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Provisional Peer-Reviewed Toxicity Values for

1-Bromo-2-Chloroethane
(CASRN 107-04-0)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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Center for Public Health and Environmental Assessment
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Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at https://ecomments.epa.gov/pprtv.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-*S*-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure-activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

DRAFT PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1-BROMO-2-CHLOROETHANE (CASRN 107-04-0)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established U.S. Environmental Protection Agency (U.S. EPA) guidance on human health toxicity value derivations.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing adverse human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and

limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

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

QUESTIONS REGARDING PPRTVs

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA ORD CPHEA website at https://ecomments.epa.gov/pprtv.

1. INTRODUCTION

1-Bromo-2-chloroethane (CASRN 107-04-0) belongs to the class of compounds known as halogenated alkanes. 1-Bromo-2-chloroethane currently has no commercial uses, but small amounts may be imported and used for research and development (U.S. EPA, 2015b). It is listed under the U.S. Environmental Protection Agency (U.S. EPA) Toxic Substances Control Act (TSCA) Significant New Use Rule (SNUR), which requires notification of the U.S. EPA prior to manufacturing, importing, or processing of a chemical substance for a significant new use (e.g., commercial purpose) (U.S. EPA, 2015c). Former uses of 1-bromo-2-chloroethane include as a solvent for cellulose esters and ethers, in organic synthesis, and as a fumigant for fruits and vegetables (Lewis and Hawley, 2007). 1-Bromo-2-chloroethane is listed on TSCA's public inventory (U.S. EPA, 2015a), but it is not registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2015).

1-Bromo-2-chloroethane can be produced by the reaction of bromine and chlorine on ethylene gas (Lewis and Hawley, 2007). However, it is no longer produced in the United States because of potential carcinogenic activity based on its in vitro mutagenicity and the carcinogenicity of the structurally similar chemicals 1,2-dibromoethane and 1,2-dichloroethane (U.S. EPA, 2015b).

The empirical formula for 1-bromo-2-chloroethane is C_2H_4BrCl, and its structure is shown in Figure 1. Table 1 summarizes its physicochemical properties. 1-Bromo-2-chloroethane is a clear, colorless liquid with a sweet chloroform-like odor at room temperature (NOAA, 2015). Its high vapor pressure indicates that it will exist solely as a vapor in the atmosphere. Given its vapor pressure and moderate estimated Henry's law constant, it is likely to volatilize from either dry or moist soil surfaces and from water surfaces. The high water solubility and low soil adsorption coefficient indicate that it will have the potential to leach to groundwater or undergo runoff after a rain event. However, volatilization to the atmosphere is expected to be the main transport pathway. Estimated hydrolysis half-lives of 3 and 32 years at pH 8 and 7, respectively, indicate that hydrolysis is not likely to be an important fate process.

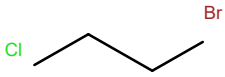


Figure 1. 1-Bromo-2-Chloroethane (CASRN 107-04-0) Structure

Table 1. Physicochemical Properties of 1-Bromo-2-Chloroethane (CASRN 107-04-0)

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	107[a]
Melting point (°C)	−16.3[a]
Density (g/cm^3)	1.63 (predicted average)[a]
Vapor pressure (mm Hg at 20°C)	33.1[a]
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mol/L)	4.79×10^{-2} [a]
Octanol-water partition coefficient (log K_{ow})	1.86 (predicted average)[a]
Henry's law constant (atm-m^3/mol at 25°C)	9.09×10^{-4} [a]
Soil adsorption coefficient K_{oc} (L/kg)	55.1 (predicted average)[a]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	3.22×10^{-13} (predicted average)[a]
Atmospheric half-life (days)	42 (estimated)[c]
Relative vapor density (air = 1)	4.94[b]
Molecular weight (g/mol)	143[a]
Flash point (closed cup, °C)	NA

[a]U.S. EPA CompTox Chemicals Dashboard (as of June 2021; https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID4024775#properties).
[b]NOAA (2015).
[c]U.S. EPA (2012).

NA = not applicable.

No toxicity values are available for 1-bromo-2-chloroethane from U.S. EPA or other agencies/organizations (see Table 2).

Table 2. Summary of Available Toxicity Values for 1-Bromo-2-Chloroethane (CASRN 107-04-0)

Source[a]	Value	Notes	Reference[b]
Noncancer			
IRIS	NV	NA	U.S. EPA (2020c)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	NV	NA	U.S. EPA (2018)
ATSDR	NV	NA	ATSDR (2018)
IPCS	NV	NA	IPCS (2020)
CalEPA	NV	NA	CalEPA (2019)
OSHA	NV	NA	OSHA (2020a); OSHA (2020b)
NIOSH	NV	NA	NIOSH (2018)
ACGIH	NV	NA	ACGIH (2020)
HEEP	NV	NA	U.S. EPA (1985)
Cancer			
IRIS	NV	NA	U.S. EPA (2020c)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	NV	NA	U.S. EPA (2018)
NTP	NV	NA	NTP (2016a)
IARC	NV	NA	IARC (2018)
CalEPA	NV	NA	CalEPA (2019)
ACGIH	NV	NA	ACGIH (2020)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.
[b]Reference date is the publication date for the database and not the date the source was accessed.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in November 2017 and updated in May 2021, for studies relevant to the derivation of provisional toxicity values for 1-bromo-2-chloroethane (CASRN 107-04-0). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE[1] (including TSCATS1), and Web of Science. The following resources were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), U.S. EPA TSCATS2/TSCATS8e, U.S. EPA High Production Volume (HPV), Chemicals via IPCS INCHEM, Japan Existing Chemical Data Base (JECDB), Organisation for Economic Cooperation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

[1]Note that this version of TOXLINE is no longer updated (https://www.nlm.nih.gov/databases/download/toxlinesubset.html); therefore, it was not included in the literature search update from May 2021.

2. REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

As shown in Tables 3A and 3B, there are no potentially relevant short-term, subchronic, chronic, developmental, or reproductive toxicity studies of 1-bromo-2-chloroethane in humans or animals exposed by oral or inhalation routes. The phrase "statistical significance" or the term "significant," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**Reference**	**Notes**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					

ND = no data.

Table 3B. Summary of Potentially Relevant Cancer Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**Reference**	**Notes**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					

ND = no data.

2.1. HUMAN STUDIES

2.1.1. Oral Exposures

No human studies following oral exposure to 1-bromo-2-chloroethane have been identified.

2.1.2. Inhalation Exposures

No human studies following inhalation exposure to 1-bromo-2-chloroethane have been identified.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures

No animal studies following oral exposure to 1-bromo-2-chloroethane have been identified.

2.2.2. Inhalation Exposures

No animal studies following inhalation exposure to 1-bromo-2-chloroethane have been identified.

2.3. OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Toxicity data for 1-bromo-2-chloroethane are limited to acute lethality values reported in secondary sources, an acute oral hepatotoxicity study, an acute intraperitoneal (i.p.) injection study, and genotoxicity studies.

2.3.1. Acute Toxicity in Animals

An oral median lethal dose (LD_{50}) value of 64 mg/kg was identified for 1-bromo-2-chloroethane in rats [Frear (1969) as cited in NLM (2016)]; no further data regarding acute oral toxicity were reported. Valade (1957), as cited in U.S. EPA (1985), reported a 30-minute median lethal concentration (LC_{50}) value of 15,000−25,000 mg/m^3 for 1-bromo-2-chloroethane in unspecified laboratory animals. This study also indicated that acute inhalation of "several alkyl halides" caused ataxia in dogs, rats, and guinea pigs; however, it is unclear whether these halides included 1-bromo-2-chloroethane.

Moody et al. (1980) treated male Sprague Dawley rats with 1-bromo-2-chloroethane via gavage and found decreases in cytochrome P450 (CYP450) content of hepatic microsomes to 51% of controls, as well as alterations in relative content of fatty acids within hepatic microsomes 18 hours after exposure to a single dose (0.15 mL/kg). A high correlation between CYP450 loss and decreased arachidonic acid, increased linoleic acid, and increased oleic acid was observed.

Significant mortality was observed in male B6C3F1 mice (5/11 treated animals) at 24 hours following a single i.p. injection of 1.5 mmol/kg (215 mg/kg) of 1-bromo-2-chloroethane. Statistically significant increases in serum sorbitol dehydrogenase (SDH), alanine aminotransferase (ALT), and blood urea nitrogen (BUN) and relative liver and kidney weights were also observed at this dose (Storer and Conolly, 1983). No mortalities or liver or kidney effects were noted at ≤1 mmol/kg (143 mg/kg); no other endpoints were evaluated.

2.3.2. Genotoxicity

Overview: Studies evaluating the potential genotoxicity of 1-bromo-2-chloroethane are summarized below (see Table 4 for details). Available data indicate that 1-bromo-2-chloroethane and/or its metabolites display genotoxic, mutagenic, clastogenic, and deoxyribonucleic acid (DNA) damaging activity.

Table 4. Summary of 1-Bromo-2-Chloroethane (CASRN 107-04-0) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References (comments)
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100	0, 1.6, 3.0, 4.7, 6.8, 8.1 µmol/plate	+ (TA1535, TA100) – (TA1537, TA1538, TA98)	+ (TA1535, TA100) – (TA1537, TA1538, TA98)	A concentration-dependent increase in revertants was observed in TA1535 and TA100 with or without metabolic activation (rat liver S9 fractions). The addition of S9 activation did not significantly increase the mutagenic response.	Barber et al. (1981)
Mutation	*S. typhimurium* strains TA1530, TA1535, and TA1538	0−15 µmol/plate	+ (TA1530, TA1535) - (TA1538)	NT	A concentration-dependent increase in revertants was observed without metabolic activation.	Brem et al. (1974)
Mutation	*S. typhimurium* strains TA100 and TA98	0, 33, 100, 200, 333, 667, 1,000, 1,500, 2,000 µg/plate	+ (TA100, TA98)	+ (TA100) – (TA98)	In TA100, the number of revertants was increased >twofold at ≥667 µg/plate without metabolic activation and ≥333 µg/plate with metabolic activation. In TA98, the number of revertants was increased >twofold at ≥333 µg/plate without metabolic activation.	NTP (1990)
Mutation	*S. typhimurium* strains TA100 and TA102	NR	+	(see comments)	Preincubation assay. It is unclear from the abstract whether or not metabolic activation was used.	Hughes et al. (1987) (abstract only)

Table 4. Summary of 1-Bromo-2-Chloroethane (CASRN 107-04-0) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References (comments)
Mutation	*S. typhimurium* strains TA1535/pK233-2 (empty plasmid) TA1535/DM11 (bacterial dichloromethane dehalogenase) TA1535/GST 5-5 (rat GST) TA1535/GST T1 (human GST)	0−10.0 µM (DM11); 0−150 µM (GST 5-5, GST T1, and control plasmid pK233-2)	− (pK233-2)	+ (DM11, GST 5-5, GST T1)	Metabolic activation was achieved using *S. typhimurium* TA1535 cells expressing mammalian theta-class GSH transferases (rat GST 5-5 or human GST T1) or a bacterial dichloromethane dehalogenase (DM11). A concentration-dependent increase in revertants was observed for each of the enzymes induced; an increase in revertants was not observed in TA1535 with the expression plasmid only. The numbers of revertants/µM per plate for GST 5-5, GST T1, and DM11 were 45, 3.3, and 2,200, respectively. It was <0.1 for the plasmid only.	Wheeler et al. (2001)
Mutation	*S. typhimurium* strain TA100	0−4.0 mM	+	+	Metabolic activation was tested either with rat GSH added or rat GSH + rat liver cytosol (S100). The number of revertants following GSH + S100 activation was increased almost fourfold over GSH only or without a metabolizing system.	van Bladeren et al. (1981)
DNA damage (SOS/*umu* chromotest)	*S. typhimurium* strains TA1535/pSK1002 (empty plasmid) NM5004 (rat GST 5-5 and *umuC-lac Z* operon)	0−0.5 mM	− (pSK1002)	+ (NM5004)	Strain NM5004 was generated by introducing a plasmid *S. typhimurium* TA1535 cells containing both rat GSH transferase (GST 5-5) cDNA and the *umuC-lac Z* operon. *Umu* gene expression was increased in a dose-dependent manner for NM5004 at noncytotoxic concentrations. Cytotoxicity was observed at ≥0.25 mM in the NM5004 strain.	Shimada et al. (1996)

