0		– (0-9.95)		
				Office workers	0		– (0-4.20)		
		Mort	SMR	All workers	5	–	1.57 (0.51-3.67)	–	
				Manufacturing workers	5		2.12 (0.69-4.96)		
				Office workers	0		– (0-3.63)		
				By Job Classification					
				Product workers	4	–	2.77 (0.75-7.09)	–	
				Maintenance workers	1		1.73 (0.04-9.66)		
				Laboratory workers	0		– (0-9)		
				Office workers	0		– (0-3.63)		
Saberi Hosnijeh *et al.* (2013)	Unexposed subjects	Inc	HR	**Myeloid Leukemias**					Age, sex, smoking status, alcohol intake, and country
				Low exposure	39	42,987	1.15 (0.78-1.70)	0.08	
				High exposure	17	11,140	1.60 (0.95-2.69)		
				Lymphoid Leukemias					
				Low exposure	51	42,987	1.06 (0.75-1.50)	0.22	
				High exposure	8	11,140	0.52 (0.25-1.06)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					Age, sex, race, rank, and education
				Cumulative exposure level (µg/L-months)[l] with 10 yr lag					
				No/low (0-45)	43	–	0.73 (0.46-1.16)	–	
				Medium/high (> 45-601)	23		1.47 (0.97-2.23)		
	CL Marines & Navy personnel with exposure < 2 µg/L-months[l]			Low (2-45)	17		**2.54 (1.27-5.08)**		
				Medium (> 45-110)	11		1.46 (0.66-3.20)		
				High (> 110-601)	12		1.69 (0.77-3.67)		
Bove *et al.* (2014b)	CL civilian employees with no/low exposure[m]	Mort	HR	**CL Civilian Employees**					Age, sex, race, blue- or white-collar occupation, and education
				Cumulative exposure level with 10 yr lag					
				Medium	1	–	0.36 (0.04-3.52)	–	
				High	8		1.25 (0.31-5.10)		
	CL civilian employees with < median exposure			≥ Median	–		1.38 (0.35-5.43)		
Koh *et al.* (2014)	Korean general population	Mort	SMR	All workers	3	–	1.46 (0.30-4.27)	–	Age, sex, and calendar period
		Inc	SIR		3	–	2.71 (0.56-7.91)		
Bassig *et al.* (2015)	Unexposed women living in urban Shanghai	Inc	HR	**Myeloid Leukemias**					Age, ever smoking, and education
				All exposed	4	–	0.74 (0.26-2.11)	–	
				By duration of exposure (yrs)					
				1-11	0	–	–	–	
				12-21	0	–	–		
				> 21	4	–	2.23 (0.77-6.44)		
				By cumulative exposure (mg/m^3-yrs)					
				≤ 59.3	0	–	–	–	
				> 59.3	4	–	1.44 (0.50-4.14)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Collins *et al.* (2015)	US general population	Mort	SMR	**All Leukemia**					Age, sex, race, and calendar yr
				All workers	20	–	1.21 (0.74-1.97)	–	
				30+ yrs since first exposure	15	–	1.23 (0.69-2.02)	–	
				By cumulative exposure (ppm-yrs)					
				0-3.9	3	–	0.60 (0.12-1.76)	0.15	
				4.0-24.9	7	–	1.23 (0.49-2.53)		
				25+	10	–	1.72 (0.86-3.17)		
				Total Lymphoid Leukemia					
				All workers	4	–	0.93 (0.25-2.39)	–	
				30+ yrs since first exposure	3	–	0.82 (0.17-2.40)	–	
				By cumulative exposure (ppm-yrs)					
				0-3.9	1	–	0.78 (0.02-4.36)	0.53	
				4.0-24.9	1	–	0.68 (0.02-3.78)		
				25+	2	–	1.31 (0.16-4.72)		
				Total Myeloid Leukemia					
				All workers	8	–	1.25 (0.54-2.47)	–	
				30+ yrs since first exposure	7	–	1.35 (0.54-2.77)	–	
				By cumulative exposure (ppm-yrs)					
				0-3.9	0	–	0.0 (0.0-1.79)	0.24	
				4.0-24.9	4	–	1.78 (0.48-4.54)		
				25+	4	–	1.93 (0.53-4.94)		
Stenehjem *et al.* (2015)	Never exposed to benzene	Inc	HR	**Myeloid Leukemias**					
				Ever exposed to benzene	15	–	1.39 (0.51-3.82)	–	Age, ever daily smoker, benzene exposure from other work
	Never exposed to benzene (first employment offshore before 1980)			Ever exposed to benzene (first employment offshore before 1980)	7	–	1.79 (0.32-10)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
	Never exposed to benzene (first employment offshore during or after 1980)			Ever exposed to benzene (first employment offshore during or after 1980)	8	–	1.20 (0.35-4.14)		
	Unexposed to benzene			*Cumulative exposure (ppm-yrs)*					
				Unexposed	6	–	Ref	0.188	
				Tertile 1 (< 0.001-0.037)	5	–	1.12 (0.31-4.01)		
				Tertile 2 (> 0.037-0.123)	4	–	1.12 (0.30-4.23)		
				Tertile 3 (0.124-0.948)	6	–	2.24 (0.65-7.71)		
				Cumulative peak exposure (> 3 ppm)					
				Unexposed	6	–	Ref	0.330	
				Tertile 1	5	–	1.51 (0.44-5.18)		
				Tertile 2	6	–	2.46 (0.75-8.10)		
				Tertile 3	4	–	1.97 (0.51-7.69)		
				Duration of exposure (yrs)					
				0	6	–	Ref	0.508	
				> 0-5.49	5	–	1.07 (0.30-3.80)		
				5.5-12.9	6	–	1.80 (0.52-6.24)		
				13-33.5	4	–	1.47 (0.37-5.88)		
				Average exposure intensity (ppm)					
				Unexposed	6	–	Ref	0.209	
				Tertile 1 (< 0.001-0.007)	2	–	0.45 (0.09-2.31)		
				Tertile 2 (> 0.007-0.013)	8	–	2.41 (0.77-7.53)		
				Tertile 3 (> 0.013-0.040)	5	–	1.66 (0.48-5.74)		

Study	Statistical Analysis								
	Reference Group	**Outcome Type**	**Risk Metric**	**Group**	**Exposed Cases[a]**	**Expected Cases[a]**	**Risk Estimate (95% CI)**	**p_{Trend}**	**Covariates Controlled For**
				Average peak exposure (> 3 ppm)					
				Unexposed	6	–	Ref	0.234	
				Tertile 1	6	–	2.09 (0.63-6.86)		
				Tertile 2	4	–	1.53 (0.42-5.58)		
				Tertile 3	5	–	2.19 (0.65-7.36)		
ATSDR (2018b)	CP Marines & Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					
				Cumulative Exposure Level[n,o]					Age and sex
				Low	80	–	1.08 (0.66-1.78)	–	
				Medium	41		0.76 (0.44-1.30)		
				High	4		**0.28 (0.09-0.83)**		
	CL Marines & Navy personnel with low exposure			Medium	41		0.70 (0.47-1.03)		
				High	4		**0.26 (0.09-0.72)**		

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; Exp = Expected; HR = Hazard Ratio; Inc = Incidence; mo = Month; Mort = Mortality; NJ = New Jersey; Obs = Observed; OR = Odds Ratio; ppm = Parts per Million; Ref = Reference; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; TVOC = Total Volatile Organic Compound; US = United States; VC = Vinyl Chloride; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Aksoy *et al.* (1974) reported that the incidence rate of leukemia was 13/100,000 in workers and 6/100,000 in the general population, and that these two rates were statistically significantly different ($p > 0.02$).
(c) Results for all continuously exposed workers were reported in Wong (1987a) and cumulative and duration of exposure results were reported in Wong (1987b). Analyses considering employees with intermittent exposures had similar results to those reported for employees with continuous exposures (Wong, 1987a,b). Wong (1987b) reported no associations between benzene exposure and combined instances of leukemia and aleukemia based on the category of max peak exposure (*i.e.*, <25, 25-100, or >100 ppm), first exposure before or after 30 years of age, or when accounting for latency (*i.e.*, <10, 10-19, or ≥20 years). There were no unexposed leukemia and aleukemia cases, so an RR could not be calculated by Wong (1987b).
(d) Probability of exposure based on 4-point exposure rating scale: "no exposure," which is defined as administrative positions; "low exposure," which is defined as staff with duties that occasionally required vessel inspections; "moderate exposure," which is defined as staff with inspection duties that did not regularly include hull structures or regular inspection of hull structures in geographic areas where chemicals were not major cargo items; and "high exposure," which is defined as persons who performed hull inspections at ports where vessels transported chemicals (Blair *et al.*, 1989).
(e) Honda *et al.* (1995) report risk estimates only for certain stratifications of selected characteristics, risk estimates for other stratifications without a statistically significant risk estimate were not reported.

(f) Fu *et al*. (1996) reports results for an Italian and English cohort separately. I only include results from the English cohort here. I include results from the Italian cohort reported in Costantini *et al*. (2003), which has a longer period of follow-up.
(g) The constant exposure category consists of workers who were always exposed at the indicated levels (Hayes *et al*., 1997).
(h) There was conflicting information on the time period of the standardized rates used. The text notes that rates from 1992 were used and applied to the other years (1979-1993), but the results table indicates that rates from 1979-1993 were used (Bulbulyan *et al*., 1999).
(i) Lewis *et al.* (2000a) and Huebner *et al.* (2004) both evaluate leukemia risk in petroleum and chemical workers at Exxon facilities in Louisiana, Texas, and New Jersey. Huebner *et al.* (2004) provides the longest duration of follow up and reports results for the Baton Rouge, Louisiana, and Baytown, Texas, facilities, which I report here. I report the results from Lewis *et al.* (2000a) for participants at the Bayway, New Jersey, facility, and all three facilities combined, which were not reported in Huebner *et al.* (2004).
(j) Rinsky *et al*. (2002) reported that sex did not have a statistically significant effect on the relationship between cumulative benzene exposure and leukemia. However, they qualified this statement by noting that the number of female workers is so small that an effect would be difficult to detect.
(k) Lewis *et al.* (2003) only reported SMR results when the number of cases/deaths was > 5, or if < 5 when statistically significant.
(l) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al*., 2014a). I report the values consistent with the text definition.
(m) To evaluate exposure-response relationships, the authors evaluated continuous and log10 continuous cumulative exposures (µg/L-yr). The beta coefficients were not statistically significant; however, the log10 transformed beta coefficient was statistically significant ($p = 0.05$) for Marines and Navy personnel (Bove *et al*., 2014a,b).
(n) Categorized as low exposure (< 50th percentile), medium exposure (≥ 50th percentile to < 90th percentile), and high exposure (≥ 90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018b).
(o) There was complete correlation (gamma coefficient > 0.99) between the categorical variables for TCE, benzene, VC and TVOCs; the authors only reported results based on TCE analyses (ATSDR, 2018b).

Table H.3 Benzene and Acute Lymphocytic Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Wong *et al.* (1993)	US general population	Mort	SMR	Land-based terminal employees	2	–	1.259 (0.152-4.545)	–	Age, sex, race, and calendar period
				Marine employees	1	–	0.795 (0.020-4.416)		
Collingwood *et al.* (1996)	US general population	Mort	SMR	All males	1	0.8	1.25 (0.03-6.96)	–	Age, sex, race, and calendar period
Divine *et al.* (1999b)	US general population	Mort	SMR	All employees	5	4.9	1.01 (0.32-2.35)	–	Age, sex, and race
				Employed < 1950	5	3.8	1.33 (0.42-3.11)		
Wong *et al.* (2001a)	US general population	Mort	SMR	Male employees	0	0.36	0.0 (0.0-10.352	–	Age, sex, race, and calendar period
				By Job Category: Male Employees					
				Maintenance	0	0.14	0.0 (0.0-27.128)	–	
				Process	0	0.12	0.0 (0.0-30.425)		
				By Duration of Employment (Yrs): Male Employees					
				< 10	0	–	0.0 (0.0-33.323)	–	
				10-29	0		0.0 (0.0-19.893)		
				30+	0		0.0 (0.0-61.253)		
				By Time Since First Employment (Yrs): Male Employees					
				< 20	0	–	0.0 (0.0-36.133)	–	
				20-39	0		0.0 (0.0-28.929)		
				40+	0		0.0 (0.0-29.103)		
Wong *et al.* (2001b)	US general population	Mort	SMR	All male employees	0	1.23	0.0 (0.0-2.992)	–	Age, sex, race, and calendar period
				By Job Category: Male Employees					
				Maintenance	0	0.64	0.0 (0.0-5.776)	–	
				Process	0	0.50	0.0 (0.0-7.312)		
				By Duration of Employment (Yrs): Male Employees					
				All male employees					
				< 10	0	–	0.0 (0.0-14.026)	–	
				10-29	0		0.0 (0.0-9.028)		
				30+	0		0.0 (0.0-6.572)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Male maintenance employees					
				< 10	0	–	0.0 (0.0-15.145)	–	
				10-29	0		0.0 (0.0-15.674)		
				30+	0		0.0 (0.0-23.097)		
				Male process employees					
				< 10	0	–	0.0 (0.0-19.011)	–	
				10-29	0		0.0 (0.0-19.286)		
				30+	0		0.0 (0.0-30.959)		
				By Time Since First Employment (Yrs): Male Employees					
				All male employees					
				< 20	0	–	0.0 (0.0-12.414)	–	
				20-39	0		0.0 (0.0-9.853)		
				40+	0		0.0 (0.0-6.571)		
				Male maintenance employees					
				< 20	0	–	0.0 (0.0-21.096)	–	
				20-39	0		0.0 (0.0-17.240)		
				40+	0		0.0 (0.0-14.767)		
				Male process employees					
				< 20	0	–	0.0 (0.0-24.487)	–	
				20-39	0		0.0 (0.0-21.949)		
				40+	0		0.0 (0.0-19.858)		
				By Yr of First Hire: Male Employees					
				< 1950	0	0.92	0.0 (0.0-4.000)	–	
				≥ 1950	0	0.31	0.0 (0.0-11.876)		
Lewis *et al.* (2003)	Canadian general population	Inc	SIR	Males	2	1.42	–[b]	–	Age, sex, and calendar period
				Females	0	0.42			
				By Duration of Employment for Male Workers (Yrs)					
				< 10	0	0.40	–[b]	–	
				≥ 10-< 20	0	0.28			
				≥ 20	0	0.06			
		Mort	SMR	Males	1	0.90		–	
				Females	0	0.28			

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Huebner *et al.* (2004)	Louisiana and Texas general populations	Mort	SMR	**By Work Location**					Age, sex, race, and calendar period
				Baton Rouge	2	0.89	–	–	
				Baytown	2	1	–		
				For Employees Hired < 1950					
				Baton Rouge	1	0.55	–	–	
				Baytown	1	0.61	–		
				For Employees Hired ≥ 1950					
				Baton Rouge	1	0.33	–	–	
				Baytown	1	0.39	–		
Sorahan *et al.* (2005)	England and Wales general population	Mort	SMR	All exposed workers	0	0.83	0 (0-4.44)	–	Age, sex, and calendar yr
Tsai *et al.* (2007)	US general population	Mort	SMR	Total cohort	3	1.81	1.66 (0.34-4.84)	–	Age, sex, race, calendar period
				≥ 10 yrs of employment	3	1.07	2.80 (0.58-8.19)		
				≥ 20 yrs of employment	2	0.74	2.70 (0.33-9.76)		
Kirkeleit *et al.* (2008)	Norway's general working population	Inc	RR	**Upstream Operators Offshore[c]**					Age at inclusion into cohort, sex, yr of first exposure, and education
				All workers	1	–	2.17 (0.29-16.6)	–	

Notes:
CI = Confidence Interval; Inc = Incidence; Mort = Mortality; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; US = United States; yr = Year.
– = Not Reported.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Lewis *et al.* (2003) only reported SMR results when the number of cases/deaths was > 5, or if < 5 when statistically significant.
(c) The category "upstream operator offshore" contained workers who mainly worked in the production and processing unit. This includes job categories such as process technicians, laboratory engineers, control operators, and other job groups involved in the production process including stabilization, separation, and fractionation of the crude oil, natural gas, and natural gas liquids (Kirkeleit *et al.*, 2008).

Table H.4 Benzene and Acute Myeloid Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Wong *et al.* (1993)	US general population	Mort	SMR	Land-based terminal employees	13	–	1.505 (0.800-2.572)	–	Age, sex, race, and calendar period
				Marine employees	5	–	0.742 (0.240, 1.733)		
Collingwood *et al.* (1996)	US general population	Mort	SMR	All males	4	4.2	0.95 (0.26-2.44)	–	Age, sex, race, and calendar period
Lynge *et al.* (1997)	Danish, Finnish, Norwegian, and Swedish general populations	Inc	SIR	**Males**					Age and sex
				Overall	13	9.14	1.4 (0.8-2.4)	–	
				Females					
				Overall	0	1.23	–	–	
Divine *et al.* (1999b)	US general population	Mort	SMR	All employees	20	15.5	1.29 (0.78-1.99)	–	Age, sex, and race
				Period of employment					
				Employed < 1950	19	12.2	1.55 (0.93-2.43)	–	
				Employed ≥ 1950	1	3.3	0.30 (0-1.68)		
Wong *et al.* (2001a)	US general population	Mort	SMR	Male employees	1	2.20	0.454 (0.011-2.528)	–	Age, sex, race, and calendar period
				By Job Category: Male Employees					
				Maintenance	0	0.83	0.0 (0.0-4.430)	–	
				Process	1	0.72	1.394 (0.035-7.765)		
				By Duration of Employment (Yrs): Male Employees					
				< 10	0	–	0.0 (0.0-7.069)	–	
				10-29	1		0.806 (0.020-4.494)		
				30+	0		0.0 (0.0-8.341)		
				By Time Since First Employment (Yrs): Male Employees					
				< 20	0	–	0.0 (0.0-9.585)	–	
				20-39	0		0.0 (0.0-3.577)		
				40+	1		1.269 (0.032-7.072)		
Wong *et al.* (2001b)	US general population	Mort	SMR	All male employees	12	8.15	1.472 (0.761-2.572)	–	Age, sex, race, and calendar period
				By Job Category: Male Employees					
				Maintenance	8	4.31	1.855 (0.801-3.656)	–	
				Process	4	3.28	1.221 (0.333-3.127)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				By Duration of Employment (Yrs): Male Employees					
				All male employees					
				< 10	2	–	1.610 (0.195-5.816)	–	
				10-29	7		**2.768 (1.113-5.704)**		
				30+	3		0.685 (0.141-2.002)		
				Male maintenance employees					
				< 10	2	–	1.530 (0.185-5.526)	–	
				10-29	4		2.287 (0.623-5.856)		
				30+	2		1.593 (0.193-5.756)		
				Male process employees					
				< 10	1	–	0.958 (0.024-5.340)	–	
				10-29	2		1.396 (0.169-5.043)		
				30+	1		1.251 (0.031-6.971)		
				By Time Since First Employment (Yrs): Male Employees					
				All male employees					
				< 20	1	–	0.949 (0.024-5.286)	–	
				20-39	5		1.588 (0.515-3.705)		
				40+	6		1.520 (0.558-3.309)		
				Male maintenance employees					
				< 20	1	–	1.583 (0.040-8.820)	–	
				20-39	3		1.655 (0.341-4.836)		
				40+	4		2.143 (0.584-5.486)		
				Male process employees					
				< 20	2	–	3.207 (0.388-11.585)	–	
				20-39	1		0.706 (0.018-3.933)		
				40+	1		0.810 (0.020-4.512)		
				By Yr of First Hire: Male Employees					
				< 1950	11	6.60	1.667 (0.832-2.984)	–	
				≥ 1950	1	1.55	0.644 (0.016-3.588)		
Collins *et al.* (2003)	Illinois mortality rate	Mort	SMR	**ANLL by Cumulative Exposure (ppm-yrs)**					Age
				No exposure	2	2.6	0.8 (0.1-2.8)	–	
				< 1	1	0.7	1.4 (0.1-5.1)		
				1-6	2	0.7	2.7 (0.3-9.9)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				> 6	2	0.9	2.2 (0.3-8.1)		
				ANLL by Peak Exposure (Number of Days with Peak Exposure Over 100 ppm)					
				None	5	3.9	1.3 (0.4-3.0)	–	
				< 7	0	0.2	0.0 (0.0-10.2)		
				7-40	0	0.4	0.0 (0.0-10.4)		
				> 40	2	0.5	4.1 (0.5-14.9)		
Lewis *et al.* (2003)	Canadian general population	Inc	SIR	**AML**					Age, sex, and calendar period
				Males	3	3.79	–[b]	–	
				Females	2	1.54			
				By duration of employment for male workers (yrs)					
				< 10	1	1.27	–[b]	–	
				≥ 10-< 20	1	0.84			
				≥ 20	0	0.23			
		Mort	SMR	Males	3	2.37		–	
				Females	0	0.90			
		Inc	SIR	**ANLL**					
				Males	4	4.13	–[b]	–	
				Females	2	1.66			
				By duration of employment for male workers (yrs)					
				< 10	1	1.38	–[b]	–	
				≥ 10-< 20	1	0.91			
				≥ 20	0	0.25			
		Mort	SMR	Males	4	2.48		–	
				Females	0	0.95			
Bloemen *et al.* (2004)	US general population and local populations	Mort	SMR	**No Lag**					Age, sex, race, and calendar period
				By duration of exposure (yrs)					
				< 5	2	–	0.82 (0.10-2.97)	–	
				5-9	1		2.20 (0.06-12.23)		
				10+	1		1.37 (0.03-7.66)		
				By cumulative exposure (ppm-yrs)					
				< 28.3	2	–	0.87 (0.11-3.13)	–	
				28.3-79.1	1		1.47 (0.04-8.17)		
				79.1+	1		1.61 (0.04-8.95)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				By average intensity (ppm)					
				< 5	0	–	0.00 (0.00-2.64)	–	
				5-14	3		2.66 (0.55-7.76)		
				15+	1		0.92 (0.02-5.13)		
				15 Yr Lag					
				By duration of exposure (yrs)					
				< 5	3	–	1.18 (0.24-3.46)	–	
				5-9	0		0.00 (0.00-8.33)		
				10+	1		1.58 (0.04-8.79)		
				By cumulative exposure (ppm-yrs)					
				< 28.3	3	–	1.26 (0.26-3.69)	–	
				28.3-79.1	0		0.00 (0.00-5.65)		
				79.1+	1		1.71 (0.04-9.51)		
				By average intensity (ppm)					
				< 5	3	–	0.93 (0.19-2.73)	–	
				5-14	1		2.65 (0.07-14.74)		
				15+	0		0.00 (0.00-146.28)		
Huebner *et al.* (2004)	Louisiana and Texas general populations	Mort	SMR	**By Work Location**					Age, sex, race, and calendar period
				Baton Rouge	11	7.23	1.52 (0.76-2.72)	–	
				Baytown	12	5.62	**2.13 (1.10-3.73)**		
				For Employees Hired < 1950					
				Baton Rouge	11	5.69	1.93 (0.96-3.46)	–	
				Baytown	9	4.35	2.07 (0.95-3.93)		
				For Employees Hired ≥ 1950					
				Baton Rouge	0	1.54	–	–	
				Baytown	3	1.27	2.36 (0.49-6.88)		
				By Duration of Employment (Yrs) for 20+ Yrs of Latency					
				Baton Rouge					
				< 15	0	0.16	–	–	
				15-29	1	1.63	–		
				30+	10	4.66	**2.15 (1.03-3.95)**		
				Baytown					
				< 15	0	0.17	–	–	

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				15-29	1	1.38	–		
				30+	9	3.37	**2.67 (1.22-5.07)**		
				By < 1950 Hire Group: Baton Rouge					
				< 1940	5	1.60	**3.12 (1.01-7.28)**	–	
				1940-1944	4	2.85	1.41 (0.38-3.60)		
				1945-1949	2	1.24	–		
Sorahan *et al.* (2005)	England and Wales general populations	Mort	SMR	**All Exposed Workers by Leukemia Subtype**					Age, sex, and calendar yr
				AML	12	6.60	1.82 (0.94-3.18)	–	
				AMoL	0	0.25	0 (–)		
				ANLL[c]	14	7.65	**1.83 (1.00-3.07)**		
		Inc	SIR	ANLL[c]	12	7.3	1.65 (0.85-2.88)		
Tsai *et al.* (2007)	US general population	Mort	SMR	**AML**					Age, sex, race, time period
				Total cohort	11	12.16	0.90 (0.45-1.62)	–	
				≥ 10 yrs of employment	7	7.84	0.89 (0.36-1.84)	–	
				≥ 20 yrs of employment	6	5.71	1.05 (0.39-2.29)	–	
				ANLL					
				Total cohort	12	12.41	0.97 (0.50-1.69)	–	
				≥ 10 yrs of employment	8	8.02	1.00 (0.43-1.97)	–	
				≥ 20 yrs of employment	7	5.85	1.20 (0.48-2.46)	–	
Kirkeleit *et al.* (2008)	Norway's general working population	Inc	RR	**Upstream Operators Offshore[d]**					Age at inclusion into cohort, sex, yr of first exposure, and education
				All workers	6	6	**2.89 (1.25-6.67)**	–	
				By period of first exposure					
				1981-1985	5	–	3.26 (1.28-8.30)	–	
				1986-2003	1		1.76 (0.24-12.86)		
				Offshore Workers Combined					
				By period of first exposure					
				1981-1985	7	–	**2.24 (1.00-5.01)**	–	
				1986-2003	4		1.23 (0.44-3.44)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Saberi Hosnijeh *et al.* (2013)	Unexposed subjects	Inc	HR	Low exposure	–	–	1.06 (0.63-1.81)	0.28	Age, sex, smoking status, alcohol intake, and count
				High exposure	–	–	1.52 (0.78-2.98)		
Collins *et al.* (2015)	US general population	Mort	SMR	**AML**					Age, sex, race, and calendar yr
				All workers	5	–	1.11 (0.36-2.58)	–	
				30+ yrs since first exposure	4	–	1.07 (0.29-2.74)	–	
				By cumulative exposure (ppm-yrs)					
				0-3.9	0	–	0.0 (0.0-2.50)	0.88	
				4.0-24.9	3	–	1.87 (0.39-5.47)		
				25+	2	–	1.39 (0.17-5.03)		
				ANLL					
				All workers	5	–	1.04 (0.34-2.44)	–	
				30+ yrs since first exposure	4	–	1.02 (0.28-2.60)	–	
				By cumulative exposure (ppm-yrs)					
				0-3.9	0	–	0.0 (0.0-2.38)	0.60	
				4.0-24.9	3	–	1.77 (0.37-5.18)		
				25+	2	–	1.30 (0.16-4.69)		
Stenehjem *et al.* (2015)	Never exposed to benzene	Inc	HR	Ever exposed to benzene	8	–	2.18 (0.47-10)	–	Age, ever daily smoker, benzene exposure from other work
	Never exposed to benzene (first employment offshore before 1980)			Ever exposed to benzene (first employment offshore before 1980)	5	–	–	–	

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
	Never exposed to benzene (first employment offshore during or after 1980)			Ever exposed to benzene (first employment offshore during or after 1980)	3	–	0.86 (0.15-4.82)	–	
	Unexposed to benzene			**Cumulative Exposure (ppm-yrs)**					
				Unexposed	2	–	Ref	0.052	
				Tertile 1 (< 0.001-0.037)	2	–	1.40 (0.18-11)		
				Tertile 2 (> 0.037-0.123)	1	–	0.85 (0.08-9.29)		
				Tertile 3 (0.124-0.948)	5	–	4.85 (0.88-27)		
				Cumulative Peak Exposure (> 3 ppm)					
				Unexposed	2	–	Ref	0.166	
				Tertile 1	2	–	1.95 (0.27-14)		
				Tertile 2	3	–	3.52 (0.61-20)		
				Tertile 3	3	–	3.92 (0.59-26)		
				Duration of Exposure (Yrs)					
				0	2	–	Ref	0.880	
				> 0-5.49	3	–	2.04 (0.33-13)		
				5.5-12.9	4	–	3.39 (0.67-17)		
				13-33.5	1	–	0.97 (0.08-11)		
				Average Exposure Intensity (ppm)					
				Unexposed	2	–	Ref	0.092	
				Tertile 1 (< 0.001-0.007)	1	–	0.76 (0.07-8.67)		
				Tertile 2 (> 0.007-0.013)	3	–	2.51 (0.41-15)		
				Tertile 3 (> 0.013-0.040)	4	–	3.47 (0.63-19)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				Average Peak Exposure (> 3 ppm)					
				Unexposed	2	–	1.00 (Ref)	0.056	
				Tertile 1	2	–	2.17 (0.31-15)		
				Tertile 2	2	–	2.21 (0.30-16)		
				Tertile 3	4	–	4.87 (0.90-26)		
Rhomberg *et al.* (2016)	US mortality rates	Mort	SMR	**By Cumulative Exposure (ppm-yrs), 5 Yr Lag[e]**					Age, sex, race, and calendar yr
				ANLL					
				< 1.54	0	0.54	0.00 (0.00-6.80)	–	
				1.54-6.29	0	0.48	0.00 (0.00-7.70)		
				6.39-20.24	0	0.51	0.00 (0.00-7.27)		
				20.25-78.06	1	0.56	1.78 (0.04-9.90)		
				≥ 78.07	7	0.69	**10.21 (4.1-21.04)**		
				AML					
				< 1.54	0	0.45	0.00 (0.00-8.26)	–	
				1.54-6.29	0	0.41	0.00 (0.00-8.93)		
				6.39-20.24	0	0.43	0.00 (0.00-8.58)		
				20.25-78.06	0	0.48	0.00 (0.00-7.68)		
				≥ 78.07	6	0.58	**10.27 (3.77-22.36)**		

Notes:
AML = Acute Myeloid Leukemia; AMoL = Acute Monocytic Leukemia; ANLL = Acute Nonlymphocytic Leukemia; CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; ppm = Parts per Million; Ref = Reference; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; US = United States; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Lewis *et al.* (2003) only reported SMR results when the number of cases/deaths was > 5, or if < 5 when statistically significant.
(c) Includes acute leukemias of unspecified cell type (Sorahan *et al.*, 2005).
(d) The category "upstream operator offshore" contained workers who mainly worked in the production and processing unit. This includes job categories such as process technicians, laboratory engineers, control operators, and other job groups involved in the production process including stabilization, separation, and fractionation of the crude oil, natural gas, and natural gas liquids (Kirkeleit *et al.*, 2008).
(e) Analyses by 0, 10, 15, and 20 yr lags were also provided. Based on the results, the relevant exposure window for benzene appeared to be within 10 years of cancer death. Similar associations were generally observed for all exposure groups for each lag period; however, ANLL analyses with a 20 year lag had a statistically significant result for the lowest exposure group (< 1.54 ppm-years), for which there were five deaths observed and SMR = 4.69 (95% CI: 1.52-10.95) (Rhomberg *et al.*, 2016).

Table H.5 Benzene and Chronic Myeloid Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
Wong *et al.* (1993)	US general population	Mort	SMR	Land-based terminal employees	1	–	0.258 (0.006, 1.433)	–	Age, sex, race, and calendar period
				Marine employees	4	–	1.329 (0.362-3.398)		
Collingwood *et al.* (1996)	US general population	Mort	SMR	All males	1	1.9	0.53 (0.01-2.93)	–	Age, sex, race, and calendar period
Wong *et al.* (2001a)	US general population	Mort	SMR	Male employees	2	1.02	1.956 (0.237-7.066)	–	Age, sex, race, and calendar period
				By Job Category: Male Employees					
				Maintenance	1	0.39	2.536 (0.063-14.128)	–	
				Process	0	0.34	0.0 (0.0-10.838)		
				By Duration of Employment (Yrs): Male Employees					
				< 10	1	–	3.442 (0.086-19.180)	–	
				10-29	1		1.793 (0.045-9.993)		
				30+	0		0.0 (0.0-21.159)		
				By Time Since First Employment (Yrs): Male Employees					
				< 20	2	–	7.295 (0.931-27.800)	–	
				20-39	0		0.0 (0.0-8.613)		
				40+	1		0.762 (0.019-4.246)		
Wong *et al.* (2001b)	US general population	Mort	SMR	All male employees	5	3.81	1.314 (0.426-3.066)	–	Age, sex, race, and calendar period
				By Job Category: Male Employees					
				Maintenance	3	2.05	1.464 (0.302-4.278)	–	
				Process	0	1.57	0.0 (0.0-2.354)		
				By Duration of Employment (Yrs): Male Employees					
				All male employees					
				< 10	1	–	1.542 (0.039-8.592)	–	
				10-29	2		1.508 (0.183-5.449)		
				30+	2		1.092 (0.132-3.945)		
				Male maintenance employees					
				< 10	0	–	0.0 (0.0-5,432)	–	
				10-29	2		2.373 (0.287-8.572)		
				30+	1		1.895 (0.047-10.561)		
				Male process employees					
				< 10	0	–	0.0 (0.0-6.346)	–	

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
				10-29	0		0.0 (0.0-5.655)		
				30+	0		0.0 (0.0-11.057)		
				By Time Since First Employment (Yrs): Male Employees					
				All male employees					
				< 20	0	–	0.0 (0.0-5.127)	–	
				20-39	2		1.424 (0.172-5.145)		
				40+	3		1.783 (0.368-5.211)		
				Male maintenance employees					
				< 20	0	–	0.0 (0.0-8.483)	–	
				20-39	3		3.741 (0.772-10.933)		
				40+	0		0.0 (0.0-4.539)		
				Male process employees					
				< 20	0	–	0.0 (0.0-9.132)	–	
				20-39	0		0.0 (0.0-5.894)		
				40+	0		0.0 (0.0-6.863)		
				By Yr of First Hire: Male Employees					
				< 1950	4	2.96	1.352 (0.369-3.463)	–	
				≥ 1950	1	0.85	1.179 (0.029-6.569)		
Lewis *et al.* (2003)	Canadian general population	Inc	SIR	Males	0	2.84	–[b]	–	Age, sex, and calendar period
				Females	1	0.86	–[b]		
				By Duration of Employment for Male Workers (Yrs)					
				< 10	0	0.96	–[b]	–	
				≥ 10-< 20	0	0.64	–[b]		
				≥ 20	0	0.16	–[b]		
		Mort	SMR	Males	1	1.46	–[b]	–	
				Females	0	0.43	–[b]		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Adjusted For
Huebner *et al.* (2004)	Louisiana and Texas general populations	Mort	SMR	**By Work Location**					Age, sex, race, and calendar period
				Baton Rouge	5	2.75	1.82 (0.59-4.25)	–	
				Baytown	4	2.61	1.54 (0.42-3.93)		
				For Employees Hired < 1950					
				Baton Rouge	4	1.93	2.08 (0.57-5.32)	–	
				Baytown	2	1.82	–		
				For Employees Hired ≥ 1950					
				Baton Rouge	1	0.82	–	–	
				Baytown	2	0.78	–		
Sorahan *et al.* (2005)	England and Wales general population	Mort	SMR	All exposed workers	2	2.57	0.78 (0.09-2.81)	–	Age, sex, and calendar yr
Tsai *et al.* (2007)	US general population	Mort	SMR	Total cohort	3	4.53	0.66 (0.14-1.93)	–	Age, race, time period
				≥ 10 yrs of employment	2	2.87	0.70 (0.08-2.52)	–	
				≥ 20 yrs of employment	2	2.01	1.00 (0.12-3.59)	–	
Saberi Hosnijeh *et al.* (2013)	Unexposed subjects	Inc	HR	Low exposure	–	–	1.00 (0.45-2.22)	0.30	Age, sex, smoking status, alcohol intake, and country
				High exposure	–	–	1.97 (0.75-5.19)		

Notes:
CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; Mort = Mortality; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; US = United States; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) Lewis *et al.* (2003) only reported SMR results when the number of cases/deaths was > 5, or if < 5 when statistically significant.

