



TOXICOLOGICAL REVIEW

OF

Trichloroethylene

(CAS No. 79-01-6)

**In Support of Summary Information on the
Integrated Risk Information System (IRIS)**

October 2009

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U.S. Environmental Protection Agency
Washington, DC

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GUIDE TO READERS OF THIS DOCUMENT

Due to the length of the TCE toxicological review, it is recommended that Chapters 1 and 6 be read prior to Chapters 2–5.

Chapter 1 is the standard introduction to an IRIS Toxicological Review, describing the purpose of the assessment and the guidelines used in its development.

Chapter 2 is an exposure characterization that summarizes information about TCE sources, releases, media levels and exposure pathways for the general population (occupational exposure is also discussed to a lesser extent).

Chapter 3 describes the toxicokinetics and physiologically based pharmacokinetic (PBPK) modeling of TCE and metabolites (PBPK modeling details are in Appendix A).

Chapter 4 is the hazard characterization of TCE. Section 4.1 summarizes the evaluation of epidemiologic studies of cancer and TCE (qualitative details in Appendix B; meta-analyses in Appendix C). Each of the Sections 4.2–4.9 provides self-contained summary and syntheses of the epidemiologic and laboratory studies on TCE and metabolites, organized by tissue/type of effects, in the following order: genetic toxicity, central nervous system (CNS), kidney, liver, immune system, respiratory tract, reproduction and development, and other cancers. Additional details are provided in Appendix D for CNS effects and Appendix E for liver effects. Section 4.10 summarizes the available data on susceptible lifestages and populations. Section 4.11 describes the overall hazard characterization, including the weight of evidence for noncancer effects and for carcinogenicity.

Chapter 5 is the dose-response assessment of TCE. Section 5.1 describes the dose-response analyses for noncancer effects, and Section 5.2 describes the dose-response analyses for cancer. Additional computational details are described in Appendix F for noncancer dose-response analyses, Appendix G for cancer dose-response analyses based on rodent bioassays, and Appendix H for cancer dose-response analyses based on human epidemiologic data.

Chapter 6 is the summary of the major conclusions in the characterization of TCE hazard and dose response.

**CONTENTS of TOXICOLOGICAL REVIEW for TRICHLOROETHYLENE
(CAS No. 79-01-6)**

LIST OF TABLES.....	xv
LIST OF FIGURES	xxvii
LIST OF ABBREVIATIONS AND ACRONYMS	xxx
FOREWORD	xxxvii
AUTHORS, CONTRIBUTORS, AND REVIEWERS	xxxviii
ACKNOWLEDGMENTS	xlii
EXECUTIVE SUMMARY	xliii
1. INTRODUCTION	1-1
2. EXPOSURE CHARACTERIZATION	2-1
2.1. ENVIRONMENTAL SOURCES	2-2
2.2. ENVIRONMENTAL FATE	2-6
2.2.1. Fate in Terrestrial Environments.....	2-6
2.2.2. Fate in the Atmosphere.....	2-6
2.2.3. Fate in Aquatic Environments.....	2-7
2.3. EXPOSURE CONCENTRATIONS	2-7
2.3.1. Outdoor Air—Measured Levels.....	2-7
2.3.2. Outdoor Air—Modeled Levels	2-10
2.3.3. Indoor Air.....	2-11
2.3.4. Water.....	2-13
2.3.5. Other Media.....	2-15
2.3.6. Biological Monitoring.....	2-16
2.4. EXPOSURE PATHWAYS AND LEVELS.....	2-17
2.4.1. General Population.....	2-17
2.4.1.1. Inhalation.....	2-17
2.4.1.2. Ingestion	2-18
2.4.1.3. Dermal.....	2-20
2.4.1.4. Exposure to TCE Related Compounds.....	2-21
2.4.2. Potentially Highly Exposed Populations.....	2-22
2.4.2.1. Occupational Exposure.....	2-22
2.4.2.2. Consumer Exposure	2-23
2.4.3. Exposure Standards.....	2-24
2.5. EXPOSURE SUMMARY.....	2-24
3. TOXICOKINETICS	3-1
3.1. ABSORPTION.....	3-2
3.1.1. Oral.....	3-2
3.1.2. Inhalation.....	3-4
3.1.3. Dermal.....	3-11
3.2. DISTRIBUTION AND BODY BURDEN.....	3-11
3.3. METABOLISM.....	3-19

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CONTENTS (continued)

3.3.1.	Introduction	3-19
3.3.2.	Extent of Metabolism	3-20
3.3.3.	Pathways of Metabolism	3-23
3.3.3.1.	Cytochrome P450-Dependent Oxidation	3-23
3.3.3.2.	Glutathione (GSH) Conjugation Pathway	3-40
3.3.3.3.	Relative Roles of the Cytochrome P450 (CYP) and Glutathione (GSH) Pathways	3-54
3.4.	TRICHLOROETHYLENE (TCE) EXCRETION	3-57
3.4.1.	Exhaled Air	3-57
3.4.2.	Urine	3-59
3.4.3.	Feces	3-61
3.5.	PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING OF TRICHLOROETHYLENE (TCE) AND ITS METABOLITES	3-62
3.5.1.	Introduction	3-62
3.5.2.	Previous Physiologically Based Pharmacokinetic (PBPK) Modeling of Trichloroethylene (TCE) for Risk Assessment Application	3-62
3.5.3.	Development and Evaluation of an Interim “Harmonized” Trichloroethylene (TCE) Physiologically Based Pharmacokinetic (PBPK) Model	3-64
3.5.4.	Physiologically Based Pharmacokinetic (PBPK) Model for Trichloroethylene (TCE) and Metabolites Used for This Assessment	3-67
3.5.4.1.	Introduction	3-67
3.5.4.2.	Updated Physiologically Based Pharmacokinetic (PBPK) Model Structure	3-67
3.5.4.3.	Specification of Physiologically Based Pharmacokinetic (PBPK) Model Parameter Prior Distributions	3-68
3.5.4.4.	Dose Metric Predictions	3-72
3.5.5.	Bayesian Estimation of Physiologically Based Pharmacokinetic (PBPK) Model Parameters, and Their Uncertainty and Variability	3-72
3.5.5.1.	Updated Pharmacokinetic Database	3-72
3.5.5.2.	Updated Hierarchical Population Statistical Model	3-81
3.5.5.3.	Use of Interspecies Scaling to Update Prior Distributions in the Absence of Other Data	3-82
3.5.5.4.	Implementation	3-84
3.5.6.	Evaluation of Updated Physiologically Based Pharmacokinetic (PBPK) Model	3-85
3.5.6.1.	Convergence	3-85
3.5.6.2.	Evaluation of Posterior Parameter Distributions	3-87
3.5.6.3.	Comparison of Model Predictions With Data	3-96
3.5.6.4.	Summary Evaluation of Updated Physiologically Based Pharmacokinetic (PBPK) Model	3-112
3.5.7.	Physiologically Based Pharmacokinetic (PBPK) Model Dose Metric Predictions	3-113

This document is a draft for review purposes only and does not constitute Agency policy.

CONTENTS (continued)

3.5.7.1.	Characterization of Uncertainty and Variability	3-113
3.5.7.2.	Implications for the Population Pharmacokinetics of Trichloroethylene (TCE)	3-128
3.5.7.3.	Overall Evaluation of Physiologically Based Pharmacokinetic (PBPK) Model-Based Internal Dose Predictions	3-135
4.	HAZARD CHARACTERIZATION	4-1
4.1.	EPIDEMIOLOGIC STUDIES ON CANCER AND TRICHLOROETHYLENE (TCE)—METHODOLOGICAL OVERVIEW	4-1
4.2.	GENETIC TOXICITY	4-29
4.2.1.	Trichloroethylene (TCE)	4-30
4.2.1.1.	DNA Binding Studies	4-30
4.2.1.2.	Bacterial Systems—Gene Mutations	4-32
4.2.1.3.	Fungal and Yeast Systems—Gene Mutations, Conversions and Recombination	4-35
4.2.1.4.	Mammalian Systems Including Human Studies	4-37
4.2.1.5.	Summary	4-49
4.2.2.	Trichloroacetic Acid (TCA)	4-50
4.2.2.1.	Bacterial Systems—Gene Mutations	4-50
4.2.2.2.	Mammalian Systems	4-52
4.2.2.3.	Summary	4-56
4.2.3.	Dichloroacetic Acid (DCA)	4-57
4.2.3.1.	Bacterial and Fungal Systems—Gene Mutations	4-57
4.2.3.2.	Mammalian Systems	4-61
4.2.3.3.	Summary	4-62
4.2.4.	Chloral Hydrate	4-63
4.2.4.1.	DNA Binding Studies	4-63
4.2.4.2.	Bacterial and Fungal Systems—Gene Mutations	4-70
4.2.4.3.	Mammalian Systems	4-71
4.2.4.4.	Summary	4-74
4.2.5.	Dichlorovinyl Cysteine (DCVC) and S-Dichlorovinyl Glutathione (DCVG)	4-74
4.2.6.	Trichloroethanol (TCOH)	4-79
4.2.7.	Synthesis and Overall Summary	4-80
4.3.	CENTRAL NERVOUS SYSTEM (CNS) TOXICITY	4-84
4.3.1.	Alterations in Nerve Conduction	4-85
4.3.1.1.	Trigeminal Nerve Function: Human Studies	4-85
4.3.1.2.	Nerve Conduction Velocity—Human Studies	4-90
4.3.1.3.	Trigeminal Nerve Function: Laboratory Animal Studies	4-90
4.3.1.4.	Discussion and Conclusions: Trichloroethylene (TCE)-Induced Trigeminal Nerve Impairment	4-91