Table 4. Summary of 1-Bromo-2-Chloroethane (CASRN 107-04-0) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References (comments)
DNA damage (SOS/*umu* chromotest)	*S. typhimurium* strains TA1535/pSK1002 (empty plasmid) NM5004 (rat GST 5-5 and *umuC-lac Z* operon)	0−0.1 mM	− (pSK1002)	+ (NM5004)	Strain NM5004 was generated as describe above by Shimada et al. (1996). *Umu* gene expression was increased in a dose-dependent manner for NM5004 at noncytotoxic concentrations. Cytotoxicity was observed at 0.1 mM in the NM5004 strain.	Oda et al. (1996)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mitotic malsegregation	*Aspergillus nidulans* diploid strain P1	0, 6.0, 12.0, 18.0, 24.0 mM	+	+	The number of malsegregations was significantly elevated at ≥12.0 mM; survival was <50% at ≥18.0 mM.	Crebelli et al. (1995)
Mitotic recombination (wing-spot test)	*Drosophila melanogaster* (*flr*^{3} × *mwh*); 48-h inhalation exposure	0, 0.31 µg/L	+	+	The tested concentration was based on the calculated LC_{50}. The frequency of wing spots at the LC_{50} was significantly elevated by 17-fold compared with controls.	Chroust et al. (2006)
Genotoxicity studies in mammalian cells in vitro						
HGPRT mutation (6-thioguanine resistance)	CHO cells	+S9: 0, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 1.0 mM; −S9: 0, 0.5, 1, 2, 3, 4, 6, 8 mM	+	+	A concentration-dependent increase in mutants was observed with and without metabolic activation; the mutagenic activity was fourfold greater with metabolic activation (rat liver S9 mix) than without S9. Enhancement by S9 mix did not occur when the NADPH pool was reduced (via omission of NADP from the S9 fraction). Cell survival (relative to untreated control) was reduced by >50% at 6 mM without S9 and 1 mM with S9.	Tan and Hsie (1981)
CAs	CHL cells	0.1−0.5 mg/mL (6 h; ±S9) 0.5−3.0 mg/mL (24 h; −S9) 0.5−4.0 mg/mL (48 h); −S9	+ (24 h; 48 h) − (6 h)	+ (6 h)	NA	Japan Chemical Industry Ecology-Toxicology Information Center (1996) as cited in NLM (2005)

Table 4. Summary of 1-Bromo-2-Chloroethane (CASRN 107-04-0) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References (comments)
Genotoxicity studies in mammals in vivo						
DNA damage (DNA unwinding assay)	Male B6C3F1 mice (six/group); single i.p. injection; sacrifice 4 h after exposure; hepatic cell nuclei were harvested	0, 0.5, 0.75, 1.0 mmol/kg	+	+	1-Bromo-2-chloroethane induced 8.9, 15.8, and 24.7% reduction in double-stranded DNA in liver cells harvested from mice exposed to 0.5, 0.75, and 1.0 mM/kg (72, 107, and 143 mg/kg), respectively, compared with control.	Storer and Conolly (1983)

[a]+ = positive; ± = weakly positive; − = negative.

CA = chromosomal aberration; cDNA = complementary DNA; CHL = Chinese hamster lung; CHO = Chinese hamster ovary (cell line cells); DNA = deoxyribonucleic acid; GSH = glutathione; GST = glutathione-*S*-transferase; HGPRT = hypoxanthine-guanine phosphoribosyltransferase; i.p. = intraperitoneal; LC_{50} = median lethal concentration; NA = not applicable; NADP = nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of NADP; NR = not reported, NT = not tested.

1-Bromo-2-chloroethane is mutagenic in bacterial and mammalian cells in vitro, both with and without metabolic activation (Wheeler et al., 2001; NTP, 1990; Hughes et al., 1987; Barber et al., 1981; Tan and Hsie, 1981; van Bladeren et al., 1981; Brem et al., 1974). Addition of glutathione-*S*-transferases (GST) or glutathione (GSH) with or without S100 into *Salmonella typhimurium* bacterial test systems enhanced mutagenicity, indicating that GSH conjugation results in the formation of mutagenic metabolites (Wheeler et al., 2001; van Bladeren et al., 1981). In the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) system, mutagenicity was enhanced in the presence of an S9 metabolic activation fraction; this enhancement did not occur when nicotinamide adenine dinucleotide phosphate (NADP) was omitted from the S9 fraction, suggesting that CYP450 enzymes could be involved in the increased metabolic activation (Tan and Hsie, 1981).

Chromosomal damage and mitotic malsegregation/recombination have been induced by 1-bromo-2-chloroethane in mammalian cells and nonmammalian eukaryotic organisms. 1-bromo-2-chloroethane induced chromosomal aberrations (CAs) in Chinese hamster lung (CHL) cells, both in the presence and absence of a metabolic activation system, in a study by the Japan Chemical Industry Ecology-Toxicology Information Center, available only as a brief summary in the Chemical Carcinogenesis Research Information System (CCRIS) (NLM, 2005). 1-Bromo-2-chloroethane also induced mitotic malsegregation in *Aspergillus nidulans* (Crebelli et al., 1995) and mitotic recombination in *Drosophila melanogaster* (Chroust et al., 2006).

DNA damage has been reported in bacterial cells exposed to 1-bromo-2-chloroethane in the presence of GSTs (Oda et al., 1996; Shimada et al., 1996). DNA damage was assessed in the SOS/*umu* test system, which measures the induction of DNA damage responsive *umuC* gene expression by cellular β-galactosidase activity produced by an *umuC-lac Z* fusion gene. Shimada et al. (1996) constructed a strain of *S. typhimurium* for use in the SOS/*umu* test system that possessed enhanced GST activity by introducing a rat GST 5-5 cDNA plasmid into *S. typhimurium* TA1535 (resulting in strain NM5004). Expression of the *umuC* gene was not increased in the tester TA1535 strain containing only the empty plasmid (pSK1002), but it was increased in a dose-related manner in the NM5004 strain expressing rat GST. These data suggest that GSH conjugates of 1-bromo-2-chloroethane were DNA-reactive intermediates.

DNA damage was also observed in liver cells from male B6C3F1 mice following a single i.p. dose of 1-bromo-2-chloroethane at greater than or equal to 0.5 mmol/kg (72 mg/kg) (Storer and Conolly, 1983). Liver cell nuclei harvested from exposed mice showed a dose-related decrease in the percentage of double-stranded DNA observed (indicating a dose-related increase in DNA damage), as assessed by an alkaline DNA unwinding/hydroxylapatite batch chromatography method.

In summary, 1-bromo-2-chloroethane displayed mutagenic activity among in vitro models employing bacterial and mammalian cells, and this mutagenic activity was increased concomitantly with an increase in GSH conjugation (Wheeler et al., 2001; NTP, 1990; Hughes et al., 1987; Tan and Hsie, 1981; van Bladeren et al., 1981; Brem et al., 1974). Increased CYP450 activity (as suggested by manipulating NADP levels within the S9 fraction) promoted elevated mutagenicity in a CHO/HGPRT model system, indicating a potential role for CYP450 in the mutagenicity resulting from 1-bromo-2-chloroethane metabolism (Tan and Hsie, 1981). Chromosomal aberrations and mitotic malsegregation were increased in both nonmammalian eukaryotic organisms and mammalian cell model systems (Chroust et al., 2006; NLM, 2005; Crebelli et al., 1995). Lastly, the induction of DNA damage in bacterial systems, as well as in in

vivo liver cells of male B6C3F1 mice, occurred in a dose-dependent manner after 1-bromo-2-chloroethane exposure (Oda et al., 1996; Shimada et al., 1996; Storer and Conolly, 1983).

2.3.3. Absorption, Distribution, Metabolism, and Excretion Studies

Available in vivo and in vitro data indicate that 1-bromo-2-chloroethane is metabolized by a GSH conjugation pathway (Jean and Reed, 1992; Marchand and Reed, 1989). GSH conjugation was demonstrated in vivo by the detection of *S*-(2-chloroethyl)glutathione (CEG) and its hydrolysis product, *S*-(2-hydroxyethyl)glutathione (HEG), in the bile of bile-duct-cannulated rats following intravenous (i.v.) injection with 75 mg/kg 1-bromo-2-chloroethane (Marchand and Reed, 1989). The total amount of CEG detected in bile was 2% of the administered dose. Marchand and Reed (1989) suggested that the low levels of CEG detected in bile may result from rapid conversion of CEG to other metabolites (e.g., HEG) or intrahepatic transport of CEG into plasma rather than bile. Data from the structurally similar dihaloalkanes 1,2-dichloroethane and 1,2-dibromoethane indicate that once formed, CEG will cyclize to form an electrophilic episulfonium ion in vivo, which subsequently binds to DNA [reviewed by Guengerich (1994) and Dekant and Vamvakas (1993)].

In isolated rat hepatocytes, 1-bromo-2-chloroethane was metabolized to HEG, *S*-(carboxymethyl)glutathione (CMG), and *S,S′*-(1,2-ethanediyl)bis(glutathione) (EDG) conjugates. HEG was produced in the largest amounts, followed by EDG and CMG (Jean and Reed, 1992). HEG and EDG are products of direct GSH conjugation (EDG results from conjugation at both carbon atoms), whereas CMG is formed after an initial oxidation to 2-haloacetaldehyde metabolites (Jean and Reed, 1992). Formation of GSH conjugates was concomitant with intracellular GSH depletion, measured as an 84% decrease in intracellular GSH levels in response to 1-bromo-2-chloroethane treatment. The addition of extracellular GSH into the incubation medium increased the formation of EDG conjugates by 179% (Jean and Reed, 1992). Combined, these data suggest that GSH conjugation is a primary and likely rate-limiting step in the metabolic activation of 1-bromo-2-chloroethane.

No data are available on the absorption, distribution, or excretion of 1-bromo-2-chloroethane.

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF PROVISIONAL REFERENCE DOSES

No studies have been identified regarding toxicity of 1-bromo-2-chloroethane to humans by oral exposure. Animal studies of oral exposure to 1-bromo-2-chloroethane are limited to acute studies of inadequate design, duration, and scope to support derivation of a subchronic or chronic provisional reference dose (p-RfD). As a result of the limitations of the available oral toxicity data for 1-bromo-2-chloroethane, subchronic and chronic p-RfDs are not derived directly. Instead, screening subchronic and chronic p-RfDs are derived in Appendix A using an alternative analogue approach. Based on the overall analogue approach presented in Appendix A, 1,2-dibromo-3-chloropropane is selected as the most appropriate analogue for 1-bromo-2-chloroethane for deriving a screening subchronic and chronic p-RfD (see Table 5).

3.2. DERIVATION OF PROVISIONAL REFERENCE CONCENTRATIONS

No studies have been identified on the toxicity of 1-bromo-2-chloroethane to humans by inhalation exposure. Animal studies of inhalation exposure to 1-bromo-2-chloroethane are limited to a single acute lethality study of inadequate design, duration, and scope to support derivation of a subchronic or chronic provisional reference concentrations (p-RfCs). Due to lack of adequate inhalation toxicity data for 1-bromo-2-chloroethane, subchronic and chronic p-RfCs are not derived directly. Instead, screening subchronic and chronic p-RfCs are derived in Appendix A using an alternative analogue approach. Based on the overall analogue approach presented in Appendix A, 1,2-dibromo-3-chloropropane is selected as the most appropriate analogue for 1-bromo-2-chloroethane for deriving a screening subchronic and chronic p-RfC (see Table 5).