Table H.6 Benzene and MDS Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Collins *et al.* (2015)	US general population	Mort	SMR	All workers	1	–	6.48 (0.17-38.15)	–	Age, sex, race, and calendar yr
				30+ yrs since first exposure	1		6.88 (0.17-38.32)	–	
				Cumulative Exposure (ppm-yrs)					
				0-3.9	0	–	0.0 (0.0-72.29)	0.11	
				4.0-24.9	0	–	0.00 (0.00-64.58)		
				25+	1	–	25.05 (0.63-139.58)		
Sorahan and Mohammed (2016)	General populations of England, Wales, and Scotland	Inc	SRR	**Petroleum Distribution Workers, Aged 15-84**					Age, sex, calendar period and country
				All workers	17	23.13	0.73 (0.43-1.18)	–	
				Yr of registration					
				1995-2000	5	6.34	0.79 (0.26-1.84)	0.73	
				2001-2005	6	7.54	0.80 (0.29-1.73)		
				2006-2011	6	9.25	0.65 (0.24-1.41)		
				Period from hire (yrs)					
				1-19	–	–	–	0.95	
				20-29	0	0.64	0 (0-5.76)		
				30-39	5	5.69	0.88 (0.29-2.05)		
				≥ 40	12	16.80	0.71 (0.37-1.25)		
				Period of commencing employment					
				1946-1949	3	3.53	0.85 (0.18-2.48)	0.78	
				1950-1959	5	8.56	0.58 (0.19-1.36)		
				1960-1969	9	9.11	0.99 (0.45-1.88)		
				1970-1974	0	1.94	0 (0-1.90)		
				Duration of employment (yrs)					
				1-9	6	7.57	0.79 (0.29-1.73)	0.96	
				10-19	4	6.88	0.58 (0.16-1.49)		
				≥ 20	7	8.68	0.81 (0.32-1.66)		
				Petroleum Distribution Workers, Aged 15-99					
				All workers	21	27.25	0.77 (0.48-1.18)	–	
				Yr of registration					
				1995-2000	6	6.96	0.86 (0.32-1.88)	0.86	
				2001-2005	6	8.60	0.70 (0.26-1.52)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				2006-2011	9	11.69	0.77 (0.35-1.46)		
				Period from hire (yrs)					
				1-19	–	–	–	0.81	
				20-29	0	0.65	0 (0-5.68)		
				30-39	5	5.91	0.85 (0.27-1.97)		
				≥ 40	16	20.70	0.77 (0.44-1.26)		
				Period of commencing employment					
				1946-1949	5	4.81	1.04 (0.34-2.43)	0.61	
				1950-1959	6	10.56	0.57 (0.21-1.24)		
				1960-1969	10	9.87	1.01 (0.49-1.86)		
				1970-1974	0	2.00	0 (0-1.84)		
				Duration of employment (yrs)					
				1-9	7	8.75	0.80 (0.32-1.65)	0.99	
				10-19	6	8.38	0.72 (0.26-1.56)		
				≥ 20	8	10.12	0.79 (0.34-1.56)		
				Oil Refinery Workers, Aged 15-84					
				All workers	29	35.76	0.81 (0.54-1.16)	–	
				Yr of registration					
				1995-2000	12	10.36	1.16 (0.60-2.02)	0.27	
				2001-2005	7	11.58	0.60 (0.24-1.25)		
				2006-2011	10	13.82	0.72 (0.35-1.33)		
				Period from hire (yrs)					
				1-19	–	–	–	0.08	
				20-29	2	0.71	2.82 (0.34-1,0.18)		
				30-39	5	4.82	1.04 (0.34-2.42)		
				≥ 40	22	30.24	0.73 (0.46-1.10)		
				Period of commencing employment					
				1946-1949	3	4.87	0.62 (0.13-1.80)	0.26	
				1950-1959	16	22.67	0.71 (0.40-1.15)		
				1960-1969	8	5.90	1.36 (0.59-2.67)		
				1970-1974	2	2.32	0.86 (0.10-3.11)		
				Duration of employment (yrs)					
				1-9	17	14.97	1.14 (0.66-1.82)	**0.03**	

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
				10-19	6	6.11	0.98 (0.36-2.14)		
				≥ 20	6	14.68	0.41 (0.15-0.89)		
				Oil Refinery Workers, Aged 15-99					
				All workers	36	43.39	0.83 (0.58-1.15)	–	
				Yr of registration					
				1995-2000	13	11.47	1.13 (0.60-1.94)	0.34	
				2001-2005	9	13.62	0.66 (0.30-1.25)		
				2006-2011	14	18.29	0.77 (0.42-1.28)		
				Period from hire (yrs)					
				1-19	–	–	–	0.12	
				20-29	2	0.71	2.82 (0.34-1,0.18)		
				30-39	5	4.96	1.01 (0.33-2.35)		
				≥ 40	29	37.72	0.77 (0.51-1.10)		
				Period of commencing employment					
				1946-1949	5	6.77	0.74 (0.24-1.72)	0.42	
				1950-1959	21	28.00	0.75 (0.46-1.15)		
				1960-1969	8	6.28	1.27 (0.55-2.51)		
				1970-1974	2	2.37	0.84 (0.10-3.05)		
				Duration of employment (yrs)					
				1-9	18	17.41	1.03 (0.61-1.63)	**0.05**	
				10-19	10	7.80	1.28 (0.61-2.36)		
				≥ 20	8	18.18	**0.44 (0.19-0.87)**		

Notes:
CI = Confidence Interval; Inc = Incidence; MDS = Myelodysplastic Syndrome; Mort = Mortality; ppm = Parts per Million; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; SRR = Standardized Risk Ratio; US = United States; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.

Table H.7 Benzene and Leukemia Case-Control Study Characteristics

Study	Location	Outcome Type	Leukemia Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Bernard *et al.* (1984)	UK	Inc	Lymphoid	1979-1981	M	≥ 15	42	Regional Histopathology Lymphoma Panel, Regional Cancer Registry, weekly enquiry of clinicians and laboratories	152	Hospital in-patient population	In-person employment history interview
Wilcosky *et al.* (1984)	US	Mort	Lymphatic	1964-1974	M	40-84	10	Cohort of male rubber workers	1,336	Cohort of male rubber workers	Work history records were linked to data on all authorized solvent usage in the plant by process area and yr
Ciccone *et al.* (1993)	Italy	Inc	Leukemia, AML	1989-1990	M	15-74	AML: 50 CML: 17 MDS: 19	Main Hospital of Torino, Italy	246	Main Hospital of Torino, Italy and a random sample of the population of Torino, Italy	Self-report *via* questionnaire and expert opinion
Greenland *et al.* (1994)	US	Mort	Leukemia	1969-1984	M[a]	21-90[b]	22	Employee pension records (subset validated)	1,202	Workers at same transformer-manufacturing facility[c]	JEM from job history records[d]
Schnatter *et al.* (1996a) [Schnatter *et al.*, 1996b]	Canada	Mort	Leukemia	1964-1983	M	Average age at first exposure: 28.7 (cases), 31.7 (controls)	14	Canadian petroleum workers cohort	115	Canadian petroleum workers cohort	Estimated by industrial hygienists

Study	Location	Outcome Type	Leukemia Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Nilsson *et al.* (1998)	Sweden	Inc	Leukemia	1961-1987	M	20-64	1960 cohort: 18 1970 cohort: 12	Swedish National Cancer Register and national censuses	1960 cohort: 159 1970 cohort: 132	National censuses	Employment as a seaman on a tanker, obtained from the Swedish Registry of Seamen
Bjork *et al.* (2001)	Sweden	Inc	Ph+CML[e]	1976-1993	B	Cases: $\bar{x}$ = 51 (31-71) Controls: $\bar{x}$ = 52 (31-72)	226	Patients cytogenetically analyzed at the Department of Clinical Genetics, Lund, Sweden	251	General population of Southern Sweden, selected by Statistics Sweden	Interview, assessment by occupational hygienists, and a Finnish JEM
Blair *et al.* (2001)	US	Inc	Leukemia,[f] AML, ALL, CML, MDS	1980-1983	M	≥ 30	Leukemia: 513 AML: 132 ALL: 13 CML: 46 Myelodysplasia: 58	IA Cancer Registry and MN hospital surveillance network	1,087	RDD, HCFA, and state death certificates	In-person interview/ standardized questionnaire on lifetime occupational history, and JEM
Guenel *et al.* (2002)	France	Inc	Leukemia, acute leukemia, chronic leukemia, AML, ALL, CML	1978-1989	M	45.5 (mean age at diagnosis)	72	EDF-GDF company cancer register	285	Active EDF-GDF worker cohort	JEM, evaluation by occupational health professionals, time-weighted average based on occupation

Study	Location	Outcome Type	Leukemia Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Adegoke *et al.* (2003)	China	Inc	Leukemia, ALL, AML, CML	1987-1989	B	≥ 15	486	Shanghai Cancer Registry	502	Random selection from Shanghai Resident Registry	Interview on lifetime job history, self-reported benzene exposure, and JEM
Albin *et al.* (2003)	Sweden	Inc	MDS	1976-1993	B	Cases median: 72, Controls median: 71	330	Department of Clinical Genetics, Lund University Hospital	337	Swedish National Bureau of Statistics	Occupational history *via* telephone interview
Glass *et al.* (2003)	Australia	Inc	Leukemia, ANLL, CML	1981-1999	M	26-79	79	Health Watch cohort study	395	Health Watch cohort study	Interview, self-reported job history, task-based algorithm based on occupational history
Costantini *et al.* (2008)	Italy	Inc	Leukemia, AML	1991-1993	B	20-74	586	Local and major city hospitals, regional cancer institutes, and the Varese Cancer Registry[g]	1,278	Demographic files of municipalities	Occupational history from in-person interview/questionnaire, and JEM
Kaufman *et al.* (2009)[h]	Thailand	Inc	Myeloid, AML, CML	1997-2003	B	≥ 18	AML: 87 CML: 44	Siriraj Hospital	756	Hospital	Occupational exposure to benzene from in-person interviews

Study	Location	Outcome Type	Leukemia Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Irons *et al.* (2010)	China	Inc	MDS-U, RA, RAEB, RCMD, and RCUD	2003-2007	B	≥ 18	29	29 Shanghai hospitals	58[i]	29 Shanghai hospitals	Work history combined with at least one of the following: exposure measurement records based on job and location; records for surrogate factories, industries or jobs; literature assessment; assessment of regulatory and technology changes; monitoring from nearby facilities; and task simulations
Wong *et al.* (2010)	Residents of Shanghai, China	Inc	AML	2003-2007	B	$\bar{x}$ = 49.92 (cases); $\bar{x}$ = 49.98 (controls)	722	Shanghai Hospitals	1,444	Shanghai Hospitals	Benzene exposure was assigned by experts using occupational history from in-person interviews
Lv *et al.* (2011)	China	Inc	MDS, RAEB, RCMD	2003-2006	B	Median: 59 (cases), 61 (controls)	403	27 hospitals in Shanghai, China	806	27 hospitals in Shanghai, China	In-person questionnaire and expert opinion

Study	Location	Outcome Type	Leukemia Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Talibov *et al.* (2014)	Finland, Iceland, Norway, Denmark, and Sweden	Inc	AML	1961-2005	B	67 (median)	14,982	Nordic Occupational Cancer Study cohort	74,505	Nordic Occupational Cancer Study cohort	JEM, occupational information from census records
Copley *et al.* (2017) [Wong *et al.*, 2010]	China	Inc	MDS, RCMD, RAEB	–	B	18+	604	29 hospitals in Shanghai, China	1,193	29 hospitals in Shanghai, China	In-person questionnaire, estimated using historic database from the Shanghai Institute of Public Health Supervision, surrogate factory monitoring, historical Chinese literature, and specific task simulations
Linet *et al.* (2019)	China	Inc	AML, MDS, AML/MDS, CML	1972-1999	B	–	AML: 36 MDS: 8 CML: 18	NCI-CAPM cohort	1,500	NCI-CAPM cohort	JEM based on factory records and subject questionnaires
Forsell *et al.* (2020)	Sweden	Inc	Leukemia, ANLL, AML, myeloid	1985-2014	M	20-85	121	Swedish Seafarers' Registry, Swedish Cancer Registry	450	Swedish Seafarers' Registry	Employment as a seafarer on a tanker
Linet *et al.* (2020)	China	Inc	ALL	1972-1999	B	–	10	NCI-CAPM cohort	1,500	NCI-CAPM cohort	Exposure modelling using historic monitoring

Study	Location	Outcome Type	Leukemia Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Yarosh *et al.* (2021)	US	Inc	De Novo MDS, Therapy Related MDS	2010-2014	B	20-85	383	Minnesota Cancer Reporting System	682	Minnesota State Driver's License and Identification Card List	Self-administered questionnaire
Anwar *et al.* (2022)	Pakistan	Inc	MDS	2010-2018	B	–	150	National Institute of Blood Diseases and Bone Marrow Transplantation	450	Patients for trivial ailments and attendants of patients	Self-report *via* questionnaire

Notes:
ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; ANLL = Acute Nonlymphocytic Leukemia; B = Both Male and Female; CML = Chronic Myeloid Leukemia; EDF-GDF = Electricite de France-Gaz de France; IA = Iowa; Inc = Incidence; JEM = Job-Exposure Matrix; M = Male; MDS = Myelodysplastic Syndrome; MDS-U = Myelodysplastic Syndrome-Unclassifiable; MN = Minnesota; Mort = Mortality; NCI-CAPM = National Cancer Institute-Chinese Academy of Preventive Medicine; Ph+CML = Philadelphia Chromosome Positive Chronic Myeloid Leukemia; RA = Refractory Anemia; RAEB = Refractory Anemia with Excess Blasts; RCMD = Refractory Cytopenia with Multiple Dysplasia; RCUD = Refractory Cytopenia with Unilineage Dysplasia; RDD = Random Digit Dialing; UK = United Kingdon; US = United States; yr = Year.
$\bar{x}$ = Mean; – = Not Reported.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) Participants restricted to white males (Greenland *et al.*, 1994).
(b) Age at death (Greenland *et al.*, 1994).
(c) Controls consisted "of workers who died of causes thought to be unrelated to the exposures under study" (Greenland *et al.*, 1994).
(d) Benzene was used at the company between approximately 1920-1950 for "general cleaning during machine assembly operations" (Greenland *et al.*, 1994).
(e) Philadelphia chromosome positive CML (Bjork *et al.*, 2001).
(f) All leukemias analysis includes myelodysplasia and other unspecified leukemias (Blair *et al.*, 2001).
(g) Based on information from Costantini *et al.* (2001, 2008).
(h) No cases of lymphoid leukemias were exposed to benzene so risk was not estimated for ALL (Kaufman *et al.*, 2009).
(i) Cases were matched by sex and exact age to two cases from a randomized group of MDS cases with no documented benzene exposure (Irons *et al.*, 2010).

Table H.8 Benzene and Leukemia Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases[a]	Exposed Controls[a]	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Bernard *et al.* (1984)	Inc	RR	**Lymphatic Leukemia**					Sex and geographic area
			No occupational benzene exposure (M)	–	–	Ref	–	
			Occupational exposure to benzene (M)	–	–	3.06 (0.98-11.97)		
Wilcosky *et al.* (1984)	Mort	OR	**Lymphatic Leukemia**					Age, sex, and race
			Unexposed	–	–	Ref	–	
			Cumulative exposure > 1 yr	4	–	2.5 (–)		
Ciccone *et al.* (1993)	Inc	OR	**By Exposure Level Among Men**					Age, sex, area of residence and birth, and smoking
			Benzene unexposed	74	226	Ref	–	
			Benzene exposed	12	20	1.7 (0.6-5.5)		
Greenland *et al.* (1994)	Mort	OR	No or indirect exposure	–	–	Ref	–	Age and yr of death
			Direct exposure	–	–	0.90 (0.26-3.08)		
			No exposure	–	–	Ref	–	Age at death, death yr, and hire yr
			97th percentile of control exposure[b]	–	–	1.4 (0.64-3.2)		
Schnatter *et al.* (1996a)	Mort	OR	**Cumulative Benzene Exposure (ppm-yrs) by Quartiles (5 Yr Lag)**					Age and sex
			0.0-0.17	3	–	Ref	–	
			0.18-0.49	7	–	NC (0.33-NC)		
			0.50-7.9	1	–	1.09 (0.02-23.9)		
			8.0-219.8	3	–	1.81 (0.17-25.7)		
			Cumulative Benzene Exposure (ppm-yrs) by Tertiles (5 Yr Lag)					
			0.0-0.22	4	–	Ref	–	
			0.23-5.49	7	–	2.15 (0.42-15.00)		
			5.50-219.8	3	–	0.86 (0.10-7.34)		
			Cumulative Benzene Exposure (ppm-yrs) by Median, 75th, and 90th Percentiles (5 Yr Lag)					
			0.0-0.49	10	–	Ref	–	
			0.50-7.99	1	–	0.21 (0.0-1.71)		
			8.0-19.99	1	–	0.53 (0.01-5.80)		
			20.0-219.8	2	–	0.96 (0.09-6.81)		
			Intensity of Benzene Exposure (Mean ppm) (5 Yr Lag)					
			0.0-0.01	10	–	Ref	–	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases[a]	Exposed Controls[a]	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			> 0.01-0.19	1	–	0.39 (0.01-4.14)		
			0.20-0.49	1	–	0.18 (0.00-1.39)		
			0.50-6.16	2	–	0.96 (0.09-6.81)		
			Maximum Intensity of Benzene Exposure (ppm) (5 Yr Lag)					
			< 0.5	10	–	Ref	–	
			0.5-0.99	0	–	1.00 (0.0-7.57)		
			≥ 1.0	4	–	1.02 (0.21-4.26)		
			Maximum Rank of Dermal Exposure (No Lag)					
			Low	8	–	Ref	–	
			Medium	4	–	0.61 (0.12-2.51)		
			High	2	–	0.47 (0.04-2.86)		
Nilsson *et al.* (1998)	Inc	OR	**1960 Cohort (Leukemia)**					Age and sex
			Employed on crude oil tanker only	4	–	2.4 (0.8-7.4)	–	
			1970 Cohort (Leukemia)					
			Employed on chemical or product tanker	4	–	1.6 (0.4-6.0)	–	
			Employed on crude oil tanker only	1	–	0.6 (0.1-5.4)		
Blair *et al.* (2001)	Inc	OR	**All Leukemias (Including Myelodysplasia) By Intensity of Exposure**					Age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking, and first degree relative with a lymphatic or hematopoietic tumor
			Unexposed	–	–	Ref	–	
			Low	121	282	0.9 (0.7-1.1)		
			High	10	19	1.0 (0.5-2.3)		
Guenel *et al.* (2002)	Inc	OR	**Electric Utility Workers by Benzene Exposure (Unit[c]-yrs)**					Age, asbestos, chlorinated solvents, and coal tars
			Leukemia					
			0	48	207	Ref	$p = 0.30$	
			> 0 < 1.1	6	38	0.7 (0.2-1.9)		
			≥ 1.1 < 5.5	7	20	1.1 (0.4-3.2)		
			≥ 5.5 < 16.8	5	12	1.4 (0.4-5.7)		
			≥ 16.8	6	8	3.1 (0.3-30.4)		
			Acute leukemia					Age
			Never exposed	31	118	Ref	**$p = 0.05$**	
			> 0 < 1.1	1	18	0.3 (0.1-1.6)		
			≥ 1.1 < 5.5	1	13	0.3 (0.1-2.3)		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases[a]	Exposed Controls[a]	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			≥ 5.5 < 16.8	2	8	1.2 (0.2-6.8)		
			≥ 16.8	6	6	**4.6 (1.2-17.4)**		
			Chronic leukemia					
			Never exposed	16	74	Ref	–	
			> 0 < 1.1	4	18	1.1 (0.3-3.8)		
			≥ 1.1 < 5.5	4	6	3.2 (0.7-13.9)		
			≥ 5.5 < 16.8	2	3	1.7 (0.3-9.3)		
			≥ 16.8	0	2	–		
			Leukemia Benzene Exposure Due to Solvent Use					
			Only exposed due to solvents (U[c]-yrs)					
			0	50	209	Ref	$p = 0.06$	
			> 0 < 1.1	6	37	0.7 (0.3-1.7)		
			≥ 1.1 < 5.5	7	21	1.3 (0.5-3.2)		
			≥ 5.5 < 16.8	5	12	1.8 (0.6-5.5)		
			≥ 16.8	4	6	3.1 (0.8-11.8)		
			Yr of first exposure					
			Never exposed	48	207	Ref	$p = 0.40$	
			< 1960	11	25	2.1 (0.9-4.7)		
			1960-1969	7	27	1.2 (0.5-2.8)		
			≥ 1970	6	26	1.0 (0.4-2.5)		
			Duration of exposure (yrs)					
			Never exposed	48	207	Ref	**$p = 0.02$**	
			0-9	10	52	0.8 (0.4-1.7)		
			10-19	7	17	2.0 (0.7-5.2)		
			≥ 20	7	9	**3.8 (1.3-11.1)**		
			Mean intensity of exposure (units[c])					
			Never exposed	48	207	Ref	**$p = 0.05$**	
			0-0.16	7	39	0.8 (0.3-1.9)		
			0.16-0.56	6	19	1.3 (0.5-3.4)		
			0.56-1.98	7	13	2.2 (0.8-5.6)		
			≥ 1.98	4	7	2.7 (0.7-11.4)		
			2 yr lag[d] (unit[c]-yrs)					
			Never exposed	48	207	Ref	**$p = 0.01$**	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases[a]	Exposed Controls[a]	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			> 0 < 1.1	6	39	0.7 (0.3-1.6)		
			≥ 1.1 < 5.5	7	19	1.5 (0.6-3.7)		
			≥ 5.5 < 16.8	5	13	1.8 (0.6-5.3)		
			≥ 16.8	6	7	**4.3 (1.3-14.8)**		
Adegoke *et al.* (2003)	Inc	OR	**Exposure Based on Lifetime Job from Self-Report**					Age, sex, and income
			Benzene exposure: Never	424	462	Ref	–	
			Benzene exposure: Ever	62	40	**1.7 (1.1-2.6)**		
			Benzene exposure: < 15 yrs	34	30	1.2 (0.7-2.1)	**<0.01**	
			Benzene exposure: ≥ 15 yrs	28	10	**3.3 (1.6-6.9)**		
			By sex					Age and income
			Men					
			Never	222	238	Ref	–	
			Ever	34	27	**1.5 (0.8-2.5)**		
			Women					
			Never	202	224	Ref	–	
			Ever	28	13	**2.3 (1.2-4.6)**		
			Exposure Based on Lifetime Job from Self-Report Combined with JEM Assessment					Age, sex, and income
			Benzene exposure: Never	420	457	Ref	–	
			Benzene exposure: Ever	65	45	**1.6 (1.1-2.4)**		
Glass *et al.* (2003)	Inc	OR	**Cumulative Lifetime Benzene Exposure (ppm-yrs)**					Age and smoking status
			≤ 1	3	138	Ref	–	
			> 1-2	6	56	3.9 (0.9-17.1)		
			> 2-4	8	67	6.1 (1.4-26.0)		
			> 4-8	3	64	2.4 (0.4-13.6)		
			> 8-16	6	53	**5.9 (1.3-27.0)**		
			> 16	7	17	**98.2 (8.8-1,090)**		
			By Start Date in Industry					
			Before 1965	15	63	Ref	–	
			1965-1975	12	60	0.9 (0.3-3.2)		
			1975 or later	6	42	1.0 (0.2-4.8)		
			By Duration of Employment (Yrs) (Truncated at Date of Diagnosis)					
			≤ 11	15	77	Ref	–	
			> 11-17	18	83	0.7 (0.2-2.5)		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases[a]	Exposed Controls[a]	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			> 17-22.5	12	81	1.2 (0.3-5.4)		
			> 22.5-29	16	80	0.4 (0.1-1.9)		
			> 29-43	18	74	0.4 (0.1-2.7)		
			By Exposure to Benzene Concentrate					
			No	28	163	Ref	–	
			Yes	5	2	6.3 (1.1-36)		
			By Exposure Intensity (ppm)					
			≤ 0.1	5	65	Ref	–	
			> 0.1-0.2	9	26	1.2 (0.3-4.9)		
			> 0.2-0.4	4	25	0.5 (0.1-3.2)		
			> 0.4-0.8	4	11	0.6 (0.1-6.2)		
			> 0.8-1.6	3	31	0.2 (0.0-2.0)		
			> 1.6-3.2	6	6	0.4 (0.0-6.1)		
			> 3.2	2	1	1.6 (0.1-38)		
Costantini *et al.* (2008)	Inc	OR	**Leukemia by Level of Exposure**					Age, gender, education, and study area
			Unexposed	355	811	Ref	–	
			Very low/low	16	50	0.5 (0.3-0.9)		
			Medium/high	25	32	1.3 (0.7-2.3)		
Kaufman *et al.* (2009)	Inc	OR	**Any Myeloid Leukemia**					Age, sex, income, cellphone use, other solvent exposure, occupational and non-occupational pesticide exposure, pesticide used near the home, working with powerlines, and living near powerlines
			No exposure	–	–	Ref	–	
			Any exposure	9	11	**3.9 (1.3-11)**		
Forsell *et al.* (2020)	Inc	OR	**Leukemia**					Age at first sea service, age at first tanker service
			Never worked on a tanker	–	–	Ref	–	
			Tankers	71		1.07 (0.68-1.67)	–	
			Tankers pre-1985	64		1.17 (0.70-1.93)	–	
			Tankers post-1985	7		0.81 (0.34-1.95)	–	
			Tankers pre-1985, > 5 yrs cumulative time	17		1.11 (0.57-2.18)	–	
			Tankers pre-1985, < 5 yrs cumulative time	47		1.19 (0.70-2.02)	–	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases[a]	Exposed Controls[a]	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			Leukemia, Latency Period (Yrs)					
			Never worked on a tanker	–	–	Ref	–	
			≤ 15	3		0.47 (0.13-1.62)		
			15-19	8		**3.10 (1.17-8.22)**		
			≥ 20	60		1.05 (0.64-1.72)		
			Leukemia, Time Since Last Exposure (Yrs)					
			Never worked on a tanker	–	–	Ref	–	
			≤ 5	8		0.68 (0.30-1.54)		
			6-10	12		2.00 (0.94-4.28)		
			11-15	8		1.02 (0.45-2.32)		
			16-20	12		1.68 (0.80-3.51)		
			> 20	31		0.89 (0.51-1.55)		
			Myeloid Leukemia					
			Never worked on a tanker	–	–	Ref	–	
			Tankers	25		0.86 (0.41-1.81)		
			Tankers pre-1985	25		1.34 (0.55-3.29)		
			Tankers post-1985	0		–		
			Tankers pre-1985, > 5 yrs cumulative time	5		0.91 (0.27-3.05)		
			Tankers pre-1985, < 5 yrs cumulative time	20		1.53 (0.61-3.83)		

Notes:
CI = Confidence Interval; Inc = Incidence; JEM = Job-Exposure Matrix; M = Male; Mort = Mortality; NC = Not Calculable; OR = Odds Ratio; ppm = Parts per Million; Ref = Reference; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.
(b) "The 97th percentile was chosen because it was usually close to the maximum case exposure at each site, and so estimates based on it would be rough estimates of the maximum possible effect among these subjects" (Greenland *et al.*, 1994).
(c) Guenel *et al.* (2002) reported that "Because of uncertainties regarding the true exposure levels, we used arbitrary units of benzene concentration to estimate exposure intensity. However, our exposure 'units' can be converted roughly into milligram per cubic meter or in parts per million, in order to compare out results with findings in other benzene exposed workers."
(d) Results for 5 and 10 year lags were similar (Guenel *et al.*, 2002).

Table H.9 Benzene and ALL Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
Blair *et al.* (2001)	Inc	OR	**By Intensity of Exposure**					Age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking, and first degree relative with a lymphatic or hematopoietic tumor
			Unexposed	–	–	Ref	–	
			Low	3	282	0.7 (0.2-2.5)		
			High	0	19	–		
Guenel *et al.* (2002)	Inc	OR	**Benzene Exposure in Electric Utility Workers (in U[a]-yrs)**					Age
			Never exposed	9	37	Ref	0.16	
			> 0 to < 5.5	1	7	0.6 (0.1-5.3)		
			≥ 5.5	2	4	3.3 (0.3-43.3)		
Adegoke *et al.* (2003)	Inc	OR	**Exposure Based on Lifetime Job from Self-Report**					Age, sex, and income
			Benzene exposure: Never	72	462	Ref	–	
			Benzene exposure: Ever	9	40	1.5 (0.7-3.3)		
			Benzene exposure: < 15 yrs	4	30	0.8 (0.3-2.4)	0.12	
			Benzene exposure: ≥ 15 yrs	5	10	**3.9 (1.3-11.8)**		
			Exposure Based on Lifetime Job from Self-Report Combined with JEM Assessment					
			Benzene exposure: Never	72	457	Ref	–	
			Benzene exposure: Ever	9	45	1.3 (0.6-2.9)		
Linet *et al.* (2020)	Inc	HR	**Exposed *Versus* Non-exposed Workers with ≥ 2 Yr Lag**					Sex and calendar yr
			Benzene unexposed	2	–	Ref	–	
			Benzene exposed	8	–	2.10 (0.52-13.91)		
			Cumulative Exposure Categories (ppm-yrs) with ≥ 2 Yr Lag					
			0	2	–	Ref	0.37	
			> 0 to < 5	1		–		
			5 to < 40	1		2.03 (0.45, 9.19))		
			40 to < 100	3		–		
			100 to < 300	0		1.87 (0.34, 10.21)		
			≥ 300	3		–		
			Continuous Cumulative Benzene Exposure at 100 ppm-yrs with Lags					
			≥ 2 yr lag	–	–	1.21 (< 1, 3.53)	0.37	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariates Controlled For
			2 to < 10 yr lag			1.69 (< 1, 7.85)	0.31	
			≥ 10 yr lag			1.19 (< 1, 3.43)	0.49	

Notes:
ALL = Acute Lymphocytic Leukemia; CI = Confidence Interval; HR = Hazard Ratio; Inc = Incidence; JEM = Job-Exposure Matrix; OR = Odds Ratio; Ref = Reference; ppm = Parts per Million; U = Unit; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Guenel *et al.* (2002) reported that "Because of uncertainties regarding the true exposure levels, we used arbitrary units of benzene concentration to estimate exposure intensity. However, our exposure 'units' can be converted roughly into milligram per cubic meter or in parts per million, in order to compare out results with findings in other benzene exposed workers."