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CONTENTS (continued)

4.3.2.	Auditory Effects	4-93
4.3.2.1.	Auditory Function: Human Studies	4-93
4.3.2.2.	Auditory Function: Laboratory Animal Studies	4-95
4.3.2.3.	Summary and Conclusion of Auditory Effects	4-99
4.3.3.	Vestibular Function	4-101
4.3.3.1.	Vestibular Function: Human Studies	4-101
4.3.3.2.	Vestibular Function: Laboratory Animal Data	4-101
4.3.3.3.	Summary and Conclusions for the Vestibular Function Studies	4-102
4.3.4.	Visual Effects	4-103
4.3.4.1.	Visual Effects: Human Studies	4-103
4.3.4.2.	Visual Effects: Laboratory Animal Data	4-105
4.3.4.3.	Summary and Conclusion of Visual Effects	4-107
4.3.5.	Cognitive Function	4-108
4.3.5.1.	Cognitive Effects: Human Studies	4-108
4.3.5.2.	Cognitive Effects: Laboratory Animal Studies	4-110
4.3.5.3.	Summary and Conclusions of Cognitive Function Studies	4-112
4.3.6.	Psychomotor Effects	4-113
4.3.6.1.	Psychomotor Effects: Human Studies	4-113
4.3.6.2.	Psychomotor Effects: Laboratory Animal Data	4-116
4.3.6.3.	Summary and Conclusions for Psychomotor Effects	4-121
4.3.7.	Mood Effects and Sleep Disorders	4-122
4.3.7.1.	Effects on Mood: Human Studies	4-122
4.3.7.2.	Effects on Mood: Laboratory Animal Findings	4-122
4.3.7.3.	Sleep Disturbances	4-123
4.3.8.	Developmental Neurotoxicity	4-123
4.3.8.1.	Human Studies	4-123
4.3.8.2.	Animal Studies	4-124
4.3.8.3.	Summary and Conclusions for the Developmental Neurotoxicity Studies	4-128
4.3.9.	Mechanistic Studies of Trichloroethylene (TCE) Neurotoxicity	4-128
4.3.9.1.	Dopamine Neuron Disruption	4-128
4.3.9.2.	Neurochemical and Molecular Changes	4-130
4.3.10.	Potential Mechanisms for Trichloroethylene (TCE)-Mediated Neurotoxicity	4-134
4.3.11.	Overall Summary and Conclusions—Weight of Evidence	4-137
4.4.	KIDNEY TOXICITY AND CANCER	4-141
4.4.1.	Human Studies of Kidney	4-141
4.4.1.1.	Nonspecific Markers of Nephrotoxicity	4-141
4.4.1.2.	End-Stage Renal Disease	4-147
4.4.2.	Human Studies of Kidney Cancer	4-147
4.4.2.1.	Studies of Job Titles and Occupations with Historical Trichloroethylene (TCE) Usage	4-148

This document is a draft for review purposes only and does not constitute Agency policy.

CONTENTS (continued)

4.4.2.2.	Cohort and Case-Controls Studies of Trichloroethylene (TCE) Exposure.....	4-159
4.4.2.3.	Examination of Possible Confounding Factors.....	4-163
4.4.2.4.	Susceptible Populations—Kidney Cancer and Trichloroethylene (TCE) Exposure.....	4-166
4.4.2.5.	Meta-Analysis for Kidney Cancer.....	4-167
4.4.3.	Human Studies of Somatic Mutation of von Hippel-Lindau (VHL) Gene.....	4-172
4.4.4.	Kidney Noncancer Toxicity in Laboratory Animals.....	4-177
4.4.5.	Kidney Cancer in Laboratory Animals.....	4-184
4.4.5.1.	Inhalation Studies of Trichloroethylene (TCE).....	4-184
4.4.5.2.	Gavage and Drinking Water Studies of Trichloroethylene (TCE).....	4-185
4.4.5.3.	Conclusions: Kidney Cancer in Laboratory Animals.....	4-187
4.4.6.	Role of Metabolism in Trichloroethylene (TCE) Kidney Toxicity.....	4-188
4.4.6.1.	<i>In Vivo</i> Studies of the Kidney Toxicity of Trichloroethylene (TCE) Metabolites.....	4-188
4.4.6.2.	<i>In Vitro</i> Studies of Kidney Toxicity of Trichloroethylene (TCE) and Metabolites.....	4-196
4.4.6.3.	Conclusions as to the Active Agents of Trichloroethylene (TCE)-Induced Nephrotoxicity.....	4-197
4.4.7.	Mode(s) of Action for Kidney Carcinogenicity.....	4-198
4.4.7.1.	Hypothesized Mode of Action: Mutagenicity.....	4-198
4.4.7.2.	Hypothesized Mode of Action: Cytotoxicity and Regenerative Proliferation.....	4-202
4.4.7.3.	Additional Hypothesized Modes of Action with Limited Evidence or Inadequate Experimental Support.....	4-204
4.4.7.4.	Conclusions About the Hypothesized Modes of Action.....	4-206
4.4.8.	Summary: Trichloroethylene (TCE) Kidney Toxicity, Carcinogenicity, and Mode-of-Action.....	4-208
4.5.	LIVER TOXICITY AND CANCER.....	4-210
4.5.1.	Liver Noncancer Toxicity in Humans.....	4-210
4.5.2.	Liver Cancer in Humans.....	4-217
4.5.3.	Experimental Studies of Trichloroethylene (TCE) in Rodents—Introduction.....	4-231
4.5.4.	Trichloroethylene (TCE)-Induced Liver Noncancer Effects.....	4-233
4.5.4.1.	Liver Weight.....	4-234
4.5.4.2.	Cytotoxicity.....	4-238
4.5.4.3.	Measures of DNA Synthesis, Cellular Proliferation, and Apoptosis.....	4-245
4.5.4.4.	Peroxisomal Proliferation and Related Effects.....	4-248
4.5.4.5.	Oxidative Stress.....	4-250
4.5.4.6.	Bile Production.....	4-251

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CONTENTS (continued)

