



**TOXICOLOGICAL REVIEW**

**OF**

**TRICHLOROETHYLENE**

(CAS No. 79-01-6)

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

*September 2011*

## **DISCLAIMER**

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## 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 a 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 in 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.

Appendix I contains the summary of EPA's response to major external peer review and public comments.

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## LIST OF ABBREVIATIONS AND ACRONYMS

[ <sup>14</sup> C]TCE	[ <sup>14</sup> C]-radiolabeled TCE
1,2-DCVC	S-(1,2-dichlorovinyl)-L-cysteine
17-β-HSD	17-β-hydroxy steroid dehydrogenase
8-OHdG	8-hydroxy-2' deoxyguanosine
ACO	acyl CoA oxidase
ADAF	age-dependent adjustment factor
ADME	absorption, distribution, metabolism, and excretion
AIC	Akaike's Information Criteria
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANCA	antineutrophil-cytoplasmic antibody
ANOVA	analysis of variance
AOAA	a beta-lyase inhibitor
ASD	autism spectrum disorder
ASPEN	Assessment System for Population Exposure Nationwide
AST	aspartate aminotransferase
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
BUN	blood urea nitrogen
CA DHS	California Department of Health Services
CH	chloral hydrate
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CO <sub>2</sub>	carbon dioxide
CoA	coenzyme A
cRfC	candidate RfC
cRfD	candidate RfD
CRT	choice reaction time
CYP	cytochrome P450

## LIST OF ABBREVIATIONS AND ACRONYMS (continued)

DAL	dichloroacetyl lysine
DASO <sub>2</sub>	diallyl sulfone
DBP	dibutyl phthalate
DCA	dichloroacetic acid
DCAA	dichloroacetic anhydride
DCAC	dichloroacetyl chloride
DCE	dichloroethylene
DCVC	S-dichlorovinyl-L-cysteine (collectively, the 1,2- and 2,2- isomers)
DCVG	S-dichlorovinyl-L-glutathione (collectively, the 1,2- and 2,2- isomers)
DEHP	di(2-ethylhexyl) phthalate
DHEAS	dehydroepiandrosterone sulphate
DNA	deoxyribonucleic acid
DNP	dinitrophenol
DPM	disintegrations per minute
dsDNA	double-stranded DNA
EC <sub>x</sub>	concentration of the chemical at which x% of the maximal effect is produced
EEG	electroencephalograph
EPA	U.S. Environmental Protection Agency
ERG	electroretinogram
ESRD	end stage renal disease
FAA	fumarylacetoacetate
FDVE	fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether
FMO	flavin mono-oxygenase
FOB	functional observational battery
FSH	follicle-stimulating hormone
G6PDH	glucose 6-p dehydrogenase
GABA	gamma-amino butyric acid
G-CSF	granulocyte colony stimulating factor
GD	gestation day
GGT	γ-glutamyl transpeptidase or γ-transpeptidase
GI	gastrointestinal
GIS	geographic information system
GSD	geometric standard deviation
GSH	glutathione
GSSG	oxidized GSH
GST	glutathione-S-transferase
GT	glutamyl transferase
H&E	hematoxylin and eosin
H <sub>2</sub> O	water
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCl	hydrochloric acid
HDL-C	high density lipoprotein-cholesterol
HEC	human equivalent concentration

## LIST OF ABBREVIATIONS AND ACRONYMS (continued)

HED	human equivalent dose
HgCl <sub>2</sub>	mercuric chloride
HH	Hamberger and Hamilton
HPLC	high-performance liquid chromatography
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
IFN	interferon
IgE	immunoglobulin E
IGF-II	insulin-like growth factor-II (gene)
IL	interleukin
IPCS	International Programme on Chemical Safety
IUGR	intrauterine growth restriction
JEM	job-exposure matrix
JTEM	job-task-exposure matrix
LC	lethal concentration
LCL	lower confidence limit
LDH	lactate dehydrogenase
LEC <sub>x</sub>	lowest effective concentration corresponding to an extra risk of x%
LH	luteinizing hormone
lnPBC	blood-air partition coefficient
lnQCC	cardiac output
lnVMAXC	VMAX for oxidation
lnVPRC	ventilation-perfusion ratio
LOAEL	lowest-observed adverse effect level
LOH	loss of heterozygosity
LORR	loss of righting reflex
MA	maleylacetone
MA DPH	Massachusetts Department of Public Health
MAA	maleylacetoacetate
MCA	monochloroacetic acid
MCMC	Markov chain Monte Carlo
MCP	methylclofenapate
MDA	malondialdehyde
MLE	maximum likelihood estimate
MNU	methyl nitrosourea