Table H.10 Benzene and AML Leukemia Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Ciccone *et al.* (1993)	Inc	OR	**Occupational Exposure and Presence of Clonal Chromosome Abnormalities (Males)**					Age, sex, smoking
			Not exposed	–	–	Ref	–	
			Possible exposure	7	–	–	–	
			Probable exposure	3	–	0.7 (0.1-4.4)	–	
Blair *et al.* (2001)	Inc	OR	**By Intensity of Exposure**					Age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking, and first degree relative with a lymphatic or hematopoietic tumor
			Unexposed	–	–	Ref	–	
			Low	30	282	0.8 (0.5-1.3)		
			High	3	19	1.1 (0.3-3.9)		
Guenel *et al.* (2002)	Inc	OR	**Benzene Exposure in Electric Utility Workers (in U-yrs)**					Age
			Never exposed	20	74	Ref	0.14	
			> 0 < 5.5	1	20	0.2 (0.1-1.4)		
			≥ 5.5	5	9	2.4 (0.7-8.5)		
Adegoke *et al.* (2003)	Inc	OR	**Exposure Based on Lifetime Job from Self-Report**					Age, sex, and income
			Benzene exposure: Never	212	462	Ref	–	
			Benzene exposure: Ever	24	40	1.4 (0.8-2.3)		
			Benzene exposure: < 15 yrs	12	30	0.8 (0.4-1.7)	**0.01**	
			Benzene exposure: ≥ 15 yrs	12	10	**2.9 (1.2-7.0)**		
			Exposure Based on Lifetime Job from Self-Report Combined with JEM Assessment					
			Benzene exposure: Never	210	457	Ref	–	
			Benzene exposure: Ever	26	45	1.3 (0.8-2.2)		
Glass *et al.* (2003)	Inc	OR	**Cumulative Lifetime Benzene Exposure (ppm-yrs)**					Age
			≤ 4	–	–	Ref	–	
			> 4-8	–	–	0.52 (0.05-5.0)		
			> 8	–	–	**7.17 (1.27-40.4)**		
Costantini *et al.* (2008)	Inc	OR	**By Exposure Level**					Age, gender, education, and study area
			Unexposed	133	811	Ref	–	
			Very low/low	3	50	0.3 (0.1-1.0)		
			Medium/high	6	32	0.9 (0.4-2.3)		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Kaufman *et al.* (2009)	Inc	OR	No exposure	–	–	Ref	–	Age, sex, income, cellphone use, other solvent exposure, occupation and non-occupational pesticide exposure, pesticide used near the home, working with powerlines, and living near powerlines.
			Any exposure	6	11	**4.9 (1.4-17)**		
Wong *et al.* (2010)	Inc	OR	**Multivariable Model**					Age, sex, education, alcohol, home/workplace renovation, living on a farm, planting crops, raising livestock or animals, farm workers, metal milling and processing, solvents, toluene, xylene, petroleum fuels, kerosene, gasoline, agricultural industry, insecticides, herbicides, fertilizers, glues and adhesives, inks, and pigments
			Never	–	–	Ref	–	
			Ever	78	113	1.20 (0.84-1.71)		
			Length of Exposed Jobs (Yrs)					Age, sex
			Non-exposed	644	1,331	Ref	0.84	
			≤ 10	43	45	**1.99 (1.29-3.07)**		
			11-20	21	30	1.44 (0.82-2.51)		
			> 20	14	38	0.74 (0.39-1.39)		
			Maximum Exposure (EGS)					
			Non-exposed	644	1,331	Ref	**0.01**	
			EGS1 (< 1 mg/m^3)	40	70	1.18 (0.79-1.76)		
			EGS2 (1-10 mg/m^3)	20	25	1.63 (0.90-2.94)		
			EGS3 and 4 (> 10 mg/m^3)	18	18	**2.05 (1.05-3.98)**		
			Yr of First Exposure (Decades)					
			Non-exposed	644	1,331	Ref	–	
			1940-1959	8	12	1.33 (0.54-3.26)		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			1960-1979	22	46	0.97 (0.57-1.62)		
			1980-1999	36	49	1.57 (1.00-2.46)		
			2000 and later	12	6	**4.18 (1.56-11.15)**		
Talibov *et al.* (2014)	Inc	HR	**Cumulative Exposure with 10 Yr Lag (ppm/yr)**					Country, sex, yr of birth, aliphatic and alicyclic hydrocarbons, methylene chloride, other organic solvents, perchloroethylene, 1,1,1-trichloroethane, trichloroethylene, toluene, formaldehyde, and ionizing radiation
			Occupationally unexposed	–	–	Ref	0.33	
			≤ 3.7	430	1,999	1.02 (0.84-1.24)		
			3.7-13.6	310	1,633	0.88 (0.71-1.11)		
			> 13.6	68	418	0.80 (0.56-1.15)		
			Sex-Specific Cumulative Exposure with 10 Yr Lag (ppm/yr)					
			Male					
			Occupationally unexposed	–	–	Ref	0.18	
			≤ 3.7	350	1,515	1.12 (0.87-1.44)		
			3.7-13.6	264	1,414	0.89 (0.69-1.18)		
			> 13.6	63	405	0.76 (0.51-1.13)		
			Female					
			Occupationally unexposed	–	–	Ref	0.59	
			≤ 3.7	81	486	0.86 (0.60-1.22)		
			3.7-13.6	45	213	1.10 (0.69-1.74)		
			> 13.6	5	17	2.02 (0.58-7.04)		
			Age-Specific Cumulative Exposure with 10 Yr Lag (ppm/yr)					
			< 50 yrs					
			Occupationally unexposed	–	–	Ref	0.65	
			≤ 1.34	55	255	1.07 (0.66-1.71)		
			1.34-5	29	219	0.69 (0.36-1.29)		
			> 5	18	44	2.24 (0.99-5.08)		
			≥ 50 yrs					
			Occupationally unexposed	–	–	Ref	0.25	
			≤ 1.34	173	836	1.05 (0.82-1.36)		
			1.34-5	222	1,033	0.97 (0.76-1.24)		
			> 5	311	1,663	0.82 (0.63-1.07)		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Linet *et al.* (2019)	Inc	ERR	**AML**					Age, sex, calendar period, and time since first employed in a study factory
			Cumulative exposure (per 100 ppm-yrs) 2 to < 10 yrs before diagnosis[a]					
			All participants	–	–	0.19 (< 0-0.97)	0.24	
			First exposure < 30 yrs	–	–	**1.16 (0.07-5.0)**	**0.02**	
			First exposure ≥ 30 yrs	–	–	-0.14 (< -0.14-0.24)	0.36	
			Average intensity of exposure (per 10 ppm) 2 to < 10 yrs before diagnosis[a]					
			All participants	–	–	0.18 (< 0-0.77)	0.13	
			First exposure < 30 yrs	–	–	**0.93 (0.11-3.78)**	**0.007**	
			First exposure ≥ 30 yrs	–	–	**1.16 (0.07-5.0)**	**0.02**	
		RR	*Cumulative exposure (ppm-yrs) 2-yr lag*					
			0	9	–	Ref	–	
			> 0 to < 40	8	–	0.94 (0.34-2.53)		
			40 to 199	12	–	1.92(0.79-4.77)		
			200 to < 400	5	–	2.41 (0.71-7.34)		
			≥ 400	2	–	0.80 (0.12-3.29)		
			AML and MDS Combined					
			Cumulative exposure (ppm-yrs) 2 to < 10 yrs before diagnosis by age (yrs) at first exposure					
			All ages					
			0	13	–	Ref	0.08	
			> 0 to < 5	6		1.48 (0.50-3.91)		
			5 to < 40	6		0.74 (0.25-1.94)		
			40 to < 100	9		**2.52 (1.02-6.08)**		
			≥ 100	10		1.84 (0.60-5.01)		
		ERR	Per 100 ppm-yrs	–		0.30 (-0.02-1.09)		
		RR	***< 30 yrs***					
			0	4	–	Ref	**0.004**	
			> 0 to < 40	4		1.12 (0.27-4.29)		
			40 to < 100	6		**5.58 (1.65-19.68)**		
			≥ 100	6		**4.50 (1.22-16.68)**		
		ERR	Per 100 ppm-yrs	–	–	**1.45 (0.21-5.70)**		
		RR	***≥ 30 yrs***					
			0	9	–	Ref	0.55	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			> 0 to < 5	3		1.02 (0.22-3.51)		
			5 to < 40	5		0.78 (0.23-2.34)		
			40 to < 100	3		1.22 (0.32-3.95)		
			≥ 100	4		0.87 (0.22-2.87)		
		ERR	Per 100 ppm-yrs	–	–	-0.080 (< 0-0.44)		
		RR	*Average intensity (ppm) 2 to < 10 yrs before diagnosis by age (yrs) at first exposure*					
			All ages					
			0	13	–	Ref	0.06	
			> 0 to < 5	8		0.80 (0.31-1.97)		
			5 to < 40	7		2.29 (0.84-5.79)		
			40 to < 100	7		1.68 (0.64-4.21)		
			≥ 100	9		2.59 (0.97-6.57)		
		ERR	Per 10 ppm	–	–	0.22 (-0.004-0.78)		
		RR	***< 30 yrs***					
			0	4	–	Ref	**0.002**	
			> 0 to < 5	2		0.68 (0.10-3.18)		
			5 to < 40	4		**4.18 (1.03-15.95)**		
			40 to < 100	4		3.44 (0.84-13.12)		
			≥ 100	6		**6.58 (1.80-24.15)**		
		ERR	Per 10 ppm	–	–	**1.09 (0.19-4.14)**		
		RR	***≥ 30 yrs***					
			0	9	–	Ref	0.82	
			> 0 to < 5	6		0.78 (0.25-2.24)		
			5 to < 40	3		1.32 (0.28-4.59)		
			40 to < 100	3		0.94 (0.24-3.03)		
			≥ 100	3		1.06 (0.22-3.82)		
		ERR	Per 10 ppm	–	–	-0.024 (< 0-0.33)		
Forsell *et al.* (2020)	Inc	OR	**AML**					Age at first sea service, age at first tanker service
			Never worked on a tanker	–	–	Ref	–	
			Tankers	4		0.35 (0.06-1.95)		
			Tankers pre-1985	4		0.95 (0.08-11.1)		
			Tankers post-1985	0		–		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			Tankers pre-1985, > 5 yrs cumulative time	2		–		
			Tankers pre-1985, < 5 yrs cumulative time	2		–		
			ANLL					
			Never worked on a tanker	–	–	Ref	–	
			Tankers	10		0.74 (0.22-2.57)		
			Tankers pre-1985	10		1.75 (0.30-10.1)		
			Tankers post-1985	0		–		
			Tankers pre-1985, > 5 yrs cumulative time	4		4.51 (0.51-39.7)		
			Tankers pre-1985, < 5 yrs cumulative time	6		1.29 (0.20-8.44)		

Notes:
AML = Acute Myeloid Leukemia; ANLL = Acute Nonlymphocytic Leukemia; CI = Confidence Interval; EGS = Exposure Group Score; ERR = Excess Rate Ratio; HR = Hazard Ratio; Inc = Incidence; JEM = Job-Exposure Matrix; MDS = Myelodysplastic Syndrome; OR = Odds Ratio; ppm = Parts per Million; Ref = Reference; RR = Relative Risk; U = Unit; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Linet *et al.* (2019) also evaluated risk by categories of cumulative exposure and average exposure intensity. They also evaluated excess risk per unit of exposure based on exposure ≥10 years before diagnosis. The only association observed was with average benzene exposure intensities between 9 to <25 ppm and incidence of AML and MDS combined (RR = 2.79, 95% CI: 1.24-6.16), but there was no association with lower or higher levels of benzene exposure.

Table H.11 Benzene and Chronic Myeloid Leukemia Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Blair *et al.* (2001)	Inc	OR	**By Intensity of Exposure**					Age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking, and first degree relative with a lymphatic or hematopoietic tumor
			Unexposed	–	–	Ref	–	
			Low	11	282	0.9 (0.4-1.8)		
			High	0	19	–		
Bjork *et al.* (2001)[a]	Inc	OR	Unexposed	190	215	Ref	–	Age, sex, and county of residence
			Occupational, hobby, or lifestyle benzene exposure ≤ 20 yrs before diagnosis	24	23	1.2 (0.66-2.3)		
Guenel *et al.* (2002)	Inc	OR	**Benzene Exposure in Electric Utility Workers (in U-yrs)**					Age
			Never exposed	7	35	Ref	0.85	
			> 0 < 5.5	5	13	1.9 (0.5-7.1)		
			≥ 5.5	1	4	1.2 (0.1-11.4)		
Adegoke *et al.* (2003)	Inc	OR	**Exposure Based on Lifetime Job from Self-Report**					Age, sex, and income
			Benzene exposure: Never	65	462	Ref	–	
			Benzene exposure: Ever	14	40	2.5 (1.3-4.9)		
			Benzene exposure: < 15 yrs	7	30	1.7 (0.7-4.0)	**0.01**	
			Benzene exposure: ≥ 15 yrs	7	10	**5.0 (1.8-13.9)**		
			Exposure Based on Lifetime Job from Self-Report Combined with JEM Assessment					
			Benzene exposure: Never	64	457	Ref	–	
			Benzene exposure: Ever	15	45	**2.4 (1.3-4.7)**		
Glass *et al.* (2003)	Inc	OR	**Cumulative Lifetime Benzene Exposure (ppm-yrs)**					Age
			≤ 4	–	–	1.00	–	
			> 4-8	–	–	–		
			> 8	–	–	0.91 (0.08-9.8)		
Kaufman *et al.* (2009)	Inc	OR	No exposure	–	–	Ref	–	Age, sex
			Any exposure	3	11	5.0 (–)		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Linet *et al*. (2019)	Inc	RR	**Exposure 2 to < 10 Yrs Before Diagnosis**					Age, sex, and calendar period
			Cumulative exposure (ppm-yrs)					
			0	6	–	Ref	0.39	
			> 0 to < 40	5	–	1.08 (0.30-3.71)		
			≥ 40	7	–	2.26 (0.71-7.66)		
		ERR	Per 100 ppm-yrs	–	–	-0.24 (-1.22-0.17)		
		RR	*Average intensity (ppm)*					
			0	6	–	Ref	0.44	
			> 0 to < 9	7	–	1.36 (0.44-4.36)		
			≥ 9	5	–	1.88 (0.51-5.77)		
		ERR	Per 10 ppm	–	–	-0.14 (-0.76-0.13)		
		RR	**Exposure ≥ 10 Yrs Before Diagnosis**					
			Cumulative exposure (ppm-yrs)					
			0	6	–	Ref	0.94	
			> 0 to < 100	7	–	2.10 (0.68-6.70)		
			≥ 100	5	–	1.85 (0.49-6.84)		
		ERR	Per 100 ppm-yrs	–	–	-0.005 (-0.20-0.082)		
		RR	*Average intensity (ppm)*					
			0	6	–	Ref	0.57	
			> 0 to < 9	6	–	2.07 (0.62-6.94)		
			≥ 9	6	–	1.94 (0.58-6.53)		
		ERR	Per 10 ppm	–	–	-0.067 (-0.43-0.10)		

Notes:
CI = Confidence Interval; ERR = Excess Rate Ratio; Inc = Incidence; JEM = Job-Exposure Matrix; OR = Odds Ratio; ppm = Parts per Million; Ref = Reference; RR = Relative Risk; U = Unit; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Bjork *et al*. (2001) reported 12 cases and 13 controls with uncertain exposures. These participants are excluded from this analysis.

Table H.12 Benzene and MDS Leukemia Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Blair *et al.* (2001)	Inc	OR	**By Intensity of Exposure**					Age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking, and first degree relative with a lymphatic or hematopoietic tumor
			Unexposed	43[a]	786[a]	Ref	–	
			Low	12	282	0.7 (0.4-1.4)		
			High	3	19	2.6 (0.7-9.7)		
Albin *et al.* (2003)	Inc	OR	No benzene exposure	284	280	Ref	–	Age, sex, and county of residence
			Benzene exposed	29	30	0.95 (0.54-1.7)		
Irons *et al.* (2010)	Inc	OR	**Benzene Signal[b] Cases**					Age and sex
			Unexposed cases	–	–	Ref	–	
			RCMD	16		0.58 (0.24-1.4)		
			RAEB	2		1.4 (0.19-11.1)		
			MDS-U	7		**11.12 (1.34-92.4)**		
			RCUD	2		1.0 (0.18-5.46)		
			RA	2		0.67 (0.13-3.3)		
Lv *et al.* (2011)	Inc	OR	**All MDS**					Age and sex
			Lifetime benzene exposure (yrs)					
			None	385	797	Ref	**0.001**	
			Ever (current and former)	18	9	**4.33 (1.88-10.00)**		
			≤ 10	8	5	**3.67 (1.09-12.33)**		
			> 10	10	4	**5.00 (1.57-15.94)**		
			Exposure level (mg/m³)					
			None	385	797	Ref	**0.00**	
			< 1	4	6	1.6 (0.43-5.96)		
			1-10	1	1	2.00 (0.13-31.98)		
			> 10	13	2	**12.54 (2.82-55.65)**		
			Weekly exposure					
			None	385	797	Ref	**0.001**	
			1-3 times (2-3 hours each)	8	4	**4.00 (1.37-170)**		
			Daily (6-8 hours per day)	10	5	**4.88 (1.28-18.60)**		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			Adjusted benzene model					Age, sex, TB drugs, diabetes medication, traditional Chinese medicine, distance to high voltage lines, new building, smoking, alcohol, pesticides, herbicides, gasoline, glues, hair dye, and education
			Unexposed	385	797	Ref	–	
			Ever exposed	–	–	**3.73 (1.32-10.51)**		
			RAEB					Age and sex
			Lifetime benzene exposure (yrs)					
			None	96	196	Ref	0.91	
			Ever (current and former)	3	2	3.00 (0.5-17.95)		
			≤ 10	0	0	–		
			> 10	3	2	2 (0.28-14.20)		
			Exposure level (mg/m^3)					
			None	96	196	Ref	0.11	
			< 1	0	3	–		
			1-10	0	0	–		
			> 10	3	0	–		
			Weekly exposure					
			None	96	196	Ref	0.31	
			1-3 times (2-3 hours each)	2	1	4.00 (0.36-44.11)		
			Daily (6-8 hours per day)	1	1	2.00 (0.13-32.00)		
			Adjusted benzene model					Age, sex, TB drugs, diabetes medication, traditional Chinese medicine, distance to high voltage lines, new building, smoking, alcohol, pesticides, herbicides, gasoline, glues, hair dye, and education
			Unexposed	385	797	Ref	–	
			Ever exposed	–	–	4.94 (0.66-36.87)	–	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
			RCMD					Age and sex
			Lifetime benzene exposure (yrs)					
			None	251	521	Ref	**0.004**	
			Ever (current and former)	12	5	**5.66 (1.81-17.64)**		
			≤ 10	6	3	**5.31 (1.05-26.77)**		
			> 10	6	2	**6.00 (1.21-29.72)**		
			Exposure level (mg/m³)					
			None	251	521	Ref	**0.005**	
			< 1	3	2	6.00 (0.62-57.68)		
			1-10	1	1	2.00 (0.13-31.98)		
			> 10	8	2	**7.56 (1.60-35.73)**		
			Weekly exposure					
			None	251	521	Ref	**0.01**	
			1-3 times (2-3 hours each)	4	2	4.00 (0.73-21.84)		
			Daily (6-8 hours per day)	7	3	**6.31 (1.29-30.74)**		
			Adjusted benzene model					Age, sex, TB drugs, diabetes medication, traditional Chinese medicine, distance to high voltage lines, new building, smoking, alcohol, pesticides, herbicides, gasoline, glues, hair dye, and education
			Unexposed	385	797	Ref	–	
			Ever exposed	–	–	**5.99 (1.19-30.16)**		

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Copley *et al.* (2017)	Inc	OR	**All MDS, Average Benzene Exposure (ppm)[a]**					Age, sex, BMI, education, farm residence, diesel fuel, metal machining, TB medication, diabetes, and welding
			Unexposed	531	1,126	Ref	**< 0.01**	
			< 0.3	22	37	1.68 (0.93-3.00)		
			0.3-2.9	14	16	1.94 (0.88-4.26)		
			3.0-11.9	11	3	**5.35 (1.44-19.9(**		
			≥ 12.0	26	11	**3.47 (1.65-7.28)**		
			RCMD, Average Benzene Exposure (ppm)[a]					Age, sex, education, farm residence, herbicides, metals, TB medication, diabetes, smoking
			Unexposed	380	809	Ref	**< 0.01**	
			< 0.3	14	27	1.71 (0.84-3.49)		
			0.3-2.9	12	10	**3.19 (1.25-8.12)**		
			3.0-11.9	9	3	**5.38 (1.36-21.3)**		
			≥ 12.0	18	8	**3.75 (1.53-9.21)**		
			RAEB, Average Benzene Exposure (ppm)					Age, sex, smoking, fertilizer exposure, metal machining, diabetes, BMI
			Unexposed	93	185	Ref	0.95	
			< 0.3	7	8	1.73 (0.55-5.41)		
			0.3-2.9	1	5	0.31 (0.03-3.36)		
			3.0+	2	3	0.81 (0.11-5.78)		
Linet *et al.* (2019)	Inc	ERR	**MDS**					Age, sex, calendar period, and time since first employed in a study factory
			Cumulative exposure (per 100 ppm-yrs) 2 to < 10 yrs before diagnosis[c]					
			All participants	–	–	1.28 (< 0-18.12)	0.09	
			First exposure < 30 yrs	–	–	**0.35 (0.13-∞)**	**0.03**	
			First exposure ≥ 30 yrs	–	–	0.35 (< 0-19.69)	0.55	
			Average intensity of exposure (per 10 ppm) 2 to < 10 yrs before diagnosis[c]					
			All participants	–	–	0.58 (< 0-7.26)	0.18	
			First exposure < 30 yrs	–	–	**∞ (0.016-∞)**	**0.05**	
			First exposure ≥ 30 yrs	–	–	**∞ (0.13-∞)**	**0.03**	

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{Trend}	Covariate Adjustment
Yarosh *et al.* (2021)	Inc	OR	**De Novo MDS[d]**					Age, sex, previous radiation therapy, personal history of cancer, chemotherapy, smoking, autoimmune disease
			No exposure to benzene	–	–	Ref	–	
			Previous Exposure to benzene	54	77	1.48 (1.00-2.19)		
			Therapy Related MDS[e]					
			No exposure to benzene	–	–	Ref	–	
			Previous Exposure to benzene	6	77	1.34 (0.40-4.48)		
			MDS in Individuals with Personal Histories of Cancer					Age, sex
			De novo MDS[d]					
			No exposure to benzene	–	–	Ref	–	
			Previous exposure to benzene	13	17	1.41 (0.62-3.20)		
			Therapy-related MDS[e]					
			No exposure to benzene	–	–	Ref	–	
			Previous exposure to benzene	4	17	0.81 (0.23-2.90)		
Anwar *et al.* (2022)	Inc	OR	Not exposed to benzene	78	283	Ref	–	Age and sex
			Exposed to benzene	72	167	**1.564 (1.077-2.272)**		

Notes:
AML = Acute Myeloid Leukemia; BMI = Body Mass Index; CI = Confidence Interval; ERR = Excess Rate Ratio; Inc = Incidence; MDS = Myelodysplastic Syndrome; MDS-U = Myelodysplastic Syndrome-Unclassifiable; OR = Odds Ratio; ppm = Parts per Million; RA = Refractory Anemia; RAEB = Refractory Anemia with Excess Blasts; RCMD = Refractory Cytopenia with Multiple Dysplasia; RCUD = Refractory Cytopenia with Unilineage Dysplasia; Ref = Reference; RR = Relative Risk; TB = Tuberculosis; yr = Year.
∞ = Infinity; – = Not Reported.
Bolded values indicate statistical significance.
(a) In an additional analysis combining the two highest exposure groups, similar statistically significant effect estimates were reported (Copley *et al.*, 2017).
(b) Benzene signal cases were defined as individuals exposed to > 67 mg/m^3 of benzene for at least 6 months with a mean exposure duration of 144 months (Irons *et al.*, 2010).
(c) Linet *et al.* (2019) also evaluated risk per unit of cumulative exposure and average exposure intensity based on exposure in the period ≥ 10 years before diagnosis and reported no associations.
(d) De novo MDS is defined as "all subtypes other than therapy-related" (Yarosh *et al.*, 2021).
(e) Therapy-related MDS is defined as "occurring after previous exposure to chemotherapy or radiation therapy administered for cancer or other diseases" (Yarosh *et al.*, 2021).

Table H.13 Benzene and Leukemia Meta-Analyses and Pooled Study Results

Study	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Included Study Designs	Statistical Model	Group	Risk Estimate	Risk Estimate (95% CI)
Raabe and Wong (1996)	Meta-analysis	Mort	ALL	19	Cohort	Meta-SMR	All US and UK studies	SMR	1.16 (0.81-1.61)
			AML	19					0.96 (0.81-1.13)
			CML	19					0.89 (0.68-1.15)
Lamm *et al.* (2009)	Meta-analysis	Inc	CML	6	Case-control	Fixed effects	All studies	OR	1.003 (0.94-1.07)
Khalade *et al.* (2010)	Meta-analysis	Inc & Mort	Leukemia	15	Cohort & case-control	Random effects	**Any Exposure**		
							All studies	ES	**1.72 (1.37-2.17)**
				8		Fixed effects	**Cumulative Exposure (ppm-yrs)[a]**		
							Low (>0-<40)	ES	**1.64 (1.13-2.39)**
				6			Medium (40-<100)		**1.90 (1.26-2.89)**
				7			High (≥100)		**2.62 (1.57-4.39)**
			AML	8			**Any Exposure**		
							All studies	ES	**1.38 (1.15-1.64)**
				4			**Cumulative Exposure (ppm-yrs)[b]**		
							Low (>0-<40)	ES	1.94 (0.95-3.95)
				2			Medium (40-<100)		2.32 (0.91-5.94)
				2			High (≥100)		**3.20 (1.09-9.45)**
			CML	5			**Any Exposure**		
							All studies	ES	1.05 (0.83-1.34)
Vlaanderen *et al.* (2011)	Meta-analysis	Inc & Mort	AML	21	Cohort	Random effects	**Stratification by Exposure Assessment Quality[c]**		
							All studies (A-D)	mRR	**1.68 (1.35-2.10)[d]**
				10			A-C		**1.73 (1.26-2.38)**
				9			A-B		**1.82 (1.25-2.66)**
				6			A		**2.32 (1.55-3.**47)
			ALL	17			All studies (A-D)		**1.44 (1.03-2.02)**
				4			A-C		1.26 (0.5-3.16)
				4			A-B		1.26 (0.5-3.16)
				1			A		2.80 (0.27-29.23)
Schnatter *et al.* (2012)[e]	Pooled	Inc	AML	3	Nested case-control		**Cumulative Exposure (ppm-yrs)**		
							≤ 0.348	OR	Ref
							0.348-2.93		1.04 (0.50-2.19)
							> 2.93		1.39 (0.68-2.85)
			CML				≤ 0.348		Ref

Study	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Included Study Designs	Statistical Model	Group	Risk Estimate	Risk Estimate (95% CI)
						Conditional logistic regression with penalized smoothing splines	0.348-2.93		**5.04 (1.45-17.5)**
							> 2.93		2.20 (0.63-7.68)
			MDS				≤ 0.348		Ref
							0.348-2.93		1.73 (0.55-5.47)
							> 2.93		**4.33 (1.31-14.3)**
			AML				**Average Exposure Intensity (ppm)**		
							≤ 0.016	OR	Ref
							0.016-0.081		1.97 (0.87-4.50)
							0.081-0.259		1.41 (0.61-3.30)
							> 0.259		1.90 (0.86-4.18)
			CML				≤ 0.016		Ref
							0.016-0.081		1.75 (0.62-4.98)
							0.081-0.259		2.17 (0.69-6.88)
							> 0.259		0.91 (0.25-3.28)
			MDS				≤ 0.016		Ref
							0.016-0.081		1.99 (0.51-7.76)
							0.081-0.259		1.85 (0.51-6.75)
							> 0.259		3.12 (0.90-10.8)
			AML				**Maximum Exposure Intensity (ppm)**		
							≤ 0.016	OR	Ref
							0.016-0.118		1.49 (0.65-3.37)
							0.118-0.413		1.35 (0.59-3.07)
							> 0.413		1.65 (0.75-3.63)
			CML				≤ 0.016		Ref
							0.016-0.118		1.25 (0.40-3.95)
							0.118-0.413		2.12 (0.77-5.82)
							> 0.413		0.59 (0.15-2.37)
			MDS				≤ 0.016		Ref
							0.016-0.118		1.46 (0.35-6.02)
							0.118-0.413		1.82 (0.51-6.52)
							> 0.413		2.81 (0.79-10.1)
			AML				**Duration of Employment (Yrs)**		
							≤ 15.6	OR	Ref
							15.6-28		0.96 (0.46-2.01)

Study	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Included Study Designs	Statistical Model	Group	Risk Estimate	Risk Estimate (95% CI)
							> 28		1.70 (0.75-3.87)
			CML				≤ 15.6		Ref
							15.6-28		3.13 (0.93-10.6)
							> 28		1.42 (0.35-5.67)
			MDS				≤ 15.6		Ref
							15.6-28		0.77 (0.23-2.53)
							> 28		1.74 (0.61-4.99)
			AML				**Peak Exposure > 3 ppm[f]**		
							None	OR	Ref
							Yes		1.50 (0.82-2.75)
			CML				None		Ref
							Yes		0.67 (0.29-1.54)
			MDS				None		Ref
							Yes		2.48 (0.97-6.35)
Vlaanderen *et al.* (2012)[g]	Meta-analysis	Inc & Mort	CML	17	Cohort	Random effects	**Stratification by Exposure Assessment Quality[c]**		
							All studies (A-D)	mRR	1.23 (0.93-1.63)
				6			A-C		1.44 (0.82-2.53)
				6			A-B		1.44 (0.82-2.53)
				3			A		1.68 (0.74-3.84)
Mundt *et al.* (2021)	Meta-analysis	Inc & Mort	AML	27	Cohort & case-control	Random effects	Overall	MRR	**1.30 (1.09-1.55)[h]**
				8			High exposure subcategories		**1.65 (1.13-2.41)**
				5			Low exposure subcategories		1.54 (0.89-2.66)
				14			Any exposure		1.14 (0.93-1.39)
				18	Cohort		Cohort studies		**1.29 (1.02-1.63)[h]**
				9	Case-control		Case-control studies		**1.34 (1.03-1.75)**
			CML	18	Cohort & case-control		Overall		1.25 (1.00-1.55)
				3			High exposure subcategories		**2.79 (1.44-5.40)**
				2			Low exposure subcategories		1.93 (0.64-5.82)
				13			Any exposure		1.11 (0.87-1.40)

Study	Study Type	Outcome Type	Cancer Type	Number of Studies in Analysis	Included Study Designs	Statistical Model	Group	Risk Estimate	Risk Estimate (95% CI)
				13	Cohort		Cohort studies		1.13 (0.89-1.45)
				5	Case-control		Case-control studies		**1.93 (1.05-3.56)**
			MDS	9	Cohort & case-control		Overall		**1.87 (1.39-2.52)**
				6			High exposure subcategories		**1.80 (1.18-2.75)**
				2			Low exposure subcategories		**2.29 (1.51-3.48)**
				1			Any exposure		1.64 (0.83-3.22)
				4	Cohort		Cohort studies		**1.94 (1.19-3.18)[h]**
				5	Case-control		Case-control studies		**1.85 (1.28-2.67)**
			ML	7	Cohort		Overall		**1.56 (1.10-2.20)**
				4			High exposure subcategories		1.28 (0.87-1.88)
				1			Low exposure subcategories		2.24 (0.65-7.71)
				2			Any exposure		**2.15 (1.29-3.58)**
				7			Cohort studies		**1.56 (1.10-2.20)[h]**

Notes:
ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid Leukemia; CI = Confidence Interval; CML = Chronic Myeloid Leukemia; ES = Effect Size; Inc = Incidence; MDS = Myelodysplastic Syndrome; ML = Myeloid Leukemia; Mort = Mortality; mRR = Meta-Relative Risk; OR = Odds Ratio; ppm = Parts per Million; Ref = Reference; RR = Relative Risk; SMR = Standardized Mortality Ratio; UK = United Kingdom; US = United States; yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.
(a) Khalade *et al.* (2010) reported a dose-response trend between leukemia and average cumulative exposure to benzene in a separate meta-regression model (p_{trend} = 0.015).
(b) Khalade *et al.* (2010) reported no dose-response trend between AML and average cumulative exposure to benzene in a separate meta-regression model (p_{trend} = 0.813).
(c) Exposure assessment was rated as follows: A, quantitative exposure estimates for benzene; B, semiquantitative estimates of benzene exposure or quantitative estimates of exposures containing benzene; C, some industrial hygiene sampling results; D, qualitative indication that benzene exposure had occurred (Vlaanderen *et al.*, 2011, 2012).
(d) Significant evidence for between study heterogeneity ($p < 0.1$) (Vlaanderen *et al.*, 2011).
(e) The AML results presented in Schnatter *et al.* (2012) are identical to those presented in Rushton *et al.* (2014); the CML results presented in Schnatter *et al.* (2012) are identical to those presented in Glass *et al.* (2014). Therefore, we do not present results from Rushton *et al.* (2014) or Glass *et al.* (2014) here.
(f) Peak exposure > 3 ppm is defined as, "at least one year employment in jobs likely experiencing > 3 ppm for 15-60 minutes at least weekly" (Schnatter *et al.*, 2012).
(g) The AML results presented in Vlaanderen *et al.* (2012) are identical to those presented in Vlaanderen *et al.* (2011). Therefore, we do not present AML results from Vlaanderen *et al.* (2012) here.
(h) Mundt *et al.* (2021) reported statistically significant publication bias ($p < 0.05$).

Attachment I

Benzene Animal Carcinogenicity Studies

List of Tables

Table I.1 Benzene and Leukemia Chronic Oral Study Results

Table I.2 Benzene and Leukemia Chronic Inhalation Study Results

Table I.3 Benzene and Leukemia Chronic Toxicity Study Quality Overview

Table I.4 Benzene and Leukemia Chronic Toxicity Study Quality Assessment

Table I.1 Benzene and Leukemia Chronic Oral Study Results

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-d)	Cancer Outcome	
						Leukemia	MNCL
Maltoni *et al.* (1983, 1985, 1988b, 1989); Maltoni and Scarnato (1979)[a]	Sprague-Dawley rat	52	Until spontaneous death	30 M	0	0/30	NR
				30 M	50	0/30	NR
				35 M	250	4/35	NR
				30 F	0	1/30	NR
				30 F	50	2/30	NR
				35 F	250	1/35	NR
	Sprague-Dawley rat	104		50 M	0	3/50	NR
				40 M	500	1/40	NR
				50 F	0	1/50	NR
				40 F	500	3/40	NR
	Wistar rat	104		40 M	0	1/40	NR
					500	2/40	NR
				40 F	0	3/40	NR
					500	4/40	NR
	Swiss mouse	78		40 M	0	5/40	NR
					500	5/40	NR
				40 F	0	8/40	NR
					500	8/40	NR
	RF/J mouse	52		45 M	0	17/45	NR
					500	26/45*	NR
				40 F	0	14/40	NR
					500	24/40*	NR

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-d)	Cancer Outcome	
						Leukemia	MNCL
Huff *et al*. (1989); NTP (1986b)[b]	F3344/N rat	104	104 wks	50 M	0	NR	7/50
					50	NR	2/50
					100	NR	4/50
					200	NR	6/50
				50 F	0	NR	6/50
					25	NR	7/50
					50	NR	6/50
					100	NR	9/50*
	B6C3 mouse			50 M	0	NR	0/49
					25	NR	0/48
					50	NR	0/50
					100	NR	0/49
				50 F	0	NR	0/49
					25	NR	0/45
					50	NR	0/50
					100	NR	0/49

Notes:
F = Females; IARC = International Agency for Research on Cancer; M = Males; mg/kg-d = Milligram per Kilogram per Day; MNCL = Malignant Mononuclear Cell Leukemia; NR = Not Reported; NTP = National Toxicology Program; Wk = Week.
* = $p < 0.05$.
(a) I calculated incidences from the percentage reported in Maltoni *et al*. (1989), which differ from the percentages reported in Maltoni *et al*. (1983). Maltoni *et al*. (1983, 1985, 1988b, 1989) and Maltoni and Scarnato (1979) did not report any statistical analyses. An IARC Working Group conducted statistical analysis of the Maltoni data using Fisher exact tests (IARC, 2018).
(b) NTP (1986b) noted that "the lymphoma or leukemia data should be viewed as all lymphoma for evaluation purposes," and that the incidences of MNCL "are in the range observed in vehicle control female F344/N rats at the same laboratory (8/50-13/50) and therefore are not considered to be clearly related to administration of benzene."

Table I.2 Benzene and Leukemia Chronic Inhalation Study Results

Study	Strain/Species	Exposure Duration	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Cancer Outcome		
						Leukemia	Chronic Myelogenous Leukemia	Acute Myelogenous Leukemia
Snyder *et al.* (1978)	Sprague-Dawley rat	Lifetime	Lifetime	27 M	0	0/27	NR	NR
				45 M	300	0/45	NR	NR
	AKR/J mouse			60 M	0	0/60	NR	NR
					300	0/60	NR	NR
Snyder *et al.* (1980)	AKR/J mouse	Lifetime	Lifetime	50 M	0	0/50	NR	NR
					100	0/50	NR	NR
	C57BL/6J mouse			40 M	0	0/40	NR	NR
					300	1/40	NR	NR
Maltoni *et al.* (1982, 1983, 1985, 1989)[a]	Sprague-Dawley rat	104 wks	Until spontaneous death	158 M	0	12/158	NR	NR
				75 M	200-300	6/75	NR	NR
				149 F	0	1/149	NR	NR
				60 F	0	2/60	NR	NR
				54 F	200-300	0/54	NR	NR
				65 F	200-300	0/65	NR	NR
Goldstein *et al.* (1982)	CD-1 mouse	Lifetime	Lifetime	40	0	NR	0/40	0/40
					300	NR	1/40	1/40
	AKR mouse			50	0	NR	0/50	0/50
					100	NR	0/50	0/50
				80	0	NR	0/80	0/80
					300	NR	0/80	0/80
	Sprague-Dawley rat			40	0	NR	0/40	0/40
					100	NR	1/40	0/40
				27	0	NR	NR	NR
				45	300	NR	NR	NR
	C57BL mouse			40	0	NR	NR	NR
					300	NR	NR	NR

Study	Strain/Species	Exposure Duration	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Cancer Outcome		
						Leukemia	Chronic Myelogenous Leukemia	Acute Myelogenous Leukemia
Snyder *et al.* (1984)[b]	Sprague-Dawley rat	Lifetime	Lifetime	40 M	0	NR	0/40	0/40
					100	NR	1/40	0/40
Snyder *et al.* (1988)[c]	C57BL/6 mouse	Lifetime	Lifetime	60 M	0	NR	NR	NR
					300	NR	NR	NR
	CD-1 mouse			60 M	0	NR	NR	NR
					300	NR	NR	NR

Notes:
F = Female; IARC = International Agency for Research on Cancer; M = Male; NR = Not Reported; ppm = Parts per Million; Wk = Week.
(a) Incidences were calculated from the percentage reported in Maltoni *et al.* (1989), which differ from the percentages reported in Maltoni *et al.* (1983). Maltoni *et al.* (1983, 1985, 1988b, 1989) did not report any statistical analyses.
(b) Snyder *et al.* (1984) concluded that benzene caused leukemia because rats rarely develop leukemia, even after treatment with known leukemogens. There were two control groups for female animals; one group was exposed as embryos and the other was exposed as pregnant breeders.
(c) Incidences and statistics for Snyder *et al.* (1988) reported in IARC (2018).