4.5.4.7.	Summary: Trichloroethylene (TCE)-Induced Noncancer Effects in Laboratory Animals	4-253
4.5.5.	Trichloroethylene (TCE)-Induced Liver Cancer in Laboratory Animals....	4-254
4.5.5.1.	Negative or Inconclusive Studies of Mice and Rats.....	4-254
4.5.5.2.	Positive Trichloroethylene (TCE) Studies of Mice.....	4-262
4.5.5.3.	Summary: Trichloroethylene (TCE)-Induced Cancer in Laboratory Animals.....	4-264
4.5.6.	Role of Metabolism in Liver Toxicity and Cancer.....	4-264
4.5.6.1.	Pharmacokinetics of Chloral Hydrate (CH), Trichloroacetic Acid (TCA), and Dichloroacetic Acid (DCA) From Trichloroethylene (TCE) Exposure.....	4-265
4.5.6.2.	Comparisons Between Trichloroethylene (TCE) and Trichloroacetic Acid (TCA), Dichloroacetic Acid (DCA), and Chloral Hydrate (CH) Noncancer Effects	4-265
4.5.6.3.	Comparisons of Trichloroethylene (TCE)-Induced Carcinogenic Responses With Trichloroacetic Acid (TCA), Dichloroacetic Acid (DCA), and Chloral Hydrate (CH) Studies	4-282
4.5.6.4.	Conclusions Regarding the Role of Trichloroacetic Acid (TCA), Dichloroacetic Acid (DCA), and Chloral Hydrate (CH) in Trichloroethylene (TCE)-Induced Effects in the Liver	4-307
4.5.7.	Mode of Action (MOA) for Trichloroethylene (TCE) Liver Carcinogenicity	4-308
4.5.7.1.	Mutagenicity.....	4-308
4.5.7.2.	Peroxisome Proliferator Activated Receptor Alpha (PPAR α) Receptor Activation.....	4-310
4.5.7.3.	Additional Proposed Hypotheses and Key Events with Limited Evidence or Inadequate Experimental Support	4-316
4.5.7.4.	Mode of Action (MOA) Conclusions.....	4-325
4.6.	IMMUNOTOXICITY AND CANCERS OF THE IMMUNE SYSTEM.....	4-331
4.6.1.	Human Studies	4-331
4.6.1.1.	Noncancer Immune-Related Effects	4-331
4.6.1.2.	Cancers of the Immune System, Including Childhood Leukemia	4-343
4.6.2.	Animal Studies	4-373
4.6.2.1.	Immunosuppression.....	4-373
4.6.2.2.	Hypersensitivity.....	4-381
4.6.2.3.	Autoimmunity	4-384
4.6.2.4.	Cancers of the Immune System.....	4-397
4.6.3.	Summary	4-400
4.6.3.1.	Noncancer Effects	4-400
4.6.3.2.	Cancer.....	4-401

This document is a draft for review purposes only and does not constitute Agency policy.

CONTENTS (continued)

4.7.	RESPIRATORY TRACT TOXICITY AND CANCER.....	4-403
4.7.1.	Epidemiologic Evidence.....	4-403
4.7.1.1.	Chronic Effects: Inhalation	4-403
4.7.1.2.	Cancer.....	4-403
4.7.2.	Laboratory Animal Studies	4-415
4.7.2.1.	Respiratory Tract Animal Toxicity	4-415
4.7.2.2.	Respiratory Tract Cancer.....	4-423
4.7.3.	Role of Metabolism in Pulmonary Toxicity.....	4-427
4.7.4.	Mode of Action for Pulmonary Carcinogenicity.....	4-432
4.7.4.1.	Mutagenicity via Oxidative Metabolism.....	4-432
4.7.4.2.	Cytotoxicity Leading to Increased Cell Proliferation.....	4-434
4.7.4.3.	Additional Hypothesized Modes of Action with Limited Evidence or Inadequate Experimental Support.....	4-435
4.7.4.4.	Conclusions About the Hypothesized Modes of Action	4-436
4.7.5.	Summary and Conclusions.....	4-438
4.8.	REPRODUCTIVE AND DEVELOPMENTAL TOXICITY	4-440
4.8.1.	Reproductive Toxicity.....	4-440
4.8.1.1.	Human Reproductive Outcome Data	4-440
4.8.1.2.	Animal Reproductive Toxicity Studies	4-444
4.8.1.3.	Discussion/Synthesis of noncancer reproductive toxicity findings.....	4-460
4.8.2.	Cancers of the Reproductive System.....	4-466
4.8.2.1.	Human Data.....	4-467
4.8.2.2.	Animal studies.....	4-480
4.8.2.3.	Mode of Action for Testicular Tumors	4-482
4.8.3.	Developmental Toxicity	4-483
4.8.3.1.	Human Developmental Data	4-483
4.8.3.2.	Animal Developmental Toxicology Studies	4-506
4.8.3.3.	Discussion/Synthesis of Developmental Data.....	4-530
4.9.	OTHER SITE-SPECIFIC CANCERS	4-547
4.9.1.	Esophageal Cancer	4-547
4.9.2.	Bladder Cancer	4-556
4.9.3.	Central Nervous System and Brain Cancers	4-562
4.10.	SUSCEPTIBLE LIFESTAGES AND POPULATIONS	4-563
4.10.1.	Lifestages.....	4-567
4.10.1.1.	Early Lifestages.....	4-568
4.10.1.2.	Later Lifestages	4-577
4.10.2.	Other Susceptibility Factors	4-578
4.10.2.1.	Gender	4-578
4.10.2.2.	Genetic Variability	4-583
4.10.2.3.	Race/Ethnicity	4-585
4.10.2.4.	Pre-Existing Health Status.....	4-585
4.10.2.5.	Lifestyle Factors and Nutrition Status.....	4-586

This document is a draft for review purposes only and does not constitute Agency policy.

CONTENTS (continued)

4.10.3. Uncertainty of Database for Susceptible Populations	4-589
4.11. HAZARD CHARACTERIZATION	4-589
4.11.1. Characterization of Noncancer Effects.....	4-589
4.11.1.1. Neurotoxicity.....	4-589
4.11.1.2. Kidney Toxicity.....	4-594
4.11.1.3. Liver Toxicity.....	4-595
4.11.1.4. Immunotoxicity	4-597
4.11.1.5. Respiratory Tract Toxicity	4-598
4.11.1.6. Reproductive Toxicity	4-599
4.11.1.7. Developmental Toxicity	4-600
4.11.2. Characterization of Carcinogenicity.....	4-604
4.11.2.1. Summary Evaluation of Epidemiologic Evidence of Trichloroethylene (TCE) and Cancer	4-604
4.11.2.2. Summary of Evidence for Trichloroethylene (TCE) Carcinogenicity in Rodents	4-612
4.11.2.3. Summary of Additional Evidence on Biological Plausibility	4-614
4.11.3. Characterization of Factors Impacting Susceptibility	4-620
5. DOSE-RESPONSE ASSESSMENT	5-1
5.1. DOSE-RESPONSE ANALYSES FOR NONCANCER ENDPOINTS	5-1
5.1.1. Modeling Approaches and Uncertainty Factors for Developing Candidate Reference Values Based on Applied Dose.....	5-3
5.1.2. Candidate Critical Effects by Effect Domain.....	5-7
5.1.2.1. Candidate Critical Neurological Effects on the Basis of Applied Dose.....	5-7
5.1.2.2. Candidate Critical Kidney Effects on the Basis of Applied Dose.....	5-11
5.1.2.3. Candidate Critical Liver Effects on the Basis of Applied Dose.....	5-15
5.1.2.4. Candidate Critical Body Weight Effects on the Basis of Applied Dose.....	5-16
5.1.2.5. Candidate Critical Immunological Effects on the Basis of Applied Dose.....	5-16
5.1.2.6. Candidate Critical Respiratory Tract Effects on the Basis of Applied Dose.....	5-19
5.1.2.7. Candidate Critical Reproductive Effects on the Basis of Applied Dose.....	5-19
5.1.2.8. Candidate Critical Developmental Effects on the Basis of Applied Dose.....	5-25
5.1.2.9. Summary of cRfCs, cRfDs, and Candidate Critical Effects.....	5-30
5.1.3. Application of Physiologically Based Pharmacokinetic (PBPK) Model to Inter- and Intraspecies Extrapolation for Candidate Critical Effects	5-33
5.1.3.1. Selection of Dose Metrics for Different Endpoints.....	5-33

This document is a draft for review purposes only and does not constitute Agency policy.