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

The noncancer screening provisional reference values for 1-bromo-2-chloroethane are summarized in Table 5.

Table 5. Summary of Noncancer Reference Values for 1-Bromo-2-Chloroethane (CASRN 107-04-0)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rabbit/M	Reduced germ cell number	1×10^{-3}	NOAEL (HED)	0.3 (based on analogue POD)	300	Foote et al. (1986a, b) as cited in U.S. EPA (2006)
Screening chronic p-RfD (mg/kg-d)	Rabbit/M	Reduced germ cell number	1×10^{-4}	NOAEL (HED)	0.3 (based on analogue POD)	3,000	Foote et al. (1986a, b) as cited in U.S. EPA (2006)
Screening subchronic p-RfC (mg/m^3)	Rabbit/M	Testicular toxicity	6×10^{-4}	NOAEL (HEC)	0.17 (based on analogue POD)	300	Rao et al. (1982) as cited in U.S. EPA (2006)
Screening chronic p-RfC (mg/m^3)	Rabbit/M	Testicular toxicity	6×10^{-5}	NOAEL (HEC)	0.17 (based on analogue POD)	3,000	Rao et al. (1982) as cited in U.S. EPA (2006)

HEC = human equivalent concentration; HED = human equivalent dose; M = male(s); NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Although the scientific literature provides information on the mutagenicity and genotoxicity of 1-bromo-2-chloroethane, no studies have been conducted to directly assess its carcinogenicity. Under the U.S. EPA Cancer Guidelines (U.S. EPA, 2005), there is *"Inadequate Information to Assess the Carcinogenic Potential"* of 1-bromo-2-chloroethane (see Table 6).

Within the current U.S. EPA Cancer Guidelines (U.S. EPA, 2005), there is no standard methodology to support the identification of a weight-of-evidence (WOE) descriptor and derivation of provisional cancer risk estimates for data-poor chemicals using an analogue approach. In the absence of an established framework, a screening evaluation of potential carcinogenicity is provided using the methodology described in Appendix B. This evaluation determined that there was a qualitative level of *concern for potential carcinogenicity* for 1-bromo-2-chloroethane (see Appendix C).

Table 6. Cancer WOE Descriptor for 1-Bromo-2-Chloroethane (CASRN 107-04-0)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No human data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	No adequate chronic-duration animal cancer bioassays are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No adequate chronic-duration animal cancer bioassays are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No studies are available assessing the carcinogenic potential of 1-bromo-2-chloroethane in humans or animals.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available. No adequate chronic-duration animal cancer bioassays are available.

NA = not applicable; NS = not selected; WOE = weight of evidence.

3.5. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

The absence of suitable data precludes development of cancer risk estimates for 1-bromo-2-chloroethane (see Table 7).

Table 7. Summary of Cancer Risk Estimates for 1-Bromo-2-Chloroethane (CASRN 107-04-0)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Risk Estimate	Principal Study
Screening p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
Screening p-IUR $(\mu g/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

APPENDIX A. SCREENING NONCANCER PROVISIONAL VALUES

Due to the lack of evidence described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional toxicity values for 1-bromo-2-chloroethane. However, some information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the provisional reference values to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there could be more uncertainty associated with deriving an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the CPHEA.

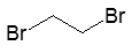
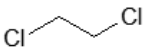
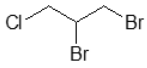
APPLICATION OF AN ALTERNATIVE ANALOGUE APPROACH

The analogue approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for analogue analysis are presented in Wang et al. (2012). Three types of potential analogues (structural, metabolic, and toxicity-like) are identified to facilitate the final analogue chemical selection. The analogue approach may or may not be route-specific or applicable to multiple routes of exposure. All information was considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable analogue both toxicologically and chemically.

Structural Analogues

An initial analogue search focused on the identification of structurally similar chemicals with toxicity values from the Integrated Risk Information System (IRIS), PPRTVs, Agency for Toxic Substances and Disease Registry (ATSDR), or California Environmental Protection Agency (CalEPA) databases to leverage the body of well-characterized chemical-class information. As described in Wang et al. (2012), structural similarity for analogues is evaluated using the National Library of Medicine's (NLM's) ChemIDplus database (ChemIDplus, 2021) and the Organisation for Economic Co-operation and Development (OECD) Toolbox. Both structural similarity approaches were used to calculate structural similarity using the Tanimoto method. Three structural analogues to 1-bromo-2-chloroethane that have oral and/or inhalation toxicity values were identified: 1,2-dibromoethane (U.S. EPA, 2004), 1,2-dichloroethane (U.S. EPA, 2010), and 1,2-dibromo-3-chloropropane (U.S. EPA, 2006, 2003). Table A-1 summarizes the analogues' physicochemical properties and similarity scores. ChemIDplus similarity scores were available only for 1,2-dibromoethane (92%) and 1,2-dichloroethane (68%). OECD Quantitative Structure-Activity Relationship (QSAR) pairwise toolbox similarity scores were similar for all three candidate analogues (24−33%) and the target chemical. The target compound and all candidate analogues are expected to be bioavailable by oral and inhalation routes (based on water solubility and K_{ow} values). A range of vapor pressure values (0.580−78.9 mm Hg at 25°C) is identified for 1-bromo-2-chloroethane and relevant analogue chemicals, suggesting that these compounds may exhibit differences in volatility. All of the candidate analogues are considered appropriate structural analogues based on the approach described in Wang et al. (2012).

Table A-1. Physicochemical Properties of 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues[a]

Property	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane (2R and 2S Isomers)
Structure				
CASRN	107-04-0	106-93-4	107-06-2	96-12-8
Molecular weight	143	188	99	236
OECD QSAR Toolbox similarity score (%)[b]	100	33	33	24
ChemIDplus similarity score (%)[c]	100	92	68	NV
Melting point (°C)	−16.3	9.8	−35.3	6.04
Boiling point (°C)	107	132	83.2	196
Vapor pressure (mm Hg at 25°C)	33.1	11.2	78.9	0.580
Henry's law constant (atm-m^3/mole at 25°C)	9.09×10^{-4}	6.50×10^{-4}	1.18×10^{-3}	2.93×10^{-4} (predicted)
Water solubility (mol/L)	4.79×10^{-2}	2.11×10^{-2}	8.68×10^{-2}	4.71×10^{-3}
Octanol-water partition coefficient (log K_{ow})	1.86 (predicted)	1.96	1.48	2.96

[a]Data represent average values as reported on the U.S. EPA's CompTox Chemicals Dashboard unless otherwise specified (https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID4024775#properties). Data accessed June 2021.
[b]OECD (2018).
[c]ChemIDplus advanced similarity scores (ChemIDplus, 2021).

NV = not available; OECD =Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship.

Metabolic Analogues

Table A-2 summarizes available toxicokinetic data for 1-bromo-2-chloroethane and the structurally similar compounds identified as candidate analogues.

Absorption, Distribution, and Excretion

No data are available to describe the absorption, distribution, or excretion of 1-bromo-2-chloroethane. Oral absorption is rapid and extensive for all three candidate analogue compounds (U.S. EPA, 2004; ATSDR, 2001; Gingell et al., 1987). Absorption is also rapid and extensive following inhalation exposure to 1,2-dibromoethane and 1,2-dichloroethane (U.S. EPA, 2004; ATSDR, 2001). There are no data available on the rate or extent of absorption following inhalation exposure to 1,2-dibromo-3-chloropropane. Widespread distribution to multiple organs and excretion primarily in the urine has been demonstrated for all three candidate analogue compounds (U.S. EPA, 2004; ATSDR, 2001; Gingell et al., 1987).

Table A-2. Comparison of Available ADME Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

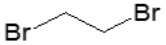
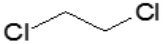
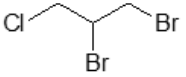
Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane (2R and 2S isomers)
Structure				
CASRN	107-04-0	106-93-4	107-06-2	96-12-8
Absorption				
Rate and extent of oral absorption	ND	Rat: rapid and extensive (C_{max} within 30 min; >80% of dose absorbed)	Rat: rapid and extensive (C_{max} within 15 min; >80% of dose absorbed)	Rat: rapid and extensive (C_{max} within 5−40 min; >80% of dose absorbed)
Rate and extent of inhalation absorption	ND	Rat: rapid and extensive (C_{max} within 20 min; 40 to <60% of dose absorbed)	Rat: rapid and extensive (C_{max} within 1−3 h; >80% of dose absorbed)	ND
Human blood-gas partition coefficient[a]	29.2	ND	19.5	ND
Rat blood-gas partition coefficient[a]	52.7	119	30.4	ND
Distribution				
Extent of distribution	ND	Rat and mouse: wide distribution to multiple organs; covalent binding to tissues (kidney, stomach, liver, and testis after oral exposure; nasal mucosa, liver, lung, kidney, and small intestine after i.p. injection)	Rat: wide distribution to multiple organs; transplacental distribution was demonstrated	Rat: wide distribution to multiple organs; V_d = 4.98 L/kg (oral)

Table A-2. Comparison of Available ADME Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

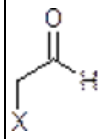
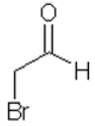
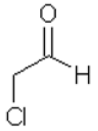
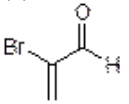
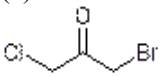
Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane (2R and 2S isomers)
Metabolism—oxidation by CYP450				
Primary reactive metabolites	By analogy to 1,2-dibromoethane and 1,2-dichloroethane: (1) 2-bromo-acetaldehyde; (2) 2-chloro-acetaldehyde  X = Br, Cl By analogy to 1,2-dibromoethane and 1,2-dichloroethane: (3) HBr, HCl	Demonstrated: (1) 2-bromo-acetaldehyde  Demonstrated: (2) HBr	Demonstrated: (1) 2-chloro-acetaldehyde  Demonstrated: (2) HCl	Demonstrated: (1) 2-bromoacrolein  (2) 2-chloro-3-(bromomethyl) oxirane  (3) 1-bromo-3-chloroacetone  Demonstrated: (4) HBr, HCl

Table A-2. Comparison of Available ADME Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

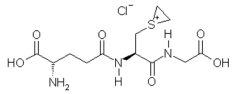
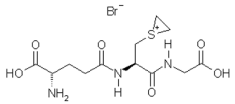
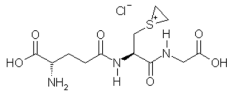
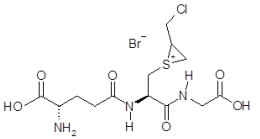
Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane (2R and 2S isomers)
Potential role in toxicity	By analogy to 1,2-dibromoethane and 1,2-dichloroethane: (1) Forms DNA adducts (2) Lipid peroxidation (3) Protein binding	Demonstrated: (1) Forms DNA adducts (2) Lipid peroxidation (3) Protein binding	Demonstrated: (1) Forms DNA adducts (2) Lipid peroxidation (3) Protein binding	Demonstrated: (1) 2-bromoacrolein and 2-chloro-3-(bromomethyl) oxirane are direct-acting mutagens in *Salmonella* (2) 2-bromoacrolein forms DNA adducts
Metabolism—GSH conjugation[b]				
Primary reactive metabolites	Inferred from CEG as primary GSH conjugate: (1) HBr released during GSH conjugation (HCl released in minor amounts) By analogy to 1,2-dichloroethane: (2) Reactive episulfonium ion formed following cyclization of GSH adduct 	Inferred from BEG as GSH conjugate: (1) HBr released during GSH conjugation Demonstrated: (2) Reactive episulfonium ion formed following cyclization of GSH adduct 	Inferred from CEG as GSH conjugate: (1) HCl released during GSH conjugation Demonstrated: (2) Reactive episulfonium ion formed following cyclization of GSH adduct 	Inferred from CBPG as primary GSH conjugate: (1) HBr released during GSH conjugation (HCl released in minor amounts) Demonstrated: (2) Reactive episulfonium ion formed following cyclization of GSH adduct 