Table I.3 Benzene and Leukemia Chronic Toxicity Study Quality Overview

Parameter	Summary
Reporting	Most studies reported information on the species; the test article name; the experimental design; the levels, duration, and route of exposure; and the outcome assessment methods.
Allocation	All studies indicated that animals were randomly allocated to dose groups.
Bias	There was no indication of bias due to co-exposures, vehicle, diet, palatability, husbandry, or health status.
Sample	Only the Huff *et al.* (1989) and NTP (1986b) study, Snyder *et al.* (1988), and the Maltoni *et al.* (1982, 1983, 1985, 1989) inhalation bioassays had adequate sample sizes. All animals were accounted for throughout each study.
Chemical Administration and Characterization	All studies took steps to ensure the exposure levels were accurate. Only the Huff *et al.* (1989) and NTP (1986b) study identified the benzene source and confirmed purity. Snyder *et al.* (1984, 1988) identified the benzene source but did not confirm purity.
Exposure Conditions	The duration of exposure varied considerably among studies; five chronic bioassays exposed animals for 104 wks (Maltoni *et al.*, 1982, 1983, 1985, 1988b, 1989; Huff *et al.*, 1989; NTP, 1986b), but two were 52 wks (Maltoni *et al.*, 1983, 1985, 1988b, 1989; Maltoni and Scarnato, 1979) and one was 78 wks (Maltoni *et al.*, 1983, 1985, 1988b, 1989). In eight bioassays, rodents were treated and observed throughout their lifespan (Snyder *et al.*, 1978, 1980, 1984, 1988; Goldstein *et al.*, 1982). A single dose was tested in four chronic oral bioassays (Maltoni *et al.*, 1983, 1985, 1988b, 1989) and eight inhalation bioassays (Snyder *et al.*, 1978, 1980, 1984, 1988; Goldstein *et al.*, 1982). Only three oral bioassays tested more than one dose (Maltoni *et al.*, 1983, 1985, 1988b, 1989; Maltoni and Scarnato, 1979; Huff *et al.*, 1989; NTP, 1986b). Snyder *et al.* (1980, 1978) reported that treatment with 300 ppm benzene resulted in high animal mortality, so the effects of benzene on lymphoma could not be assessed.
Outcome Assessment	Maltoni *et al.* (1983, 1985, 1988b, 1989) examined animals after spontaneous death rather than after sacrifice. Also, Gift *et al.* (2013) re-analyzed the results from several oral and inhalation bioassays conducted at the Ramazzini Institute (RI) (where the Maltoni *et al.* [1983, 1985, 1988b, 1989] and Maltoni and Scarnato [1979] studies were conducted) and concluded that the proper health status of experimental animals may not have been maintained. Gift *et al.* (2013) also noted that "the quality and availability of tissues for pathology slides may suffer in the RI life span protocol due to tissue autolysis." Snyder *et al.* (1978, 1980, 1984, 1988) and Goldstein *et al.* (1982) also observed animals over their entire lifespan. In the Huff *et al.* (1989) and NTP (1986b) study, mice were observed for 104 wks. Finally, there were high rates of tumors observed in control animals in several studies (Huff *et al.*, 1989; NTP, 1986b), which makes it difficult to determine whether lymphomas in dosed animals were caused by benzene.

Notes:
NTP = National Toxicology Program; ppm = Parts per Million; Wk = Week.

Table I.4 Benzene and Leukemia Chronic Toxicity Study Quality Assessment

Study	Strengths	Weaknesses	Human Relevance
Chronic – Oral			
Maltoni *et al.* (1983, 1985, 1988b, 1989); Maltoni and Scarnato (1979)	Reporting Allocation Bias	**Sample:** Small sample size **Chemical Administration and Characterization:** Did not identify benzene source or report purity **Exposure Conditions:** Exposure duration too short in some bioassays **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Huff *et al.* (1989); NTP (1986b)	Reporting Allocation Bias Sample Chemical Administration and Characterization Exposure Conditions (rats) Outcome Assessment (rats)	**Exposure Conditions:** Exposure period too long (mice) **Outcome Assessment:** Observation period too long (mice)	**Limited:** Low study quality (mice)
Chronic – Inhalation			
Snyder *et al.* (1978)	Reporting Allocation Bias	**Sample:** Small sample size (controls) **Chemical Administration and Characterization:** Did not identify benzene source or report purity **Exposure Conditions:** Only one concentration tested; lifetime exposure **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Snyder *et al.* (1980)	Reporting Allocation Bias	**Sample:** Small sample size (C57BL/6J mice) **Chemical Administration and Characterization:** Did not identify benzene source or report purity **Exposure Conditions:** Only one dose tested; lifetime exposure **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Maltoni *et al.* (1982, 1983, 1985)	Reporting Allocation Bias Sample Exposure Conditions	**Chemical Administration and Characterization:** Did not identify benzene source or report purity **Outcome Assessment:** Observation period too long	**Limited:** Low study quality

Study	Strengths	Weaknesses	Human Relevance
Goldstein *et al.* (1982)	Reporting Bias	**Allocation:** Did not specify whether random **Sample:** Small sample size **Chemical Administration and Characterization:** Did not identify benzene source, report purity, or ensure reported exposure levels were accurate **Exposure Conditions:** Lifetime exposure **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Snyder *et al.* (1984)	Reporting Allocation Bias	**Sample:** Small sample size **Chemical Administration and Characterization:** Did not conduct independent verification of chemical purity **Exposure Conditions:** Only one dose tested; lifetime exposure **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Snyder *et al.* (1988)	Reporting Allocation Bias Sample	**Chemical Administration and Characterization:** Did not conduct independent verification of chemical purity **Exposure Conditions:** Only one dose tested; lifetime exposure **Outcome Assessment:** Observation period too long	**None:** No leukemia findings

Attachment J

Vinyl Chloride Epidemiology Studies

List of Tables

Table J.1 Vinyl Chloride and Leukemia Cohort Study Characteristics

Table J.2 Vinyl Chloride and Leukemia Cohort Study Results

Table J.3 Vinyl Chloride and Leukemia Case-Control Study Characteristics

Table J.4 Vinyl Chloride and AML Case-Control Study Results

Table J.5 Vinyl Chloride and Myelodysplastic Syndromes Case-Control Study Results

Table J.6 Vinyl Chloride and Leukemia Meta-Analysis Results

Table J.1 Vinyl Chloride and Leukemia Cohort Study Characteristics

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Thériault and Allard (1981)	Canada	VC plant and industrial complex production workers	M	–	1,321	1948-1972	Union lists, company payrolls, and interviews with worker/next of kin/ co-workers	Mort	Leukemia	Death certificates and histopathological confirmation	1948-1977
Smulevich *et al.* (1988)	USSR	VC & PVC plant workers	B	–	3,232	1939-1977	Registry from plant's administrative department, attendance journals, and lists of shops	Mort	Leukemia and aleukemia	Death certificate, medical history, and necropsy protocols	1939-1977
Ward *et al.* (2001) [Simonato *et al.*, 1991]	Europe[a]	Workers in the VC industry	M	–	12,700	–	Factory records and JEM	Inc & Mort	Leukemia	Death certificates, cancer registry records, and medical records	1955-1997[b]
Bove *et al.* (2014a)	US	Marines & Navy personnel at CL & CP	B	CL & CP: 20-49[c]	CL: 154,932 CP: 154,969	1975-1985	Assignment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008
Bove *et al.* (2014b)	US	Civilian employees at CL & CP	B	CL: 31-58[c] CP: 34-60[c]	CL: 4,647 CP: 4,690	1973-1985	Employment at base, or average monthly levels in drinking water on base, based on groundwater fate and transport models	Mort	Leukemia	SSA and NDI	1979-2008

Study	Location	Study Population				Exposure Characterization		Cancer Outcome			
		Population	Sex	Age (Yrs)	N	Exposure Period	Exposure Ascertainment	Outcome Type	Type	Ascertainment	Follow-Up Period
Carreón *et al.* (2014)	US	Workers at a chemical manufacturing plant	B	Median at first employment: 23 (range: 17-65)	1,874	1946-2006	Assignment to the PVC, vinyl department <1995, jobs in shipping, packing and warehousing, rubber compounds, quality control, and research and development, jobs with assignment throughout the plant, and workers with no assigned department <1995	Mort	Leukemia and aleukemia	NDI, NDI Plus, and Florida Department of Health	1960-2007
Mundt *et al.* (2017) [Cooper, 1981; Tabershaw and Gaffey, 1974; Wong *et al.*, 1991; Mundt *et al.*, 2000]	US	VC or PVC resin manufacturing workers	M	$\bar{x}$ = 28[d]	9,951	1942-1972	Employment ≥1 yr at factory	Mort	Leukemia and aleukemia	SSA, NDI, and death certificates	1942-2013
ATSDR (2018b)[e]	US	Marines & Navy personnel & civilian employees at CL & CP	B	Marines & Navy Personnel CL and CP: 50-54[f] Civilian Employees CL: 60-64[f] CP: ≥65[f]	Marines & Navy Personnel CL: 50,684 CP: 8,615 Civilian Employees CL: 2,168 CP: 1,425	Marines & Navy Personnel 1975-1985 Civilian Employees 1972-1985	Average monthly levels in drinking water at base residence (Marines & Navy personnel) or in the Hadnot Point distribution system (civilians), based on groundwater fate and transport models	Inc	Leukemia	Self-report confirmed by medical records or death certificates	Marines & Navy Personnel 1975-2012 Civilian Employees 1972-2012
Fedeli *et al.* (2019)	Italy	VC production and polymerization facility workers	M	–	1,658	1956-1985	JEM and work histories	Mort	Leukemia	Regional mortality register	1973-2017

Notes:
ATSDR = Agency for Toxic Substances and Disease Registry; B = Both Males and Females; CL = Camp Lejeune; CP = Camp Pendleton; Inc = Incidence; JEM = Job-Exposure Matrix; M = Males; Mort = Mortality; NDI = National Death Index; PVC = Polyvinyl Chloride; SSA = Social Security Administration; US = United States; USSR = Union of Soviet Socialists Republics; VC = Vinyl Chloride; Yr = Year.

$\bar{x}$ = Mean; – = Not Reported.
When a study population was evaluated in multiple studies, I only tabulated the results from the study with the longest follow-up time, unless otherwise specified. Other studies of the same cohort or same population are listed in square brackets below the study for which I tabulated results.
(a) This is a multicenter study and the includes cohorts from factories in Italy, Norway, Sweden, and the UK, however, information on incidence was not available for subjects from Italian factories (Ward *et al*., 2001).
(b) Period of follow-up varied by factory (n = 19) and outcome type. The earliest year of follow-up among all factories and outcome types was 1955, and the latest year of follow-up was 1997 (Ward *et al*., 2001).
(c) Median age from start to end of follow-up (Bove *et al*., 2014a,b).
(d) Mean age at hire (Mundt *et al*., 2017).
(e) Ages and population sizes are reflective of Marines, Navy personnel, and civilian respondents to the 2011-2012 morbidity survey and do not include the 5,263 Marines, Navy personnel, and civilian respondents to the 1999-2002 ATSDR Survey, some of whom were included in this analysis (ATSDR, 2018b).
(f) Median age at survey or death (ATSDR, 2018b).

Table J.2 Vinyl Chloride and Leukemia Cohort Study Results

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Thériault and Allard (1981)	Province of Quebec mortality rates from 1971	Mort	SMR	**All Leukemias**					
				All exposed workers	1	1.67	0.60 (–)	–	Age and sex
	Unexposed workers at industrial complex		RR		1	–	1.15 (0.07-17.80)	–	
				All exposed workers (≥15 yr observation period)	1	–	0.59 (–)	–	
Smulevich *et al.* (1988)	City population where the plant is located (1959, 1969, and 1975)	Mort	SMR	**All Leukemias and Aleukemia**					
				All VC and PVC workers	–	–	**5.00** (–)	–	–
				Male VC and PVC workers	3		4.29 (–)		Sex
				Female VC and PVC workers	2		6.67 (–)		
Ward *et al.* (2001)	National mortality rates from the WHO	Mort	SMR	**All Leukemia**					
				All subjects	22	–	0.87 (0.54-1.31)	–	Age, sex, calendar period, and country
	Cancer registry rates	Inc	SIR	All subjects	16[b]	–	0.81 (0.46-1.31)	–	
Bove *et al.* (2014a)	CP Marines & Navy personnel	Mort	HR	**CL Marines & Navy Personnel**					
				Cumulative exposure level (µg/L-mos)[c] with 10 yr lag					
				No/low (0-205)	43	–	0.80 (0.51-1.26)	–	Age, sex, race, rank, and education
				Medium/high (>205-2,800)	23		1.37 (0.90-2.08)		
				Low (>1-205)	15		1.85 (0.93-3.68)		
	CL Marines & Navy personnel with exposure ≤1 µg/L-mos[d]			Medium (>205-500)	10		1.27 (0.58-2.80)		
				High (>500-2,800)	13		1.63 (0.78-3.43)		

Study	Statistical Analysis								
	Reference Group	Outcome Type	Risk Metric	Group	Exposed Cases[a]	Expected Cases[a]	Risk Estimate (95% CI)	p_{trend}	Covariates Controlled For
Bove *et al.* (2014b)	CL civilian employees with no/low exposure[d,e]	Mort	HR	**CL Civilian Employees**					
				Cumulative exposure level with 10 yr lag					
				Medium	2	–	1.01 (0.14-7.45)	–	Age, sex, race, blue- or white-collar occupation, and education
				High	8		1.72 (0.33-8.83)		
	CL civilian employees with <median exposure			≥Median	–		1.44 (0.37-5.63)		
	CL civilian employees with no/low exposure[e]			*Average exposure level with 10 yr lag*					
				Medium	–	–	1.64 (0.31-8.73)	–	Age, sex, race, blue- or white-collar occupation, and education
				High	–	–	1.95 (0.37-10.43)	–	
Carreón *et al.* (2014)	US general population	Mort	SMR	All Workers	3	–	0.69 (0.14-2.00)	–	Age, sex, race, and calendar yr
				Duration of employment (ds)					
				<90	0	–	0 (0-5.02)	–	Age, sex, race, and calendar yr
				≥90	3		0.82 (0.17-2.41)		
Mundt *et al.* (2017)	NIOSH state-specific rates for white men	Mort	SMR	**Leukemia and Aleukemia**					Age, sex, and calendar yr
				All workers	71	63.3	1.12 (0.88-1.41)	–	
ATSDR (2018b)	CP Marines and Navy personnel	Inc	OR	**CL Marines & Navy Personnel**					
				Cumulative exposure level[f,g]					
				Low	80	–	1.08 (0.66-1.78)	–	Age and sex
				Medium	41		0.76 (0.44-1.30)		
				High	4		**0.28 (0.09-0.83)**		
	CL Marines and Navy personnel with low exposure			Medium	41		0.70 (0.47-1.03)		
				High	4		**0.26 (0.09-0.72)**		
Fedeli *et al.* (2019)	Italian regional mortality rates	Mort	SMR	All VC workers	10	–	1.07 (0.58-1.99)	–	Age and calendar yr

Notes:
CI = Confidence Interval; CL = Camp Lejeune; CP = Camp Pendleton; D = Day; HR = Hazard Ratio; Inc = Incidence; Mo = Month; Mort = Mortality; NIOSH = National Institute for Occupational Safety and Health; OR = Odds Ratio; PVC = Polyvinyl Chloride; RR = Relative Risk; SIR = Standardized Incidence Ratio; SMR = Standardized Mortality Ratio; TCE = Trichloroethylene; UK = United Kingdom; US = United States; VC = Vinyl Chloride; WHO = World Health Organization; Yr = Year.
– = Not Reported.

Bolded values indicate statistical significance.

(a) Observed cases and expected cases for SMR and SIR analyses, and exposed cases and exposed non-cases for other analyses.

(b) This multicentric study includes cohorts from factories from Italy, Norway, Sweden, and the UK, however, information on incidence was not available for subjects from Italian factories, which likely contributed to the lower incidence count (Ward *et al*., 2001).

(c) Exposure groups are unclear. Table S.3 reports the exposure groups as "no/very low" and "low to high" cumulative exposures, but the text reports, "For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3)" (Bove *et al*., 2014a). I report the values consistent with the text definition.

(d) To evaluate exposure-response relationships, the authors evaluated continuous and $\log_{10}$ continuous cumulative exposures (µg/L-yr). The beta coefficients were nonsignificant (Bove *et al*., 2014a,b).

(e) Bove *et al*. (2014b) report a positive monotonic exposure response relationship. This trend was not evaluated for statistical significance.

(f) Categorized as low exposure (<50th percentile), medium exposure (≥50th percentile to <90th percentile), and high exposure (≥90th percentile); for female Marines and Navy personnel, cut points were based on the 75th and 90th percentiles because the 50th percentile for TCE exposure was 0 µg/L-mos (ATSDR, 2018b).

(g) There was complete correlation (gamma coefficient > 0.99) between the categorical variable for TCE and the categorical variable for vinyl chloride; the authors only reported results based on TCE analyses (ATSDR, 2018b).

Table J.3 Vinyl Chloride and Leukemia Case-Control Study Characteristics

Study	Location	Outcome Type	Cancer Type	Study Period	Study Population						Exposure Ascertainment
					Sex	Age (Yrs)	Cases		Controls		
							N	Source	N	Source	
Poynter *et al.* (2017)	US	Inc	AML, MDS	2005-2010	B	20-85	420	MCSS	701	MN driver's license or ID card records	Self-reported *via* questionnaire

Notes:
AML = Acute Myeloid Leukemia; B = Both Females and Males; ID = Identification; Inc = Incidence; MCSS = Minnesota Cancer Surveillance System; MDS = Myelodysplastic Syndromes; MN = Minnesota; US = United States; Yr = Year.

Table J.4 Vinyl Chloride and AML Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{trend}	Covariate Adjustment
Poynter *et al.* (2017)	Inc	OR	No vinyl chloride or plastic exposure	378	1,287	Ref	0.08	Age, sex, household income, smoking, radiation exposure, having lived on a farm or in rural area ≥1 yr
			<5 yrs exposure	11	10	**2.81 (1.14-6.92)**		
			≥5 yrs exposure	16	49	1.03 (0.57-1.86)		

Notes:
AML = Acute Myeloid Leukemia; CI = Confidence Interval; Inc = Incidence; OR = Odds Ratio; Ref = Reference; Yr = Year.
Bolded values indicate statistical significance.

Table J.5 Vinyl Chloride and Myelodysplastic Syndromes Case-Control Study Results

Study	Outcome Type	Statistical Analysis						
		Risk Metric	Group	Exposed Cases	Exposed Controls	Risk Estimate (95% CI)	p_{trend}	Covariate Adjustment
Poynter *et al.* (2017)	Inc	OR	No vinyl chloride or plastic exposure	241	1,325	Ref	–	Age, sex, household income, smoking, radiation exposure, having lived on a farm or in rural area ≥1 yr
			<5 yrs exposure	4	10	–		
			≥5 yrs exposure	20	50	**2.05 (1.15-3.63)**		

Notes:
CI = Confidence Interval; Inc = Incidence; OR = Odds Ratio; Yr = Year.
– = Not Reported.
Bolded values indicate statistical significance.

Table J.6 Vinyl Chloride and Leukemia Meta-Analysis Results

Study	Outcome Type	Cancer Type	Number of Studies in Analysis	Study Type	Statistical Model	Group	Risk Estimate	Risk Estimate (95% CI)
Boffetta *et al*. (2003)	Mort	Leukemia	2[a]	Cohort	Random-effects	Multicenter pooled studies	SMR	0.91 (0.69-1.21)

Notes:
CI = Confidence Interval; Mort = Mortality; SMR = Standardized Mortality Ratio.
(a) Boffetta *et al*. (2003) reported a *p* value for heterogeneity of 0.8.

Attachment K

Vinyl Chloride Animal Carcinogenicity Studies

List of Tables

Table K.1 Vinyl Chloride and Leukemia Chronic Ingestion Study Results

Table K.2 Vinyl Chloride and Leukemia Chronic Inhalation Study Results

Table K.3 Vinyl Chloride and Leukemia Chronic Intraperitoneal Injection Study Results

Table K.4 Vinyl Chloride and Leukemia Chronic Toxicity Study Quality Overview

Table K.5 Vinyl Chloride and Leukemia Chronic Toxicity Study Quality Evaluation

Table K.1 Vinyl Chloride and Leukemia Chronic Ingestion Study Results

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Dose (mg/kg-d)	Leukemia
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)[a]	Sprague-Dawley rat	52-59	Until spontaneous death	40 M	0	1/40
					3.33	0/40
					16.65	0/40
					50	1/40
				40 F	0	1/40
					3.33	0/40
					16.65	1/40
					50	0/40
	Sprague-Dawley rat			75 M	0	4/75
					0.03	3/75
					0.3	4/75
					1	1/74
				75 F	0	3/75
					0.03	1/75
					0.3	0/73
					1	5/75
Feron *et al.* (1981)[b]	Wistar rat	135	M: 135 wks F: 144 wks	80 M	0	1/80
				60 M	1.7	0/60
				60 M	5.0	1/60
				80 M	14.1	1/80
				80 M	300	3/80
		144		80 F	0	1/80
				60 F	1.7	2/60
				60 F	5.0	1/60
				80 F	14.1	0/60
				80 F	300	1/80

Notes:
F = Female; M = Male; mg/kg-d = Milligram per Kilogram per Day; Wk = Week.
(a) I used the "corrected number of animals" as the denominators for reporting incidences of leukemia.
(b) Vinyl chloride was administered as a polyvinyl chloride (PVC) powder with vinyl chloride monomer (VCM). Doses of 1.7, 5, and 14.1 mg/kg-d were administered *via* feed. The 300 mg/kg-d dose was administered *via* gavage, but there was no gavage control group. The exposure duration is the point at which 75% of the control rats were dead. The results here are for rats found dead or sacrificed *in extremis* or terminal (not for scheduled sacrifice at 26 or 52 wks) (Feron *et al.*, 1981).

Table K.2 Vinyl Chloride and Leukemia Chronic Inhalation Study Results

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Leukemia
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)[a]	Sprague-Dawley rat	52	Until spontaneous death	30 M	0	0/29
					50	0/30
					250	1/29
					500	0/30
					2,500	0/30
					6,000	0/29
					10,000	0/30
				30 F	0	1/29
					50	0/30
					250	0/30
					500	2/30
					2,500	1/30
					6,000	0/30
					10,000	2/30
	Sprague-Dawley rat	52		85 M	0	5/85
				60 M	100	1/60
					150	2/59
					200	1/60
				100 F	0	2/100
				60 F	100	1/60
					150	0/60
					200	0/60
	Sprague-Dawley rat	52		30 M	30,000	0/30
				30 F		0/30
	Sprague-Dawley rat	52		50 M	0	6/48
				150 M	50	7/144
				50 F	0	2/50

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Leukemia
				150 M	50	3/150
	Sprague-Dawley rat	52		60 M	0	3/60
					1	3/58
					5	3/59
					10	3/59
					25	4/60
				60 F	0	3/60
					1	0/60
					5	2/60
					10	1/60
					25	3/60
	Wistar rat	52		120-130 M	0	10/94
					1	8/99
	Wistar rat	52		40 M	0	4/38
				30 M	50	3/28
					250	1/27
					500	2/28
					2,500	0/25
					6,000	0/26
					10,000	0/27
Holmberg *et al.* (1976)	NMRI mouse	52	Until moribund or spontaneous death	12 M	0	NR
					50	NR
				12 F	0	NR
					50	NR

Study	Strain/Species	Exposure Duration (Wks)	Observation Period	Treatment Groups (n, Sex)	Concentration (ppm)	Leukemia
Lee *et al.* (1978)	CD-1 mouse	52	52 wks	36 M	0	NR
					50	NR
					250	NR
					1,000	NR
				36 F	0	NR
					50	NR
					250	NR
					1,000	NR
	CD rat	52		36 M	0	NR
					50	NR
					250	NR
					1,000	NR
				36 F	0	NR
					50	NR
					250	NR
					1,000	NR
Maltoni and Cotti (1988)[b]	Sprague-Dawley rat	76	Until spontaneous death	60 F adults	0	2/60
				54 F adults	2,500	0/54
				307 M & F embryos	0	13/307
				127 M & F embryos	2,500	0/127

Notes:
F = Female; M = Male; NR = Not Reported; ppm = Parts per Million; Wk = Week.
(a) I used the "corrected number of animals" as the denominators for reporting incidences of leukemia.
(b) I calculated these incidences based off the percentages provided in Table 9 of Maltoni and Cotti (1988). Adult breeders were exposed by inhalation for 76 wks. Offspring were exposed from gestational day (GD) 12 by the transplacental route and then by inhalation for 76 wks (Maltoni and Cotti, 1988).

Table K.3 Vinyl Chloride and Leukemia Chronic Intraperitoneal Injection Study Results

Study	Strain/Species	Exposure Duration	Observation Period	Treatment Groups (n, Sex)	Concentration (mg/mL)	Leukemia
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)[a]	Sprague-Dawley rats	NR	Until spontaneous death	30 M	0	0/28
		2 times at 2 mo intervals			4.25	0/28
		3 times at 2 mo intervals				0/30
		4 times at 2 mo intervals				1/26
		NR		30 F	0	1/27
		2 times at 2 mo intervals			4.25	0/28
		3 times at 2 mo intervals				0/30
		4 times at 2 mo intervals				0/30

Notes:
F = Female; M = Male; Mo = Month; NR = Not Reported.
(a) I used the "corrected number of animals" as the denominators for reporting incidences of leukemia.

Table K.4 Vinyl Chloride and Leukemia Chronic Toxicity Study Quality Overview

Parameter	Summary
Reporting	Most bioassays reported information on the species; the test article name; the experimental design; the levels, duration, and route of exposure; and the outcome evaluation methods. Feron *et al.* (1981), Maltoni and Lefemine (1975), Maltoni *et al.* (1981, 1984), and Maltoni and Cotti (1988) were the only studies that said they examined the hematopoietic system and reported leukemia findings.
Allocation	Only Feron *et al.* (1981) indicated that allocation to dose groups was random.
Bias	There was no indication of bias due to co-exposures, vehicle, diet, palatability, husbandry, or health status.
Sample	Most bioassays had adequate sample sizes; exceptions were Holmberg *et al.* (1976), Lee *et al.* (1978), Maltoni and Lefemine (1975), and Maltoni *et al.* (1981, 1984) for ingestion, inhalation, and intraperitoneal exposure. All animals were accounted for only in the studies by Holmberg *et al.* (1976) and Maltoni and Cotti (1988).
Chemical Administration and Characterization	Three studies (Feron *et al.*, 1981; Lee *et al.*, 1978; Maltoni and Cotti, 1988) provided adequate information on chemical source, purity, or composition; independently verified chemical purity; and took steps to ensure reported exposure levels were accurate. The remaining bioassays did not.
Exposure Conditions	The duration of exposure was not adequate in any study: 12 chronic bioassays exposed rats and mice for 52 wks (Maltoni and Lefemine, 1975; Maltoni *et al.*, 1981, 1984; Holmberg *et al.*, 1976; Lee *et al.*, 1978), and one chronic bioassay exposed animals for 76 wks (Maltoni and Cotti, 1988). These exposure durations are too short to evaluate carcinogenicity. Feron *et al.* (1981) exposed animals for 135-144 wks, based on the point at which 75% of the control rats were dead. Two chronic bioassays tested only a single concentration of vinyl chloride (Feron *et al.*, 1981; Maltoni and Cotti, 1988). Therefore, the studies have limited human relevance.
Outcome Assessment	Lee *et al.* (1978) used a reliable, valid, sensitive, and specific outcome assessment method; however, the observation period was too short (52 wks). In the other bioassays (Feron *et al.*, 1981; Maltoni and Lefemine, 1975; Maltoni *et al.*, 1981, 1984; Holmberg *et al.*, 1976; Maltoni and Cotti, 1988), animals were observed over their entire lifetime and examined until moribund or spontaneous death, which could have biased results.

Note:
Wk = Week.

Table K.5 Vinyl Chloride and Leukemia Chronic Toxicity Study Quality Evaluation

Study	Strengths	Weaknesses	Human Relevance
Chronic – Ingestion			
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	Reporting Bias	**Allocation:** Did not specify whether random **Sample:** Not all animals are accounted for **Chemical Administration and Characterization:** Did not identify vinyl chloride source or report or confirm purity **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Feron *et al.* (1981)	Reporting Allocation Bias Chemical Administration and Characterization	**Sample:** Not all animals are accounted for **Exposure Conditions:** Exposure duration too long **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Chronic – Inhalation			
Maltoni and Lefemine (1975); Maltoni *et al.* (1981, 1984)	Reporting Bias	**Allocation:** Did not specify whether random **Sample:** Not all animals were accounted for **Chemical Administration and Characterization:** Did not identify vinyl chloride source or report or confirm purity **Exposure Conditions:** Exposure duration too short **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Holmberg *et al.* (1976)	Bias	**Reporting:** No leukemia data **Allocation:** Did not specify whether random **Sample:** Small sample size **Chemical Administration and Characterization:** Did not identify vinyl chloride source or confirm purity **Exposure Conditions:** Exposure duration too short and only one dose tested **Outcome Assessment:** Observation period too long	**None:** No leukemia data

Study	Strengths	Weaknesses	Human Relevance
Lee *et al*. (1978)	Bias Chemical Administration and Characterization	**Reporting:** No leukemia data **Allocation:** Did not specify whether random **Sample:** Small sample size and not all animals were accounted for **Exposure Conditions:** Exposure duration too short **Outcome Assessment**: Observation period too short	**None:** No leukemia data
Maltoni and Cotti (1988)	Reporting Chemical Administration and Characterization Bias Sample	**Allocation:** Did not specify whether random **Exposure Conditions:** Exposure duration too short and only one dose tested **Outcome Assessment:** Observation period too long	**Limited:** Low study quality
Chronic – Intraperitoneal Injection			
Maltoni and Lefemine (1975); Maltoni *et al*. (1981, 1984)	Reporting Bias	**Allocation:** Did not specify whether random **Sample:** Not all animals were accounted for **Chemical Administration and Characterization:** Did not identify vinyl chloride source or report or confirm purity **Exposure Conditions:** Exposure duration too short and only one dose tested **Outcome Assessment:** Observation period too long	**Limited:** Low study quality

Attachment L

Curriculum Vitae

Julie E. Goodman, Ph.D., DABT, FACE, ATS
Principal
Julie.Goodman@gradientcorp.com

Areas of Expertise

Epidemiology, toxicology, systematic review, evidence integration, meta-analysis, carcinogenesis, dose-response analysis, product safety, risk assessment, risk communication.

Education & Certifications

Ph.D., Environmental Health Sciences/Toxicology, Johns Hopkins Bloomberg School of Public Health, 2002

Sc.M., Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2000

S.B., Environmental Engineering, Massachusetts Institute of Technology, 1996

Diplomate, American Board of Toxicology (DABT), 2005; recertified 2010, 2015, 2020, 2025

Fellow, American College of Epidemiology (FACE), 2014

Fellow, Academy of Toxicological Sciences (ATS), 2014; recertified 2019, 2024

Professional Experience

2004 – Present GRADIENT, Boston, MA
Principal. Evaluate toxicity and epidemiology data in the context of causation analysis and human health risk assessments. Focus on substances in consumer products, pharmaceuticals, and medical devices, and chemicals in the workplace and the environment.

2009 – 2017 HARVARD T. H. CHAN SCHOOL OF PUBLIC HEALTH, Boston, MA
Adjunct Faculty Member. Department of Epidemiology. Co-instructor of course entitled, "Research Synthesis & Meta-analysis."

2002 – 2004 NATIONAL CANCER INSTITUTE, Bethesda, MD
Cancer Prevention Fellow. Conducted a number of molecular epidemiology studies analyzing the relationships between inflammatory gene polymorphisms and colon cancer risk. Instrumental in the development of a powerful statistical tool for cancer risk assessment.