CONTENTS (continued)

5.1.3.2.	Methods for Inter- and Intraspecies Extrapolation Using Internal Doses.....	5-45
5.1.3.3.	Results and Discussion of p-RfCs and p-RfDs for Candidate Critical Effects.....	5-62
5.1.4.	Uncertainties in cRfCs and cRfDs.....	5-63
5.1.4.1.	Qualitative Uncertainties.....	5-63
5.1.4.2.	Quantitative Uncertainty Analysis of Physiologically Based Pharmacokinetic (PBPK) Model-Based Dose Metrics for Lowest-Observed-Adverse-Effect Level (LOAEL) or No-Observed-Adverse-Effect Level (NOAEL)-Based Point of Departures (PODs).....	5-66
5.1.5.	Summary of Noncancer Reference Values.....	5-76
5.1.5.1.	Preferred Candidate Reference Values (cRfCs, cRfD, p-cRfCs and p-cRfDs) for Candidate Critical Effects.....	5-76
5.1.5.2.	Reference Concentration.....	5-82
5.1.5.3.	Reference Dose.....	5-85
5.2.	DOSE-RESPONSE ANALYSIS FOR CANCER ENDPOINTS.....	5-88
5.2.1.	Dose-Response Analyses: Rodent Bioassays.....	5-88
5.2.1.1.	Rodent Dose-Response Analyses: Studies and Modeling Approaches.....	5-88
5.2.1.2.	Rodent Dose-Response Analyses: Dosimetry.....	5-96
5.2.1.3.	Rodent Dose-Response Analyses: Results.....	5-109
5.2.1.4.	Uncertainties in Dose-Response Analyses of Rodent Bioassays.....	5-119
5.2.2.	Dose-Response Analyses: Human Epidemiologic Data.....	5-130
5.2.2.1.	Inhalation Unit Risk Estimate for Renal Cell Carcinoma Derived from Charbotel et al. (2006) Data.....	5-130
5.2.2.2.	Adjustment of the Inhalation Unit Risk Estimate for Multiple Sites.....	5-137
5.2.2.3.	Route-to-Route Extrapolation Using Physiologically Based Pharmacokinetic (PBPK) Model.....	5-141
5.2.3.	Summary of Unit Risk Estimates.....	5-144
5.2.3.1.	Inhalation Unit Risk Estimate.....	5-144
5.2.3.2.	Oral Unit Risk Estimate.....	5-146
5.2.3.3.	Application of Age-Dependent Adjustment Factors.....	5-147
6.	MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE.....	6-1
6.1.	HUMAN HAZARD POTENTIAL.....	6-1
6.1.1.	Exposure.....	6-1
6.1.2.	Toxicokinetics and Physiologically-Based Pharmacokinetic (PBPK) Modeling.....	6-2
6.1.3.	Noncancer Toxicity.....	6-3

This document is a draft for review purposes only and does not constitute Agency policy.

CONTENTS (continued)

- 6.1.3.1. Neurological Effects..... 6-4
- 6.1.3.2. Kidney Effects..... 6-5
- 6.1.3.3. Liver Effects..... 6-6
- 6.1.3.4. Immunological Effects..... 6-7
- 6.1.3.5. Respiratory Tract Effects..... 6-8
- 6.1.3.6. Reproductive Effects..... 6-8
- 6.1.3.7. Developmental Effects..... 6-9
- 6.1.4. Carcinogenicity..... 6-11
- 6.1.5. Susceptibility..... 6-17
- 6.2. DOSE-RESPONSE ASSESSMENT..... 6-18
 - 6.2.1. Noncancer Effects..... 6-18
 - 6.2.1.1. Background and Methods..... 6-18
 - 6.2.1.2. Uncertainties and Application of Uncertainty Factors (UFs)..... 6-19
 - 6.2.1.3. Candidate Critical Effects and Reference Values..... 6-23
 - 6.2.1.4. Noncancer Reference Values..... 6-28
 - 6.2.2. Cancer..... 6-31
 - 6.2.2.1. Background and Methods..... 6-31
 - 6.2.2.2. Inhalation Unit Risk Estimate..... 6-32
 - 6.2.2.3. Oral Unit Risk Estimate..... 6-34
 - 6.2.2.4. Uncertainties in Cancer Dose-Response Assessment..... 6-35
 - 6.2.2.5. Application of Age-Dependent Adjustment Factors..... 6-40
- 6.3. OVERALL CHARACTERIZATION OF TCE HAZARD AND DOSE RESPONSE..... 6-41
- REFERENCES..... R-1
- APPENDIX A: PBPK MODELING OF TCE AND METABOLITES–DETAILED METHODS AND RESULTS..... A-1
- APPENDIX B: SYSTEMATIC REVIEW OF EPIDEMIOLOGIC STUDIES ON CANCER AND TRICHLOROETHYLENE (TCE) EXPOSURE..... B-1
- APPENDIX C: META-ANALYSIS OF CANCER RESULTS FROM EPIDEMIOLOGICAL STUDIES..... C-1
- APPENDIX D: NEUROLOGICAL EFFECTS OF TRICHLOROETHYLENE..... D-1
- APPENDIX E: ANALYSIS OF LIVER AND COEXPOSURE ISSUES FOR THE TCE TOXICOLOGICAL REVIEW..... E-1
- APPENDIX F: TCE NONCANCER DOSE-RESPONSE ANALYSES..... F-1

This document is a draft for review purposes only and does not constitute Agency policy.

CONTENTS (continued)

APPENDIX G: TCE CANCER DOSE-RESPONSE ANALYSES WITH RODENT
CANCER BIOASSAY DATA G-1

APPENDIX H: LIFETABLE ANALYSIS AND WEIGHTED LINEAR REGRESSION
BASED ON RESULTS FROM CHARBOTEL ET AL..... H-1

LIST OF TABLES

2-1. TCE metabolites and related parent compounds 2-1

2-2. Chemical properties of TCE 2-2

2-3. Properties and uses of TCE related compounds 2-3

2-4. Toxics Release Inventory (TRI) releases of TCE 2-4

2-5. Concentrations of trichloroethylene in ambient air 2-8

2-6. TCE ambient air monitoring data 2-9

2-7. Mean TCE air levels across monitors by land setting and use (1985 to 1998)..... 2-9

2-8. Concentrations of trichloroethylene in water based on pre-1990 studies 2-13

2-9. Levels in food 2-16

2-10. TCE levels in whole blood by population percentile..... 2-17

2-11. Modeled 1999 annual exposure concentrations for trichloroethylene 2-18

2-12. Preliminary estimates of TCE intake from food ingestion 2-20

2-13. Preliminary intake estimates of TCE and TCE-related chemicals..... 2-21

2-14. Years of solvent use in industrial degreasing and cleaning operations 2-23

2-15. TCE standards..... 2-24

3-1. Blood:air PC values for humans 3-5

3-2. Blood:air PC values for rats and mice 3-6

3-3. Air and blood concentrations during exposure to TCE in humans..... 3-7

3-4. Retention of inhaled TCE vapor in humans..... 3-8

3-5. Uptake of TCE in human volunteers following 4 hour exposure to 70 ppm 3-8

3-6. Concentrations of TCE in maternal and fetal blood at birth..... 3-13

3-7. Distribution of TCE to rat tissues following inhalation exposure 3-14

3-8. Tissue:blood partition coefficient values for TCE..... 3-16

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

3-9.	Age-dependence of tissue:air partition coefficients in rats.....	3-17
3-10.	Predicted maximal concentrations of TCE in rat blood following a 6-hour inhalation exposure.....	3-17
3-11.	Tissue distribution of TCE metabolites following inhalation exposure.....	3-18
3-12.	Binding of ¹⁴ C from [¹⁴ C]TCE in rat liver and kidney at 72 hours after oral administration of 200 mg/kg [¹⁴ C]TCE.....	3-19
3-13.	<i>In vitro</i> TCE oxidative metabolism in hepatocytes and microsomal fractions.....	3-26
3-14.	<i>In vitro</i> kinetics of trichloroethanol and trichloroacetic acid formation from chloral hydrate in rat, mouse, and human liver homogenates.....	3-29
3-15.	<i>In vitro</i> kinetics of DCA metabolism in hepatic cytosol of mice, rats, and humans.....	3-31
3-16.	TCOH and TCA formed from CH <i>in vitro</i> in lysed whole blood of rats and mice or fractionated blood of humans.....	3-33
3-17.	Reported TCA plasma binding parameters.....	3-34
3-18.	Partition coefficients for TCE oxidative metabolites.....	3-35
3-19.	Urinary excretion of trichloroacetic acid by various species exposed to trichloroethylene.....	3-37
3-20.	P450 isoform kinetics for metabolism of TCE to CH in human, rat, and mouse recombinant P450s.....	3-38
3-21.	P450 isoform activities in human liver microsomes exhibiting different affinities for TCE.....	3-39
3-22.	Comparison of peak blood concentrations in humans exposed to 100 ppm TCE for 4 hours.....	3-43
3-23.	GSH conjugation of TCE in liver and kidney cellular fractions in humans, male F344 rats, and male B6C3F1 mice.....	3-44
3-24.	Kinetics of TCE metabolism via GSH conjugation in male F344 rat kidney and human liver and kidney cellular and subcellular fractions.....	3-45
3-25.	GGT activity in liver and kidney subcellular fractions of mice, rats, and humans.....	3-50
3-26.	Multispecies comparison of whole-organ activity levels of GGT and dispeptidase.....	3-51

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

3-27. Comparison of hepatic *in vitro* oxidation and conjugation of TCE..... 3-55

3-28. Estimates of DCVG in blood relative to inhaled TCE dose in humans exposed to 50 and 100 ppm..... 3-56