Table A-2. Comparison of Available ADME Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane (2R and 2S isomers)
Potential role in toxicity	By analogy to all potential analogues: (1) Forms DNA adducts By analogy to 1,2-dibromoethane and 1,2-dibromo-3-chloropropane: (2) Causes DNA damage in cells including spermatocytes Demonstrated: (3) Mutagenicity among genotoxicity assays mediated by GSH activity	Demonstrated: (1) Forms DNA adducts, (2) Causes DNA damage in hepatocytes and spermatocytes (unscheduled DNA synthesis)	Demonstrated: (1) Forms DNA adducts, (2) Binds to protein and DNA in kidney and liver	Demonstrated: (1) Forms DNA adducts, (2) Causes DNA damage in multiple tissues including kidneys and testes (unscheduled DNA synthesis), (3) DNA strand breaks in spermatocytes, (4) DNA damage is correlated with tissue injury at higher doses
Excretion				
Half-life in blood (h)	ND	ND	Rat, oral: <1	Rat, oral: 2.64
Route of excretion	ND	Rat, oral: 60 to <80% urine <20% feces <20% exhaled air (form not indicated)	Rat, oral: 60 to <80% urine <20% feces 20 to <40% excreted unchanged in exhaled air Rat, inhalation: >80% urine <20% feces <20% as CO_2 in exhaled air	Rat, oral: 40 to <60% urine <20% feces 20 to <40% exhaled air (<1% unmetabolized; 20% as CO_2)

Table A-2. Comparison of Available ADME Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane (2R and 2S isomers)
References	Guengerich (1994); Dekant and Vamvakas (1993); Jean and Reed (1992); Gargas et al. (1989); Marchand and Reed (1989); Guengerich et al. (1987); van Bladeren et al. (1981); Wheeler et al. (2001); Shimada et al. (1996)	U.S. EPA (2004); Gargas et al. (1989); Guengerich et al. (1987); NTP (2021)	ATSDR (2001); Gargas et al. (1989); Guengerich et al. (1987)	Guengerich (1994); van Beerendonk et al. (1994); Dekant and Vamvakas (1993); Humphreys et al. (1991); Pearson et al. (1990); Dohn et al. (1988); Omichinski et al. (1988a); Omichinski et al. (1988b); Gingell et al. (1987); Guengerich et al. (1987)

[a]Values represent means in the case of multiple studies.
[b]Metabolism information was categorized as: (1) experimentally **demonstrated,** (2) **inferred from** other experimental data for the same compound, or (3) **by analogy** to experimental data for a different compound.

ADME = absorption, distribution, metabolism, and excretion; BEG = *S*-(2-bromoethyl)glutathione; Br = bromine; CBPG = *S*-(3-chloro-2-bromopropyl) glutathione; CEG = *S*-(2-chloroethyl)glutathione; C_{max} = maximum concentration; Cl = chlorine; CO_2 = carbon dioxide; CYP450 = cytochrome P450; DNA = deoxyribonucleic acid; GSH = glutathione; HBr = hydrogen bromide; HCl = hydrogen chloride; i.p. = intraperitoneal; ND = no data; V_d = volume of distribution.

Metabolism

Each of the candidate analogue compounds is metabolized by a cytochrome P450 (CYP450) oxidation pathway and a direct glutathione (GSH) conjugation pathway. Contributions from both pathways are presumed by analogy for the target compound as well; however, experimental data for 1-bromo-2-chloroethane (the target compound) are available only for the GSH conjugation pathway. Formation of a reactive episulfonium ion occurs, or is expected to occur, for all compounds. Although metabolic pathways are similar among the target chemical and potential analogues, available data indicate that the rate of GSH conjugation and the specific products of oxidative metabolism differ between compounds.

Studies suggest that GSH conjugation leads to the formation of reactive intermediates for the target compound and potential analogues. As discussed in the "Absorption, Distribution, Metabolism, and Excretion" (ADME) section in the main document, 1-bromo-2-chloroethane was metabolized to *S*-(2-chloroethyl)glutathione (CEG) in bile-duct-cannulated rats (Marchand and Reed, 1989). GSH conjugation to CEG is also suggested by formation of *S*-(2-hydroxyethyl)glutathione (HEG), a hydrolysis product of CEG, in isolated rat hepatocytes (Jean and Reed, 1992). Metabolic studies with 1,2-dichloroethane (which also forms CEG by GSH conjugation) report that once formed, CEG cyclizes to form an electrophilic episulfonium ion in vivo, which subsequently binds to deoxyribonucleic acid (DNA) [reviewed by Guengerich (1994); Dekant and Vamvakas (1993)]. Similar electrophilic metabolites (i.e., episulfonium ions) were also produced following GSH conjugation to 1,2-dibromoethane to form *S*-(2-bromoethyl)glutathione (BEG) and to 1,2-dibromo-3-chloropropane to form *S*-(3-chloro-2-bromopropyl) glutathione (CBPG), also resulting in DNA and protein binding and subsequent damage to DNA (NTP, 2021; U.S. EPA, 2004; ATSDR, 2001; Guengerich, 1994; van Beerendonk et al., 1994; Dekant and Vamvakas, 1993; Pearson et al., 1990; Dohn et al., 1988; Omichinski et al., 1988b; Omichinski et al., 1988a; Guengerich et al., 1987). The rate of GSH conjugation is anticipated to be faster for the brominated compounds compared with 1,2-dichloroethane because of the increased relative reactivity of the bromine versus the chlorine leaving group. This is demonstrated by the initial GSH conjugation products identified for both 1-bromo-2-chloroethane and the proposed analogue 1,2-dibromo-3-chloropropane. When both chlorine and bromine substituents are present, GSH conjugation occurs preferentially at the brominated site (yielding CEG and CBPG, respectively) (Dekant and Vamvakas, 1993; Jean and Reed, 1992; Humphreys et al., 1991; Marchand and Reed, 1989). The concomitant release of hydrogen bromide (HBr) (with minor release of hydrogen chloride [HCl]) is inferred (i.e., not experimentally demonstrated) by the preference for GSH conjugation at the brominated site. Halogen reactivity (i.e., bromine vs. chlorine) is expected to have less influence on the rate of the cyclization reaction that occurs subsequent to GSH conjugation, because the reacting centers are held in close proximity to each other, resulting in rapid formation of the episulfonium ion from the GSH adduct in all cases.

Oxidative metabolites differ among the candidate analogue compounds. CYP450-mediated oxidation of 1,2-dibromoethane and 1,2-dichloroethane results in the production of haloacetaldehyde metabolites that can cause lipid peroxidation and bind to cellular proteins and DNA (NTP, 2021; U.S. EPA, 2004; ATSDR, 2001). HBr and HCl are released during the formation of the haloacetaldehyde metabolite (NTP, 1991; van Bladeren et al., 1981). Although not experimentally demonstrated, this pathway is expected for the target compound as well, based on analogy to the candidate analogue compounds. Oxidative metabolism of 1,2-dibromo-3-chloroethane produces three primary metabolites (2-bromoacrolein, 2-chloro-3-[bromomethyl] oxirane, 1-bromo-3-chloroacetone) (Pearson et al., 1990; Dohn et al.,

1988; Omichinski et al., 1988b), none of which can be produced by oxidation of the target compound due to structural constraints. Both HBr and HCl are released during the formation of 2-bromoacrolein, while only HBr is released during the formation of 2-chloro-3-(bromomethyl) oxirane and 1-bromo-3-chloroacetone (Omichinski et al., 1988b). 2-Bromoacrolein and 2-chloro-3-(bromomethyl) oxirane are electrophilic and have been shown to be clastogenic and direct-acting mutagens in *Salmonella* (van Beerendonk et al., 1994; Pearson et al., 1990). 2-Bromoacrolein has also been demonstrated to bind to DNA, and the resulting adducts have been characterized (van Beerendonk et al., 1994).

Because of the preference for relative reactivity of the bromine versus the chlorine leaving group during GSH conjugation, 1,2-dibromoethane and 1,2-dibromo-3-chloropropane are favored as metabolic analogues over 1,2-dichloroethane. Assuming that both CYP450 oxidation and GSH conjugation are equally relevant to the toxicity of the target compound, 1,2-dibromoethane is the most appropriate choice as a metabolic analogue. If the GSH conjugation pathway predominates in its relevance to toxicity, 1,2-dibromo-3-chloropropane may be a more appropriate metabolic analogue.

Toxicity-Like Analogues—Oral

Table A-3 summarizes available oral toxicity values for 1-bromo-2-chloroethane and the compounds identified as potential structural analogues.

Table A-3. Comparison of Available Oral Toxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

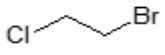
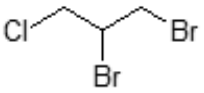
Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane
Structure				
CASRN	107-04-0	106-93-4	107-06-2	96-12-8
Repeated-dose toxicity—subchronic				
POD (mg/kg-d)	NA	NA	58	0.7
POD type	NA	NA	LOAEL	NOAEL
Subchronic UF_C	NA	NA	3,000 (UF_A, UF_D, UF_H, UF_L)	300 (UF_A, UF_D, UF_H)
Subchronic p-RfD (mg/kg-d)	NA	NA	2×10^{-2}	2×10^{-3}
Critical effects[a]	NA	NA	Increased absolute kidney weight in female rats	Male reproductive toxicity (reduced germ cell number)
Species	NA	NA	Rat	Rabbit
Duration	NA	NA	13 wk	10 wk
Route (method)	NA	NA	Drinking water	Drinking water
Source	NA	NA	U.S. EPA (2010)	U.S. EPA (2006)
Repeated-dose toxicity—chronic				
POD (mg/kg-d)	NA	27	58	0.7
POD type	NA	LOAEL (ADJ)	LOAEL	NOAEL
Chronic UF_C	NA	3,000 (UF_A, UF_D, UF_H, UF_L)	10,000 (UF_A, UF_D, UF_H, UF_L, UF_S)	3,000 (UF_A, UF_D, UF_H, UF_S)
Chronic RfD/p-RfD (mg/kg-d)	NA	9×10^{-3}	6×10^{-3} (screening)	2×10^{-4}
Critical effects[a]	NA	Liver peliosis, testicular atrophy, and adrenal cortical degeneration	Increased absolute kidney weight in female rats	Testicular toxicity (reduced germ cell number)
Species	NA	Rat (M and F)	Rat	Rabbit
Duration	NA	49 wk (M); 61 wk (F)	13 wk	10 wk
Route (method)	NA	Gavage in corn oil (5 d/wk)	Drinking water	Drinking water
Source	NA	U.S. EPA (2004)	U.S. EPA (2010)	U.S. EPA (2006)

Table A-3. Comparison of Available Oral Toxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane
Acute oral lethality data				
Rat oral LD_{50} (mg/kg)	64	55−420	670−967	170
Toxicity at rat LD_{50}	NR	NR	NR	NR
Source	U.S. EPA (2020b); U.S. EPA (1985)	U.S. EPA (2020b); U.S. EPA (2004)	U.S. EPA (2020a)	U.S. EPA (2020b)

[a]Exposure-response arrays were prepared to illustrate the dose-response relationship for testicular, kidney, and liver effects across the candidate analogue compounds (Figures A-1, A-2, and A-3, respectively).