Continuing Education Courses and Other Training

- Introduction to Open-Access Computational Toxicology Tools (web course), Society of Toxicology 2020 Annual Meeting, April 2020
- Protecting Human Research Participants Online Course, National Institutes of Health (NIH) Office of Extramural Research, 2015
- Tools and Technologies in Translational Toxicology, Society of Toxicology 2013 Annual Meeting, San Antonio, TX, March 2013

- Use of Expert Elicitation to Inform Decisionmaking, Society for Risk Analysis 2012 Annual Meeting, San Francisco, CA, December 2012
- Novel Statistical Challenges in Environmental Epidemiology Workshop, 3rd North American Congress of Epidemiology, Montreal, Canada, June 2011
- Comparative Biology of the Lung, Society of Toxicology 2010 Annual Meeting, Salt Lake City, UT, March 2010
- Introduction to the Benchmark Dose Methodology and Interactive Application of United States Environmental Protection Agency (US EPA) Benchmark Dose Software (BMDS), Version 2.1, Society for Risk Analysis 2010 Annual Meeting, Salt Lake City, UT, December 2010
- Green Innovation for Business Conference (Moderator, Green Chemistry and Greenwashing Workshops), Boston, MA, June 2009
- Decision-making for Recommendations and Communication Based on the Totality of Food-related Research, International Life Sciences Institute Workshop, Washington, DC, December 2008
- 2008 Board of Health Certification Program, Massachusetts Association of Health Boards, Marlborough, MA, November 2008
- What is Evolutionary Epidemiology? American College of Epidemiology Annual Meeting, Tucson, AZ, September 2008
- Research Ethics in Studying Genes and the Environment in Diabetes Among Ethnic Minorities, American College of Epidemiology Annual Meeting, Tucson, AZ, September 2008
- Use of Data for Development of Uncertainty Factors in Non-Cancer Risk Assessment, Society of Toxicology 47th Annual Meeting, Seattle, WA, March 2008
- International Society of Regulatory Toxicology and Pharmacology Workshop: Conducting and Assessing the Results of Endocrine Screening, Bethesda, MD, February 2008
- Assessment of Abuse Liability and Physical Dependence, Northeast Chapter Society of Toxicology Annual Meeting, Groton, CT, October 2007
- Practical Issues and Procedures for Preclinical Safety Testing, 2007 BioReliance Toxicology Technical Seminars, Boston, MA, October 2007
- Introduction to Pharmacoepidemiology: Practical Applications and Analytic Methods, American College of Epidemiology 25th Annual Meeting, Ft. Lauderdale, FL, September 2007
- SAS Programming I: Essentials, SAS Institute, Boston, MA, July 2007
- Introduction to Bayesian Modeling of Epidemiologic Data, Society for Epidemiologic Research 40th Annual Meeting, Boston, MA, June 2007
- Systematic Review and Meta-analysis, Society for Epidemiologic Research 40th Annual Meeting, Boston, MA, June 2007
- The Biology and Toxicology of the Peri- and Post-natal Development, Society of Toxicology 46th Annual Meeting, Charlotte, NC, March 2007
- Reproductive Toxicity Testing: Study Designs, Evaluation, Interpretation, and Risk Assessment, Society of Toxicology 45th Annual Meeting, San Diego, CA, March 2006
- Project Managers Bootcamp I, PSMJ Resources, Inc., Cambridge, MA, April 2005
- Development and Interpretation of Toxicokinetic Data for Risk and Safety Assessment, Society of Toxicology 44th Annual Meeting, New Orleans, LA, March 2005
- Survival Analysis, Graduate Summer Institute of Epidemiology and Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, June 2003
- Speaking on the Job, Cancer Prevention Fellowship Program, National Cancer Institute (NCI), Rockville, MD, February 2003
- Grants and Grantsmanship Workshop, Cancer Prevention Fellowship Program, NCI, Rockville, MD, January 2003
- Spotted Gene Expression Microarray Workshop, Advanced Technology Center, NCI, Gaithersburg, MD, October 2002
- Laboratory of Cellular Carcinogenesis and Tumor Promotion/Laboratory of Human Carcinogenesis/Laboratory of Experimental Carcinogenesis Interlaboratory Seminar, Monthly, 2002-2004
- Division of Cancer Prevention, Office of Preventive Oncology Colloquia Series on Cancer Prevention Topics, Weekly, 2002-2004

- Radiation Safety for Authorized Users, NIH Radiation Safety Branch, Bethesda, MD, Sept. 2002
- Molecular Prevention Course, NCI Summer Curriculum in Cancer Prevention, Rockville, MD, August 2002
- Principles & Practice of Cancer Prevention and Control Course, NCI Summer Curriculum in Cancer Prevention, Rockville, MD, July-August 2002

Professional Activities

- Member, American College of Epidemiology (ACE) Ethics & Policy Committee, 2024-Present
- Philanthropy Liason, National Charity League, 2023-Present
- Member, Evidence-based Toxicology Collaboration (EBTC) Interim Scientific Advisory Council (iSAC), November 2021-Present
- Member, Board of Directors, Academy of Toxicological Sciences, 2020-2023, 2024-Present
- Chair, Communications Committee, Academy of Toxicological Sciences, 2021-2022
- Member, Communications Committee, Academy of Toxicological Sciences, 2020-2021
- Canton, Massachusetts, COVID Task Force, 2020-Present
- Scientific Advisory Board Member, National Stone, Sand, and Gravel Association, 2019-Present
- Invited Lecturer, "Introduction to Meta-analysis," Northeastern College of Professional Studies, May 8, 2019
- Invited Participant, "Excellence in Risk Analysis," Society for Risk Analysis (SRA) Workshop, June 2018
- Reviewer, R21 Hurricane Applications, National Institutes of Health (NIH), January 2018
- Member, Regis College Doctoral Thesis Committee, 2015-2017
- Reviewer, R21 NIH Exploratory/Developmental Research Grant Proposal, NIH, September 2017
- Invited Panelist, Cancer Prevention Fellowship Program (CPFP) Alumni Career Panel, September 2016
- Reviewer, K99 Career Research Grant Proposal, NIH, July 2016
- Invited Lecturer, "An Introduction to Meta-analysis," Johns Hopkins Bloomberg School of Public Health, April 5, 2016
- Member, Scientific Advisory Council, Evidence-based Toxicology Collaboration (EBTC) at Johns Hopkins Bloomberg School of Public Health, December 2015-November 2021
- Invited Observer, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*: *Volume 113: Some Organochlorine Insecticides and Some Chlorophenoxy Herbicides*, Lyon, France, June 2015
- Mentor, Society of Toxicology Mentor Match Program, January 2015-Present
- Member, Speaker Bureau, Society of Toxicology, July 2014-2016
- Chair, "Implementing NRC Recommendations: IRIS," SRA Annual Meeting, 2014
- Member, California Breast Cancer Research Program (CBCRP) Chemicals Testing and Occupational Exposures Review Panel, November 2014
- Proposal Reviewer, Scientific Panel, California Breast Cancer Research Program (CBCRP), June 2014
- Invited Epidemiology Panel Member, The International Council of Chemical Associations Long-Range Research Initiative and Joint Research Centre Workshop, "What is Safe? Integrating Multi-Disciplinary Approaches for Decision Marking about the Human Health and Environmental Impacts of Chemicals." Lugano, Switzerland, June 2014
- Proposal Reviewer, John Templeton Foundation, 2014
- Co-Chair, "Understanding Weight of Evidence: Exploring Different Approaches to Integrating Evidence from Diverse Data Streams," Society of Toxicology, 2014
- Co-Chair, "Epidemiology for Toxicologists: What the Numbers Really Mean," Society of Toxicology, 2014
- Best Paper Awards Selection Committee, Risk Assessment Section, Society of Toxicology, 2014
- Peer Reviewer, Provisional Peer-Reviewed Toxicity Values for Styrene-Acrylonitrile (SAN Trimer), US EPA Draft Document, December 2013
- Keynote Speaker and Scientific Committee Member, Isocyanates & Health Conference, April 2013
- Presidential Task Force Member, Strategic Plan, American College of Epidemiology, 2013

- Proposal Reviewer, National Science Foundation, 2013
- Invited Participant, ILSI Health and Environmental Sciences Institute Emerging Issue Workshop: Evaluating Causality in Epidemiology, October 2012
- Invited Panel Member, "Using Mode of Action to Support the Development of a Multipollutant Science Assessment," US EPA Workshop, May 2012
- Editorial Board Member, *Carcinogenesis*, 2012-2014
- Invited Participant on "Improving Science-Based Regulation," The George Washington University Regulatory Studies Center and the Center for Risk Science and Public Health, January 2012
- Member, Massachusetts Environmental Justice Assistance Network (EJAN), 2010-Present
- Board Member, American College of Epidemiology, 2011-2013
- Nominating Committee, Society of Toxicology, 2009-2011
- Elected Member, Canton, Massachusetts Board of Health, 2008-Present
- Editorial Board Member, *The Open Biomarkers Journal*, 2008-Present
- Managing Editor, *Journal of Environmental Protection Science*, 2008-2010
- Member, Canton, Massachusetts Medical Reserve Corps, 2007-Present
- Peer Reviewer, *Texas Commission on Environmental Quality, Development Support Document for Nickel and Inorganic Nickel Compounds, Preliminary Draft*, May 2009
- Invited Observer, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 100, Meeting C: Metals, Particles and Fibres*, Lyon, France, March 2009
- Abstract Awards Selection Committee, Risk Assessment Section, Society of Toxicology, 2008
- Secretary/Treasurer, Risk Assessment Specialty Section, Society of Toxicology, 2007-2009
- Editorial Board Member, *Journal of Environmental Protection Science*, 2007-2008
- Guest Lecturer, Cancer Epidemiology, University of Maryland, 2004
- Member, Cancer Prevention Fellowship Scientific Education Committee, NCI, 2003
- Guest Lecturer, Xenobiotic Metabolism, Johns Hopkins Bloomberg School of Public Health, 2001-2002
- Reviewer: *African Journal of Biotechnology; American Journal of Ophthalmology; American Journal of Pathology; Annals of Epidemiology; Applied Economics Letters; Biomarkers & Prevention; BMC Medical Research Methodology; Cancer Epidemiology; Cancer Genetics and Cytogenetics; Cancer Research; Carcinogenesis; Chemical Research in Toxicology; Chemico-Biological Interactions; CHEST; Clinical Cancer Research; Critical Reviews in Toxicology; Environmental Health Perspectives; Environment International; Environmental Science & Technology; Epidemiology; Food Science & Nutrition; Global Epidemiology; Human and Experimental Toxicology; Inhalation Toxicology; International Journal Of Environmental Health Research; International Journal of Environmental Research and Public Health; Journal of Cellular Biochemistry; Journal of Clinical Epidemiology; Jornal de Pediatria; Journal of Exposure Science and Environmental Epidemiology; Journal of Human and Ecological Risk Assessment; Journal of Occupational and Environmental Medicine; Journal of Toxicology and Environmental Health, Part A: Current Issues; Medical Journal of Australia; NeuroToxicology; PeerJ; Pharmacogenetics; Preventive Medicine Reports; Regulatory Toxicology and Pharmacology; Risk Analysis; Safety and Health at Work; Scientific Reports (Nature Publishing Group); Toxicology; Toxicology and Applied Pharmacology; Toxicological Sciences; Trends in Food Science & Technology*

Honors and Awards

- Best Poster Award, Environment, Health & Safety Poster Session, Polyurethanes Technical Conference, October 2018
- Distinguished Alumna Award, Johns Hopkins University, April 2015
- Chauncey Starr Distinguished Young Risk Analyst Award, Society for Risk Analysis, 2014
- Best Overall Abstract, Risk Assessment Specialty Session, Society of Toxicology, San Antonio, TX, 2013
- International Dose-Response Society Outstanding New Investigator Award, 2012
- Top 10% Best Overall Abstracts in Risk Assessment, Risk Assessment Specialty Section, Society of Toxicology, Seattle, WA, 2008

- Fellows Award for Research Excellence: $1,000 Travel Award, National Institutes of Health, Bethesda, MD, 2004
- Honorable Mention Poster Presentation, Center for Cancer Research 4th Annual Fellows and Young Investigators Retreat, Williamsburg, VA, March 2004
- Graduate Student Travel Award, Gordon Research Conference on Hormonal Carcinogenesis, 1999, 2001
- Travel Award, Third World Congress on Alternatives and Animal Use in the Life Sciences, Bologna, Italy, 1999
- Howard Hughes Predoctoral Fellowship Award, 1997-2002
- NIEHS Training Grant Graduate Fellowship Award, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 1996-1997
- Tau Beta Pi, National Engineering Honor Society, 1995-1996
- Chi Epsilon, National Civil Engineering Honor Society, 1994-1996

Professional Affiliations

American College of Epidemiology; Society for Risk Analysis; Society for Risk Analysis New England Chapter; Society of Toxicology; American Board of Toxicology; Academy of Toxicological Sciences; International Dose-Response Society

Selected Projects

Manufacturer: Evaluated whether potential exposures to ammonium perfluorooctanoate (APFO) and perfluorooctanoic acid (PFOA) emissions from a manufacturing facility could have caused specific cancer and non-cancer health outcomes in certain individuals.

Manufacturer: Evaluated whether certain cancers could have been caused by exposure to an alleged NDMA impurity in a pharmaceutical.

Trade Association: Conducted a systematic review of gas cooking or indoor nitrogen dioxide (NO_2) and asthma or wheeze in children.

Food company: Reviewed applicable US FDA requirements for new dietary ingredients and proposed a framework where alternative test data could be used to reduce or replace traditional animal toxicity testing.

Trade Organization: Created a database and conducted hazard assessments for approximately 800 chemicals.

Town: Reviewed a cancer cluster analysis conducted by the state and communicated findings to the community.

University: Described the main features of internal dose time courses that are important when pharmacodynamics are governed by an activation threshold. Presented the adverse outcome pathway (AOP) for NLRP3-induced chronic inflammatory diseases as a case study.

Trade Organization: Evaluated the Consumer Product Safety Commission's Final Rule: Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates, including the methods used to calculate Hazard Index values.

Cleaning Products Company: Determined whether several ingredients of several cleaning products could have caused or exacerbated several claimed health effects (such as respiratory effects) in individuals using the products or working in areas where the products were used.

Public School: Evaluated school facility information and environmental assessments that have been conducted on lead in school drinking water. Quantified typical student exposures and estimated health risks. Evaluated exposures and risks of PEX replacement pipes.

Research Organization: Estimated dietary phthalate intake based on data from the National Health and Nutrition Examination Survey (NHANES), a program of studies of United States residents conducted at the Centers for Disease Control and Prevention (CDC).

Trade Association: Reviewed and provided comments to the United States Environmental Protection Agency (US EPA) on its assessment plan for an updated arsenic health risk assessment.

Trade Organization: Developed a framework for a systematic, objective, and transparent evaluation of the evidence for non-cancer causation that requires reviewers to conduct a systematic study quality analysis and consider how the evidence from several realms impacts the interpretation of others.

Electric Utility: Evaluated the potential non-cancer and cancer health effects from exposure to coal combustion residuals (CCR) as a whole, and arsenic and chromium specifically, as reported in epidemiology and toxicity studies. Determined whether potential exposures to CCR contributed to current or future health effects, or warrant medical monitoring.

Trade Organization: Determined the safety of benzoic acid and its salts when used as preservatives in food and soft drinks based on an evaluation of pharmacokinetic data in rodents and humans, and human clinical studies of sodium benzoate administered as a therapeutic drug.

Children's Personal Care Product Manufacturer: Conducted a comprehensive hazard and risk assessment using data reported by various research and regulatory agencies, and specific risk assessments for individual preservatives, to determine whether there could be health risks for children from regular use of personal care products containing these preservatives.

Trade Organization: Evaluated the association between coffee generally, and acrylamide specifically, and cancer risk in the context of California's Proposition 65.

Trade Association: Conducted two comprehensive critical weight-of-evidence (WoE) reviews of studies bearing on the ability of very low bisphenol a (BPA) exposures to affect reproduction and development *via* endocrine disruption. These analyses were presented to several state legislative committees, all of which were considering bans on BPA.

Trade Organization: Conducted a survey of nearly 50 WoE frameworks to evaluate best practices for determining causation. Defined the key concepts of WoE analyses and their application to particular problems, and articulated the best practices from among the spectrum of approaches.

Food Manufacturer: Evaluated the significance of lead in imported hot sauces after a journal article reported that some of the products contained elevated levels of lead. Prepared a critique and summary of the study findings, and compared lead levels to US FDA limits. Evaluated the potential impact of the lead exposures on blood lead levels.

Trade Organization: Evaluated potential health risks from BPA in epoxy-lined metal cans based on both peer-reviewed scientific literature and regulatory agency risk assessments.

Personal Care Product Company: Conducted a risk assessment of zinc oxide in sunblock.

Trade Association: Critically evaluated the Environmental Benefits Mapping and Analysis Program – Community Edition (BenMAP-CE) that US EPA uses in the risk assessments for ozone (O_3) and particulate matter (PM) as part of its NAAQS evaluation.

Chemical Company: Evaluated the utility of using epidemiology data in human health risk assessment and regulatory decision-making for the insecticide, chlorpyrifos.

Trade Organization: Performed an O_3 mortality risk assessment using US EPA's Environmental Benefits Mapping and Analysis Program (BenMAP). Evaluated mortality risks by conducting a series of sensitivity analyses to assess how alterative model inputs impacted risk results.

Hospitals: Conducted screening level risk assessment for contaminants, including hexavalent chromium and polycyclic aromatic hydrocarbons, in product residue on surgical instruments used for medical procedures at several hospitals.

Industrial Consortium: Contributed to a toxicity and risk assessment in a class-action lawsuit by residents claiming adverse health effects from TCE and PCE in groundwater. Participated in a quantitative analysis of ingestion exposure, showering exposure, potential health risks, and proposed medical monitoring.

Water Supply Company: Evaluated potential health effects of arsenic, lead, and chlorination disinfection byproducts in drinking water.

City: Evaluated whether a career as a firefighter is associated with brain or lung cancer.

Consumer Product Company: Reviewed the safety testing required for a pesticide to be registered in the US; the potential risks and benefits of DEET; and standards, guidelines, and recommendations for using DEET.

Law firm: Evaluated whether air pollution may have increased the incidence and prevalence of several health conditions, including several cancers, in a city in Israel.

Trade Organization: Evaluated whether there is a scientific consensus regarding the potential health effects of asbestos compared to other elongate mineral particles, and whether any differences should be considered for testing guidelines.

Consumer Product Company: Critically reviewed epidemiology studies of specific consumer products.

Mining Company: Assessed the potential health risks of residents exposed to nickel as result of residing near a surface lateritic nickel mine and ferronickel smelter based on air, water, soil, and sediment data collected as part of the mine's environmental monitoring program.

Trade Association: Conducted a systematic review ozone exposure and metabolic syndrome.

Trade Organization: Critically reviewed parabens and weight gain epidemiology, toxicology, and mode-of-action evidence.

Waste Disposal Company: Evaluated the scientific evidence regarding radiation exposure and renal cell carcinoma in general and the likelihood that this cancer could have been caused by exposure to radionuclides from living in proximity to a landfill containing radioactive waste.

Trade Organization: Reviewed a cancer cluster investigation and epidemiology studies of pediatric leukemia and lymphoma, pediatric brain cancer, and pediatric Ewing sarcoma.

Trade Organization: Critically reviewed epidemiology research on air pollution and COVID.

Trade Organization: Evaluated and provided comments on US EPA's draft risk evaluation for trichloroethylene. Focused on the meta-analyses of kidney cancer, liver cancer, and non-Hodgkin's lymphoma.

Non-Profit Research Institute: Developed an *in silico*-based health-protective screening approach for inhaled chemicals.

Law firm: Evaluated the potential human carcinogenicity of formaldehyde and methyl *tert*-butyl ether (MTBE).

Trade Organization: Conducted a systematic review of long-term exposure to fine particulate matter ($PM_{2.5}$) and all-cause mortality.

Waste Management Company: Evaluated whether specific health conditions, including cancer, were likely attributable to exposures to Radium 226, Thorium 230, or Uranium 238 that originated from a landfill.

Farm: Evaluated whether certain health conditions could be caused by exposures to nitrate in drinking water or hydrogen sulfide or ammonia in air and, if so, under what exposure conditions.

Trade Organization: Conducted a WoE analysis of talc and ovarian cancer, including a quantitative bias analysis of epidemiology studies.

Trade Organization: Evaluated the association between personal $PM_{2.5}$ exposures and ambient $PM_{2.5}$ concentrations, and the implications for the interpretation of epidemiology studies that estimate personal exposure based on ambient concentrations.

Private Company: Assessed whether appropriate epidemiology methods were used to evaluate a potential pediatric cancer cluster in a military housing complex. Evaluated whether public health and environmental investigations used methodologically sound analyses.

Consumer Product Company: Determined whether a framework for assessing the hazard of cleaning product ingredients was sufficient to support "non-toxic" claims on product packaging for a household cleaner.

Consumer Product Company: Evaluated the historical state of knowledge regarding the toxicity of butadiene and the development of myelodysplastic syndrome.

Railroad Company: Summarized the historical states of knowledge regarding the toxicity of vermiculite and asbestos in the railroad industry.

Trade Organization: Conducted a systematic review of metallic nickel and cancer.

Trade Organization: Evaluated best practices for evidence integration in National Ambient Air Quality Standards (NAAQS) Integrated Science Assessments (ISAs).

State Environmental Agency: Quantitatively evaluated how uncertainty and bias can impact epidemiology associations between air pollutants and respiratory morbidity at low exposures.

Law Firm: Evaluated the potential lung cancer, mesothelioma, and interstitial fibrosis risks from exposure to chrysotile asbestos from brakes based on epidemiology studies of vehicle brake repair workers and industrial hygiene, mode-of-action, and toxicology data.

Chemical Company: Evaluated and provided comments on US EPA's Toxicological Review of Libby Amphibole Asbestos. Interacted with several regulatory agencies throughout the interagency process of the Integrated Risk Information System (IRIS) review.

Trade Organization: Evaluated systematic review methods used by US EPA in IRIS and Toxic Substances Control Act (TSCA) evaluations.

Pesticide Companies: Evaluated the use of neurodevelopmental epidemiology studies by the US EPA in the re-registration process for organophosphate pesticides.

Consumer Product Company: Determined whether aspiration of a laundry pod caused long-term health effects in an infant.

Consumer Product Company: Evaluated the implications of a new toxicity study of an ingredient in a consumer product for adults and children who use the product and workers who manufacture the product. Provided an analysis of the potential Globally Harmonized System of Classification and Labeling of Chemicals (GHS) and Safety Data Sheet (SDS) implications of a the ingredient.

Trade Organization: Assessed whether a post-market skin patch epidemiology study should be used for risk assessment.

Trade Organization: Evaluated emission limits for several chemicals defined in certification guidelines for a consumer product.

Trade Organization: Reviewed and provided comments on Health Canada's Draft Screening Assessment Report and Risk Management Scope for talc.

Municipality: Evaluated whether childhood blood lead levels in a city appeared to be impacted by increases in water lead levels. Assessed the potential beneficial impact of the City's distribution of point-of-use water filters to residents.

Trade Organization: Developed detailed criteria for exposure characterization that can be used when designing future epidemiology studies and for evaluating completed studies to determine how their results should be considered in a regulatory setting.

Trade Organization: Determined whether nickel should be classified as a reproductive or developmental toxicant under California EPA's Proposition 65.

Consumer Product Company: Developed a statistical approach for a clinical study of a medical device.

Trade Organization: Performed a detailed quantitative analysis to determine the reliability and adequacy of the T25 Carcinogenic Potency Method for inhalation exposures of inorganic substances. This method is used to classify carcinogenic substances according to the European Union's guidance for Classification, Labelling and Packaging of Substances and Mixtures.

Law Firm: Evaluated the potential side effects and dose-response relationships for cosmetic botulinum toxin injections from reviews of clinical trials and FDA warning labels. Assessed whether claimed health effects in an individual existed prior to an injection with botulinum toxin, were included among the documented side effects of the toxin, or were indicative of systemic toxicity.

Trade Organization: Critically reviewed the draft recommendation for a non-health-based BPA occupational exposure limit (OEL) proposed by the Dutch Expert Committee on Occupational Health and Safety (DECOS). Derived and recommended a health-based BPA OEL that is consistent with European Commission directives.

Law Firm: Evaluated nickel concentrations in an urban neighborhood using air monitoring data. Assessed the cancer and non-cancer health risks of exposure to nickel in air and dust among residents.

Trade Organization: Evaluated the association between short-term exposures to $PM_{2.5}$ and hospital admissions for cardiovascular diseases.

Research Organization: Evaluated the impact of respiratory infections, outdoor pollen, and socioeconomic status on associations between $PM_{2.5}$ and ozone and pediatric asthma hospital admissions.

Research Organization: Critically reviewed the epidemiology literature on exposure to $PM_{2.5}$ and several birth outcomes.

Trade Organization: Reviewed and commented on the International Agency for Research on Cancer (IARC) Preamble, which summarizes the underlying scientific principles of the IARC Monographs, which evaluate the carcinogenic hazards of chemicals and other substances.

Baby Product Company: Evaluated whether a teething ring product contained more Bisphenol A than is permitted under Proposition 65.

Energy Company: Evaluated whether working on the site of a former Manufactured Gas Plant may have contributed to kidney cancer.

Steel Company: Assessed the state of knowledge related to employment in a steel mill or steel plant and asbestos-related disease to understand when the scientific community began to study the hazards of asbestos among steelworkers and when it was reasonable for a steel manufacturing company to have known that exposure to asbestos-containing materials could potentially lead to the development of respiratory disease in steelworkers.

Trade Organization: Evaluated US EPA's calculation of an inhalation unit risk (IUR) in its "Toxicological Review for Trichloroethylene in Support of Summary Information on the IRIS."

Trade Organization: Developed standards for epidemiology studies similar to good laboratory practice (GLP) standards, which are intended to assure the quality and integrity of non-clinical laboratory studies.

Manufacturer: Critically reviewed the quality of case-control studies conducted in North America that assessed the associations between captan exposure and the risk of multiple myeloma. Conducted a quantitative bias/uncertainty analysis of these studies.

Trade Organization: Evaluated the basis for the American Conference of Governmental Industrial Hygienists (ACGIH) lowering the Threshold Limit Value for toluene diisocyanate.

Law Firm: Evaluated exposure to O-toluidine and bladder cancer risk.

Law Firm: Evaluated exposures to landfill gases, including hydrogen sulfide, and potential health effects from these exposures in individuals residing near a municipal solid waste landfill. Evaluated potential odor impacts and the differences between odor perception and adverse health effects.

Trade Organization: Reviewed literature regarding several air toxics and health endpoints and provided recommendations on a proposed regulation in California to monitor communities for air pollution-attributable health effects.

Trade Organization: Critically reviewed the harmonized carcinogenicity classification and labeling for cobalt metal developed to comply with the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation by RIVM (Netherlands National Institute for Public Health and the Environment).

Toy Manufacturer: Evaluated whether brain injury could occur as a primary consequence of ingesting toy beads containing 1,4-butadiene, or as a secondary consequence of experiencing coma-like symptoms following ingestion of the beads.

Pharmaceutical Company: Assessed whether on-label use of a pharmaceutical increased cardiovascular disease risk based on randomized controlled trials and observational epidemiology studies.

US EPA: Contributed to the design of a model describing several frequently encountered toxicity endpoints in terms of a series of progressive pathophysiological steps.

Pharmaceutical Company: Performed an in-depth analysis of the toxicology and epidemiology data of a specific drug to determine whether the company could have anticipated potential adverse side effects in humans.

Pharmaceutical Company: In the context of a patent infringement lawsuit, performed an independent analysis of efficacy and toxicity data from animal experiments to determine if claims in the patent could be challenged.

Government Agency: Critically evaluated an epidemiology study of exposures and health outcomes in indigenous and Afro-Colombian communities living near a nickel mine and smelter and discussed with the government agency that conducted the study.

Chemical Company: Conducted a meta-analysis of epidemiology studies that evaluated the use of a pharmaceutical during labor and dystocia.

Trade Association: Evaluated whether atherosclerosis development is a plausible mode of action for PM in cardiovascular pathogenesis, and whether this is supported by epidemiology evidence.

Trade Association: Critically reviewed the draft recommendation for a non-health-based OEL for di- and triisocyanates proposed by the DECOS of the Health Council of the Netherlands.

Trade Organization: Developed a database of epidemiology studies of occupational exposures to pesticides and cancer.

Trade Organization: Critically reviewed the epidemiology literature on long-term exposure to ambient ozone and asthma development.

Manufacturer: Evaluated the health risks of potential carbon monoxide exposures at a proposed bridge near a manufacturing facility.

Consumer Product Company: Systematically reviewed epidemiology, toxicity, exposure and transport, and mechanistic studies to evaluate whether personal use of cosmetic talc increases ovarian cancer risk.

Trade Organization: Evaluated whether an alternative form of the sulfur dioxide (SO_2) NAAQS would be as public health protective as the then-current form.

Trade Organization: Critically reviewed the approach US EPA used to quantify health co-benefits when assessing the impacts of the Clean Power Plan. Evaluated the scientific validity of the models, data sources, and assumptions underlying US EPA's calculations.

Chemical Company: Evaluated whether exposure to odorous chemicals emitted from spray foam insulation in a residence posed a potential health risk. Compared residents' exposure to odor thresholds, toxicity criteria, and health effect levels for specific constituents emitted from the foam.

Law Firm: Assessed human health risks associated with coal-fired power plant emissions, including particulate matter, SO_2, and nitrogen oxides (NO_x), based on air modeling results and available measurement data.

Trade Organization: Conducted a systematic review of epidemiology studies that evaluated proximity to unconventional natural gas development (UNGD) and perinatal outcomes.

Chemical Company: Provided chemical-level assessments (*i.e.*, analysis of inventory status, occupational exposure limits, and available toxicity data) and product-level assessments (*i.e.*, evaluation of Good Manufacturing Practice and regulatory hurdles) for several cosmetics and consumer products.

Research Organization: Critically evaluated toxicity studies that investigated $PM_{2.5}$ and developmental and reproductive effects.

Utility Group: Evaluated potential exposures and health impacts of PM in general, as well as two specific types of PM associated with power plant operations (*i.e.*, diesel exhaust emissions and coal dust emissions).

Manufacturer: Assessed the potential health risks of saline-filled breast implants based on a review of the peer-reviewed literature and pre- and post-market studies of silicone- and saline-filled breast implants.

Pharmaceutical Company: Evaluated whether historical data support the patentability of a drug that lowers blood lipid levels. Reviewed the experimental methods (including statistics) and results of efficacy studies with the drug to confirm the original study conclusions.

Trade Associations: Facilitated research that addresses the causality of the relationship between $PM_{2.5}$ and mortality. Selected research candidates, developed a request for proposal, evaluated solicited proposals, coordinated selected researchers for data access, and organized a symposium for researchers to present and discuss their findings.

Utility Company: Evaluated health effects associated with potential exposures to chemicals, including coal tar and polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene, resulting from recreational activities in the vicinity of a former manufactured gas plant site.

Chemical Company: Evaluated whether the PAHs in an asphalt roofing underlayment would require its classification under the Occupational Safety and Hazard Administration's (OSHA) hazard communication standard.

Manufacturer: Evaluated the incidence, prevalence, risk factors, and potential alternative causes of health complaints among office workers allegedly exposed to chemicals in indoor air *via* vapor intrusion of contaminated groundwater. Also assessed whether there were any disease clusters at the site.

Trade Organization: Provided written and oral comments to the Clean Air Scientific Advisory Committee (CASAC) on exposure, epidemiology, toxicity, and mode-of-action studies and their bearing on US EPA's development of NAAQS for O_3, PM, NO_x, and sulfur oxides (SO_x) on numerous occasions.

Manufacturer: Reviewed asbestos exposure data related to the handling and installation of electrical equipment and epidemiology evidence regarding mesothelioma, lung cancer, and laryngeal cancer in electricians.

US Army: Assessed several dose-response functions, animal models, and endpoints to obtain the most appropriate model-predicted risk estimate to use in establishing a risk-based inhalation exposure criterion for vanadium pentoxide.

Appliance Manufacturer: Evaluated evidence for a cancer cluster in a neighborhood where soil containing polychlorinated biphenyl (PCBs) was historically used as landfill in a recreation area.

State Environmental Agency: Conducted WoE evaluations of the association between short-term and long-term ozone exposure and cardiovascular effects.

State Environmental Agency: Evaluated how meta-analyses have been or could be applied in the evaluation of health effects of air pollutants. Assessed the strengths and limitations of methods, issues that arise in meta-analyzing different types of data, assumptions that can influence the interpretation of results, and how bias and heterogeneity can be addressed.

Law Firm: Assessed the impact of coal-fired power plant emissions on exposures to fine PM, SO_2, and NO_2 and whether these exposures likely contribute to adverse health effects in Colorado residents.

Mining Company: Evaluated methods used to derive a proposed standard for nickel by the Province of Quebec, Canada.

Utility Company: Reviewed the historical releases of compounds associated with manufactured gas plant processes, including PAHs such as benzo[a]pyrene, and the historical understanding of risk assessment, carcinogenesis, and the toxicity of these compounds.

State Environmental Agency: Reviewed epidemiology, controlled human exposure, experimental animal, and mechanistic studies of ozone and markers of inflammation and oxidative stress.

State Environmental Agency: Critically reviewed potential uses of Next Generation (NexGen) toxicity testing methods and associated interpretation techniques in assessing the risks associated with chemical exposures (*e.g.*, in high-throughput screening programs or detailed quantitative analyses for individual data-rich chemicals).

Trade Organization: Critiqued draft templates for tabulating epidemiology and experimental animal study data for hazard identification proposed by the Developmental and Reproductive Toxicant Identification Committee (DART IC) of California's Office of Environmental Health Hazard Assessment (CalOEHHA). Proposed an alternative set of tables to systematically present data for consideration in a full evidence integration process.

State Environmental Agency: Critically reviewed epidemiology, controlled human exposure, experimental animal, and mechanistic studies of ozone and outcomes related to asthma exacerbation.

State Environmental Agency: Evaluated the relationship between ozone concentrations and asthma hospitalizations in Texas from 2001-2011.

Trade Organization: Conducted sensitivity analyses to determine how alternative assumptions impact exposure and risk estimates calculated using the US EPA Air Pollutants Exposure (APEX) Model.

Health Care Company: Analyzed the health effects of perchloroethylene and its breakdown products (trichloroethylene, 1,1-dichloroethylene, 1,2-dichloroethylene, and vinyl chloride) to address community concerns with remediation requirements. Also reviewed the bases for soil and groundwater remediation goals.

Chemical Company: Analyzed health risks from exposure to PCBs in caulking in a school in Massachusetts by analyzing potential exposures at the school and epidemiology and toxicology evidence. Also summarized the state of knowledge regarding PCBs when the school was built.

State Environmental Agency: Organized and participated in a workshop focused on the scientific evidence for ozone effects and the societal implications of lowering the ozone NAAQS.

Utility Company: Characterized and communicated exposures to chemicals, including PAHs such as benzo[a]pyrene, for occupants of residential and commercial properties constructed on the site of a former manufactured gas plant.

Trade Association: Evaluated non-cancer effects of PM.

Chemical Company: Evaluated whether inflammation and oxidative stress caused by ozone exposure are key events leading to respiratory toxicity.

Chemical Company: Conducted a WoE evaluation of PM and biomarkers of cancer.

Chemical Company: Evaluated whether there was evidence of any developmental health effects clusters at an office building. Assessed likely explanations for health claims.

Trade Association: Proposed a framework for evaluating causation that provides a structure for integrating different realms of evidence, weighing the strength of evidence for causation, and assessing the potential impact of uncertainty on the body of evidence.

Trade Organization: Critically reviewed the epidemiology literature evaluating nickel exposure and reproductive and developmental effects. Determined whether it supported a prioritization of nickel for CalOEHHA's consideration under California's Proposition 65.

Trade Organization: Evaluated whether higher regulatory limits on heavy metals in finished medical marijuana products would provide an adequate margin of safety for patients, and whether certain hydrocarbon gases could be safely used in the production of cannabis concentrates used in medical marijuana infused products.

Law Firm: Evaluated whether exposures to diesel exhaust and jet fuel are associated with lung cancer based on a literature review, agency classifications, and key epidemiology studies on which classifications are based.

Electric Utility: Evaluated the scientific basis of health impacts associated with air quality regulations that would impact an electricity generation facility. Compared air quality data in the area around the facility to health-based NAAQS.

Trade Organization: Assessed the US EPA "Framework for Human Health Risk Assessment to Inform Decision Making" and compared it to US EPA's ongoing O_3 analysis. Focused on planning and "fit for purpose," WoE, transparency, reasonableness, consistency, at-risk factors, and uncertainty and variability.

Electric Utility: Analyzed air monitoring data to determine the potential public health impacts of stack air emissions of fine PM, O_3, NO_2, and SO_2.

Trade Organization: Conducted a quantitative analysis of controlled human exposure studies to address whether there is a subset of individuals who are susceptible to health effects of criteria air pollutants at particular exposure levels, but whose response is obscured by analyzing data at the group level.

Law Firm: Analyzed human health risks posed by chemicals measured in workplace indoor air that were alleged to have originated from groundwater contaminated by a nearby recycling facility. Focused on the epidemiology of the chemicals of concern at the levels measured in the workplace and the plaintiffs' health complaints, including cancer.

Smelter: Assessed whether a smelter's permit would likely allow for SO_2 emissions that could lead to adverse health effects in the community.

Trade Organization: Reviewed the basis for the California Environmental Protection Agency's (CalEPA's) proposal to list SO_2 as a Proposition 65 developmental and reproductive toxicant. Evaluated whether the underlying studies provided sufficient and robust evidence that SO_2 causes developmental and reproductive effects.

Trade Organization: Reviewed and critiqued the assumptions and uncertainties associated with the statistical models on which US EPA's 2011 Benefits and Costs of the Clean Air Act Report was based.

Chemical Company: Evaluated US EPA's proposed national emission standards for hazardous air pollutants (NESHAPs) for mercury from major industrial boilers. Evaluated the agency's statistical approach for establishing the maximum achievable control technology (MACT) limit and determined how alternative approaches would impact the MACT derivation.

Trade Organization: Conducted meta-analyses and meta-regressions of airway hyper-responsiveness in asthmatic volunteers exposed to NO_2 in clinical studies. Presented these analyses to the US Office of Management and Budget.