3-29. Concentrations of TCE in expired breath from inhalation-exposed humans..... 3-58

3-30. Conclusions from evaluation of Hack et al. (2006), and implications for PBPK model development..... 3-65

3-31. Discussion of changes to the Hack et al. (2006) PBPK model implemented for this assessment..... 3-70

3-32. PBPK model-based dose metrics 3-73

3-33. Rodent studies with pharmacokinetic data considered for analysis..... 3-74

3-34. Human studies with pharmacokinetic data considered for analysis 3-78

3-35. Parameters for which scaling from mouse to rat, or from mouse and rat to human, was used to update the prior distributions..... 3-83

3-36. Physiological parameters: prior and posterior combined uncertainty and variability 3-88

3-37. Distribution parameters: prior and posterior combined uncertainty and variability 3-90

3-38. Absorption parameters: prior and posterior combined uncertainty and variability 3-92

3-39. TCE metabolism parameters: prior and posterior combined uncertainty and variability 3-93

3-40. Metabolite metabolism parameters: prior and posterior combined uncertainty and variability 3-94

3-41. Estimates of the residual error 3-98

3-42. Summary comparison of updated PBPK model predictions and *in vivo* data in mice..... 3-100

3-43. Summary comparison of updated PBPK model predictions and *in vivo* data used for “calibration” in rats..... 3-103

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

3-44.	Summary comparison of updated PBPK model predictions and <i>in vivo</i> data used for “out-of-sample” evaluation in rats	3-106
3-45.	Summary comparison of updated PBPK model predictions and <i>in vivo</i> data used for “calibration” in humans	3-109
3-46.	Summary comparison of updated PBPK model predictions and <i>in vivo</i> data used for “out-of-sample” evaluation in humans	3-111
3-47.	Posterior predictions for representative internal doses: mouse.....	3-123
3-48.	Posterior predictions for representative internal doses: rat.....	3-124
3-49.	Posterior predictions for representative internal doses: human	3-125
3-50.	Degree of variance in dose metric predictions due to incomplete convergence, combined uncertainty and population variability, uncertainty in particular human population percentiles, model fits to <i>in vivo</i> data.	3-136
4-1.	Description of epidemiologic cohort and proportionate mortality ratio (PMR) studies assessing cancer and TCE exposure	4-2
4-2.	Case-control epidemiologic studies examining cancer and TCE exposure	4-9
4-3.	Geographic-based studies assessing cancer and TCE exposure	4-19
4-4.	Standards of epidemiologic study design and analysis use for identifying cancer hazard and TCE exposure.	4-21
4-5.	Summary of criteria for meta-analysis study selection.....	4-25
4-6.	TCE genotoxicity: bacterial assays.....	4-33
4-7.	TCE genotoxicity: fungal and yeast systems	4-36
4-8.	TCE genotoxicity: mammalian systems—gene mutations and chromosome aberrations.....	4-38
4-9.	TCE genotoxicity: mammalian systems—micronucleus, sister chromatic exchanges.....	4-43
4-10.	TCE genotoxicity: mammalian systems—unscheduled DNA synthesis, DNA strand breaks/protein crosslinks, cell transformation.....	4-47
4-11.	Genotoxicity of Trichloroacetic acid—bacterial systems.....	4-51

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

4-12. TCA Genotoxicity—mammalian systems 4-54

4-13. Genotoxicity of dichloroacetic acid 4-58

4-14. Genotoxicity of dichloroacetic acid—mammalian systems 4-59

4-15. Chloral hydrate genotoxicity: bacterial, yeast and fungal systems 4-64

4-16. Chloral hydrate genotoxicity: mammalian systems—all genetic endpoints,
in vitro 4-66

4-17. Chloral hydrate genotoxicity: mammalian systems—all genetic damage, *in vivo* 4-68

4-18. TCE GSH conjugation metabolites genotoxicity 4-76

4-19. Genotoxicity of trichloroethanol 4-80

4-20. Summary of human trigeminal nerve and nerve conduction velocity studies 4-86

4-21. Summary of animal trigeminal nerve studies 4-91

4-22. Summary of human auditory function studies 4-94

4-23. Summary of animal auditory function studies 4-97

4-24. Summary of mammalian sensory studies—vestibular and visual systems 4-102

4-25. Summary of human visual function studies 4-104

4-26. Summary of animal visual system studies 4-106

4-27. Summary of human cognition effect studies 4-109

4-28. Summary of animal cognition effect studies 4-111

4-29. Summary of human choice reaction time studies 4-114

4-30. Summary of animal psychomotor function and reaction time studies 4-117

4-31. Summary of animal locomotor activity studies 4-119

4-32. Summary of human developmental neurotoxicity associated with TCE
exposures 4-124

4-33. Summary of mammalian *in vivo* developmental neurotoxicity studies—oral
exposures 4-126

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

4-34. Summary of animal dopamine neuronal studies..... 4-130

4-35. Summary of neurophysiological, neurochemical, and neuropathological effects with TCE exposure 4-132

4-36. Summary of *in vitro* ion channel effects with TCE exposure..... 4-134

4-37. Summary of human kidney toxicity studies..... 4-143

4-38. Summary of human studies on TCE exposure and kidney cancer..... 4-149

4-39. Summary of case-control studies on kidney cancer and occupation or job title..... 4-156

4-40. Summary of human studies on somatic mutations of the VHL gene..... 4-174

4-41. Summary of renal toxicity and tumor findings in gavage studies of trichloroethylene by NTP (1990)..... 4-179

4-42. Summary of renal toxicity and tumor findings in gavage studies of trichloroethylene by NCI (1976)..... 4-181

4-43. Summary of renal toxicity findings in gavage studies of trichloroethylene by Maltoni et al. (1988) 4-181

4-44. Summary of renal toxicity and tumor incidence in gavage studies of trichloroethylene by NTP (1988)..... 4-182

4-45. Summary of renal toxicity and tumor findings in inhalation studies of trichloroethylene by Maltoni et al. (1988)..... 4-183

4-46. Summary of renal tumor findings in inhalation studies of trichloroethylene by Henschler et al. (1980) and Fukuda et al. (1983)..... 4-185

4-47. Summary of renal tumor findings in gavage studies of trichloroethylene by Henschler et al. (1984) and Van Duuren et al. (1979)..... 4-187

4-48. Summary of histological changes in renal proximal tubular cells induced by chronic exposure to TCE, DCVC, and TCOH..... 4-190

4-49. Summary of human liver toxicity studies 4-212

4-50. Selected results from epidemiologic studies of TCE exposure and cirrhosis..... 4-215

4-51. Selected results from epidemiologic studies of TCE exposure and liver cancer 4-219

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

4-52. Summary of liver tumor findings in gavage studies of trichloroethylene by NTP (1990) 4-255

4-53. Summary of liver tumor findings in gavage studies of trichloroethylene by NCI (1976)..... 4-256

4-54. Summary of liver tumor incidence in gavage studies of trichloroethylene by NTP (1988) 4-257

4-55. Summary of liver tumor findings in inhalation studies of trichloroethylene by Maltoni et al. (1988) 4-258

4-56. Summary of liver tumor findings in inhalation studies of trichloroethylene by Henschler et al. (1980) and Fukuda et al. (1983)..... 4-259

4-57. Summary of liver tumor findings in gavage studies of trichloroethylene by Henschler et al. (1984)..... 4-260

4-58. Studies of immune parameters and trichloroethylene in humans 4-333

4-59. Case-control studies of autoimmune diseases with measures of trichloroethylene exposure 4-341

4-60. Incidence cohort studies of TCE exposure and lymphopoietic and hematopoietic cancer risk 4-347

4-61. Mortality cohort and PMR studies of TCE exposure and lymphopoietic and hematopoietic cancer risk 4-350

4-62. Case-control studies of TCE exposure and lymphopoietic cancer or leukemia 4-358

4-63. Geographic-based studies of TCE and non-Hodgkin lymphoma or leukemia in adults 4-362

4-64. Selected results from epidemiologic studies of TCE exposure and childhood leukemia..... 4-365

4-65. Summary of TCE immunosuppression studies..... 4-374

4-66. Summary of TCE hypersensitivity studies 4-382

4-67. Summary of autoimmune-related studies of TCE and metabolites in mice and rats..... 4-385

4-68. Malignant lymphomas incidence in mice exposed to TCE in gavage and inhalation exposure studies 4-398

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

4-69. Leukemia incidence in rats exposed to TCE in gavage and inhalation exposure studies 4-399