ADJ = duration adjusted; F = female(s); LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male(s); NA = not applicable; NOAEL = no-observed-adverse-effect level; NR = not reported; POD = point of departure; p-RfD = provisional reference dose; RfD = oral reference dose; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

No repeated-dose oral toxicity data are available for 1-bromo-2-chloroethane. Acute toxicity data are limited to a reported median lethal dose (LD_{50}) of 64 mg/kg-day in rats; no further information was provided [Frear (1969) as cited in NLM (2016)].

Oral toxicity values are available for 1,2-dibromoethane, 1,2-dichloroethane, and 1,2-dibromo-3-chloropropane (see Table A-3), and the data supporting these values are extensive [as cited in U.S. EPA (2010, 2006, 2004)]. The target organs of toxicity for these potential analogues include the testis, kidney, and liver (see exposure-response arrays in Figures A-1, A-2, and A-3). After review of the available data for candidate analogues, testicular effects are identified as the most sensitive toxicity target after exposure to 1,2-dibromo-3-chloropropane and 1,2-dibromoethane.

Testicular effects occurred at the lowest oral doses for 1,2-dibromoethane and 1,2-dibromo-3-chloropropane and are identified as being among the critical effects for derivation of provisional reference dose (p-RfD) values for both compounds (see Table A-3, Figure A-1). In support of this endpoint, epidemiological studies of 1,2-dibromo-3-chloropropane-exposed production workers, farmers and pesticide applicators have demonstrated impaired testicular function (decreased spermatogenesis and sperm count and altered sperm morphology) in exposed humans. The testicular toxicity of 1,2-dibromo-3-chloropropane is known to be mediated exclusively by the GSH conjugation pathway because the inhibition of this pathway completely abrogated the observed testicular effects (Omichinski et al., 1988a; Søderlund et al., 1988). Reactive episulfonium metabolites are well known to bind to DNA and promote increased rates of DNA damage. Within the context of the 1,2-dibromo-3-chloropropane database, reactive episulfonium metabolites were observed to produce increased amounts of testicular DNA damage, promote testicular necrosis and atrophy at higher doses (Søderlund et al., 1988), and in turn, impair spermatogenesis and prolong oligospermia (Meistrich et al., 2003). This same sequence of events is likely to occur for 1,2-dibromoethane and 1-bromo-2-chloroethane, which are anticipated to undergo GSH conjugation at similar rates to 1,2-dibromo-3-chloropropane due to the presence of bromine leaving groups in all three compounds. This reaction leads to

formation of the reactive episulfonium metabolites that are implicated in testicular toxicity. The absence of testicular toxicity following exposure to 1,2-dichloroethane (see Figure A-1) may be attributable to reduced episulfonium formation secondary to the expected slower rate of GSH conjugation resulting from lower reactivity of the chlorine leaving group relative to bromine (see "Metabolic Analogues" section for more details).

In the absence of repeated-exposure oral toxicity data for 1-bromo-2-chloroethane, there is no information with which to clearly identify or rule out candidate analogues based on toxicity comparisons. However, based on the expected formation of the episulfonium ion following metabolism of 1-bromo-2-chloroethane, the mechanism of action for the critical testicular effects following exposure to 1,2-dibromo-3-chloropropane (and by analogy 1,2-dibromoethane) is plausible for 1-bromo-2-chloroethane as well.

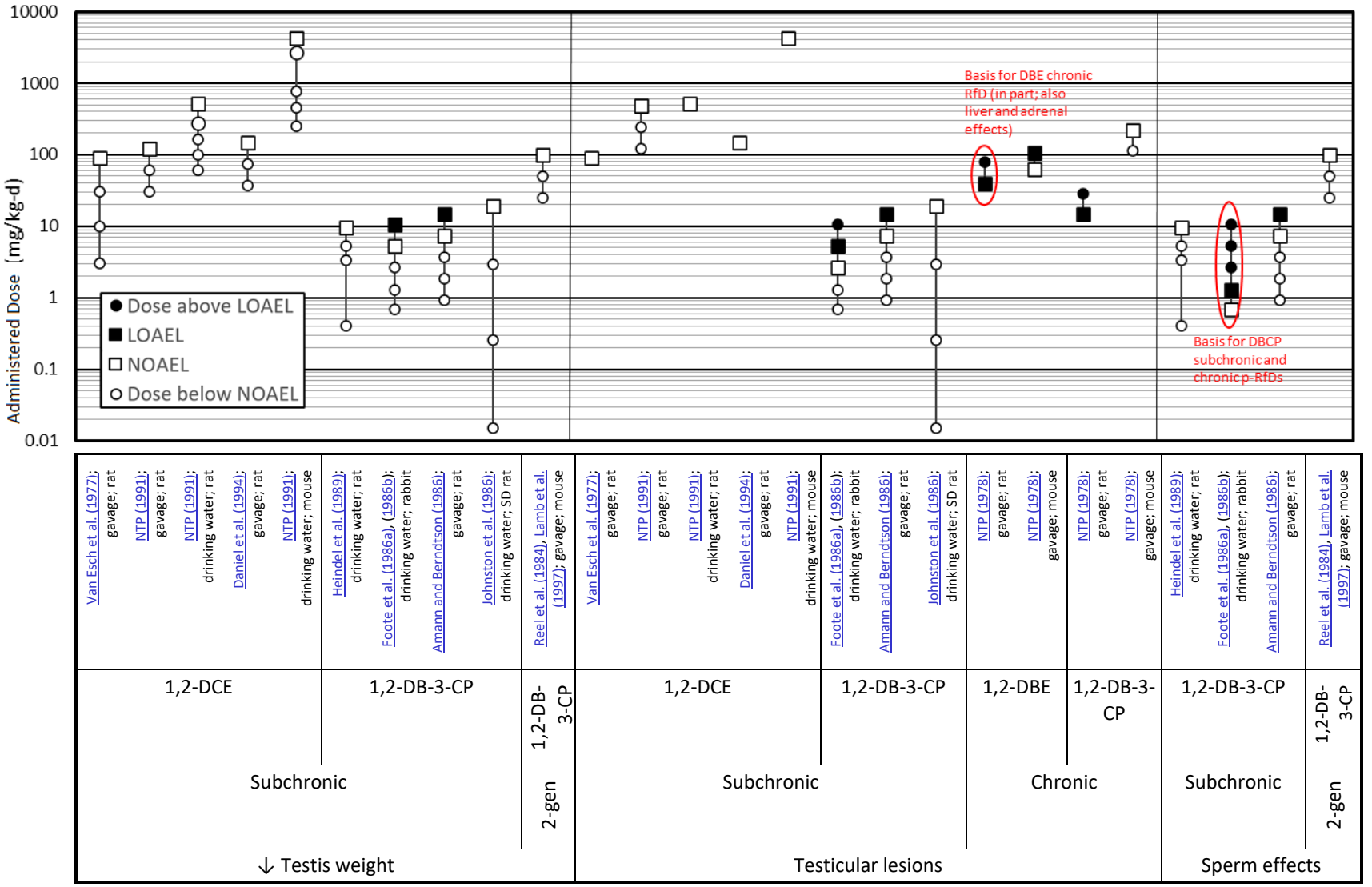


Figure A-1. Testicular Effects Following Oral Exposure to 1,2-Dichloroethane (1,2-DCE), 1,2-Dibromoethane (1,2-DBE), or 1,2-Dibromo-3-Chloropropane (1,2-DB-3-CP) [reviewed by U.S. EPA (2010, 2006, 2004)]

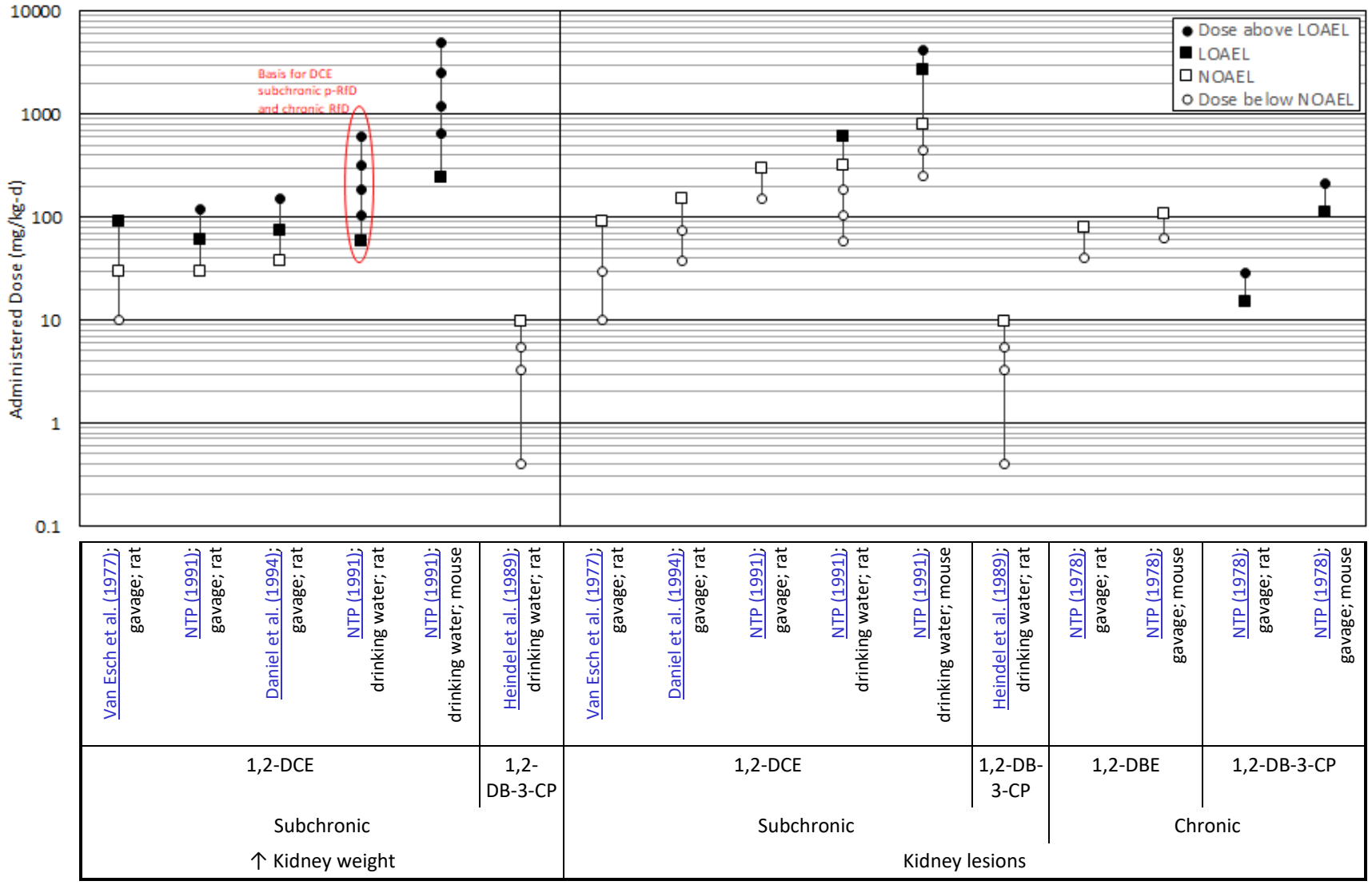


Figure A-2. Kidney Effects Following Oral Exposure to 1,2-Dichloroethane (1,2-DCE), 1,2-Dibromoethane (1,2-DBE), or 1,2-Dibromo-3-Chloropropane (1,2-DB-3-CP) [reviewed by U.S. EPA (2010, 2006, 2004)]