Trade Organization: Assessed what constitutes an adverse health effect *vs*. normal biological variation (or adaption or compensation to stressors), and the role of statistics in assessing adversity. Used airway hyper-responsiveness to SO_2 as a case study.

Health Effects Institute: Compiled and reviewed studies regarding chronic and acute toxicity guidelines for mobile source air toxicants.

Trade Organization: Evaluated studies examining low-dose exposure to BPA and effects on reproduction and development using a W approach. Discussed results in written comments and oral testimony to CalEPA in the context of whether BPA should be listed as a female reproductive toxicant under Proposition 65.

Cleaning Product Company: Evaluated toxicity of chemicals in all-natural cleaning products.

Municipality: In response to citizens' concerns, independently investigated whether there was an increased incidence of cancer in residents living near a municipal landfill. Communicated findings with city officials and residents at public meetings.

Toy Distributor: Determined whether a toxicological evaluation of a toy was sufficient for determining children's health risks. Assessed the toxicity of a chemical found in the toy, potential routes of exposure, and possible health risks.

Trade Organization: Conducted a systematic review and meta-analyses of 2,4-dichlorophenoxyacetic acid (2,4-D) and non-Hodgkin's lymphoma, gastric cancer, and prostate cancer. Participated as an observer at the IARC Monograph 113 Meeting at which 2,4-D was evaluated.

Trade Organization: Assessed whether animal, mechanistic, and epidemiology evidence is consistent with the nickel ion bioavailability model, which asserts that the carcinogenicity of nickel-containing substances is based on the bioavailability of the nickel ion at nuclear sites of target respiratory epithelial cells.

Public Agency: Evaluated the variability in water lead levels across a US city and the association between water lead levels and blood lead levels in children.

Pesticide Company: Assessed whether epidemiology, toxicology, and mechanistic evidence support chlorpyrifos being a neurobehavioral toxicant in humans at relatively low exposure levels. Evaluated evidence using recently proposed frameworks for integrating human and animal data, as well as Gradient's hypothesis-based weight-of-evidence (HBWoE) approach.

Cleaning Product Company: Evaluated the potential risks of birth defects from exposure to the chemical components of products used in floor stripping and refinishing.

Trade Organization: Conducted a critical examination of a proposal by the National Academy of Sciences that linear low-dose extrapolation should be used for non-cancer and cancer endpoints as a default because measurement error in epidemiology studies linearizes dose-response curves.

Law Firm: Reviewed specific exposure information and occupational epidemiology literature for a claim regarding a causal association between formaldehyde inhalation and acute myeloid leukemia.

Law Firm: Evaluated whether radiation should have been considered as a potential cause of an individual's mesothelioma. Analyzed both specific exposure information and toxicology and epidemiology literature on radiation and mesothelioma.

Trade Association: Using the HBWoE approach, evaluated whether epidemiology, toxicology, and mechanistic evidence supports the plausibility of formaldehyde as a human leukemogen.

Chemical Companies: Calculated a benchmark dose (BMD) for an industrial chemical using US EPA's BMD Software (BMDS). Assessed several dose-response models and evaluated the impact of using historical control data.

Trade Organization: Evaluated whether epidemiology, animal toxicity, mechanistic, and pharmacokinetic evidence indicates that toluene diisocyanate is a human carcinogen.

Trade Organization: Critically reviewed meta-analysis of respiratory cancer risk following inhalation exposure to nickel compounds. Provided comments regarding the methods, limitations, and interpretation of results throughout the conduct of this study.

Trade Organization: Conducted a pilot meta-analysis of studies bearing on the ability of very low oral exposures to BPA to affect prostate weight in rodents. Investigated the possibility of publication bias and evidence for a temporal trend in the data.

Trade Organization: Critically reviewed a draft European Union report on the state of the science regarding endocrine-disrupting chemicals. Assembled a panel of experts to determine whether the draft report constituted a complete and unbiased analysis of endocrine disruptors.

Trade Organization: Reviewed epidemiology studies assessing associations between BPA and several health effects.

Trade Association: Reviewed and prepared comments on ACGIH's proposed Threshold Limit Value for manganese. Reviewed the methodology applied by ACGIH, compared the use of published regression analyses of manganese dose-response data to benchmark dose modeling of more recent data, and identified appropriate adverse effect levels of manganese in occupational studies.

Chemical Manufacturer: Reviewed the epidemiology and mode-of-action data on acetic anhydride and cancer using a systematic WoE approach to determine whether the data are consistent with ACGIH cancer classification.

Law Firm: Evaluated epidemiology literature regarding present and future risks of cancer and non-cancer health effects in a group of individuals from inhalation exposures to trichloroethylene (TCE) and perchloroethylene (PCE).

Law Firm: Evaluated the epidemiology literature regarding cancer and non-cancer health effects of benzene, dioxin, and pentachlorophenol. Conducted a cluster analysis to determine whether individuals residing in an area with alleged exposures had increased rates of several cancers and non-cancer health effects.

Pesticide Companies: Critically reviewed epidemiology, toxicology, and mechanistic studies to assess whether exposure to atrazine in drinking water is associated with reproductive and developmental health effects.

Confidential Client: Evaluated the health effects associated with hexavalent chromium based on an assessment of the epidemiology literature. Assessed the scientific rigor of an analysis of potentially exposed individuals' survey responses.

Trade Organization: Classified, summarized, and entered relevant lead studies into the International Uniform Chemical Information Database (IUCLID) 5.2, a database for the intrinsic and hazard properties of chemical substances that companies can use to submit data under the REACH legislation in Europe.

Trade Organization: Provided written and oral testimony to the US National Toxicology Program (NTP) and its Board of Scientific Councilors regarding occupational epidemiology studies of styrene and whether styrene should be considered a human carcinogen.

Trade Organization: Developed scientifically sound approaches for incorporating human data into quantitative non-cancer risk assessment to support commentary on the ongoing US EPA revision of its dioxin assessment.

Trade Organization: Evaluated the associations between metal exposures and health outcomes using NHANES data.

Trade Organization: Conducted a WoE assessment of exposure to soluble nickel compounds and respiratory cancer risk based on animal carcinogenicity, mode-of-action, and occupational epidemiology studies.

Trade Organization: Conducted a critical review of the US EPA Toxicological Review of 1,4-Dioxane in support of "Summary Information" provided in IRIS. Proposed alternative methods to calculate the cancer slope factor and reference dose.

Law Firm: Evaluated the toxicology and epidemiology evidence regarding several pesticides and whether there was evidence for a causal association with certain birth defects.

Law Firm: Assessed recent occupational epidemiology studies of manganese and their bearing on the reference concentration (RfC).

Law Firm: Assessed whether epidemiology literature supports an association between low-level exposures to lead and IQ.

Trade Organization: Determined whether linear low-dose extrapolation should be used for non-cancer endpoints.

Law Firm: Assessed appropriateness of statistical analyses used by the Ramazzini Foundation for comparing cancer incidence rates in rats treated with MTBE and untreated rats.

Law Firm: Critically reviewed epidemiology literature of radium and osteosarcoma risk. Determined whether osteosarcoma rates were higher than expected in certain geographic regions in a southern state.

Law Firm: Critically reviewed potential health effects associated with exposure to heating oil from a basement spill.

Law Firm: Critically reviewed the epidemiology literature on the role of ionizing radiation in cancer risk in patients receiving radiation therapy, in nuclear energy facility workers, and in patients receiving Thorotrast treatments.

Chemical Company: Conducted a comprehensive review of the scientific literature on indoor dust levels of several flame retardants and an exposure assessment of each one.

Consumer Product Company: Interpreted the results of two genotoxicity screening assays in light of their sensitivity and specificity.

Toy Manufacturer: Conducted failure analyses of children's toys to determine whether proper or improper use was likely to lead to physical harm. Made recommendations regarding ways to make the toys safer.

Chemical Manufacturing Plant: Evaluated the mercury toxicology and epidemiology literature and determined whether levels in residential soil were above background and likely attributable to a nearby manufacturing plant.

Chemical Company: Conducted a critical review of neurodevelopmental toxicity studies of the flame retardant, decabromodiphenyl ether.

Petroleum Refining Company: Conducted an uncertainty analysis of the carcinogenicity of naphthalene using an HBWoE approach.

Power Plant: Critically reviewed published epidemiology studies of health effects in children residing near coal-fired power plants or coal mines. These studies examined respiratory outcomes, birth defects, and effects on physical development.

Law Firm: Analyzed health effects – including fetal, infant, and total death rates and cancer rates – and certain vital statistics in a Montana county. Compared overall health status of the county to that of the state.

Trade Organization: Evaluated and applied an uncertainty analysis focused on dioxin exposure and health effects data from key toxicology and human biomonitoring-based epidemiology studies as part of a margin-of-exposure analysis.

Law Firm: Evaluated toxicology and epidemiology evidence regarding glutaraldehyde and hydroquinone exposure and leukemia.

Trade Organization: Developed and refined a search strategy for the exposure and health effects of a chemical used in a manufacturing process using several databases, such as PubMed, Toxline, IRIS, and HSDB. Identified and screened relevant articles for inclusion in an electronic database.

Cleaning Product Company: Designed methodology for testing the presence and activity of an enzyme in a cleaning product. Determined whether this enzyme was appropriate for the product.

Wood Treatment Plant: Analyzed dioxin and PCB congeners in individuals residing near a wood treatment plant and compared them to background levels reported by NHANES. Analyzed these compounds in soil, dust, and sediment to determine whether there were elevated risks of exposure.

Small Business: Assessed whether cancer cases at a small business could be attributed to a common exposure.

Trade Association: Re-analyzed published rat testicular carcinogenicity data on MTBE using the Poly-3 statistical method to account for survival differences among treatment groups.

Pesticide Company: Analyzed US EPA's use of the lower confidence limit on the benchmark dose ($BMDL_{10}$) to determine a point of departure for the cancer risk of dimethylarsenic acid in humans.

Research Organization: Critically reviewed epidemiology literature to determine if the effects of lead and mercury on human neurological development are additive or synergistic.

Flame Retardant Company: Provided toxicological, database, and risk analysis support for product development of phosphorus-based flame retardant chemicals with low potential for health and environmental impact.

Chemical Company: Contributed to the drafting of an evidence-based argument submitted to US EPA regarding whether acetonitrile should be delisted from the US EPA's Toxic Release Inventory.

Smelter: Reviewed general and company-specific historical knowledge of human and ecological toxicity of smelter contaminants.

Manufacturer: Summarized the cancer and non-cancer effects of cobalt and nickel for a company that fabricates tungsten heavy metal alloy products.

Publications – *Journal Articles*

Rhomberg, LR; Goodman, JE; Ryman, J. 2025, Forthcoming. "Is the Science Underlying Recent Alternatives for Harmonizing Quantitative Risk Approaches Robust Enough to Replace Toxicity Thresholds in Non-Cancer Risk Assessment? " *J. Toxicol. Reg. Pol.*

Bus, JS; Su, S; Li, W; Goodman, JE. 2024. "Styrene Lung Cancer Risk Assessment: An Alternative Evaluation of Human Lung Cancer Risk Assuming Mouse Lung Tumors are Potentially Human Relevant and Operating by a Threshold-based Non-genotoxic Mode of Action." *J. Toxicol. Environ. Health B Crit. Rev.* 27(7):264-286. doi: 10.1080/10937404.2024.2380449.

Prueitt, RL; Goodman, JE. 2024. "Real-world Bisphenol A Exposure Not Linked to Microbiota Dynamics in Childhood Obesity." *mSystems.* 9(7):e0055624. doi: 10.1128/msystems.00714-24.

Boon, DN; Goodman, JE; Colonna, KJ; Espira, LM; Prueitt, RL. 2024. "A Systematic Review of the Epidemiology Evidence on Talc and Cancer." *Crit. Rev. Toxicol.* 54(6):394-417. doi: 10.1080/10408444.2024.2351081.

Prueitt, RL; Drury, NL; Shore, RA; Boon, DN; Goodman, JE. 2024. "Talc and Human Cancer: A Systematic Review of the Experimental/Animal and Mechanistic Evidence." *Crit. Rev. Toxicol.* 54(6):359-393. doi: 10.1080/10408444.2024.2349668.

Goodman, JE; Espira, LM; Zu, K; Boon, D. 2024. "Quantitative Recall Bias Analysis of the Talc and Ovarian Cancer Association." *Glob. Epidemiol.* 7:100140. doi: 10.1016/j.gloepi.2024.100140.

Li, W; Goodman, JE; Long, CM. 2024. "Population Attributable Fraction of Gas Cooking and Childhood Asthma: What Was Missed?" *Glob. Epidemiol.* 7:100141. doi: 10.1016/j.gloepi.2024.100141.

Prueitt, RL; Meakin, CJ; Drury, NL; Goodman, JE. 2024. "Evaluation of Neural Reflex Activation as a Potential Mode of Action for Respiratory and Cardiovascular Effects of Fine Particulate Matter." *Inhal. Toxicol.* 36(3):125-144. doi: 10.1080/08958378.2024.2324033.

Li, W; Zhou, J; Boon, Denali; Fan, T; Anneser, E; Goodman, J; Prueitt, RL. 2024. "Nickel in Ambient Particulate Matter and Respiratory or Cardiovascular Outcomes: A Critical Review." *Environ. Pollut.* 347:123442. doi: 10.1016/j.envpol.2024.123442

Prueitt, RL; Goodman, JE. 2024. "Evidence Evaluated by European Food Safety Authority Does Not Support Lowering the Temporary Tolerable Daily Intake for Bisphenol A." *Toxicol. Sci.* 198(2):185-190. doi: 10.1093/toxsci/kfad136.

Ebelt, S; Baxter, L; Erickson, HS; Henneman, LRF; Lange, S; Luben, TJ; Neidell, M; Rule, AM; Russel, AG; Wendt Hess, J; Burns, CJ; LaKind, JS, Goodman, JE. 2023. "Air Pollution Accountability Research: Moving from a Chain to a Web." *Glob. Epidemiol.* 6:100128. doi: 10.1016/j.gloepi.2023.100128.

Goodman, JE; Boon, DN; Jack, MM. 2023. "Perspectives on Recent Reviews of Aspartame Cancer Epidemiology." *Glob. Epidemiol.* 6:100117. doi: 10.1016/j.gloepi.2023.100117.

Goodman, JE; Anneser, EG; Khandaker, A; Boon, DN. 2023. "The Role of Study Quality in Aspartame and Cancer Epidemiology Study Reviews." *Glob. Epidemiol.* 100110. doi: 10.1016/j.gloepi.2023.100110.

Li, W; Long, C; Fan, T; Anneser, E; Chien, J; Goodman, JE. 2023. "Gas Cooking and Respiratory Outcomes in Children: A Systematic Review." *Glob. Epidemiol.* 5:100107. doi: 10.1016/j.gloepi.2023.100107.

Prueitt, RL; Hixon, ML; Fan, T; Olgun, NS; Piatos, P; Zhou, J; Goodman, JE. 2023. "Systematic Review of the Potential Carcinogenicity of Bisphenol A in Humans." *Regul. Toxicol. Pharmacol.*142:105414. doi: 10.1016/j.yrtph.2023.105414.

Goodman, JE; Ticknor, RC; Zhou, J. 2022. "Response: Alternative Approaches for Systematic Review." *Glob. Epidemiol.* doi: 10.1016/j.gloepi.2022.100091.

Goodman, JE; Becich, MJ; Bernstein, DM; Case, BW; Mandel, JH; Nel, AE; Nolan, R; Odo, NU; Smith, SR; Taioli, E; Gibbs, G. 2022. "Non-asbestiform Elongate Mineral Particles and Mesothelioma Risk: Human and Experimental Evidence." *Environ. Res.* 2022 Oct 19:114578. doi: 10.1016/j.envres.2022.114578.

Goodman, JE; Ticknor, RC; Zhou, J. 2022. "Systematic Review of Perchloroethylene and Non- Hodgkin's Lymphoma." *Glob. Epidemiol.* 4 :100077. doi: 10.1016/j.gloepi.2022.100077.

Lynch, HN; Goodman, JE; Bachman, AN. 2021. "Lung Physiology and Controlled Exposure Study Design." *J. Pharmacol. Toxicol. Methods* 112:107106. doi: 10.1016/j.vascn.2021.107106.

Dodge, DG; Engel, AM; Prueitt, RL; Peterson, MK; Goodman, JE. 2021. "US EPA's TSCA Risk Assessment Approach: A Case Study of Asbestos in Automotive Brakes." *Inhal. Toxicol.* 33(9-14):295-307. doi:10.1080/08958378.2021.1998258.

Goodman, JE; Prueitt, RL; Harbison, RD; Johnson, GT. 2021. "Re: In Defense of the Weight-of-Evidence Approach to Literature Review in the Integrated Science Assessment (Letter)." *Epidemiology* 32(4):e12. doi: 10.1097/EDE.0000000000001365.

Boomhower, SR; Long, CM; Li, W; Manidis, TD; Bhatia, A; Goodman, JE. 2021. "A Review and Analysis of Personal and Ambient $PM_{2.5}$ Measurements: Implications for Epidemiology Studies." *Inhal. Toxicol.* 204(Pt B):112019. doi: 10.1016/j.envres.2021.112019.

Goodman, JE; Li, W; Cox, LA Jr. 2021. "Commentary: Using Potential Outcomes Causal Methods to Assess Whether Reductions in $PM_{2.5}$ Result in Decreased Mortality." *Glob. Epidemiol.* 3:100052. doi: 10.1016/j.gloepi.2021.100052.

LaKind, J; Burns, C; Pottenger, L; Naiman, D; Goodman, JE; Marchitti, S. 2021. "Does Ozone Inhalation Cause Adverse Metabolic Effects in Humans? A Systematic Review." *Crit. Rev. Toxicol.* doi: 10.1080/10408444.2021.1965086.

Lynch, HN; Goodman, JE; Bachman, AN. 2021. "Lung Physiology and Controlled Exposure Study Design." *J. Pharmacol. Toxicol. Methods* doi: 10.1016/j.vascn.2021.107106.

Prueitt, RL; Li, W; Edwards, L; Zhou, J; Goodman, JE. 2021. "Systematic Review of the Association Between Long-term Exposure to Fine Particulate Matter and Mortality." *Int. J. Environ. Health Res.* doi: 10.1080/09603123.2021.1901864.

Prueitt, RL; Li, W; Chang, Y-C; Boffetta, P; Goodman, JE. 2020. "Systematic Review of the Potential Respiratory Carcinogenicity of Metallic Nickel in Humans." *Crit. Rev. Toxicol.* 50(7):605-639. doi: 10.1080/10408444.2020.1803792.

Goodman, JE; Prueitt, RL; Boffetta, P; Halsall, C; Sweetman, A. 2020."'Good Epidemiology Practice' guidelines for pesticide exposure assessment." *Int. J. Environ. Res. Public Health* 17(14):E5114. doi: 10.3390/ijerph17145114.

Cox, LA Jr.; Goodman, JE; Engel, AM. 2020. "Chronic Inflammation, Adverse Outcome Pathways, and Risk Assessment: A Diagrammatic Exposition." *Regul. Toxicol. Pharmacol.* 114:104663. doi: 10.1016/j.yrtph.2020.104663.

Goodman, JE; Kerper, LE; Prueitt, RL; Marsh, CM. 2020. "A Critical Review of Talc and Ovarian Cancer." *J. Toxicol. Environ. Health B*. 23(5):183-213. doi: 10.1080/10937404.2020.1755402.

Goodman, JE; Prueitt, RL; Harbison, RD; Johnson, GT. 2020. "Systematically Evaluating and Integrating Evidence in National Ambient Air Quality Standards Reviews." *Glob. Epidemiol.* 2:100019. doi: 10.1016/j.gloepi.2020.100019.

Goodman, JE; Mayfield, DB; Becker, RA; Hartigan, SB; Erraguntla, NK. 2020. "Recommendations for Further Revisions to Improve the International Agency for Research on Cancer (IARC) Monograph Program." *Regul. Toxicol. Pharmacol.* 113:104639. doi: 10.1016/j.yrtph.2020.104639.

Lynch, HN; Prueitt, RL; Goodman, JE. 2018. "Critique of the ACGIH 2016 Derivation of Toluene Diisocyanate Threshold Limit Values." *Regul. Toxicol. Pharmacol.* 97:189-196. doi: 10.1016/j.yrtph.2018.06.017.

Zu, K; Shi, L; Prueitt, RL; Liu, X; Goodman, JE. 2018. "Critical Review of Long-term Ozone Exposure and Asthma Development." *Inhal. Toxicol.* 30(3):99-113. doi: 10.1080/08958378.2018.1455772.

Goodman, JE; Lynch, HN; Rhomberg, LR. 2018. "Letter to the Editor re: Guyton et al. (2018), 'Application of the Key Characteristics of Carcinogens in Cancer Hazard Identification'." *Carcinogenesis* 39(8):1089-1090. doi: 10.1093/carcin/bgy066.

Goodman, JE; Zu, K; Loftus, CT; Lynch, HN; Prueitt, RL; Mohar, I; Shubin, SP; Sax, SN. 2018. "Short-term Ozone Exposure and Asthma Severity: Weight-of-evidence Analysis." *Environ. Res.* 160:391-397. doi: 10.1016/j.envres.2017.10.018.

Pedroso, FE; Angriman, FA; Endo, A; Dasenbrock, H; Storino, A; Castillo, R; Watkins, AA; Castillo-Angeles, M; Goodman, JE; Zitzman, MD. 2018. "Weight Loss after Bariatric Surgery in Obese Adolescents: A Systematic Review and Meta-analysis." *Surg. Obes. Relat. Dis.* 14 (3):413-422. doi: 10.1016/j.soard.2017.10.003.

Prueitt, RL; Lynch, HN; Zu, K; Shi, L; Goodman, JE. 2017. "Dermal Exposure to Toluene Diisocyanate and Respiratory Cancer Risk." *Environ. Int.* 109:181-192. doi:10.1016/j.envint.2017.09.017.

Cox, LA; Liu, X; Shi, L; Zu, K; Goodman, JE. 2017. "Applying Nonparametric Methods to Analyses of Short-term Fine Particulate Matter Exposure and Hospital Admissions for Cardiovascular Diseases among Older Adults." *Int. J. Environ. Res. Public Health* 14 (9):1051. doi: 10.3390/ijerph14091051.

Goodman, JE; Zu, K; Loftus, CT; Tao, G; Liu, X; Lange, SS. 2017. "Ambient Ozone and Asthma Hospital Admissions in Texas: A Time-series Analysis." *Asthma Res. Pract.* 3:6. doi: 10.1186/s40733-017-0034-1.

Goodman, JE; Kennedy, EM; Seeley, MR. 2017. "Do Individuals with Asthma Experience Airway Hyper-responsiveness After Exposure to Nitrogen Dioxide?" *Regul. Toxicol. Pharmacol.* 89:279-287. doi: 10.1016/j.yrtph.2017.07.021.

Zu, K; Pizzurro, DM; Lewandowski, TA; Goodman, JE. 2017. "Pharmacokinetic Data Reduce Uncertainty in the Acceptable Daily Intake for Benzoic Acid and Its Salts." *Regul. Toxicol. Pharmacol.* 89:83-94. doi: 10.1016/j.yrtph.2017.07.012

Goodman, JE; Loftus, CT; Liu, X; Zu, K. 2017. "Impact of Respiratory Infections, Outdoor Pollen, and Socioeconomic Status on Associations between Air Pollutants and Pediatric Asthma Hospital Admissions." *PLoS ONE* 12(7). doi: doi.org/10.1371/journal.pone.0180522. e0180522.

Bailey, LA; Kerper, LE; Goodman, JE. 2017. "Derivation of an Occupational Exposure Level for Manganese in Welding Fumes." *Neurotoxicology* doi: 10.1016/j.neuro.2017.06.009.

Zu, K; Liu, X; Shi, L; Tao, G; Loftus, CT; Lange, SS; Goodman, JE. 2017. "Concentration-response of Short-term Ozone Exposure and Hospital Admissions for Asthma in Texas." *Environ. Int.* 104:139-145. doi: 10.1016/j.envint.2017.04.006.

Hoffmann, S; de Vries, RBM; Stephens, ML; Beck, NB; Dirven, HAAM; Fowle, JR III; Goodman, JE; Hartung, T; Kimber, I; Lalu, MM; Thayer, K; Whaley, P; Wikoff, D; Tsaioun, K. 2017. "A Primer on Systematic Reviews in Toxicology." *Arch. Toxicol.* doi: 10.1007/s00204-017-1980-3.

Goodman, JE; Peterson, MK; Hixon, ML; Shubin, SP. 2017. "Derivation of an Oral Maximum Allowable Dose Level for Bisphenol A." *Regul. Toxicol. Pharmacol.* 86:312-318. doi: 10.1016/j.yrtph.2017.03.024.

Lynch, HN; Goodman, JE; Beck, NB. 2017. "More Clarity Needed in the Navigation Guide Systematic Review Framework (Letter)." *Environ. Int.* doi: 10.1016/j.envint.2017.01.011.

Goodman, JE; Loftus, CT; Zu, K. 2017. "2,4-Dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma: Results from the Agricultural Health Study and an Updated Meta-analysis." *Ann. Epidemiol.* doi: 10:1016/j.annepidem.2017.01.008.

Goodman, JE; Lynch, HN. 2017. "Improving the International Agency for Research on Cancer's Consideration of Mechanistic Evidence." *Toxicol. Appl. Pharmacol.* 319:39-46. doi: 10.1016/j.taap.2017.01.020.

Goodman, JE; Zu, K; Loftus, CT; Prueitt, R. 2017. "Letter to the Editor re: Dermal TDI Exposure is not Associated with Lung Cancer Risk." *Am. J. Ind. Med.* 60(2):221-222. doi: 10.1002/ajim.22677.

Lynch, HN; Loftus; CT; Cohen, JM; Kerper, LE; Kennedy, EM; Goodman, JE. 2016. "Weight-of-evidence Evaluation of Associations between Particulate Matter Exposure and Biomarkers of Lung Cancer." *Regul. Toxicol. Pharmacol.* 82: 53-93. doi:10.1016/j.yrtph.2016.10.006.

Prueitt, RL; Rhomberg, LR; Guan, N; Goodman, JE. 2016. "Evaluation of the Human Carcinogenicity of Toluene Diisocyanate." *Asian J. Ecotoxicol.* doi: 10.7524/AJE.1673-5897.20160112001.

Prueitt, RL; Goodman, JE. 2016. "Evaluation of Neural Reflex Activation as a Mode of Action for the Acute Respiratory Effects of Ozone." *Inhal. Toxicol.* 28(11):484-499. doi: 10.1080/08958378.2016.1213332.

Zu, K; Tao, G; Goodman, JE. 2016. "Pleural Plaques and Lung Function in the Marysville Worker Cohort: A Re-analysis." *Inhal. Toxicol.* 28(11):514-519. doi: 10.1080/08958378.2016.1210704.

Goodman, JE; Zu, K; Tao, G; Kerper, LE. 2016. "Comment on 'Exposure-response Modeling of Non-cancer Effects in Humans Exposed to Libby Amphibole Asbestos; Update' by Benson *et al.* (2015) (Letter)." *Regul. Toxicol. Pharmacol.* doi: 10.1016/j.yrtph.2016.05.014.

Rhomberg, LR; Goodman, JE; Tao, G; Zu, Ke; Chandalia, J; Williams, PRD; Allen, B. 2016. "Evaluation of Acute Non-lymphocytic Leukemia and its Subtypes with Updated Benzene Exposure and Mortality Estimates: A Lifetable Analysis of the Pliofilm Cohort." *J. Occup. Environ. Med.* 58(4):414-20. doi: 10.1097/JOM.0000000000000689.

Lynch, HN; Goodman, JE; Tabony, JA; Rhomberg, LR. 2016. "Systematic Comparison of Study Quality Criteria." *Regul. Toxicol. Pharmacol.* doi: 10.1016/j.yrtph.2015.12.017.

Cox, LA; Goodman, JE. 2016. "Letter to the Editor re: Estimating Causal Associations of Fine Particles with Daily Deaths in Boston." *Am. J. Epidemiol.* doi: 10.1093/aje/kww023.

Lamb, JC IV; Boffetta, P; Foster, WG; Goodman, JE; Hentz, KL; Rhomberg, LR; Staveley, J; Swaen, G; Van Der Kraak, G; Williams, AL. 2015. "Comments on the Opinions Published by Bergman *et al.* (2015) on 'Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals' (Lamb *et al*. 2014)." *Regul. Toxicol. Pharmacol*. 73(3):754-7. doi: 10.1016/j.yrtph.2015.10.029.

Prueitt, RL; Cohen, JM; Goodman, JE. 2015. "Evaluation of Atherosclerosis as a Potential Mode of Action for Cardiovascular Effects of Particulate Matter." *Regul. Toxicol. Pharmacol.* 73(Suppl. 2):S1-S15. doi: 10.1016/j.yrtph.2015.09.034.

Rhomberg, LR; Mayfield, DB; Goodman, JE; Butler, EL; Nascarella, MA; Williams, DR. 2015. "Quantitative Cancer Risk Assessment for Occupational Exposures to Asphalt Fumes During Built-up Roofing Asphalt (BURA) Operations." *Crit. Rev. Toxicol*. 45(10):873-918. doi: 10.3109/10408444.2015.1094450.

Goodman, JE; Loftus, CT; Zu, K. 2015. "2,4-Dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma, Gastric Cancer, and Prostate Cancer: Meta-analyses of the Published Literature." *Ann. Epidemiol.* 25(8):626-636.e4. doi: 10.1016/j.annepidem.2015.04.002.

Tao, G; Zu, K; Kerper, LE; Goodman, JE. 2015. "Comment on 'HRCT/CT and Associated Spirometric Effects of Low Libby Amphibole Asbestos Exposure' by Lockey *et al*. (2015)." *J. Occup. Environ. Med.* 57(7):e80. doi: 10.1097/JOM.0000000000000463.

Goodman, JE; Petito Boyce, C; Sax, SN; Beyer, LA; Prueitt, RL. 2015. "Rethinking Meta-analysis: Applications for Air Pollution Data and Beyond." *Risk Anal.* 35(6):1017-1039. doi: 10.1111/risa.12405.

Goodman, JE; Prueitt, RL; Sax, SN; Pizzurro, DM; Lynch, HN; Zu, K; Venditti, FJ. 2015. "Ozone Exposure and Systemic Biomarkers: Evaluation of Evidence for Adverse Cardiovascular Health Impacts." *Crit. Rev. Toxicol.* 45(5):412-452. doi: 10.3109/10408444.2015.1031371.

Goodman, JE; Kerper, LE; Zu, K; Lynch, HN; Tao, G. 2015. "Comment on 'A Systematic Review of the Association Between Pleural Plaques and Changes in Lung Function' by Kopylev *et al* (2014)." *Occup. Environ. Med*. 72(9):684-685. doi: 10.1136/oemed-2015-102894.

Goodman, JE; Sax, SN; Lange, S; Rhomberg, LR. 2015. "Are the Elements of the Proposed Ozone National Ambient Air Quality Standards Informed by the Best Available Science?" *Regul. Toxicol. Pharmacol.* 72(1):134-140. doi: 10.1016/j.yrtph.2015.04.001.

Petito Boyce, C; Goodman, JE; Sax, SN; Loftus, CT. 2015. "Providing Perspective for Interpreting Cardiovascular Mortality Risks Associated with Ozone Exposures." *Regul. Toxicol. Pharmacol.* 72(1):107-116. doi: 10.1016/j.yrtph.2015.03.009.

Zu, K; Tao, G; Long, CM; Goodman, JE; Valberg, PA. 2015. "Long-range Fine Particulate Matter from the 2002 Quebec Forest Fires and Daily Mortality in Greater Boston and New York City." *Air Qual. Atmos. Health.* doi: 10.1007/s11869-015-0332-9.

Goodman, JE; Seeley, MR; Mattuck, RL; Thakali, S. 2015. "Do Group Responses Mask the Effects of Air Pollutants on Potentially Sensitive Individuals in Controlled Human Exposure Studies?" *Regul. Toxicol. Pharmacol.* 71(3):552-564. doi: 10.1016/j.yrtph.2015.02.002.

Clark, K; Flynn, J; Goodman, JE; Zu, K; Karmaus, W; Mohr, L. 2015. "A Response to Comments by Noonan re: 'Pleural Plaques and their Effect on Lung Function in Libby Vermiculite Miners' (Letter)." *Chest* 147(3):e124-e126. doi: 10.1378/chest.14-3041.

Clark, K; Flynn, J; Goodman, JE; Zu, K; Karmaus, W; Mohr, L. 2015. "A Response to Comments by Miller re: 'Pleural Plaques and Their Effect on Lung Function in Libby Vermiculite Miners' (Letter)." *Chest* 147(3):e128-e129. doi: 10.1378/chest.14-2635.

Kerper, LE; Lynch, HN; Zu, K; Tao, G; Utell, MJ; Goodman, JE. 2015. "Systematic Review of Pleural Plaques and Lung Function." *Inhal. Toxicol.* 27(1):15-44. doi: 10.3109/08958378.2014.981349.

Goodman, JE; Prueitt, RL; Sax, SN; Lynch, HN; Zu, K; Lemay, JC; King, JM; Venditti, FJ. 2014. "Weight-of-evidence Evaluation of Short-term Ozone Exposure and Cardiovascular Effects." *Crit. Rev. Toxicol.* 44(9):725-790. doi: 10.3109/10408444.2014.937854.

Prueitt, RL; Lynch, HN; Zu, K; Sax, SN; Venditti, FJ; Goodman, JE. 2014. "Weight-of-evidence Evaluation of Long-term Ozone Exposure and Cardiovascular Effects." *Crit. Rev. Toxicol.* 44(9):791-822. doi: 10.3109/10408444.2014.937855.

Lamb, JC; Boffetta, P; Foster, WG; Goodman, JE; Hentz, KL; Rhomberg, LR; Staveley, J; Swaen, G; Van Der Kraak, G; Williams, AL. 2014. "Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals – 2012." *Regul. Toxicol. Pharmacol.* 69(1):22-40. doi: 10.1016/j.yrtph.2014.02.002.

Keum, N; Woong, J; Hoon Lee, DH; Ding, EL; Hsieh, CC; Goodman, JE; Giovannucci, EL. 2014. "Leisure-time Physical Activity and Endometrial Cancer Risk: Dose-response Meta-analysis of Epidemiological Studies." *Int. J. Cancer* 135(3):682-94. doi: 10.1002/ijc.28687.

Clark, KA; Flynn, JJ III; Goodman, JE; Zu, K; Karmaus, WJJ; Mohr, LC. 2014. "Pleural Plaques and Their Effect on Lung Function in Libby Vermiculite Miners." *Chest* 146(3):786-794. doi: 10.1378/chest.14-0043.

Goodman, JE; Prueitt, RL; Chandalia, J; Sax, SN. 2014. "Evaluation of Adverse Human Lung Function Effects in Controlled Ozone Exposure Studies." *J. Appl. Toxicol.* 34(5):516-524. doi: 10.1002/jat.2905.

Beck, NB; Becker, RA; Boobis, A; Fergusson, D; Fowle III, JR; Goodman, JE; Hoffmann, S; Lalu, M; Leist, M; Stephens, ML. 2014. "Instruments for Assessing Risk of Bias and Other Methodological Criteria of Animal Studies: Omission of Well-established Methods (Letter)." *Environ. Health Perspect.* 122(3):A66-A67. doi: 10.1289/ehp.1307727.