4-70. Selected results from epidemiologic studies of TCE exposure and lung cancer 4-404

4-71. Selected results from epidemiologic studies of TCE exposure and laryngeal cancer 4-411

4-72. Animal toxicity studies of trichloroethylene..... 4-416

4-73. Animal carcinogenicity studies of trichloroethylene 4-424

4-74. Human reproductive effects..... 4-445

4-75. Summary of mammalian *in vivo* reproductive toxicity studies—*inhalation* exposures..... 4-447

4-76. Summary of mammalian *in vivo* reproductive toxicity studies—*oral* exposures 4-449

4-77. Summary of adverse female reproductive outcomes associated with TCE exposures..... 4-461

4-78. Summary of adverse male reproductive outcomes associated with TCE exposures..... 4-463

4-79. Summary of human studies on TCE exposure and prostate cancer..... 4-469

4-80. Summary of human studies on TCE exposure and breast cancer..... 4-472

4-81. Summary of human studies on TCE exposure and cervical cancer..... 4-475

4-82. Histopathology findings in reproductive organs..... 4-481

4-83. Testicular tumors in male rats exposed to TCE, adjusted for reduced survival 4-482

4-84. Developmental studies in humans 4-484

4-85. Summary of mammalian *in vivo* developmental toxicity studies—*inhalation* exposures..... 4-507

4-86. Ocular defects observed..... 4-508

4-87. Summary of mammalian *in vivo* developmental toxicity studies—*oral* exposures..... 4-509

4-88. Types of congenital cardiac defects observed in TCE-exposed fetuses 4-517

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

4-89. Types of heart malformations per 100 fetuses 4-518

4-90. Congenital cardiac malformations 4-52

4-91. Summary of adverse fetal and early neonatal outcomes associated with TCE exposures..... 4-531

4-92. Summary of studies that identified cardiac malformations associated with TCE exposures..... 4-533

4-93. Events in cardiac valve formation in mammals and birds 4-536

4-94. Summary of other structural developmental outcomes associated with TCE exposures..... 4-540

4-95. Summary of developmental neurotoxicity associated with TCE exposures..... 4-542

4-96. Summary of developmental immunotoxicity associated with TCE exposures 4-544

4-97. Summary of childhood cancers associated with TCE exposures..... 4-546

4-98. Selected observations from case-control studies of TCE exposure and esophageal cancer 4-548

4-99. Summary of human studies on TCE exposure and esophageal cancer..... 4-551

4-100. Summary of human studies on TCE exposure and bladder cancer 4-558

4-101. Summary of human studies on TCE exposure and brain cancer 4-564

4-102. Estimated lifestage-specific daily doses for TCE in water 4-570

5-1. Neurological effects in studies suitable for dose-response, and corresponding cRfCs and cRfDs..... 5-8

5-2. Kidney, liver, and body weight effects in studies suitable for dose-response, and corresponding cRfCs and cRfDs..... 5-12

5-3. Immunological effects in studies suitable for dose-response, and corresponding cRfCs and cRfDs..... 5-17

5-4. Reproductive effects in studies suitable for dose-response, and corresponding cRfCs and cRfDs..... 5-21

5-5. Developmental effects in studies suitable for dose-response, and corresponding cRfCs and cRfDs..... 5-26

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

5-6. Ranges of cRfCs based on applied dose for various noncancer effects associated with inhalation TCE exposure 5-31

5-7. Ranges of cRfDs based on applied dose for various noncancer effects associated with oral TCE exposure 5-32

5-8. cRfCs and cRfDs and p-cRfCs and p-cRfDs for candidate critical neurological effects 5-49

5-9. cRfCs and cRfDs and p-cRfCs and p-cRfDs for candidate critical kidney effects 5-51

5-10. cRfCs and cRfDs and p-cRfCs and p-cRfDs for candidate critical liver effects 5-53

5-11. cRfCs and cRfDs and p-cRfCs and p-cRfDs for candidate critical immunological effects 5-54

5-12. cRfCs and cRfDs and p-cRfCs and p-cRfDs for candidate critical reproductive effects 5-56

5-13. cRfCs and cRfDs and p-cRfCs and p-cRfDs for candidate critical developmental effects 5-59

5-14. Comparison of “sensitive individual” HECs or HEDs for neurological effects based on PBPK modeled internal dose metrics at different levels of confidence and sensitivity, at the NOAEL or LOAEL 5-69

5-15. Comparison of “sensitive individual” HECs or HEDs for kidney and liver effects based on PBPK modeled internal dose metrics at different levels of confidence and sensitivity, at the NOAEL or LOAEL 5-70

5-16. Comparison of “sensitive individual” HECs or HEDs for immunological effects based on PBPK modeled internal dose metrics at different levels of confidence and sensitivity, at the NOAEL or LOAEL 5-72

5-17. Comparison of “sensitive individual” HECs or HEDs for reproductive effects based on PBPK modeled internal dose metrics at different levels of confidence and sensitivity, at the NOAEL or LOAEL 5-73

5-18. Comparison of “sensitive individual” HECs or HEDs for developmental effects based on PBPK modeled internal dose metrics at different levels of confidence and sensitivity, at the NOAEL or LOAEL 5-75

5-19. Lowest p-cRfCs or cRfCs for different effect domains 5-77

5-20. Lowest p-cRfDs or cRfDs for different effect domains 5-79

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

5-21. Lowest p-cRfCs for candidate critical effects for different types of effect based on primary dose metric 5-81

5-22. Lowest p-cRfDs for candidate critical effects for different types of effect based on primary dose metric 5-81

5-23. Summary of critical studies, effects, PODs, and UFs supporting the RfC 5-84

5-24. Summary of critical studies, effects, PODs, and UFs supporting the RfD 5-87

5-25. Inhalation bioassays 5-89

5-26. Oral bioassays 5-90

5-27. Specific dose-response analyses performed and dose metrics used 5-94

5-28. Mean PBPK model predictions for weekly internal dose in humans exposed continuously to low levels of TCE via inhalation (ppm) or orally (mg/kg/d) 5-109

5-29. Summary of PODs and unit risk estimates for each sex/species/bioassay/tumor type (inhalation) 5-110

5-30. Summary of PODs and unit risk estimates for each sex/species/bioassay/tumor type (oral) 5-112

5-31. Comparison of survival-adjusted results for 3 oral male rat data sets 5-116

5-32. Inhalation: most sensitive bioassay for each sex/species combination 5-120

5-33. Oral: most sensitive bioassay for each sex/species combination 5-120

5-34. Summary of PBPK model-based uncertainty analysis of unit risk estimates for each sex/species/bioassay/tumor type (inhalation) 5-127

5-35. Summary of PBPK model-based uncertainty analysis of unit risk estimates for each sex/species/bioassay/tumor type (oral) 5-128

5-36. Results from Charbotel et al. on relationship between TCE exposure and RCC 5-131

5-37. Extra risk estimates for RCC incidence from various levels of lifetime exposure to TCE, using linear cumulative exposure model 5-133

5-38. EC01, LEC01, and unit risk estimates for RCC incidence, using linear cumulative exposure model 5-134

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF TABLES (continued)

5-39. Relative contributions to extra risk for cancer incidence from TCE exposure for multiple tumor types..... 5-140

5-40. Route-to-route extrapolation of site-specific inhalation unit risks to oral slope factors..... 5-144

5-41. Estimates of age-specific water ingestion rates 5-151

5-42. Sample calculation for total lifetime cancer risk based on the kidney unit risk estimate, adjusting for potential risk at multiple sites and for potential increased early-life susceptibility and assuming a constant lifetime exposure to 1 µg/mL of TCE in drinking water 5-152

