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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.

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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

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

FFVC	(*E*,*Z*)-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_2O	water
H_2O_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

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

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

PND	postnatal day
P_{O_2}	partial pressure oxygen
POD	point of departure
PPARα	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

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).

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Weihsueh A. Chiu
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

AUTHORS

Ambuja Bale
National Center for Environmental Assessment—Immediate Office
U.S. Environmental Protection Agency
Washington, DC

Stanley Barone
National Center for Environmental Assessment—Immediate Office
U.S. Environmental Protection Agency
Washington, DC

Rebecca Brown
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Jane C. Caldwell
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Chao Chen
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Weihsueh A. Chiu
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Glinda Cooper
National Center for Environmental Assessment—Immediate Office
U.S. Environmental Protection Agency
Washington, DC

Ghazi Dannan
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Marina Evans
National Health and Environmental Effects Research Laboratory
(on detail to National Center for Environmental Assessment—Washington Office)
U.S. Environmental Protection Agency
Research Triangle Park, NC

John Fox
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Kathryn Z. Guyton
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Maureen R. Gwinn
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Jennifer Jinot
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Nagalakshmi Keshava
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

John Lipscomb
National Center for Environmental Assessment—Cincinnati Office
U.S. Environmental Protection Agency
Cincinnati, OH

Susan Makris
National Center for Environmental Assessment—Washington Office
U.S. Environmental Protection Agency
Washington, DC

Miles Okino
National Exposure Research Laboratory—Las Vegas Office
U.S. Environmental Protection Agency
Las Vegas, NV

Fred Power
National Exposure Research Laboratory—Las Vegas Office
U.S. Environmental Protection Agency
Las Vegas, NV

John Schaum
National Center for Environmental Assessment—Washington Office
Office of Research and Development
Washington, DC

Cheryl Siegel Scott
National Center for Environmental Assessment—Washington Office
Office of Research and Development
Washington, DC

REVIEWERS

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.

INTERNAL EPA REVIEWERS

Daniel Axelrad
National Center for Environmental Economics

Robert Benson
U.S. EPA Region 8

Ted Birner
National Center for Environmental Assessment—Immediate Office

Nancy Chiu
Office of Water

David Farrar
National Center for Environmental Assessment—Cincinnati Office

Lynn Flowers
National Center for Environmental Assessment—Immediate Office

Stiven Foster
Office of Solid Waste and Emergency Response

Susan Griffin
U.S. EPA Region 8

Samantha Jones
National Center for Environmental Assessment—Immediate Office

Leonid Kopylev
National Center for Environmental Assessment—Washington Office

Allan Marcus
National Center for Environmental Assessment—Immediate Office

Gregory Miller
Office of Children's Health Protection and Environmental Education

Deirdre Murphy
Office of Air Quality Planning and Standards

Marian Olsen
U.S. EPA Region 2

Peter Preuss
National Center for Environmental Assessment—Immediate Office

Kathleen Raffaele
National Center for Environmental Assessment—Washington Office

William Sette
Office of Solid Waste and Emergency Response

Bob Sonawane
National Center for Environmental Assessment—Washington Office

Suryanarayana Vulimiri
National Center for Environmental Assessment—Washington Office

Nina Ching Y. Wang
National Center for Environmental Assessment—Cincinnati Office

Paul White
National Center for Environmental Assessment—Washington Office

Marcia Bailey
U.S. EPA Region 10

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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

preferred RfC estimate of **0.001 ppm** (1 ppb or 5 μg/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 μg/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.