## LIST OF ABBREVIATIONS AND ACRONYMS (continued)

MS	mass spectrometry
MSW	multistage Weibull
NAcDCVC	N-acetyl-S-(1,2-dichlorovinyl)-L-cysteine
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate-oxidase
NAG	N-acetyl- $\beta$ -D-glucosaminidase
NAS	National Academy of Sciences
NAT	N-acetyl transferase
NCI	National Cancer Institute
NF- $\kappa$ B	nuclear factor kappa-light-chain enhancer of activated B cells
NHL	non-Hodgkin lymphoma
NK	natural killer
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NPMC	nonpurified rat peritoneal mast cells
NRC	National Research Council
NSATA	National-Scale Air Toxics Assessment
NTP	National Toxicology Program
NYS DOH	New York State Department of Health
ODE	ordinary differential equation
OECD	Organization for Economic Co-operation and Development
OFT	outflow tract
OP	oscillatory potential
OR	odds ratio
OR <sub>adj</sub>	adjusted odds ratio
PAS	periodic acid-Schiff
PBPK	physiologically based pharmacokinetics
PCEs	polychromatic erythrocytes
PCNA	proliferating cell nuclear antigen
PCO	palmitoyl-CoA oxidase
PCR	polymerase chain reaction
p-cRfC	PBPK model-based candidate RfCs
p-cRfD	PBPK model-based candidate RfDs
PEG 400	polyethylene glycol 400
PFC	plaque-forming cell
PFU	plaque-forming units
PMR	proportionate mortality ratio
PND	postnatal day
PO <sub>2</sub>	partial pressure oxygen
POD	point of departure
PPAR	peroxisome proliferator activated receptor
RBL-2H3	rat basophilic leukemia



## LIST OF ABBREVIATIONS AND ACRONYMS (continued)

RCC	renal cell carcinoma
RfC	inhalation reference concentration
RfD	oral reference dose
RNA	ribonucleic acid
RR	relative risk
RRm	summary RR
RT	reaction time
S9	metabolic activation system
SBA	serum bile acids
SC	sensitivity coefficient
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SEER	Surveillance, Epidemiology, and End Results
SES	socioeconomic status
SGA	small for gestational age
SHBG	sex-hormone binding globulin
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SNP	single nucleotide polymorphism
SRBC	sheep red blood cells
SRT	simple reaction time
SSB	single-strand breaks
SSCP	single strand conformation polymorphism
ssDNA	single-stranded DNA
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
ThX	T-helper Type X
TNF	tumor necrosis factor
TRI	Toxics Release Inventory
TSEP	trigeminal somatosensory evoked potential
TTC	total trichloro compounds
TWA	time-weighted average

## LIST OF ABBREVIATIONS AND ACRONYMS (continued)

U.S. EPA	U.S. Environmental Protection Agency
UCL	upper confidence limit
UDS	unscheduled DNA synthesis
UF	uncertainty factor
USGS	United States Geological Survey
U-TCA	urinary-TCA
U-TTC	urinary total trichloro-compounds
VEGF	vascular endothelial growth factor
VEP	visual evoked potential
<i>VHL</i>	von Hippel-Lindau
VLivC	liver volume
VOC	volatile organic compound
VSCC	voltage sensitive calcium channel
W	wakefulness
WHO	World Health Organization
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 by addressing the quality of the data and related uncertainties. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

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](mailto:hotline.iris@epa.gov) (email address).

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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, kidney, liver, immune system, 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, 2005b](#)) *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 strong for non-Hodgkin Lymphoma but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer. 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, breast. 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 for kidney tumors, and the lack of mechanistic data supporting the conclusion that any of the mode(s) of action 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, preexisting 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 RfC of **0.0004 ppm** (0.4 ppb or  $2 \mu\text{g}/\text{m}^3$ ) is based on route-to-route extrapolated results from oral studies for the critical effects of heart malformations (rats) and immunotoxicity (mice). This RfC value is further supported by route-to-route extrapolated results from an oral study of toxic nephropathy (rats). Similarly, the RfD for noncancer effects of **0.0005 mg/kg/day** is based on the critical effects of heart malformations (rats), adult immunological effects (mice), and developmental immunotoxicity (mice), all from oral studies. This RfD value is further supported by results from an oral study for the effect of toxic nephropathy (rats) and route-to-route extrapolated results from an inhalation study for the effect of increased kidney weight (rats). There is high confidence in these noncancer reference values, as they are supported by moderate-to-high confidence estimates for multiple effects from multiple studies.

For cancer, the inhalation unit risk is  $2 \times 10^{-2}$  per ppm [ $4 \times 10^{-6}$  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 NHL and liver cancer. The oral unit risk for cancer is  $5 \times 10^{-2}$  per mg/kg/day, resulting from physiologically based pharmacokinetic model-based route-to-route extrapolation of the inhalation unit risk based on the human kidney cancer risks reported in Charbotel et al. (2006) and adjusted, using human epidemiologic data, for potential risk for NHL and liver cancer. 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. There is both sufficient weight of evidence to conclude that TCE operates through a mutagenic mode of action for kidney tumors and a lack of TCE-specific quantitative data on early-life susceptibility. Generally, the application of age-dependent adjustment factors (ADAFs) is recommended when assessing cancer risks for a carcinogen with a mutagenic mode of action. However, because the ADAF adjustment applies only to the kidney cancer component of the total risk, it is likely to have a minimal impact on the total cancer risk except when exposures are primarily during early life.