LIST OF FIGURES

2-1.	Molecular structure of TCE.	2-2
2-2.	Source contribution to TCE emissions.	2-5
2-3.	Annual emissions of TCE.	2-6
2-4.	Modeled ambient air concentrations of TCE.	2-11
3-1.	Gas uptake data from closed chamber exposure of rats to TCE.	3-10
3-2.	Disposition of [¹⁴ C]TCE administered by oral gavage in mice.	3-21
3-3.	Disposition of [¹⁴ C]TCE administered by oral gavage in rats.	3-22
3-4.	Scheme for the oxidative metabolism of TCE.	3-24
3-5.	Scheme for GSH-dependent metabolism of TCE.	3-41
3-6.	Interorgan TCE transport and metabolism via the GSH pathway.	3-48
3-7.	Overall structure of PBPK model for TCE and metabolites used in this assessment.	3-69
3-8.	Schematic of how posterior predictions were generated for comparison with experimental data.	3-97
3-9.	Comparison of urinary excretion data for NAcDCVC and predictions from the Hack et al. and the updated PBPK models.	3-107
3-10.	Comparison of DCVG concentrations in human blood and predictions from the updated.	3-112
3-11.	PBPK model predictions for the fraction of intake that is metabolized under continuous inhalation and oral exposure conditions in mice, rats, and humans.	3-114
3-12.	PBPK model predictions for the fraction of intake that is metabolized by oxidation under continuous inhalation and oral exposure conditions in mice, rats, and humans.	3-115
3-13.	PBPK model predictions for the fraction of intake that is metabolized by GSH conjugation under continuous inhalation and oral exposure conditions in mice, rats, and humans.	3-116
3-14.	PBPK model predictions for the fraction of intake that is bioactivated DCVC in the kidney under continuous inhalation and oral exposure conditions in rats and humans.	3-117

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF FIGURES (continued)

3-15. PBPK model predictions for fraction of intake that is oxidized in the respiratory tract under continuous inhalation and oral exposure conditions in mice, rats, and humans 3-118

3-16. PBPK model predictions for the fraction of intake that is “untracked” oxidation of TCE in the liver under continuous inhalation and oral exposure conditions in mice, rats, and humans..... 3-119

3-17. PBPK model predictions for the weekly AUC of TCE in venous blood per unit exposure under continuous inhalation and oral exposure conditions in mice, rats, and humans 3-120

3-18. PBPK model predictions for the weekly AUC of TCOH in blood per unit exposure under continuous inhalation and oral exposure conditions in mice, rats, and humans..... 3-121

3-19. PBPK model predictions for the weekly AUC of TCA in the liver per unit exposure under continuous inhalation and oral exposure conditions in mice, rats, and humans..... 3-122

4-1. Meta-analysis of kidney cancer and overall TCE exposure..... 4-169

4-2. Meta-analysis of kidney cancer and TCE exposure—highest exposure groups..... 4-171

4-3. Relative risk estimates of liver and biliary tract cancer and overall TCE exposure. ... 4-227

4-4. Meta-analysis of liver cancer and TCE exposure—highest exposure groups 4-229

4-5. Comparison of average fold-changes in relative liver weight to control and exposure concentrations of 2 g/L or less in drinking water for TCA and DCA in male B6C3F1 mice for 14–30 days 4-267

4-6. Comparisons of fold-changes in average relative liver weight and gavage dose of male B6C3F1 mice for 10–28 days of exposure and in male B6C3F1 and Swiss mice. 4-269

4-7. Comparison of fold-changes in relative liver weight for data sets in male B6C3F1, Swiss, and NRM1 mice between TCE studies and studies of direct oral TCA administration to B6C3 F1 mice..... 4-271

4-8. Fold-changes in relative liver weight for data sets in male B6C3F1, Swiss, and NRM1 mice reported by TCE studies of duration 28–42 days using internal dose metrics predicted by the PBPK model described in Section 3.5..... 4-27

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF FIGURES (continued)

4-9. Dose-response relationship, expressed as percent incidence and fold-increase over controls, for TCE hepatocarcinogenicity in NCI 4-287

4-10. Dose-response relationship, expressed as incidence and fold-increase over controls, for TCE hepatocarcinogenicity in Maltoni et al..... 4-287

4-11. Dose-response data for hepatocellular carcinomas incidence and multiplicity, induced by DCA from DeAngelo et al. 4-288

4-12. Reported incidences of hepatocellular carcinomas and adenomas plus carcinomas in various studies in B6C3F1 mice..... 4-290

4-13. Reported incidence of hepatocellular carcinomas induced by DCA and TCA in 104-week studies..... 4-292

4-14. Effects of dietary control on the dose-response curves for changes in liver tumor incidences induced by CH in diet..... 4-296

4-15. Meta-analysis of lymphoma and overall TCE exposure..... 4-370

4-16. Meta-analysis of lymphoma and TCE exposure—highest exposure groups 4-371

5-1. Flow-chart of the process used to derive the RfD and RfC for noncancer effects. 5-2

5-2. Flow-chart for dose-response analyses of rodent noncancer effects using PBPK model-based dose metrics. 5-46

5-3. Schematic of combined interspecies, intraspecies, and route-to-route extrapolation from a rodent study LOAEL or NOAEL. 5-47

5-4. Flow-chart for uncertainty analysis of HECs and HEDs derived using PBPK model-based dose metrics. 5-67

5-5. Flow-chart for dose-response analyses of rodent bioassays using PBPK model-based dose metrics. 5-108

5-6. Flow-chart for uncertainty analysis of dose-response analyses of rodent bioassays using PBPK model-based dose metrics 5-126

5-7. Flow-chart for route-to-route extrapolation of human site-specific cancer inhalation unit risks to oral slope factors. 5-142

This document is a draft for review purposes only and does not constitute Agency policy.

LIST OF ABBREVIATIONS AND ACRONYMS

1,2-DCVC	S-(1,2-dichlorovinyl)-L-cysteine
[¹⁴ C]TCE	[¹⁴ C]-radio labeled TCE
17-β-HSD	17-β-hydroxy steroid dehydrogenase
8epiPGF	8-epiprostaglandin F2alpha
8-OHdG	8-hydroxy-2' deoxyguanosine
ADAF	age-dependent adjustment factor
ADME	absorption, distribution, metabolism, and excretion
AIC	Akaike Information Criteria
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANCA	antineutrophil-cytoplasmic antibody
ASD	autism spectrum disorder
ASPEN	Assessment System for Population Exposure Nationwide
AST	aspartate aminotrasferase
ATF-2	activating transcription factor 2
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area-under-the-curve
AV	atrioventricular
AVC	atrioventricular canal
AZ DHS	Arizona Department of Health Services
BAER	brainstem auditory-evoked response
BAL	bronchoalveolar lavage
BMD	benchmark dose
BMDL	benchmark dose lower bound
BMDS	BenchMark Dose Software
BMI	body mass index
BMR	benchmark response
BSO	buthionine-(S,R)-sulfoximine
BW	body weight

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

CA DHS	California Department of Health Services
CH	chloral hydrate
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CO ₂	carbon dioxide
CoA	coenzyme A
cRfCs	candidate RfCs
cRfDs	candidate RfDs
CRT	choice reaction time
CYP	cytochrome
DBF	D-type peroxisomal bifunctional protein
DBP	dibutyl phthalate
DCA	dichloroacetic acid
DCAC	dichloroacetyl chloride
DCE	dichloroethane
DCVC	dichlorovinyl cysteine
DCVG	S-dichlorovinyl glutathione
DCVT	S-(1,2-dichlorovinyl) thiol
DEHA	di(2-ethylhexyl) adipate
DEHP	di(2-ethylhexyl) phthalate
DHEAS	dehydroepiandrosterone sulphate
DNP	dinitrophenol
EC ₅₀	median effective concentrations
ECC	extrahepatic cholangiocarcinoma
EC _x	effective concentration corresponding to an extra risk of x%
EEG	electroencephalograph
ERG	electroretinogram
FAA	fumarylacetoacetate
FDVE	fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

FFVC	(<i>E,Z</i>)-S-(1-fluoro-2-fluoromethoxy-2-(trifluoromethyl)vinyl)-Lcysteine
FMO	flavin mono-oxygenase
FOB	functional observational battery
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony stimulating factor
G6PDH	glucose 6p dehydrogenase
GA	glomerular antigen
GABA	gamma-amino butyric acid
GD	gestation day
GGT	γ -glutamyl transpeptidase or γ -transpeptidase
GI	gastro-intestinal
GIS	geographic information system
GSD	geometric standard deviation
GSH	glutathione
GST	glutathione-S-transferase
GT	glutamyl transferase
H&E	hematoxylin and eosin
H ₂ O	water
H ₂ O ₂	hydrogen peroxide
HAP	hazardous air pollutant
HCC	hepatocellular carcinoma
HCl	hydrochloric acid
HDL-C	high density lipoprotein-cholesterol
HEC	human equivalent concentration
HED	human equivalent dose
HH	Hamberger and Hamilton
HPT	hypothalamic-pituitary-testis
i.a.	intra-arterial
i.p.	intraperitoneal
i.v.	intravenous