Ryan, BM; Zanetti KA; Robles, AI; Schetter, AJ; Goodman, JE; Hayes, RB; Huang, WY; Gunter, MJ; Yeager, M; Burdette, L; Berndt, SI; Harris CC. 2014. "Germline Variation in NCF4, an Innate Immunity Gene, is Associated with an Increased Risk of Colorectal Cancer." *Int. J. Cancer* 134(6):1399-1407. doi: 10.1002/ijc.28457.

Sax, SN; Goodman JE. 2014. "Residential Air Pollution and Lung Cancer Risk (Letter)." *Epidemiology* 25(1):159. doi: 10.1097/EDE.0000000000000011.

Goodman, JE; Petito Boyce, C; Pizzurro, DM; Rhomberg, LR. 2014. "Strengthening the Foundation of Next Generation Risk Assessment." *Regul. Toxicol. Pharmacol*. 68(1):160-170. doi: 10.1016/j.yrtph.2013.12.002.

Goodman, JE; Peterson, MK; Bailey, LA; Kerper, LE; Dodge, DG. 2014. "Electricians' Chrysotile Asbestos Exposure from Electrical Products and Risks of Mesothelioma and Lung Cancer." *Regul. Toxicol. Pharmacol.* 68(1):8-15. doi: 10.1016/j.yrtph.2013.10.008.

Goodman, JE; Prueitt, RL; Sax, SN; Bailey, LA; Rhomberg, LR. 2013. "Evaluation of the Causal Framework Used for Setting National Ambient Air Quality Standards." *Crit. Rev. Toxicol.* 43(10):829-849. doi: 10.3109/10408444.2013.837864.

Sax, SN; Zu, K; Goodman, JE. 2013. "Air Pollution and Lung Cancer in Europe (Letter)." *Lancet Oncol.* 14(11):e439-e440. doi: 10.1016/S1470-2045(13)70438-8.

Rhomberg, LR; Goodman, JE; Bailey, LA; Prueitt, RL; Beck, NB; Bevan, C; Honeycutt, M; Kaminski, NE; Paoli, G; Pottenger, LH; Scherer, RW; Wise, KC; Becker, RA. 2013. "A Survey of Frameworks for Best Practices in Weight-of-evidence Analyses." *Crit. Rev. Toxicol.* 43(9):753-784. doi: 10.3109/10408444.2013.832727.

Chang, CM; Chia, VM; Gunter, MJ; Zanetti, KA; Ryan, BM; Goodman, JE; Harris, CC; Weissfield, J; Huang, WY; Chanock, S; Yeager, M; Hayes, RB; Berndt, SI; Genetics and Epidemiology of Colorectal Cancer Consortium. 2013. "Innate Immunity Gene Polymorphisms and the Risk of Colorectal Neoplasia." *Carcinogenesis* 34(11):2512-2520. doi: 10.1093/carcin/bgt228.

Yakoob, MY; Bateman, BT; Ho, E; Hernandez-Diaz, S; Franklin JM; Goodman, JE; Hoban, RA. 2013. "The Risk of Congenital Malformations Associated with Exposure to β-blockers Early in Pregnancy: A Meta-analysis." *Hypertension* 62(2):375-381. doi: 10.1161/HYPERTENSIONAHA.111.00833.

Prueitt, RL; Rhomberg, LR; Goodman, JE. 2013. "Hypothesis-based Weight-of-evidence Evaluation of the Human Carcinogenicity of Toluene Diisocyanate." *Crit. Rev. Toxicol.* 43(5):391-435. doi: 10.3109/10408444.2013.790877.

Sax, SN; Goodman, JE. 2013. "Re: 'Is the Relation Between Ozone and Mortality Confounded by Chemical Components of Particulate Matter? Analysis of 7 Components in 57 US Communities.' (Letter)." *Am. J. Epidemiol.* 177(12):1460. doi: 10.1093/aje/kwt081.

Goodman, JE; Sax, SN. 2013. "Letter by Goodman and Sax Regarding Article, 'Controlled Exposure of Healthy Young Volunteers to Ozone Causes Cardiovascular Effects.'" *Circulation* 127(4):e432. doi: 10.1161/CIRCULATIONAHA.112.133249.

Goodman, JE; Prueitt, RL; Rhomberg, LR. 2013. "Incorporating Low-dose Epidemiology Data in a Chlorpyrifos Risk Assessment." *Dose Response* 11(2):207-219. doi: 10.2203/doseresponse.12022.

Rhomberg, LR; Goodman, JE; Prueitt, RL. 2013. "The Weight of Evidence Does Not Support the Listing of Styrene as 'Reasonably Anticipated to be a Human Carcinogen' in NTP's Twelfth Report on Carcinogens." *Hum. Ecol. Risk. Assess*. 19(1):4-27. doi: 10.1080/10807039.2012.650577.

Rhomberg, LR; Goodman, JE. 2012. "Low-dose Effects and Nonmonotonic Dose-responses of Endocrine Disrupting Chemicals: Has the Case Been Made?" *Reg. Tox. Pharmacol.* 64(1):130-133. doi: 10.1016/j.yrtph.2012.06.015.

Hajifathalian, K; Gonzalez-Gonzalez LA; Zacharias, DG; Goodman, JE. 2012. "A Meta-analysis of Human Acellular Dermis and Submuscular Tissue Expander Breast Reconstruction (Letter)." *Plast. Reconstr. Surg*. 130(6):896e. doi: 10.1097/PRS.0b013e31826d9e2e.

Rhomberg, LR; Goodman, JE; Foster, WG; Borgert, CJ; Van Der Kraak, G. 2012. "A Critique of the European Commission Document, 'State of the Art Assessment of Endocrine Disrupters.'" *Crit. Rev. Toxicol*. 42(6):465-473. doi: 10.3109/10408444.2012.690367.

Zanetti, KA; Haznadar, M; Welsh, JA; Robles, AI; Ryan, BM; McClary, AC; Bowman, ED; Goodman, JE; Bernig, T; Chanock, SJ; Harris, CC. 2012. "3' UTR and Functional Secretor Haplotypes in Mannose-binding Lectin 2 Are Associated with Increased Colon Cancer Risk in African Americans." *Cancer Res.* 72(6):1467-1477. doi: 10.1158/0008-5472.CAN-11-3073.

Tippin, BL; Levine, AJ; Materi, AM; Song, WL; Keku, TO; Goodman, JE; Sansbury, LB; Das, S; Dai, A; Kwong, AM; Lin, AM; Lin, JM; Park, JM; Patterson, RE; Chlebowski, RT; Garavito, RM; Inoue, T; Cho, W; Lawson, JA; Kapoor, S; Kolonel, LN; Le Marchand, L; Haile, RW; Sandler, RS; Lin, HJ. 2012. "Hematopoietic Prostaglandin D Synthase (HPGDS): A High Stability, Val187Ile Isoenzyme Common Among African Americans and its Relationship to Risk for Colorectal Cancer." *Prostaglandins Other Lipid Mediat.* 97(1-2):22-28. doi: 10.1016/j.prostaglandins.2011.07.006.

Prueitt, RL; Goodman, JE; Bailey, LA; Rhomberg, LR. 2011. "Hypothesis-based Weight-of-evidence Evaluation of the Neurodevelopmental Effects of Chlorpyrifos." *Crit. Rev. Toxicol.* 41(10):822-903. doi: 10.3109/10408444.2011.616877.

Rhomberg, LR; Chandalia, JK; Long, CM; Goodman, JE. 2011. "Measurement Error in Environmental Epidemiology and the Shape of Exposure-response Curves." *Crit. Rev. Toxicol.* 41(8):651-671. doi: 10.3109/10408444.2011.563420.

Rhomberg, LR; Bailey, LA; Goodman, JE; Hamade, AK; Mayfield, DB. 2011. "Is Exposure to Formaldehyde in Air Causally Associated with Leukemia? – A Hypothesis-based Weight-of-evidence Analysis." *Crit. Rev. Toxicol.* 41(7):555-621. doi: 10.3109/10408444.2011.560140.

Prueitt, RL; Goodman, JE. 2011. "The Global Burden of Ozone on Respiratory Mortality: No Clear Evidence for Association (Letter)." *Environ. Health Perspect.* 119(4):A158. doi: 10.1289/ehp.1003276.

Goodman, JE; Prueitt, RL; Thakali, S; Oller, AR. 2011. "The Nickel Ion Bioavailability Model of the Carcinogenic Potential of Nickel-containing Substances in the Lung." *Crit. Rev. Toxicol.* 41(2):142-174. doi: 10.3109/10408444.2010.531460.

Rhomberg, LR; Goodman, JE; Haber, LT; Dourson, M; Andersen, ME; Klaunig, JE; Meek, B; Price, PS; McClellan, RO; Cohen, SM. 2011. "Linear Low-dose Extrapolation for Noncancer Health Effects is the Exception, Not the Rule." *Crit. Rev. Toxicol*. 41(1):1-19. doi: 10.3109/10408444.2010.536524.

Goodman, JE. 2011. "Nickel Metal Not Associated with Lung Cancer Risk (Letter)." *Am. J. Ind. Med.* 54(5):419. doi: 10.1002/ajim.20908.

Goodman, JE; Kerper, LE; Petito Boyce, C; Prueitt, RL; Rhomberg LR. 2010. "Weight-of-evidence Analysis of Human Exposures to Dioxins and Dioxin-like Compounds and Associations with Thyroid Hormone Levels During Early Development." *Regul. Toxicol. Pharmacol.* 58(1):79-99. doi: 10.1016/j.yrtph.2010.04.008.

Goodman, JE; Hudson, TC; Monteiro, RJ. 2010. "Cancer Cluster Investigation in Residents near a Municipal Landfill." *Hum. Ecol. Risk Assess.* 16(6):1339-1359. doi: 10.1080/10807039.2010.526504.

Goodman, JE; Kerper, LE; Johnson, GT; Harbison, RD; Cordero, R; Lee, RV; Pulde, MF; Hardy, M; Stedeford, T. 2010. "(PBDE) Flame Retardants and Thyroid Hormones during Pregnancy (Letter)." *Environ. Health Perspect.* 118(12):A520. doi: 10.1289/ehp.1002782.

Goodman, JE; Johnson, GT; Harbison, HD; Lee, RE; Pulde, MF; Hardy, M; Stedeford, T. 2010. "Prenatal PBDEs and Neurodevelopment: Accuracy of Assessment (Letter)." *Environ. Health Perspect.* 118:A468-A469.

Glynn, SA; Prueitt, RL; Ridnour, LA; Boersma, BJ; Dorsey, TM; Wink, DA; Goodman, JE; Yfantis, HG; Lee, DH; Ambs, S. 2010. "COX-2 Activation Is Associated with Akt Phosphorylation and Poor Survival in ER-negative, HER2-positive Breast Cancer." *BMC Cancer* 10:626. doi: 10.1186/1471-2407-10-626.

Rhomberg, LR; Bailey, LA; Goodman JE. 2010. "Hypothesis-based Weight of Evidence: A Tool for Evaluating and Communicating Uncertainties and Inconsistencies in the Large Body of Evidence in Proposing a Carcinogenic Mode of Action – Naphthalene as an Example." *Crit. Rev. Toxicol.* 40:671-696. doi: 10.3109/10408444.2010.499504.

Goodman, JE; Dodge, DG; Bailey, LA. 2010. "A Framework for Assessing Causality and Adverse Effects in Humans with a Case Study of Sulfur Dioxide." *Regul. Toxicol. Pharmacol.* 58:308-322. doi: 10.1016/j.yrtph.2010.07.002.

Goodman, JE; Biesemeier, JA; Johnson, GT; Harbison, C; Zhu, Y; Lee, RV; Harbison, RD; Silberberg, H; Hardy, M; Stedeford, T. 2010. "Fecundability and Serum PBDE Concentrations in Women (Letter)." *Environ. Health Perspect.* 118(8):A330. doi: 10.1289/ehp.1002283.

Bailey, LA; Goodman, JE; Beck, BD. 2009. "Proposal for a Revised Reference Concentration (RfC) for Manganese Based on Recent Epidemiological Studies." *Regul. Toxicol. Pharmacol.* 55(3):330-339. doi: 10.1016/j.yrtph.2009.08.005.

Glynn, SA; Boersma, BJ; Howe, TM; Edvardsen, H; Geisler, SB; Goodman, JE; Ridnour, LA; Lonning, PE; Borresen-Dale, AL; Naume, B; Kristensen, VN; Chanock, SJ; Wink, DA; Ambs, S. 2009. "A Mitochondrial Target Sequence Polymorphism in Manganese Superoxide Dismutase Predicts Inferior Survival in Breast Cancer Patients Treated with Cyclophosphamide." *Clin. Cancer Res.* 15(12):4165-4173. doi: 10.1158/1078-0432.CCR-09-0119.

Petito Boyce, C; Sax, SN; Dodge, DG; Pollock, MC; Goodman, JE. 2009. "Human Exposure to Decabromodiphenyl Ether, Tetrabromobisphenol A, and Decabromodiphenyl Ethane in Indoor Dust." *J. Environ. Protect. Sci.* 3:75-96.

Dodge, DG; Pollock, MC; Petito Boyce, C; Goodman, JE. 2009. "Review of Brominated and Halogen-free Flame Retardant Levels in Indoor Dust." *J. Environ. Protect. Sci.* 3:58-74.

Goodman, JE; Chandalia, JK; Thakali, S; Seeley, M. 2009. "Meta-analysis of Nitrogen Dioxide Exposure and Airway Hyper-responsiveness in Asthmatics." *Crit. Rev. Toxicol.* 39(9):719-742. doi: 10.3109/10408440903283641.

Goodman, JE; Nascarella, MA; Valberg, PA. 2009. "Ionizing Radiation: A Risk Factor for Mesothelioma." *Cancer Causes Control* 20:1237-1254. doi: 10.1007/s10552-009-9357-4.

Goodman, JE. 2009. "Neurodevelopmental Effects of Decabromodiphenyl Ether (BDE-209) and Implications for the Reference Dose." *Toxicol. Appl. Pharmacol.* 54(1):91-104. doi: 10.1016/j.yrtph.2009.02.006.

Goodman, JE; Prueitt, RL; Dodge, DG; Thakali, S. 2009. "Carcinogenicity Assessment of Water-soluble Nickel Compounds." *Crit. Rev. Toxicol.* 39(5):365-417. doi: 10.1080/10408440902762777.

Prueitt, RL; Goodman, JE; Valberg, PA. 2009. "Radionuclides in Cigarettes May Lead to Carcinogenesis *via* p16INK4a Inactivation." *J. Environ. Radioact.* 100(2):157-161. doi: 10.1016/j.jenvrad.2008.11.008.

Goodman, JE; Beyer, LA; Beck, BD. 2009. "Comment on 'Evaluation of Evidence for Infection as a Mode of Action for Induction of Rat Lymphoma' by Caldwell *et al*. (Letter)." *Environ. Mol. Mutagen.* 50(1):4-5. doi: 10.1002/em.20466.

Goodman, JE; Witorsch, RJ; McConnell, EE; Sipes, IG; Slayton, TM; Yu, CJ; Franz, AM; Rhomberg, LR. 2009. "Weight-of-evidence Evaluation of Reproductive and Developmental Effects of Low Doses of Bisphenol A." *Crit. Rev. Toxicol.* 39(1):1-75. doi: 10.3109/10408440903279946.

Rhomberg, LR; Goodman, JE. 2008. "CERHR Conclusions Would Have Been Strengthened by a More Explicit Weight-of-evidence Analysis." *Birth Defects Res. B: Dev. Reprod. Toxicol.* 83(3):155-156. doi: 10.1002/bdrb.20161.

Aylward, LL; Goodman, JE; Charnley, G; Rhomberg, LR. 2008. "A Margin of Exposure Approach to Assessment of Non-cancer Risks of Dioxins Based on Human Exposure and Response Data." *Environ. Health Perspect.* 116(10):1344-1351. doi: 10.1289/ehp.11514.

Goodman, JE; Gaylor, D; Beyer, LA; Rhomberg, LR; Beck, BD. 2008. "Effects of MTBE on the Reported Incidence of Leydig Cell Tumors in Sprague-Dawley Rats: Range of Possible Poly-3 Results." *Regul. Toxicol. Pharmacol.* 50:273-284. doi: 10.1016/j.yrtph.2007.12.005.

Mechanic, LE; Luke, BT; Goodman, JE; Chanock, SJ; Harris, CC. 2008. "Polymorphism Interaction Analysis (PIA): A Method for Investigating Complex Gene-gene Interactions." *BMC Bioinformatics* 9(1):146. doi: 10.1186/1471-2105-9-146.

Aylward, LL; Charnley, G; Goodman, JE; Rhomberg, LR. 2008. "Comment on 'Chronic Disease and Early Exposure to Air-borne Mixtures. 2. Exposure Assessment' (Letter)." *Environ. Sci. Technol.* 42(6):2201.

Rhomberg, LR; Bowers, TS; Beyer, LA; Goodman, JE. 2008. "Comment on 'Residential and Biological Exposure Assessment of Chemicals from a Wood Treatment Plant' by James Dahlgren *et al*. (Letter)." *Chemosphere* 70(9):1730-1733.

Prueitt, RL; Boersma, BJ; Howe, TM; Goodman, JE; Thomas, DD; Ying, L; Pfiester, CM; Yfantis, HG; Cottrell, JR; Lee, DH; Remaley, AT; Hofseth, LJ; Wink, DA; Ambs, S. 2007. "Inflammation and IGF-I Activate the Akt Pathway in Breast Cancer." *Int. J. Cancer* 120(4):796-805. doi: 10.1002/ijc.22336.

Martin, DN; Boersma, BJ; Howe, TM; Goodman, JE; Mechanic, LE, Chanock, SJ; Ambs, S. 2006. "Association of MTHFR Gene Polymorphisms with Breast Cancer Survival." *BMC Cancer* 6:257.

Goodman, JE; McConnell, EE; Sipes, IG; Witorsch, RJ; Slayton, TM; Yu, CJ; Lewis, AS; Rhomberg, LR. 2006. "An Updated Weight of the Evidence Evaluation of Reproductive and Developmental Effects of Low Doses of Bisphenol A." *Crit. Rev. Toxicol.* 36(5):387-457.

Boersma, BJ; Howe, TM; Goodman, JE; Yfantis, HG; Lee, DH; Chanock, SJ; Ambs, S. 2006. "Association of Breast Cancer Outcome with Status of p53 and MDM2 SNP309." *J. Natl. Cancer Inst.* 98(13):911-919.

Goodman JE; Mechanic, LE; Luke, BT; Ambs, S; Chanock, S; Harris CC. 2006. "Exploring SNP-SNP Interactions and Colon Cancer Risk Using Polymorphism Interaction Analysis." *Int. J. Cancer* 118(7):1790-1797. doi: 10.1002/ijc.21523.

Goodman, JE; Bowman, ED; Chanock, S; Alberg, AJ; Harris, CC. 2004. "Arachidonate Lipoxygenase (ALOX) and Cyclooxygenase (COX) Polymorphisms and Colon Cancer Risk." *Carcinogenesis* 25(12):2467-2472. doi: 10.1093/carcin/bgh260.

Sullivan, AE; Goodman, JE; Silber, PM; Yager, JD. 2004. "Catechol-O-methyltransferase Low Activity Genotype ($COMT^{LL}$) is Associated with Low Levels of COMT Protein in Human Hepatocytes." *Cancer Lett.* 214(2):189-195. doi:10.1016/j.canlet.2004.06.033.

Goodman, JE; Hofseth, LJ; Hussain, SP; Harris, CC. 2004. "Nitric Oxide and P53 in Cancer-prone Chronic Inflammation and Oxyradical Overload Disease." *Environ. Mol. Mutagen.* 44(1):3-9. doi: 10.1002/em.20024.

Yao, J; Li, Y; Chang, M; Wu, H; Yang, X; Goodman, JE; Liu, X; Liu, H; Mesecar, AD; van Breemen, RB; Yager, JD; Bolton, JL. 2003. "Catechol Estrogen 4-hydroxyequilenin Is A Substrate and An Inhibitor of Catechol-O-methyltransferase." *Chem. Res. Toxicol.* 16(5):668-675. doi: 10.1021/tx0340549.

Goodman, JE; Jensen, LT; He, P; Yager, JD. 2002. "Characterization of Human Soluble High and Low Activity Catechol-O-methyltransferase Catalyzed Catechol Estrogen Methylation." *Pharmacogenetics* 12(7):517-528.

Goodman, JE; Lavigne, JA; Wu, K; Helzlsouer, KJ; Strickland, PT; Selhub, J; Yager, JD. 2001. "COMT Genotype, Micronutrients in the Folate Metabolic Pathway and Breast Cancer Risk." *Carcinogenesis* 22(10):1661-1665. doi: 10.1093/carcin/22.10.1661.

Lavigne, JA; Goodman, JE; Fonong, T; Odwin, S; He, P; Roberts, DW; Yager, JD. 2001. "The Effects of Catechol-O-methyltransferase Inhibition on Estrogen Metabolite and Oxidative DNA Damage Levels in Estradiol Treated MCF-7 Cells." *Cancer Res.* 61:7488-7494.

Goodman, JE; Lavigne, JA; Hengstler, JG; Tanner, B; Helzlsouer, KJ; Yager, JD. 2000. "Catechol-O-methyltransferase Polymorphism is Not Associated with Ovarian Cancer Risk." *Cancer Epidemiol. Biomarkers Prev.* 9(12):1373-1376.

Publications – *Book Chapters*

Lynch, HN; Goodman, JE. 2020. "Target sites: Skin." In *Information Resources in Toxicology (Fifth Edition)*. (Ed.: Wexler, P), Elsevier, Amsterdam, Netherlands, p585-588.

Rhomberg, LR; Lewandowski, TA; Pizzurro, DM; Goodman, JE. 2018. "Risk assessment." In *Comprehensive Toxicology (Third Edition). Volume 1: General Principles*. (Ed.: McQueen, CA), Elsevier Ltd., United Kingdom, p473-488.

Goodman, JE; Lemay, JC; Mattuck, RL; Mayfield, DB; Verslycke, TA; Zhang, J; Zu, K. 2016. "Health risk assessment." In *Environmental Science Deskbook (Release #14)*. (Ed.: Conrad, JW Jr.), Thomson Reuters, Eagan, MN, 61p.

Rhomberg, LR; Goodman, JE; Lewandowski, TA. 2014. "Risk assessment." In *Elsevier Reference Module in Biomedical Sciences*. doi:10.1016/B978-0-12-801238-3.01901-2.

Prueitt, RL; Goodman, JE. 2015. "Nickel." In *Hamilton and Hardy's Industrial Toxicology (Sixth Edition)*. (Eds.: Harbison, RD; Bourgeois, MM; Johnson, GT), John Wiley & Sons, Inc., Hoboken, NJ, p173-182.

Dodge, DG; Goodman, JE. 2015. "Perchloroethylene (Tetrachloroethylene)." In *Hamilton and Hardy's Industrial Toxicology (Sixth Edition)*. (Eds.: Harbison, RD; Bourgeois, MM; Johnson, GT), John Wiley & Sons, Inc., Hoboken, NJ, p727-732.

Dodge, DG; Goodman, JE. 2015. "Trichloroethylene." In *Hamilton and Hardy's Industrial Toxicology (Sixth Edition)*. (Eds.: Harbison, RD; Bourgeois, MM; Johnson, GT), John Wiley & Sons, Inc., Hoboken, NJ, p733-740.

Goodman, JE; Rhomberg, LR; Peterson, MK. 2015. "Bisphenol A (4,4'-Isopropylidenediphenol)." In *Hamilton and Hardy's Industrial Toxicology (Sixth Edition)*. (Eds.: Harbison, RD; Bourgeois, MM; Johnson, GT), John Wiley & Sons, Inc., Hoboken, NJ, p795-808.

Beyer, LA; Goodman, JE. 2015. "Polystyrene/Styrene." In *Hamilton and Hardy's Industrial Toxicology (Sixth Edition)*. (Eds.: Harbison, RD; Bourgeois, MM; Johnson, GT), John Wiley & Sons, Inc., Hoboken, NJ, p809-814.

Goodman, JE; Peterson, MK. 2014. "Bisphenol A." In *Encyclopedia of Toxicology (Third Edition) (Volume 1)*. (Ed.: Wexler, P), Elsevier Inc., Academic Press, p378-380.

Rhomberg, LR; Seeley, M; Verslycke, T; Goodman, JE. 2014. "Environmental hormone disruptors." In *Encyclopedia of Toxicology (Third Edition) (Volume 2)*. (Ed.: Wexler, P), Elsevier Inc., Academic Press, p514–518.

Rhomberg, LR; Goodman, JE; Lewandowski, TA. 2010. "Risk assessment." In *Comprehensive Toxicology, Second Edition, Volume 1: General Principles*. (Ed.: Bond, J), Elsevier Ltd., United Kingdom, p447-464.

Goodman, JE; Yu, CJ. 2009. "Target sites: Skin." In *Information Resources in Toxicology (Fourth Edition)*. (Ed.: Wexler, P), Elsevier, Amsterdam, Netherlands, p481-484.

Goodman, JE; Rhomberg, LR. 2009. "Bisphenol A." In *Endocrine Disrupting Chemicals in Food.* (Ed.: Shaw, I), Woodhead Publishing, Cambridge, United Kingdom, p406-436.

Publications – *Abstracts and Posters*

Boon, DN; Goodman, JE; Colonna, KJ; Espira, LM; Prueitt, RL. 2024. "A Systematic Review of Talc and Cancer Epidemiology Evidence." Presented at the Society for Risk Analysis (SRA) Annual Meeting, Austin, TX, December 8-12.

Boon, DN; Colonna, KJ; Espira, LM; Prueitt, RL; Goodman, JE. 2024. "A Systematic Review of Exposure Assessment Quality in Epidemiology Studies Evaluating Talc and Cancer." Poster #828. Presented at the ISES Annual Meeting, Montreal, Quebec, October 20-24.

Rege, S; Lewis, RJ; Li, A; Goodman, J. 2024. "Risk of Bias in Air Pollution Epidemiology." ISEE Conf. Abstr.doi: 10.1289/isee.2024.1879. Presented at ISEE 2024: 36th Annual Conference of the International Society of Environmental Epidemiology, Santiago, Chile, August 25-28.

Hixon, ML; Prueitt, RL; Goodman, JE. 2024. "Critical Analysis of Sperm Parameter Data Used as the Basis for a Tolerable Daily Intake for Bisphenol A." Abstract/Poster #:3867/P375. Presented at the Society of Toxicology (SOT) 63rd Annual Meeting and ToxExpo, Salt Lake City, UT, March 10-14.

Prueitt, RL; Hixon, ML; Goodman, JE. 2024. "Critical Evaluation of Immunotoxicity Data Used as the Basis for a Tolerable Daily Intake for Bisphenol A." Abstract/Poster #:3655/P156. Presented at the Society of Toxicology (SOT) 63rd Annual Meeting and ToxExpo, Salt Lake City, UT, March 10-14.

Goodman, JE; Boon, D; Espira, LM. 2023. "The Impact of Recall and Selection Bias on the Association Between Talc and Ovarian Cancer in Case-Control Studies." Presented at the International Conference on Using Epidemiological Studies in Health Risk Assessments, Berlin, Germany, November 9-10.

Boon, DN; Khandaker, A; Annesar, EG; Goodman, JE. 2023. "Epidemiology Study Quality Evaluation in a Systematic Review of Aspartame and Cancer Evidence." Poster #LP-61. Presented at the EUROTOX Congress 2023, Ljubljana, Slovenia, September 10-13.

Ticknor, RC; Zhou, J; Goodman, JE. 2022. "Systematic Review of Perchloroethylene and Non-Hodgkin's Lymphoma." Poster # 3928/P607. Presented at the Society of Toxicology (SOT) 61st Annual Meeting & ToxExpo, held March 27-31.

Prueitt, RL; Li, W; Zhou, J; Goodman, JE. 2021. "Systematic Review of the Association Between Long-Term Exposure to Ambient Fine Particulate Matter and Mortality." Abstract/Poster: 2304/P180. Presented at the Society of Toxicology (SOT) 60th Annual Meeting & ToxExpo, held virtually March 21-26.

Prueitt, RL; Li, AW; Chang, RY; Goodman, JE. 2020. "Systematic Review of the Potential Respiratory Carcinogenicity of Metallic Nickel in Humans." Poster # 1516/P617. Prepared for presentation at the Society of Toxicology (SOT) 59th Annual Meeting & ToxExpo, Anaheim, CA, March 15-19 (Conference cancelled).

Boomhower, SR; Goodman, JE; Li, AW; Long, CM. 2020. "A Systematic Review and Analysis of Personal and Ambient $PM_{2.5}$ Measurements: Implications for Epidemiological Studies." Poster # 1135/P177. Prepared for presentation at the Society of Toxicology (SOT) 59th Annual Meeting & ToxExpo, Anaheim, CA, March 15-19 (Conference cancelled).

Goodman, JE; Li, AW. 2020. "Using Causal Methods to Assess Whether Reductions in $PM_{2.5}$ Result in Decreased Mortality." 5p. Prepared for presentation at the Health Effects Institute (HEI)'s 2020 Annual Conference, Boston, MA, April 5-7 (Conference cancelled).

Zu, K; Goodman, JE; Prueitt, RL. 2019. "Strengthening the Evaluation of Mechanistic Evidence Categorized by the IARC 10 Key Characteristics of Carcinogens." Presented at the National Academies of Sciences, Engineering, and Medicine (NASEM) Evidence Integration Workshop, Washington, DC, June 3-4.

Goodman, JE; Johnson, G; Prueitt, RL; Zu, K. 2019. "Systematically Evaluating and Integrating Evidence in National Ambient Air Quality Standards (NAAQS) Reviews." Presented at the National Academies of Sciences, Engineering, and Medicine (NASEM) Evidence Integration Workshop, Washington, DC, June 3-4.

Zu, K; Goodman, JE; Prueitt, RL. 2019. "Evaluating Mechanistic Evidence: Beyond the IARC 10 Key Characteristic Framework for Carcinogens." Presented at the National Toxicology Program (NTP) Workshop: Converging on Cancer, Washington, DC, April 29-30.

Goodman, JE; Johnson, G; Prueitt, RL; Zu, K. 2019. "Systematically Evaluating and Integrating Evidence on Cancer in National Ambient Air Quality Standards (NAAQS) Reviews." Presented at the National Toxicology Program (NTP) Workshop: Converging on Cancer, Washington, DC, April 29-30.

Goodman, JE; Pizzurro, DM; Lemay, JC; Lewandowski, T; Zu, K. 2018. "Use of Chemical-specific Adjustment Factors in Health Risk Assessments: A Tale of Two Preservatives." Poster #175/OP02-04. Presented at EUROTOX 2018, Brussels, Belgium, September 2-5.

Prueitt, RL; Lynch, HN; Mohar, I; Goodman, JE. 2018. "Critical Evaluation of Threshold for Respiratory Effects of Toluene Diisocyanate." Poster #701/P19-27. Presented at EUROTOX 2018, Brussels, Belgium, September 2-5.

Goodman, JE; Peterson, MK; Hixon, ML; Pacheco Shubin, S. 2018. "Derivation of a Maximum Allowable Dose Level for Bisphenol A." Poster #2903/P429. Presented at the Society of Toxicology (SOT) 57th Annual Meeting, San Antonio, TX, March 11-15.

Lynch, HN; Goodman, JE; Prueitt, RL; Mohar, I. 2018. "Critical Evaluation of Thresholds for Respiratory Effects of Toluene Diisocyanate." Poster #1197/P248. Presented at the Society of Toxicology (SOT) 57th Annual Meeting, San Antonio, TX, March 11-15.

Prueitt, RL; Lynch, HN; Zu, K; Shi, L; Goodman, JE. 2018. "Evaluation of Respiratory Cancer Risk from Dermal Exposure to Toluene Diisocyanate." Poster #2820/P343. Presented at the Society of Toxicology (SOT) 57th Annual Meeting, San Antonio, TX, March 11-15.

Liu, X; Zu, K; Lam, T; Goodman, JE. 2018. "Systematic Review and Meta-analysis of Diazepam and Labor Duration." Poster #1876/P207. Presented at the Society of Toxicology (SOT) 57th Annual Meeting, San Antonio, TX, March 11-15.

Zu, K; Goodman, JE; Pizzurro, DM; Lewandowski, TA. 2018. "Use of Clinical Data to Inform Risk Assessments of Food Additives: A Case Study of Sodium Benzoate." Poster #2847/P370. Presented at the Society of Toxicology (SOT) 57th Annual Meeting, San Antonio, TX, March 11-15.

Goodman, JE; Lynch, HN; Prueitt, RL; Mohar, I. 2017. "Evaluation of ACGIH TLVs for Toluene Diisocyanate." Poster #P.178. Presented at the Society for Risk Analysis (SRA) Annual Meeting, Arlington, VA, December 10-14.

Pizzurro, DM; Zu, K; Lewandowski, TA; Goodman, JE. 2017. "Use of Pharmacokinetic Data for Adjustment Factor Derivation for Benzoate Preservatives." Presented at American College of Toxicology (ACT) 38th Annual Meeting, Palm Springs, CA, November 5-8.

Zu, K; Liu, X; Shi, L; Tao, G; Loftus, C; Lange, S; Goodman, JE. 2017. "Concentration-response of Short-term Ozone Exposure and Hospital Admissions for Asthma in Texas." Presented at the Society of Epidemiological Research 50th Annual Meeting, Seattle, WA, June 20-23.

Lynch, HN; Goodman, JE. 2017. "Risk Assessment Calls for Standard Guidelines for Exposure Characterization in Epidemiology Studies." Presented at the Society of Epidemiological Research 50th Annual Meeting, Seattle, WA, June 20-23.

Lam, T; Loftus, C; Zu, K; Kennedy, EM; Goodman, JE. 2017. "2,4-Dichlorophenoxyacetic Acid and Soft Tissue Sarcoma: Meta-analysis of the Published Literature." Presented at the Society of Epidemiological Research 50th Annual Meeting, Seattle, WA, June 20-23.

Prueitt, RL; Goodman, JE. 2017. "Mode-of-action Evaluation for Ozone-induced Respiratory Effects Through Activation of Neural Reflexes." Poster #2824/P226. Presented at the Society of Toxicology (SOT) 56th Annual Meeting, Baltimore, MD, March 12-16.

Lynch, HN; Goodman, JE; Yan, Z. 2017. "Risk Assessment Calls for Standard Guidelines for Exposure Characterization in Epidemiology Studies." Poster #1311/P534. Presented at the Society of Toxicology (SOT) 56th Annual Meeting, Baltimore, MD, March 12-16.

Zu, K; Liu, X; Goodman, JE. 2017. "Meta-analysis of Dose-response Relationships from Epidemiology Studies for Risk Assessment: A Case Study of Trans Fats and Coronary Heart Disease." Poster #1850/P424. Presented at the Society of Toxicology (SOT) 56th Annual Meeting, Baltimore, MD, March 12-16.

Lemay, JC; Zu, K; Zhang, J; Goodman, JE. 2016. "Sunscreen Safety for Kids: A Risk Assessment of a Common Preservative." Poster #MP168. Presented at the Society of Environmental Toxicology and Chemistry (SETAC) North America 37th Annual Meeting, Orlando, FL, November 6-10.