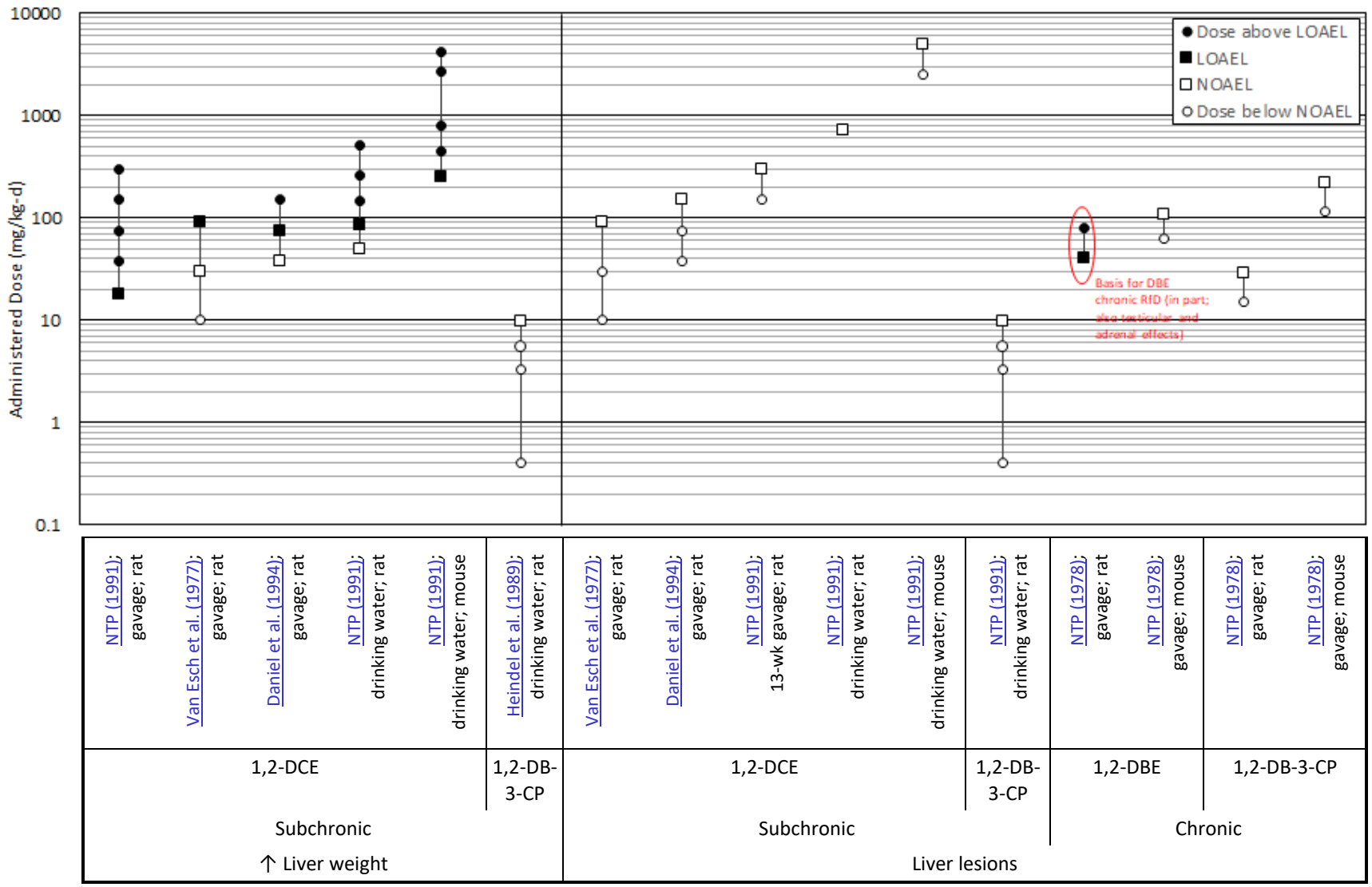


Figure A-3. Liver Effects Following Oral Exposure to 1,2-Dichloroethane (1,2-DCE), 1,2-Dibromoethane (1,2-DBE), or 1,2-Dibromo-3-Chloropropane (1,2-DB-3-CP) [reviewed by U.S. EPA (2010, 2006, 2004)]

Toxicity-Like Analogues—Inhalation

Table A-4 summarizes available inhalation toxicity values for the compounds identified as potential structural analogues for 1-bromo-2-chloroethane.

Table A-4. Comparison of Available Inhalation Toxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

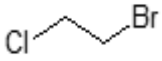
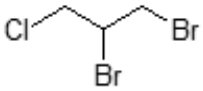
Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane
Structure				
CASRN	107-04-0	106-93-4	107-06-2	96-12-8
Repeated-dose toxicity—subchronic				
POD (mg/m^3)	NA	NA	22	0.17
POD type	NA	NA	LOAEL (ADJ)	NOAEL (HEC)
Subchronic UF_C	NA	NA	300 (UF_D, UF_H, UF_L)	100 (UF_A, UF_D, UF_H)
Subchronic p-RfC (mg/m^3)	NA	NA	7×10^{-2}	2×10^{-3}
Critical effects[a]	NA	NA	Neurobehavioral impairment (impaired visual-motor reactions)	Testicular effects (decreased absolute testis-weight, atrophy, loss of spermatogenic elements in seminiferous tubules)
Species	NA	NA	Human	Rabbit
Duration	NA	NA	No information on length of employment or duration of exposure was reported; treated as subchronic in the PPRTV assessment	14 wk
Route (method)	NA	NA	Inhalation (occupational)	Inhalation (whole body; 6 h/d, 5 d/wk)
Source	NA	U.S. EPA (2004)	U.S. EPA (2010)	U.S. EPA (2006); U.S. EPA (2003)
Repeated-dose toxicity—chronic				
POD (mg/m^3)	NA	2.8	22	0.17
POD type	NA	$BMCL_{10}$ (HEC)	LOAEL (ADJ)	NOAEL (HEC)
Chronic UF_C	NA	300 (UF_A, UF_D, UF_H)	3,000 (UF_D, UF_H, UF_L, UF_S)	1,000 (UF_A, UF_D, UF_H, UF_S)
Chronic RfC/p-RfC (mg/m^3)	NA	9×10^{-3}	7×10^{-3}	2×10^{-4}

Table A-4. Comparison of Available Inhalation Toxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Parameter	1-Bromo-2-Chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dibromo-3-Chloropropane
Critical effects[a]	NA	Suppurative inflammation of nasal cavity in female mice	Neurobehavioral impairment (impaired visual-motor reactions)	Testicular effects (decreased absolute testis weight, atrophy, loss of spermatogenic elements in seminiferous tubules)
Species	NA	Mouse	Human	Rabbit
Duration	NA	78 wk (M) 90−106 wk (F)	No information on length of employment or duration of exposure was reported; treated as subchronic in the PPRTV assessment	14 wk
Route (method)	NA	Inhalation (whole body; 6 h/d, 5 d/wk)	Inhalation (occupational)	Inhalation (whole body; 6 h/d, 5 d/wk)
Source	NA	U.S. EPA (2004)	U.S. EPA (2010)	U.S. EPA (2006); U.S. EPA (2003)
Acute inhalation lethality data				
LC_{50} (mg/m^3)	15,000−25,000 (30-min; unspecified species)	~1,500 (9 h; rat)	7,758 (4 h; rat)	ND
Source	U.S. EPA (1985)	U.S. EPA (2004)	U.S. EPA (2020a)	U.S. EPA (2020b)

[a]Exposure-response arrays were prepared to illustrate the dose-response relationship for testicular, kidney, liver, and respiratory tract effects in experimental animal inhalation studies across the candidate analogue compounds (see Figures A-4, A-5, A-6, and A-7, respectively).

ADJ = duration adjusted; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; F = female(s); HEC = human equivalent concentration; LC_{50} = median lethal concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); NA = not applicable; ND = no data; NOAEL = no-observed-adverse-effect level; POD = point of departure; PPRTV = provisional peer-reviewed toxicity value; p-RfC = provisional reference concentration; RfC = inhalation reference concentration; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

No repeated-exposure inhalation toxicity data are available for 1-bromo-2-chloroethane. Acute inhalation toxicity data are limited to a single study by Valade et al. (1957) as cited in U.S. EPA (1985), which reports a 30-minute median lethal concentration (LC_{50}) value of 15,000−25,000 mg/m^3 in unspecified laboratory animals. This study also indicates that acute inhalation of "several alkyl halides" caused ataxia in dogs, rats, and guinea pigs; however, it is unclear whether these halides included 1-bromo-2-chloroethane.

Inhalation toxicity values are available for 1,2-dichloroethane, 1,2-dibromoethane, and 1,2-dibromo-3-chloropropane (see Table A-4), and the data supporting these values are extensive [reviewed by U.S. EPA (2010, 2006, 2004, 2003)]. Target organs and systems of toxicity for potential analogues include the testis, kidney, liver, nervous system, and respiratory tract (see exposure-response arrays in Figures A-4, A-5, A-6, and A-7). Although neurobehavioral impairment was observed following occupational exposure to 1,2-dichloroethane (impaired visual-motor reactions in two of three tests), an exposure-response array was not prepared for this endpoint because no additional neurobehavioral studies were identified for any candidate analogue in humans or laboratory animals. No information is available regarding the potential mode of action (MOA) for the observed neurobehavioral effects in humans or animals. Upon review of the available inhalation toxicity data, testicular and respiratory effects are identified as the most sensitive toxicity endpoints among the candidate analogues.

Epidemiology studies of 1,2-dibromo-3-chloropropane-exposed production workers, farmers, and pesticide applicators have demonstrated impaired testicular function (decreased spermatogenesis and sperm count and altered sperm morphology) in exposed humans. Testicular effects were identified as critical effects for assessment of 1,2-dibromo-3-chloropropane inhalation toxicity in animal studies. A comparison of rat, mouse, and rabbit data indicates that the rabbit is the most sensitive of these species for testicular effects (by both inhalation and oral exposure). Oral data indicate that testicular toxicity of 1,2-dibromo-3-chloropropane is mediated exclusively by the GSH conjugation pathway (Omichinski et al., 1988a; Søderlund et al., 1988). This is likely the case also for 1,2-dibromoethane and 1-bromo-2-chloroethane, which are anticipated to undergo GSH conjugation at similar rates because of the expected similar reactivity of the bromine leaving groups. This reaction leads to the formation of the reactive episulfonium ion metabolites that are implicated in testicular toxicity (see "Toxicity-Like Analogues—Oral" section above for more details).

Inhalation exposure to the candidate analogues 1,2-dibromoethane and 1,2-dibromo-3-chloropropane in rats and mice produced respiratory tract lesions, with nasal effects occurring at lower concentrations than lesions observed in the bronchial, bronchiolar, and alveolar regions. Respiratory lesions may result, at least in part, from the production of HBr (from both CYP450 oxidation and GSH conjugation) in the respiratory tract. Nasal irritation has been observed in volunteers and laboratory animals exposed to HBr gas (NRC, 2014). By analogy, HBr formation and respiratory lesions may also be expected to occur for the 1-bromo-2-chloroethane target compound. In contrast, 1,2-dichloroethane does not produce nasal or other respiratory tract lesions following inhalation exposure. This may be partially explained by the slower release of chlorine relative to bromine during GSH conjugation, resulting in a reduced rate of generation of HCl in the respiratory tract of exposed animals (relative to HBr from the other compounds). The lack of effect by 1,2-dichloroethane supports the hypothesized role of HBr in the observed respiratory effects.

Other cytotoxic mechanisms may contribute to the nasal toxicity of 1,2-dibromoethane; these include lipid peroxidation and/or protein binding induced by anticipated or experimentally determined metabolites (e.g., 2-bromoacetaldehyde) (U.S. EPA, 2004). By analogy, formation of 2-bromoacetaldehyde and subsequent nasal and/or respiratory lesions may also be expected to occur for the 1-bromo-2-chloroethane target compound.