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

IARC	International Agency for Research on Cancer
ICC	intrahepatic cholangiocarcinoma
ICD	International Classification of Disease
ICRP	The International Commission on Radiological Protection
idPOD	internal dose points of departure
IDR	incidence density ratio
IGF-II	insulin-like growth factor-II (gene)
IL	interleukin
IRIS	Integrated Risk Information System
IUGR	intrauterine growth restriction
LDH	lactate dehydrogenase
LEC	lowest effective concentration
LEC _x	lowest effective concentration corresponding to an extra risk of x%
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
LOH	loss of heterozygosity
LORR	loss of righting reflex
MA DPH	Massachusetts Department of Public Health
MA	maleylacetone
MAA	maleylacetoacetate
MCA	monochloroacetic acid
MCMC	Markov chain Monte Carlo
MCP	methylclofenapate
MLE	maximum likelihood estimate
MMPI	Minnesota Multiphasic Personal Inventory
MNU	methyl nitrosourea
MOA	mode of action
MSW	multistage Weibull
NAC	N-acetylcysteine
NAcDCVC	N-acetyl-S-(1,2-dichlorovinyl)-L-cysteine

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

NAG	N-acetyl- β -D-glucosaminidase
NAT	N-acetyl transferase
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NHL	non-Hodgkin's lymphoma
NK	natural killer
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NPL	National Priorities List
NPMC	nonpurified rat peritoneal mast
NRC	National Research Council
NSATA	National-Scale Air Toxics Assessment
NTP	National Toxicology Program
NYS DOH	New York State Department of Health
OECD	Organization for Economic Co-operation and Development
OFT	outflow tract
OP	oscillatory potential
OR	odds ratio
p.v.	intraperivenous
PB	TCE blood-air partition coefficient
PBPK	physiologically based pharmacokinetics
PCE	perchloroethylene
PCEs	polychromatic erythrocytes
PCNA	proliferating cell nuclear antigen
PCO	palmitoyl-CoA oxidation
PCR	polymerase chain reaction
p-cRfC	PBPK model-based candidate RfCs
p-cRfD	PBPK model-based candidate RfDs
PFU	plaque-forming units

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

PND	postnatal day
PO ₂	partial pressure oxygen
POD	point of departure
PPAR α	peroxisome proliferator activated receptor alpha
QC	quality control
RBL-2H3	rat basophilic leukemia
RCC	renal cell carcinoma
RfC	inhalation reference concentration
RfD	oral reference dose
ROS	reactive oxygen species
RR	relative risk
RRp	pooled RR
RT	reaction time
S9	metabolic activation system
SBA	serum bile acids
SCEs	sister chromatid exchanges
S-D	Sprague-Dawley
SD	standard deviation
SDH	sorbitol dehydrogenase
SEER	Surveillance, Epidemiology, and End Results
SES	socio-economic status
SGA	small for gestational age
SHBG	sex-hormone binding globulin
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SRBC	sheep red blood cells
SRT	simple reaction time
SSB	single-strand breaks
TaClo	tetrahydro-beta-carbolines
TBARS	thiobarbiturate acid-reactive substances

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

TCA	trichloroacetic acid
TCAA	trichloroacetaldehyde
TCAH	trichloroacetaldehyde hydrate
TCE	trichloroethylene
TCOG	trichloroethanol-glucuronide conjugate
TCOH	trichloroethanol
TRI	Toxics Release Inventory
TSEP	trigeminal somatosensory evoked potential
TTC	total trichloro compounds
TWA	time-weighted average
UA	University of Arizona
UCL	upper confidence limit
UF	uncertainty factor
U.S. EPA	U.S. Environmental Protection Agency
USGS	United States Geological Survey
U-TCA	urinary-TCA
U-TTC	urinary total trichloro-compounds
VEGF	vascular endothelial growth factor
VEP	visual evoked potential
VHL	von Hippel-Lindau
VOC	volatile organic compound
VSCCs	voltage sensitive calcium channels
W	wakefulness
YFF	fluorescent Y-bodies

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to **trichloroethylene**. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of **trichloroethylene**.

The intent of Chapter 6, *Major Conclusions in the Characterization of Hazard and Dose Response*, is to present the major conclusions reached in the derivation of the reference dose, reference concentration and cancer assessment, where applicable, and to characterize the overall confidence in the quantitative and qualitative aspects of hazard and dose response. For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

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This document has been reviewed by U.S. EPA scientists, reviewers from other Federal agencies, and the public, and peer reviewed by independent scientists external to U.S. EPA. A summary and U.S. EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix I.

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EXECUTIVE SUMMARY

There is substantial potential for human exposure to trichloroethylene (TCE), as it has a widespread presence in ambient air, indoor air, soil, and groundwater. At the same time, humans are likely to be exposed to a variety of compounds that are either metabolites of TCE or which have common metabolites or targets of toxicity. Once exposed, humans, as well as laboratory animal species, rapidly absorb TCE, which is then distributed to tissues via systemic circulation, extensively metabolized, and then excreted primarily in breath as unchanged TCE or carbon dioxide, or in urine as metabolites.

Based on the available human epidemiologic data and experimental and mechanistic studies, it is concluded that TCE poses a potential human health hazard for noncancer toxicity to the central nervous system, the kidney, the liver, the immune system, the male reproductive system, and the developing fetus. The evidence is more limited for TCE toxicity to the respiratory tract and female reproductive system. Following U.S. Environmental Protection Agency (U.S. EPA, 2005a) *Guidelines for Carcinogen Risk Assessment*, TCE is characterized as *carcinogenic in humans by all routes of exposure*. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer. The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is compelling for non-Hodgkins Lymphoma but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer. Further support for the characterization of TCE as *carcinogenic in humans by all routes of exposure* is derived from positive results in multiple rodent cancer bioassays in rats and mice of both sexes, similar toxicokinetics between rodents and humans, mechanistic data supporting a mutagenic mode of action (MOA) for kidney tumors, and the lack of mechanistic data supporting the conclusion that any of the MOA(s) for TCE-induced rodent tumors are irrelevant to humans.

As TCE toxicity and carcinogenicity are generally associated with TCE metabolism, susceptibility to TCE health effects may be modulated by factors affecting toxicokinetics, including lifestage, gender, genetic polymorphisms, race/ethnicity, pre-existing health status, lifestyle, and nutrition status. In addition, while these some of these factors are known risk factors for effects associated with TCE exposure, it is not known how TCE interacts with known risk factors for human diseases.

For noncancer effects, the most sensitive types of effects, based either on human equivalent concentrations/doses or on candidate inhalation reference concentrations (RfCs)/oral reference doses (RfDs), appear to be developmental, kidney, and immunological (adult and developmental) effects. The neurological and reproductive effects appear to be about an order of magnitude less sensitive, with liver effects another two orders of magnitude less sensitive. The

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preferred RfC estimate of **0.001 ppm** (1 ppb or 5 $\mu\text{g}/\text{m}^3$) is based on route-to-route extrapolated results from oral studies for the critical effects of heart malformations (rats), immunotoxicity (mice), and toxic nephropathy (rats, mice), and an inhalation study for the critical effect of increased kidney weight (rats). Similarly, the preferred RfD estimate for noncancer effects of **0.0004 mg/kg/d** is based on the critical effects of heart malformations (rats), adult immunological effects (mice), developmental immunotoxicity (mice), and toxic nephropathy (rats). There is high confidence in these preferred noncancer reference values, as they are supported by moderate- to high-confidence estimates for multiple effects from multiple studies.

For cancer, the preferred estimate of the inhalation unit risk is **2×10^{-2} per ppm [4×10^{-6} per $\mu\text{g}/\text{m}^3$]**, based on human kidney cancer risks reported by Charbotel et al. (2006) and adjusted, using human epidemiologic data, for potential risk for tumors at multiple sites. The preferred estimate of the oral unit risk for cancer is **5×10^{-2} per mg/kg/d**, resulting from physiologically-based pharmacokinetic model-based route-to-route extrapolation of the inhalation unit risk estimate based on the human kidney cancer risks reported in Charbotel et al. (2006) and adjusted, using human epidemiologic data, for potential risk for tumors at multiple sites. There is high confidence in these unit risks for cancer, as they are based on good quality human data, as well as being similar to unit risk estimates based on multiple rodent bioassays. Because there is both sufficient weight of evidence to conclude that TCE operates through a mutagenic MOA for kidney tumors and a lack of TCE-specific quantitative data on early-life susceptibility, the default age-dependent adjustment factors (ADAFs) can be applied for the kidney cancer component of the unit risks for cancer; however, the application of ADAFs is likely to have a minimal impact on the total cancer risk except when exposures are primarily during early life.