Bailey, LA; Kerper, LE; Goodman, JE. 2016. "Occupational Exposure Level for Manganese in Welding Fumes Based on the Best Available Science." Presented at the Manganese 2016 Conference: Manganese Health Effects on Neurodevelopment & Neurodegenerative Diseases, New York, NY, September 25-28.

Goodman, JE; Zu, K; Tao, G; Rhomberg, LR. 2016. "Evaluation of Occupational Benzene Exposure and Leukemia Mortality: A Lifetable Analysis of the Pliofilm Cohort." Presented at the Epidemiology Congress of the Americas 2016 Annual Meeting, Miami, FL, June 21-24.

Zu, K; Tao, G; Goodman, J. 2016. "Pleural plaques and lung function in the Marysville worker cohort: A re-analysis." Presented at the Epidemiology Congress of the Americas 2016 Annual Meeting, Miami, FL, June 21-24.

Lange, SS; Tao, G; Rhomberg, LR; Goodman, JE; Dourson, ML; Honeycutt, ME. 2016. "Dose Response Curves Derived from Clinical Ozone Exposures Can Inform Public Policy." Presented at the Society of Toxicology (SOT) 55th Annual Meeting, New Orleans, LA, March 13-17.

Zu, K; Lemay, JC; Zhang, J; Goodman, JE. 2016. "A Hazard and Risk Assessment of Phenoxyethanol in Children's Personal Care Products." Presented at the Society of Toxicology (SOT) 55th Annual Meeting, New Orleans, LA, March 13-17.

Prueitt, RL; Cohen, JM; Goodman, JE. 2016. "Evaluation of Atherosclerosis as a Mode of Action for the Cardiovascular Effects of Particulate Matter." Presented at the Society of Toxicology (SOT) 55th Annual Meeting, New Orleans, LA, March 13-17.

Seeley, MR; Goodman, JE. 2016. "Evaluation of Nitrogen Dioxide and Airway Hyper-responsiveness." Presented at the Society of Toxicology (SOT) 55th Annual Meeting, New Orleans, LA, March 13-17.

Zu, K; Loftus, CT; Goodman, JE. 2015. "Non-Hodgkin's Lymphoma and 2,4-dichlorophenoxyacetic Acid: A Meta-analysis." Poster No. 022. Presented at the Society for Epidemiological Research 48th Annual Meeting, Denver, Colorado, June 19, 2015.

Rhomberg, LR; Mayfield, DB; Goodman, JE; Butler, EL; Nascarella, MA; Williams, DR. 2015. "Quantitative Cancer Risk Assessment for Occupational Exposures to Asphalt Fumes During Built-up Roofing Asphalt (BURA) Operations." Presented at the INRS 2015 Occupational Health Research Conference, Nancy, France, April 8-10.

Tao, G; Zu, K; Long, CM; Goodman, JE; Valberg, PA. 2015. "Forest-fire Fine Particulate Matter and Daily Mortality in Greater Boston and New York City." *Toxicologist* 144(1):163. Abstract 763. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Zu, K; Tao, G; Kerper, LE; Rhomberg, LR; Goodman, JE. 2015. "Evaluation of US EPA's Noncancer Risk Assessment of Libby Amphibole Asbestos." *Toxicologist* 144(1):164. Abstract 768. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Sax, SN; Pizzurro, DM; Zu, K; Lynch, HN; Prueitt, RL; Goodman, JE. 2015. "Ozone Exposure and Systemic Biomarkers: Evaluation of Evidence of Adverse Cardiovascular Health Impacts." *Toxicologist* 144(1):166-167. Abstract 778. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Prueitt, RL; Lynch, HN; Tabony, JA; Beck, NB; Goodman, JE; Rhomberg, LR 2015. "Evaluation of Study Quality Criteria Frameworks." *Toxicologist* 144(1):400. Abstract 1865. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Kerper, LE; Lynch, HN; Zu, K; Tao, G; Utell, M; Goodman, JE. 2015. "A Systematic Review of Asbestos-induced Pleural Plaques and Lung Function." *Toxicologist* 144(1):401. Abstract 1869. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Seeley, MR; Thakali, S; Goodman, JE. 2015. "Birth Defect Rates in High and Low Atrazine-use States." *Toxicologist* 144(1):462. Abstract 2151. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Loftus, CT; Goodman, JE; Zu, K. 2015. "2,4-dichlorophenoxyacetic Acid and Non-Hodgkin's Lymphoma, Gastric Cancer, and Prostate Cancer: Meta-analyses of the Published Literature." *Toxicologist* 144(1 (Supplement)):192. Abstract 2831. Presented at the Society of Toxicology (SOT) 54th Annual Meeting, San Diego, CA, March 22-26.

Goodman, JE; Lynch, HN; Prueitt, RL; Beck, NB; Tabony, JA; Rhomberg, LR. 2014. "Evaluation of Study Quality Criteria Frameworks." Presented at the Society for Risk Analysis Annual Meeting, Denver, Colorado, December 7-10.

Sax, SN; Pizzurro, DM; Zu, K; Lynch, HN; Prueitt, RL; Goodman JE. 2014. "Weight-of-evidence Evaluation of Short-term Ozone Exposure and Cardiovascular Biomarkers." Presented at the Society for Risk Analysis Annual Meeting, Denver, Colorado, December 7-10.

Lange, SS; Rhomberg, LR; Dourson, ML, Tao G, Goodman JE, Honeycutt M. 2014. "How Dose Response Curves Derived from Clinical Ozone Exposures can Inform Public Policy." Presented at the Society for Risk Analysis Annual Meeting, Denver, Colorado, December 7-10.

Kerper, LE; Lynch, HN; Mohr, LC; Goodman, JE. 2014. "Do Asbestos-induced Pleural Plaques Cause Lung Function Deficits?" *Toxicologist* 138(1):475. Abstract 1811. Presented at the Society of Toxicology (SOT) 53rd Annual Meeting, Phoenix, AZ, March 23-27.

Prueitt, RL; Sax, SN; Lynch, HN; Lemay, JC; King, JM; Goodman, JE. 2014. "Weight-of-evidence Evaluation of Short-term Ozone Exposure and Cardiovascular Effects." *Toxicologist* 138(1):475. Abstract 1810. Presented at the Society of Toxicology (SOT) 53rd Annual Meeting, Phoenix, AZ, March 23-27.

Lemay, JC; Prueitt, RL; Hixon, ML; Goodman, JE. 2013. "Distinguishing between Risks and Hazards: A Case Study of Bisphenol A." Presented at the Society for Risk Analysis Annual Meeting, Baltimore, MD, December 810. 13p.

Sax, SN; Prueitt, RL; Goodman, JE. 2013. "Weight-of-evidence Evaluation of Short-term Ozone Exposure and Cardiovascular Effects." Presented at the Society for Risk Analysis Annual Meeting, Baltimore, MD, December 8-11.

Goodman, JE, Prueitt RL, Rhomberg, LR. 2013. "Hypothesis-based Weight-of-evidence Evaluation of the Human Carcinogenicity of Toluene Diisocyanate." Presented at the Conference on Isocyanates and Health: Past, Present and Future, April 3-4.

Seeley, MR; Goodman, JE. 2013. "Is There a Subset of Susceptible Individuals in Controlled Air Pollution Studies?" *Toxicologist* 132(1):414. Abstract No. 1945. Presented at the Society of Toxicology (SOT) 52nd Annual Meeting, San Antonio, TX, March 10-14.

Prueitt, RL; Goodman, JE; Rhomberg, LR. 2013. "Hypothesis-based Weight-of-evidence Evaluation of the Human Carcinogenicity of Toluene Diisocyanate." *Toxicologist* 132(1):415. Abstract No. 1951. Presented at the Society of Toxicology (SOT) 52nd Annual Meeting, San Antonio, TX, March 10-14.

Rhomberg, LR; Goodman, JE; Bailey, EA; Prueitt, RL. 2012. "Weight-of-evidence Frameworks, Systems, and Tools: A Survey of Existing Approaches and Notes on Best Practices." Presented at the "Putting it All Together: Recent Developments in Risk Assessment Approaches" Symposium, Society for Risk Analysis Annual Meeting, San Francisco, CA, December 11. 24p.

Sax, SN; Lau, JH; Goodman, JE. 2012. "Evaluation of the BenMAP Model for Estimating Mortality Impacts of Lower Ozone Concentrations." Presented at the 22nd Annual Conference of the International Society of Exposure Science, Seattle, WA, October 28-November 1.

Bailey, LA; Goodman, JE; Beck, BD. 2012. "Revised Reference Concentration for Manganese Oxide Based on Recent Epidemiology and Pharmacokinetic Studies." *Toxicologist* 126(1):213. Abstract No. 995. Presented at the Society of Toxicology (SOT) 51st Annual Meeting, San Francisco, CA, March 11-15.

Peterson, MK; Goodman, JE. 2012. "Infant Risk and Exposure Assessment of Bisphenol A in Polycarbonate and 'BPA-free' Plastic Bottles." *Toxicologist* 126(1):319. Abstract No. 1478. Presented at the Society of Toxicology (SOT) 51st Annual Meeting, San Francisco, CA, March 11-15.

Prueitt, RL; Goodman, JE; Bailey, LA; Rhomberg, LR. 2012. "Hypothesis-based Weight-of-evidence Evaluation of the Neurodevelopmental Effects of Chlorpyrifos." *Toxicologist* 126(1):309. Abstract No. 1430. Presented at the Society of Toxicology (SOT) 51st Annual Meeting, San Francisco, CA, March 11-15.

Seeley, MR; Goodman, JE. 2012. "Is Sulfur Dioxide a Reproductive and Developmental Toxicant?" *Toxicologist* 126(1):24. Abstract No. 119. Presented at the Society of Toxicology (SOT) 51st Annual Meeting, San Francisco, CA, March 11-15.

Bailey, LA; Goodman, JE; Rhomberg, LR. 2011. "Hypothesis-based Weight-of-evidence Evaluation of Naphthalene: Carcinogenic Hazard Assessment and Mode of Action." Presented at SETAC North America 32nd Annual Meeting, Boston, MA, November 14. 1p.

Prueitt, RL; Goodman, JE. 2011. "Evaluation of Adverse Effects on Human Lung Function Caused by Ozone." *Toxicologist* 120(Suppl. 2):491. Abstract No. 2286. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Peterson, MK; Bailey, LA; Dodge, DG; Goodman, JE; Valberg, PA. 2011. "A Weight-of-evidence Evaluation of Asbestos Exposure and Mesothelioma Risk among Electricians." *Toxicologist* 120(Suppl. 2):414. Abstract No. 1935. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Goodman, JE; Mayfield, DB; Bailey, LA; Rhomberg, LR. 2011. "Weight-of-evidence Evaluation of Formaldehyde Exposure and Leukemia Risk." *Toxicologist* 120(Suppl. 2):416. Abstract No. 1944. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Mattuck, RL; Seeley, MR; Reid, KR; Goodman, JE. 2011. "Human Health Risks from Exposure to 1,4-butanediol in Craft Kit Beads." *Toxicologist* 190(Suppl. 2):332. Abstract No. 1545. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Dodge, DG; Pollock, MC; Sax, SN; Petito Boyce, C; Goodman, JE. 2011. "Risk Characterization of the Brominated Flame Retardant Decabromodiphenyl Ethane in Indoor Dust." *Toxicologist* 120(Suppl. 2):271. Abstract No. 1268. Presented at the Society of Toxicology (SOT) 50th Annual Meeting, Washington, DC, March 6-11.

Peterson, MK; Bailey, LA; Dodge, DG; Goodman, JE; Valberg, PA. 2010. "Risk Assessment of Mesothelioma Among Electricians." Presented at the Society for Risk Analysis Annual Meeting, Salt Lake City, UT, December 5-8.

Haber, LT; Prueitt, RL; Goodman, JE; Thakali, S; Patterson, J. 2010. "Report of a Workshop: An Evaluation of Hypotheses for Determining the Carcinogenic Potential of Nickel-containing Substances." Presented at the Society for Risk Analysis Annual Meeting, Salt Lake City, Utah, December 5-8. 1p.

Goodman, JE; Kerper, LE; Petito Boyce, C; Prueitt, RL; Rhomberg, LR. 2010. "Weight of Evidence Exposures Analysis of Exposures to Dioxins and Dioxin-like Compounds and Associations with Thyroid Hormone Levels during Early Development." Presented at the Society of Toxicology (SOT) 49th Annual Meeting, Salt Lake City, UT. 1p.

Prueitt, RL; Goodman, JE; Thakali, S. 2010. "An Evaluation of Hypotheses for Determining the Carcinogenic Potential of Nickel-containing Substances." Presented at the Society of Toxicology (SOT) 49th Annual Meeting, Salt Lake City, UT. 1p.

Dodge, DG; Goodman, JE; Beck, BD. 2010. "Weight-of-evidence Analysis of Hydroquinone and Leukemia." *Toxicologist* 114(1):111-112. Abstract No. 514. Presented at the Society of Toxicology (SOT) 49th Annual Meeting, Salt Lake City, UT, March 7-11.

Thakali, S; Chandalia, JK; Seeley, M; Goodman, JE. 2010. "Meta-analysis of Nitrogen Dioxide Effects on Airway Hyper-responsiveness in Asthmatics: Effects of the Types of Airway Challenge, Exposure Methods, and Activites During Exposure." *Toxicologist* 114(1):401. Abstract No. 1886. Presented at the Society of Toxicology (SOT) 49th Annual Meeting, Salt Lake City, UT, March 7-11.

Goodman, JE; Chandalia, JK; Thakali, S; Seeley, M. 2009. "Meta-analysis of Controlled Nitrogen Dioxide Exposure Studies Assessing Airway Hyper-responsiveness in Asthmatics." Presented at the Society for Risk Analysis Annual Meeting, Baltimore, MD, December 6-9.

Goodman, JE; Rhomberg, LR; Pruiett, RL. 2009. "A Weight-of-evidence Analysis of the Human Carcinogenicity of Styrene." Presented at the Annual Meeting of the American College of Epidemiology, Silver Spring, MD, September 13-15.

Prueitt, RL; Goodman, JE; Dodge, DG; Thakali, S. 2009. "A Weight-of-evidence Evaluation of the Carcinogenicity of Soluble Nickel." *Toxicologist* 108(1):328. Abstract No. 1582. Presented at the Society of Toxicology (SOT) 48th Annual Meeting, Baltimore, MD, March 15-19.

Goodman, JE; Rhomberg, LR. 2009. "A Weight-of-evidence Approach to Evaluating Epidemiological Data on Styrene Cancer Hazards." *Toxicologist* 108(1):248. Abstract No. 1190. Presented at the Society of Toxicology (SOT) 48th Annual Meeting, Baltimore, MD, March 15-19.

Beyer, LA; Beck, BD; Goodman, JE. 2009. "Background Rates of Lymphomas/Leukemias and Leydig Cell Tumors in Sprague Dawley Rats." *Toxicologist* 108(1):421. Abstract No. 2028. Presented at the Society of Toxicology (SOT) 48th Annual Meeting, Baltimore, MD, March 15-19.

Goodman, JE; Bailey, LA; Beck, BD. 2008. "Recent Occupational Studies of Manganese and their Bearing on the Reference Concentration (RfC)." Presented at the Annual Meeting of the American College of Epidemiology, Tucson, AZ, September 14-16.

Aylward, LL; Goodman, JE; Charnley, G; Rhomberg, LR. 2008. "A Margin of Exposure Approach to Assessment of Non-cancer Risks of Dioxins Based on Human Exposure and Response Data." Presented at the 28th International Symposium on Halogenated Persistent Organic Pollutants, Birmingham, England, August 17-22.

Goodman, JE; Bailey, LA; Beck, BD. 2008. "Recent Studies of the Health Effects of Manganese and the Implications for the Reference Concentration (RfC)." *Toxicologist* 102. Abstract No. 1787. Presented at the Society of Toxicology (SOT) 47th Annual Meeting, Seattle, WA, March 16-20.

Dodge, DG; Haber, LT; Kopras, E; Goodman, JE; Pagan, I; Gift, JS; Rhomberg, LR. 2008 "Case Studies for the Development of a Pathophysiological Progression Model." *Toxicologist* 102(1):245. Abstract No. 1189. Presented at the Society of Toxicology (SOT) 47th Annual Meeting, Seattle, WA, March 16-20.

Beyer, LA; Slayton, TM; Goodman, JE; Greenberg, GI; Hudson, TC; Sax, SN; Beck, BD. 2008 "Evaluation of Key Information Informing the Basis of EPA's New Recommended Ozone Standard." *Toxicologist* 102. Abstract No. 1462. Presented at the Society of Toxicology (SOT) 47th Annual Meeting, Seattle, WA, March 16-20.

Pagan, I; Haber, LT; Rhomberg, LR; Goodman, JE; Dodge, DG; Foureman, GL. 2007. "Development of a Pathophysiological Progression Model for Selected Endpoints." Presented at the Society for Risk Analysis Annual Meeting, San Antonio, TX, December 9-12.

Haber, LT; Rhomberg, LR; Goodman, JE; Dodge, DG; Zhao, QJ; Pagan, I; Foureman, GL. 2007. "Considerations Regarding the Structure and Application of a Pathophysiological Progression Model." Presented at the Society for Risk Analysis Annual Meeting, San Antonio, TX, December 9-12.

Dodge, DG; Zhao, QJ; Haber, LT; Goodman, JE; Pagan, I; Foureman, GL; Rhomberg, LR. 2007. "Case Studies for the Development of a Pathophysiological Progression Model: Fatty Liver." Presented at the Society for Risk Analysis Annual Meeting, San Antonio, TX, December 9-12.

Mechanic, LE; Luke, BT; Goodman, JE; Chanock, SJ; Harris, CC. 2007. "Polymorphism Interaction Analysis (PIA): A Method for Investigating Complex Gene-gene Interactions." Presented at Approaches to Complex Pathways in Molecular Epidemiology, Santa Ana Pueblo, NM, May 30-June 2.

Goodman, JE; Gaylor, D; Beyer, LA; Rhomberg, LR; Beck, BD. 2007. "MTBE is Not Associated with a Statistically Significant Increase in Leydig Cell Tumors in Sprague-Dawley Rats." *Toxicologist* 96(1):339. Abstract No. 1637. Presented at the Society of Toxicology (SOT) 46th Annual Meeting, Charlotte, NC, March 25-29.

Rhomberg, LR; Goodman, JE; McConnell, EE; Sipes, IG; Witorsch, RJ; Slayton, TM; Yu, CJ; Lewis, AS. 2007. "An Updated Weight of the Evidence Evaluation of Reproductive and Developmental Effects of Low Doses of Bisphenol A." *Toxicologist* 96(1):427. Abstract No. 2067. Presented at the Society of Toxicology (SOT) 46th Annual Meeting, Charlotte, NC, March 25-29.

Beyer, LA; Goodman, JE; Seeley, MR; Slayton, TM; Beck, BD. 2007. "Carcinogenicity Evaluation of Methyl Tert-butyl Ether (MTBE)." *Toxicologist* 96(1):325. Abstract No. 1569. Presented at the Society of Toxicology (SOT) 46th Annual Meeting, Charlotte, NC, March 25-29.

Zanetti, KA; Kahn, MA; Bowman, ED; Goodman, JE; Chanock, S; Harris, CC. 2007. "Compromised Complement System Increases Colon Cancer Susceptibility in African-Americans." *Proc. Am. Assoc. Cancer Res.* 48.

Schoen, A; Eldan, M; Goodman, JE; Beck, BD. 2006. "DMA_V-induced Bladder Tumors: Unique Rat Susceptibility." *Toxicologist* 90(1):448. Abstract No. 2186. Presented at the Society of Toxicology (SOT) 45th Annual Meeting, San Diego, CA, March 5-9.

Goodman, JE; Harris, CC. 2005. "GST-T1, p53, and CASPASE-8 Polymorphisms and Colon Cancer Risk." Presented at the Society of Toxicology (SOT) 44th Annual Meeting, New Orleans, LA, March 6-10.

Goodman, JE; Bowman, E; Chanock, S; Harris, CC. 2004. "Arachidonate Lipoxygenase (ALOX) and Cyclooxygenase (COX) Polymorphisms and Colon Cancer Risk." *Proc. Am. Assoc. Cancer Res.* 44.

Goodman, JE; Bowman, E; Chanock, S; Harris, CC. 2004. "ALOX & COX Polymorphisms & Colon Cancer Risk: Association with ALOX-5 G-1753A & G-1700A." Center for Cancer Research Fourth Annual Fellows and Young Investigators Retreat, Williamsburg, VA, March 9-11.

Sullivan, AE; Goodman, JE; Silber, PM; Yager, JD. 2004. "Correlation Between Catechol-O-methyltransferase Genotype and Phenotype." *Toxicologist* 88.

Sullivan, AE; Goodman, JE; Yager, JD. 2003. "Catechol-O-methyltransferase (COMT) and Catechol Estrogens in Breast Cancer." Presented at the 226th National American Chemical Society Division of Toxicology Meeting, New York, NY, September 7-11.

Goodman, JE; Sullivan, AE; He, P; Silber, PM; Yager, JD. 2003. "Correlation Between Catechol-O-methyltransferase Genotype and Phenotype." AACR Molecular and Genetic Epidemiology of Cancer Conference Proceedings, Waikoloa, HI, January 18-23.

Goodman, JE; He, P; Yager, JD. 2002. "COMT Polymorphism and Catechol Estrogen Methylation in Breast Epithelial Cell Lines." *Proc. Am. Assoc. Cancer Res.* 45.

Goodman, JE; He, P; Yager, JD. 2001. "Kinetics of High and Low Activity Human Catechol-O-methyltransferase Activity for Catechol Estrogen Methylation." *Proc. Am. Assoc. Cancer Res.* 42.

Lavigne, JA; Goodman, JE; Fonong, T; Odwin-DeCosta, S; He, P; Yager, JD. 2001. "The Effects of Catechol-O-methyltransferase Inhibition on Catechol Estrogen Levels and Oxidative DNA Damage in MCF-7 Cells." *Proc. Am. Assoc. Cancer Res.* 42.

Goodman, JE; Lavigne, JA; Hengstler, JG; Helzlsouer, KJ; Yager, JD. 2000. "Catechol-O-methyltransferase Polymorphism Not Associated with Ovarian Cancer." *Proc. Am. Assoc. Cancer Res.* 41.

Chen, JQ; Delannoy, M; Goodman, JE; Lavigne, JA; Odwin, SE; He, P; Yager, JD. 2000. "Enhanced Transcript Levels of Mitochondrial Genes, Respiratory Chain Activity, Bcl-2 Levels and Glutathione Distribution by Ethinyl Estradiol in Female Rat Hepatocytes." *Proc. Am. Assoc. Cancer Res.* 41.

Invited Lectures, Testimony, and Other Presentations

"A Case for Good Epidemiology Practice Guidelines for Regulatory Risk Assessment." Presented at the Environmental Epidemiology Committee Webinar, September 23, 2021.

"Food Safety." Presented at Gradient's Trends 75 Webinar, June 19, 2019.

"Evaluating Adverse Drug Effects in Pharmacoepidemiology Studies." Presented at Gradient's Trends 71 Webinar, February 28, 2018.

"Study Quality and Evidence Integration in the IRIS Process." Presented at the National Academies of Science, Engineering, and Medicine Review of Advances Made to the IRIS Process Workshop, Washington, DC, February 1, 2018.

"Challenges for the Agrochemical Industry." Presented at the International Society of Exposure Science (ISES) Annual Conference, Research Triangle Park, NC, October 17, 2017.

"National Ambient Air Quality Standards." Presented at the Institute for Humane Studies and the Mercatus Center Risk Analysis Seminar, Portland, OR, June 27, 2016.

"Why Epidemiologists Need Toxicologists (and Vice Versa)." Presented at the CropLife America & RISE 2016 Spring Conference, Arlington, VA, April 14, 2016.

"Systematic Review." Presented at the Asphalt Institute Spring Meeting, Nashville, TN, April 13, 2016.

"An Introduction to Meta-analysis." Presented at the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, April 5, 2016.

"Evaluation of Scoring Approaches and Consideration of an Independent Approach." Presented at the 40th Annual Winter Meeting of Toxicology Forum, Washington, DC, February 10, 2016.

"Extrapolation of Controlled Human Study Results to the US Population." Presented at the Society for Risk Analysis Annual Meeting, December 6-9, 2015.

"How a Sensitivity Analysis of Raw Data Would Strengthen EPA's Chlorpyrifos Risk Assessment." Presented at the Society for Risk Analysis Annual Meeting, December 6-9, 2015.

"The Future of Toxicology." Presented at the SPI Food Packaging Summit, November 10, 2015.

"Evaluation of Evidence EPA Cites in Support of the Ozone National Ambient Air Quality Standards for Ozone Proposed Rule." Presented at the 2015 Env-vision Conference, May 12-14, 2015.

"The Scientific Evidence Does Not Support the Administrator's Proposed Conclusion that the Primary Ozone NAAQS Should Be Between 0.065 and 0.070 ppm." Testimony at the US Environmental Protection Agency (EPA) Public Hearing on the Proposed Updates to the National Ambient Air Quality Standards (NAAQS) for Ground-level Ozone, Washington, DC, January 29, 2015.

"Risk-of-bias Analysis: Case Study of Pleural Plaques and Lung Function." Presented at the Society for Risk Analysis Annual Meeting, December 7-10, 2014.

"Is a Stricter Ozone NAAQS Supported by the Science?" Presented at the Association of Battery Recyclers 2014 Fall Meeting, October 16, 2014.

"NexGen: Are We There Yet?" Presented at the 2014 Health Effects Institute Annual Conference, May 6, 2014.

"Hypotheses and Weight-of-evidence Frameworks." Presented at the 53rd Annual Society of Toxicology Meeting, March 23, 2014.

"When an Association Indicates Causation." Presented at the 53rd Annual Society of Toxicology Meeting, March 23, 2014.

"Rethinking Meta-analysis: Applications for Air Pollution Data and Beyond." Presented at the Society for Risk Analysis Annual Meeting, December 8-11, 2013.

"Incorporation of Weight-of-evidence Best Practices in the National Ambient Air Quality Standards Review Process." Presented at the Society for Risk Analysis Annual Meeting, December 8-11, 2013.

"Bradford Hill Viewpoints and Hypothesis-based Weight of Evidence." Presented at the Society for Risk Analysis Annual Meeting, December 8-11, 2013.

"Rethinking Meta-analysis: Applications for Air Pollution Data and Beyond." Presented at the Harvard Systematic Review Symposium, October 3-4, 2013.

"A Hypothesis-based Weight-of-evidence Approach to Evaluate the Human Carcinogenicity of Isocyanates." Presented at the Isocyanates & Health Conference, April 3, 2013.

"Using Epidemiology to Analyze Neurodevelopmental Toxicity Across Species." Presented at the 52nd Annual Society of Toxicology Meeting, March 14, 2013.

"Designing Case-control Studies." Presented at the New York Medical College School of Health Science & Practice, February 21, 2013.

"Designing Cohort Studies." Presented at the New York Medical College School of Health Science & Practice, February 11, 2013.

"Systemic Reviews and Meta-analysis." Presented in the Use of Expert Elicitation to Inform Decisionmaking Workshop, Society for Risk Analysis 2012 Annual Meeting, San Francisco, CA, December 2012.

"Survival Analysis & Meta-analysis." Presented at the New York Medical College School of Health Sciences & Practice, November 8, 2012.

"Overview of the Controversy Surrounding Bisphenol A Toxicity." Presented at the Biological Relevance and Health Concerns of Genotoxicity Conference, Newark, DE, October 24, 2012.

"Biological & Statistical Interaction." Presented at the New York Medical College School of Health Sciences & Practice, October 11, 2012.

Testimony regarding "EPA's Assessment of Health Benefits Associated with $PM_{2.5}$ Reductions for the Final Mercury and Air Toxics Standards." Presented to the Subcommittee on Energy and Power, United States Congressional Committee on Energy and Commerce American Energy Initiative Hearing, Washington, DC, February 8, 2012.

"Synthesizing Evidence: An Introduction to Systematic Reviews, Meta-analysis, and Expert Elicitation." Presented at the Society for Risk Analysis 2011 Annual Meeting, Charleston, SC, December 2011.

"Why Meta-analyses and Systematic Reviews Come to Different Conclusions About Formaldehyde and Leukemia." Presented at the Society for Risk Analysis 2011 Annual Meeting, Charleston, SC, December 2011.

"The Weight of Evidence Regarding Bisphenol A and Human Health." Presented at the Society for Risk Analysis New England Chapter Meeting, Harvard School of Public Health, Boston, MA, December 2011.

Testimony regarding Air Quality and Children's Health. Presented to the Subcommittee on Clean Air and Nuclear Safety and the Subcommittee on Children's Health and Environmental Responsibility, United States Senate Committee on Environment and Public Works Hearing, Washington, DC, June 8, 2011.

"Bisphenol A and Human Health: What Does the Science Show?" Presented at the Policy of BPA Event, American Enterprise Institute, Washington, DC, June 2010.

"Human Health Risk Assessment." Presented at the Massachusetts Maritime Academy, Buzzards Bay, MA, May 2010.

"The Science Behind the Reconsideration of the Ozone NAAQS." Presented as part of the webinar, How Will EPA's New Ozone Standards Affect Your Community? April 2010.

"Weight-of-evidence Analysis of Reproductive and Developmental Health Effects of Bisphenol A." Presented at the Nypro Bisphenol A Information Event, Clinton, MA, March 2010.

"Everyday Exposures to Bisphenol A Do Not Cause Adverse Health Effects in Humans." Presented at the Harvard Extension School, Environmental Management Program, Cambridge, MA, March 2010.

"New Developments in Exploratory Research on 'Estrogenicity' – Progress Toward Validation of New Endpoints and Testing Methods." Presented at the Society of the Plastics Industry's Food, Drug, and Cosmetic Packaging Materials Committee Winter Conference, Atlanta, GA, December 2009.

"Avoiding Potential Long-term Liability through Risk Assessment for Material Selection." Presented at the 21st Annual Product Liability Conference, University of Wisconsin-Madison, Madison, WI, September 2009.

"Epidemiology and Risk Assessment." Presented at the Annual Meeting of the American College of Epidemiology, Silver Spring, MD, September 2009.

"Risk Assessment Techniques for Materials Selection." Presented as part of the Strategies for Substance Replacement in Products Webinar, May 2009.

"Investigation of Potential Cancer Clusters in Northampton, MA." Presented at the John F. Kennedy School, Northampton, MA, September 2008.

"Did Chemicals in Your Product Cause John Doe's Disease? The Toxicologist Speaks." Presented at the 20th Annual Product Liability Conference, University of Wisconsin-Madison, Madison, WI, September 2008.

"Investigation of Potential Disease Clusters in Northampton, MA: Progress Update." Presented at the Robert K. Finn Ryan Road School, Northampton, MA, October 2007.

"Investigation of Potential Disease Clusters in Northampton, MA." Presented at the Robert K. Finn Ryan Road School, Northampton, MA, May 2007.

"Single Nucleotide Polymorphisms (SNPs), Inflammation and Colon Cancer." Presented at the Cancer Prevention Fellowship Program Seminar Series, NCI, Rockville, MD, February 2004.

"The Epidemiology of Inflammation and Colon Cancer." Presented at the Laboratory of Human Carcinogenesis Meeting, NCI, Bethesda, MD, December 2003.

"Macrophage Migration Inhibitory Factor (MIF) in Inflammatory Bowel Diseases." Presented at the Laboratory of Human Carcinogenesis International Workshop, Bethesda, MD, September 2003.

"Chronic Inflammation and Colon Cancer Risk." Presented at the Cancer Prevention Fellowship Program Seminar Series, NCI, Rockville, MD, June 2003.

Attachment M

Testimony Experience

Expert Testimony
Julie E. Goodman, Ph.D., DABT, FACE, ATS
Last Four Years

Expert #	For:	Plaintiff (P)	Defendant (D)	Case #	Court	District	Date	Legal Proceeding
1	D	Amber, *et al.*	Allied Waste Transportation, Inc., *et al.*	09 L 15741	Circuit Court	State of Illinois, County of Cook	6/16/21	Deposition
2	D	Estate of Wayne D. Vetre	Town of Wells/Maine Municipal Association	218W2797	Worker's Compensation Board		12/14/21	Deposition
3	D	John C. Riegler and Kathi A. Riegler	Ford Motor Company	2:20-cv-00752-RJS-CMR	District Court	District of Utah	4/6/2022	Deposition
4	D	Pamela S. Rud and David Rud	Ford Motor Company	21-L-286	Circuit Court	State of Illinois, County of Madison	5/24/2022	Deposition
5	D	Estate of Eugene G. Hohlfeld, Sr.	Ford Motor Company, *et al.*	18-CV-251	Circuit Court	State of Wisconsin, County of Lacrosse	9/14/2022	Trial
6	D	Estate of Vincent DiFillipo, Sr.	City of Portland and Maine Municipal Association		Worker's Compensation Board		9/29/2022	Deposition
7	D	District of Columbia	Beech-Nut Nutrition Company	2021 CA 001292B	Superior Court	District of Columbia	3/2/2023	Deposition
8	D	Citizens for the Environment	Elcon Recycling Center (2003) Ltd., *et al.*	CA 36568-07-19	District Court	Haifa, Israel	5/15/2023; 5/17/2023	Trial
9	D	Vicki Lee and the Estate of Steven A. Lee	Ford Motor Company	2019CV000344	Circuit Court	State of Wisconsin, County of Grant	6/1/2023	Deposition
10	D	Robert Collins	Allied Fluid Products Corp., *et al.*	22CV021614	Superior Court	State of California, County of Alameda	6/5/2023	Deposition
11	D	Bryan Dick-Ipsen	Tri-Supply Co., *et al.*	2018-L-011367	Circuit Court	State of Illinois, Cook County	8/10/2023	Deposition
12	D	Ricky Bush, *et al.*	Clean Harbors Colfax, LLC	1:22-cv-02026-DDD-JPM	District Court	State of Louisiana, Alexandria Division	10/2/2023	Deposition
13	D	In Re: New Indy Emissions Litigation		21-CV-01480-SAL, 21-CV-01704-SAL	District Court	District of South Carolina, Rock Hill Division	10/30/2023	Deposition
14	D	William Grit	Koch Remediation and Environmental Services, LLC; *et al.*	2021-CV-000527	District Court	State of Kansas, County of Shawnee	2/16/2024	Deposition
15	D	Yehoshua Klein, *et al.*	Oil Refineries Ltd., *et al.*	CA 11278-10-19	District Court	Tel Aviv, Israel	3/12/2024	Trial
16	D	James S. Diede and Jeanne Diede	A.O. Smith Corporation., *et al.*	Civil Action No. 23-0274	Superior Court	State of Massachusetts, County of Middlesex	6/12/2024	Deposition
17	D	Stephen P. Sutton, *et al.*	W. L. Gore & Associates, Inc.	Civil Action No. 1:22-cv-1471	District Court	State of Maryland	9/11/2024	Deposition
18	D	FTCA Flint Water Cases		Civil Action No. 4:17-cv-11218	District Court	Eastern District of Michigan, Southern Division	9/19/2024; 10/9/2024	Deposition
19	D	Bruce S. Wright and Louis K. Wright	Cummins Inc., *et al.*	Civil Action No. 1:23-cv-10496	District Court	District of Massachusetts	11/20/2024	Deposition