In the absence of repeated-exposure inhalation toxicity data for 1-bromo-2-chloroethane, there is no information with which to clearly identify or rule out candidate analogues based on toxicity comparisons. However, based on the expected formation of the episulfonium ion following metabolism of 1-bromo-2-chloroethane, the mechanism of action for testicular toxicity following exposure to 1,2-dibromo-3-chloropropane (and by analogy 1,2-dibromoethane) is plausible for 1-bromo-2-chloroethane. Based on the expected formation of HBr and 2-bromoacetaldehyde following metabolism of 1-bromo-2-chloroethane, respiratory toxicity is also plausible for 1-bromo-2-chloroethane.

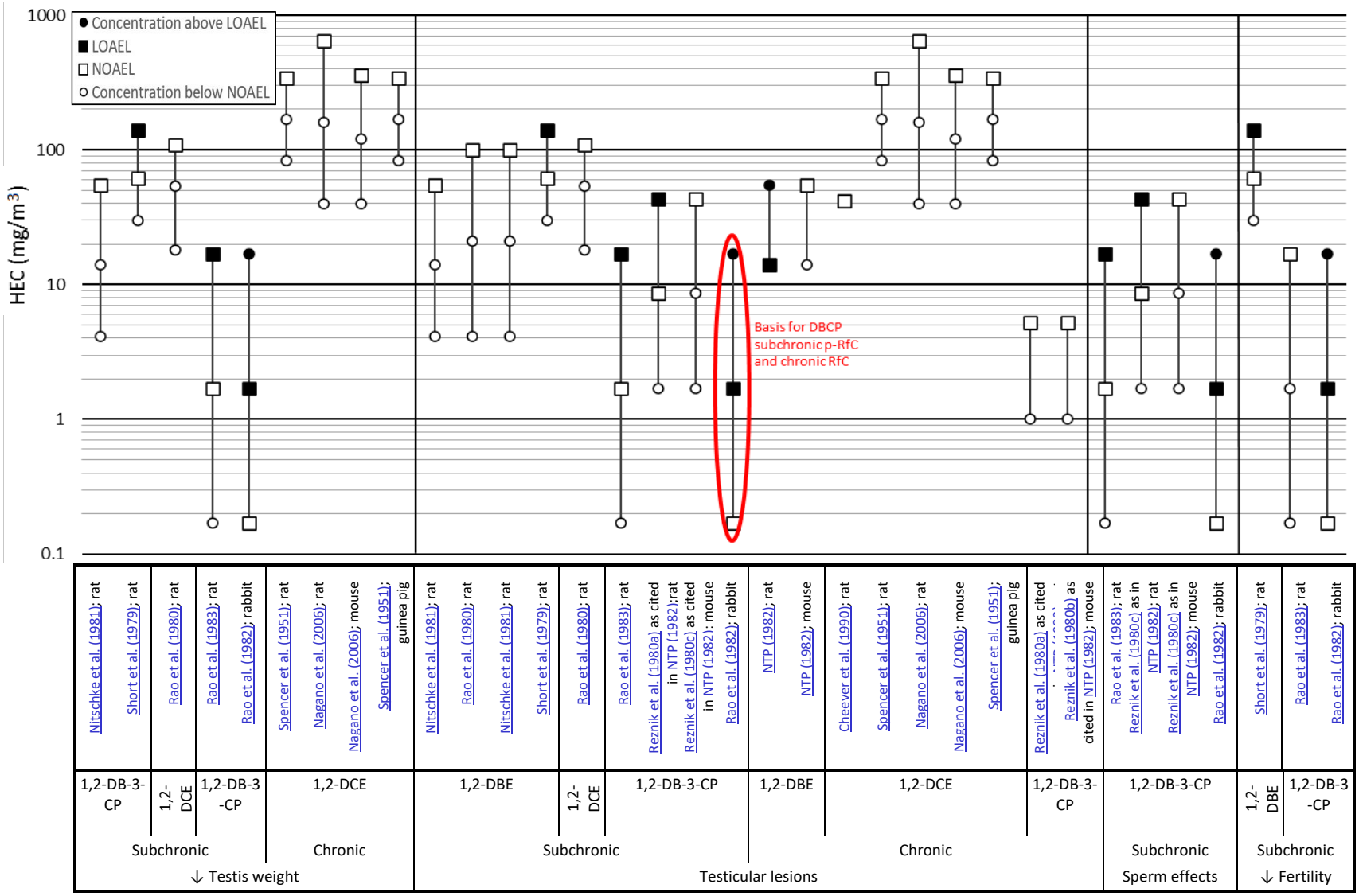


Figure A-4. Testicular Effects Following Inhalation Exposure to 1,2-Dichloroethane (1,2-DCE), 1,2-Dibromoethane (1,2-DBE), or 1,2-Dibromo-3-Chloropropane (1,2-DB-3-CP) [reviewed by U.S. EPA (2010, 2006, 2004, 2003)]

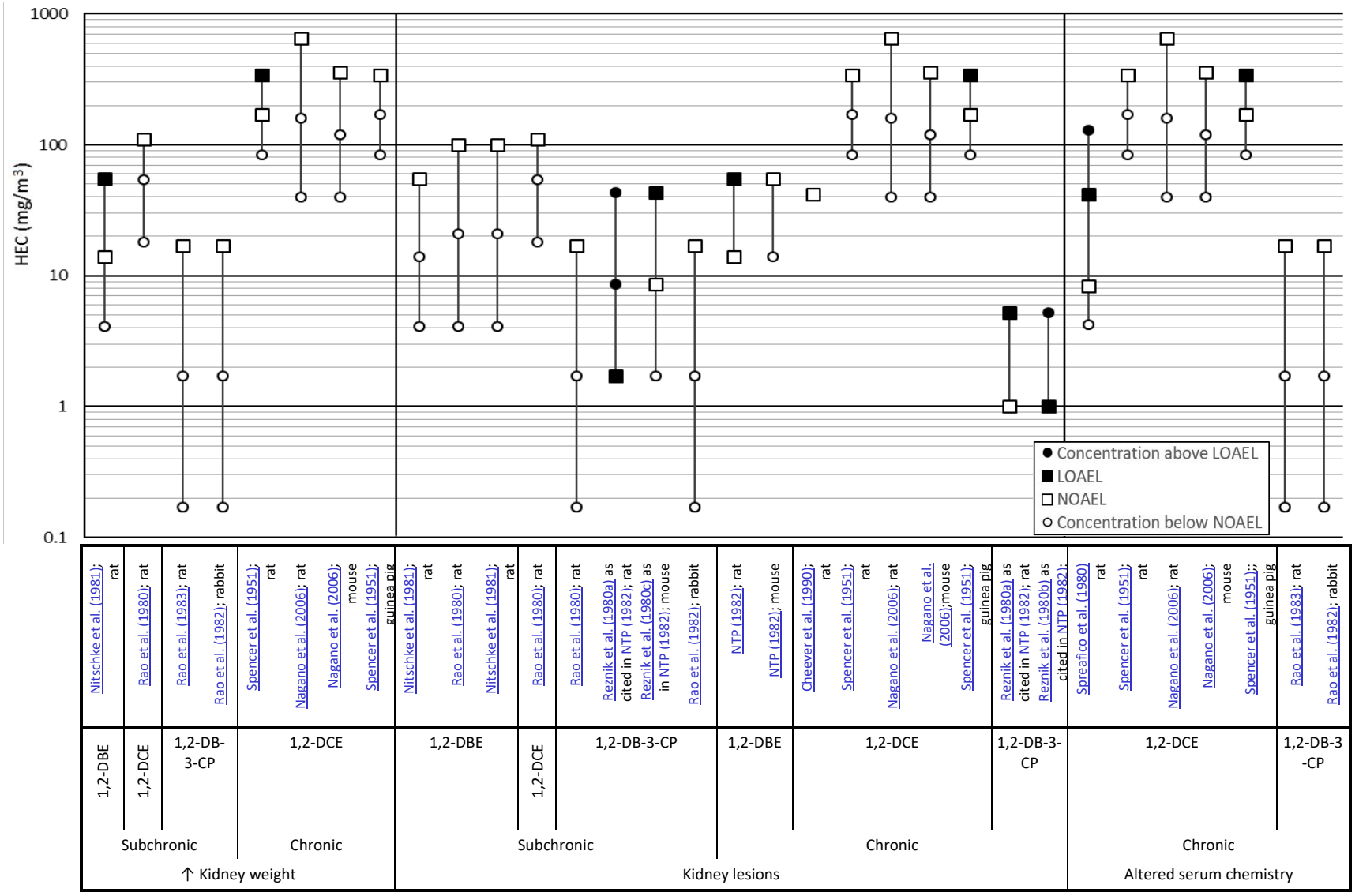


Figure A-5. Kidney Effects Following Inhalation Exposure to 1,2-Dichloroethane (1,2-DCE), 1,2-Dibromoethane (1,2-DBE), or 1,2-Dibromo-3-Chloropropane (1,2-DB-3-CP) [reviewed by U.S. EPA (2010, 2006, 2004, 2003)]

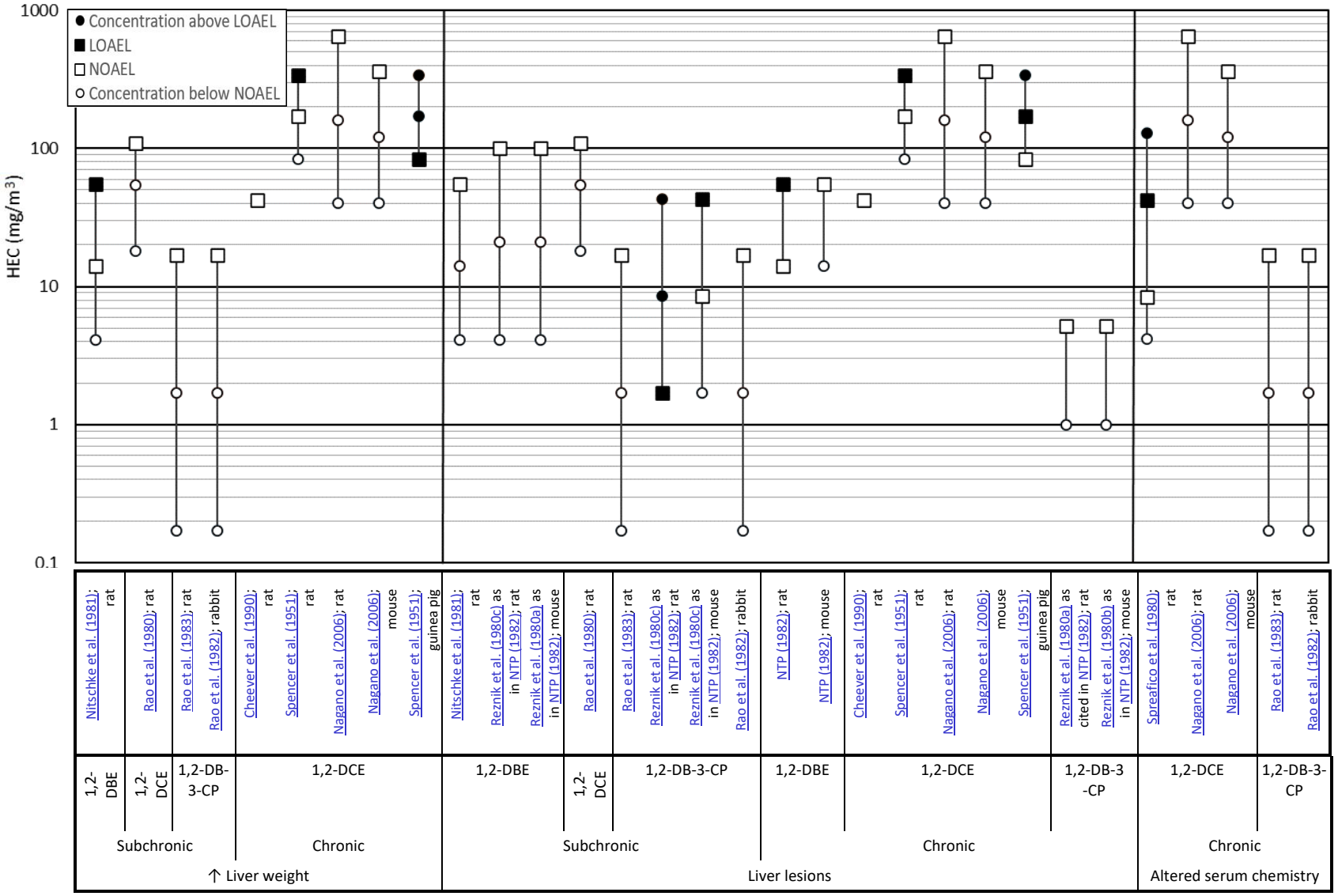


Figure A-6. Liver Effects Following Inhalation Exposure to 1,2-Dichloroethane (1,2-DCE), 1,2-Dibromoethane (1,2-DBE), or 1,2-Dibromo-3-Chloropropane (1,2-DB-3-CP) [reviewed by U.S. EPA (2010, 2006, 2004, 2003)]

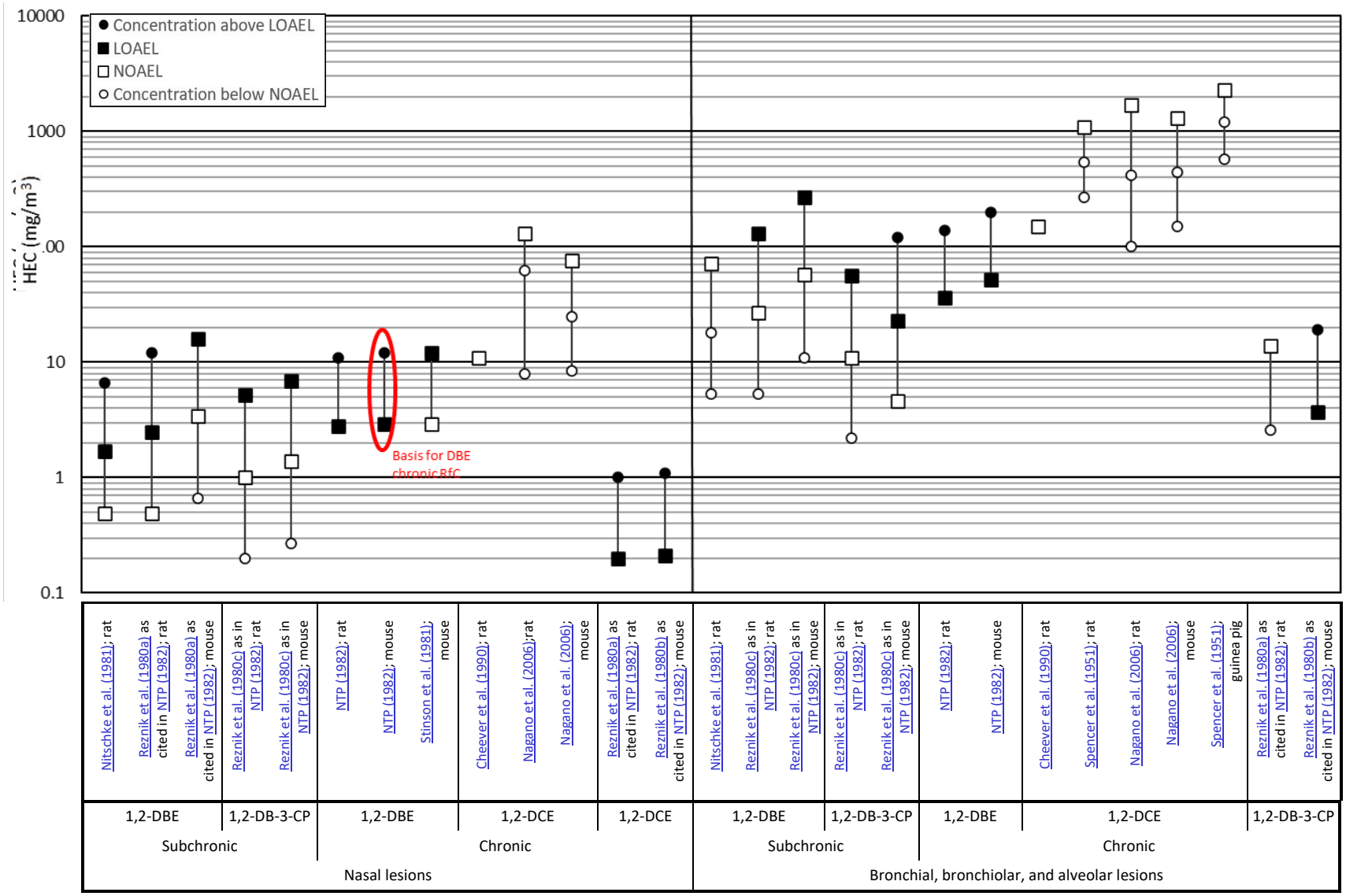


Figure A-7. Respiratory Tract Effects Following Inhalation Exposure to 1,2-Dichloroethane (1,2-DCE), 1,2-Dibromoethane (1,2-DBE), or 1,2-Dibromo-3-Chloropropane (1,2-DB-3-CP) [reviewed by U.S. EPA (2010, 2006, 2004, 2003)]

Weight-of-Evidence Approach

To select the best analogue chemical based on all of the information described within the three analogue similarity tiers prescribed in Wang et al. (2012), the following considerations are used in a weight-of-evidence (WOE) approach: (1) lines of evidence from U.S. EPA assessments are preferred; (2) biological and toxicokinetic data are preferred over the structural similarity scores; (3) lines of evidence that indicate pertinence to humans are preferred; (4) chronic studies are preferred over subchronic studies when selecting an analogue for a chronic value; (5) chemicals with more sensitive toxicity values may be favored; and (6) if there are no clear indications as to the best analogue chemical based on the other considerations, then the candidate analogue with the highest structural similarity scores may be preferred.

Oral

The WOE approach used to select the analogue compound for 1-bromo-2-chloroethane is based on mechanistic and metabolism considerations related to the most sensitive critical effect (i.e., testicular toxicity). Unlike 1,2-dibromoethane and 1,2-dibromo-3-chloropropane, 1,2-dichloroethane is not a testicular toxicant. This may be explained by differences in the rate and extent of GSH adduct formation due in part to differences in the chemical reactivity of the brominated versus the chlorinated compounds. 1,2-Dibromoethane will react more rapidly with GSH than 1,2-dichloroethane because bromide is a better chemical leaving group in comparison to the chloride. That is, the C-Br bond is more readily cleaved than is the C-Cl bond. The results of this difference are demonstrated by the metabolic products and GSH adducts formed by 1-bromo-2-chloroethane and 1,2-dibromo-3-chloropropane. In both cases, bromine is preferentially displaced when both C-Br and C-Cl bonds are available. The only GSH-conjugated product detected from 1-bromo-2-chloroethane metabolism was CEG, and episulfonium products of 1,2-dibromo-3-chloropropane contain chlorine, indicating that bromine was preferentially released during metabolism (Dekant and Vamvakas, 1993; Jean and Reed, 1992; Humphreys et al., 1991; Marchand and Reed, 1989). These data suggest that from the available identified potential analogue chemicals, chemicals with a bromine leaving group are expected to be more relevant as an analogue for 1-bromo-2-chloroethane. The presence of this group is expected to significantly influence the rate of GSH conjugation (and ultimately the rate of toxic moiety production) over analogues containing chlorine leaving groups.

By analogy, 1-bromo-2-chloroethane can be expected to form the same episulfonium ion that is formed from 1,2-dibromoethane and 1,2-dichloroethane after GSH conjugation (see Table A-2). In the initial reaction, bromine will be preferentially displaced from 1-bromo-2-chloroethane. Although this compound and 1,2-dichloroethane are both expected to lead to the same initial adduct, 1-bromo-2-chloroethane is expected to react faster because of the presence of a bromide versus chloride leaving group, leading to a higher localized concentration of the proximal toxicant. Therefore, the rate of initial adduct formation is expected to be more similar to 1,2-dibromoethane and 1,2-dibromo-3-chloropropane than to 1,2-dichloroethane. Available data suggest that the cyclization of the GSH adducts for each respective analogue is rapid and immediate, and that this step (leading to the production of the toxic episulfonium ion moiety) is not likely to be the rate-limiting step in the metabolism of the parent chemicals.

Given the demonstrated significance of the presence of a bromide leaving group in metabolism and expected toxicity, 1-bromo-2-chloroethane, 1,2-dibromoethane, and

1,2-dibromo-3-chloropropane were determined to be more appropriate analogues compared with 1,2-dichloroethane. Ultimately, 1,2-dibromo-3-chloropropane is selected as the most appropriate analogue compound for both subchronic and chronic effects because the demonstrated testicular effect of this chemical on sperm is the most sensitive measure of toxicity among the favored brominated analogues.

Inhalation

The WOE approach used to select the analogue compound for 1-bromo-2-chloroethane is based on mechanistic considerations related to sensitive effects for the candidate brominated analogues following inhalation exposure (i.e., testicular toxicity and respiratory effects). The absence of testicular and respiratory tract effects for 1,2-dichloroethane may be explained, at least in part, by a decrease in the rate and extent of GSH conjugation (i.e., bromine is a better chemical leaving group than chlorine), leading to a lower localized concentration of proximal toxicants (i.e., episulfonium ion, HCl). 1-Bromo-2-chloroethane can be expected to form both the reactive episulfonium metabolite (responsible for testicular effects) and HBr (which may contribute to respiratory lesions) at a similar rate as 1,2-dibromoethane and 1,2-dibromo-3-chloropropane. Both 1,2-dibromoethane and 1,2-dibromo-3-chloropropane release HBr during GSH conjugation, and this is expected to occur for 1-bromo-2-chloroethane. As described above, the rate of GSH conjugation among brominated compounds, rapid cyclization of GSH conjugates to generate reactive episulfonium ions, and the release of HBr during GSH conjugation suggest that the brominated analogues are more appropriate surrogate chemicals for 1-bromo-2-chloroethane than 1,2-dichloroethane. However, these characteristics do not provide a means to sufficiently differentiate amongst the brominated analogues.

Ultimately, 1,2-dibromo-3-chloropropane is selected as the analogue compound for both subchronic and chronic inhalation exposure because the demonstrated effect of this chemical on sperm is among the most sensitive measures of toxicity among the favored brominated analogues, and the relevance of this endpoint to humans is supported by the observation of similar effects in exposed workers (U.S. EPA, 2006).

NONCANCER ORAL TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Dose

Based on the overall analogue approach presented in this PPRTV assessment, 1,2-dibromo-3-chloropropane is selected as the analogue for 1-bromo-2-chloroethane for deriving a screening subchronic p-RfD. The study used for the U.S. EPA subchronic p-RfD for 1,2-dibromo-3-chloropropane was a 10-week reproductive study in rabbits [Foote et al. (1986a, b) as cited in U.S. EPA (2006)] described as follows:

> *Groups of 6 male Dutch rabbits were exposed to drinking water that provided reported DBCP intakes of 0, 0.94, 1.88, 3.75, 7.5 or 15.0 mg/kg on 5 days/week (0, 0.7, 1.3, 2.7, 5.4 or 10.7 mg/kg-day) for 10 weeks (Foote et al., 1986a, 1986b). General health, body weight, semen quality, and libido were evaluated throughout the study. Assessments of fertility (mated with untreated females) and serum levels of reproductive hormones (follicle stimulation hormone, luteinizing hormone and testosterone) were performed during the last week of the study. Endpoints evaluated following sacrifice at the end of the study*

included organ weights (liver, kidneys, testes, epididymides, accessory sex glands), quantitative histology of testes and epididymides, and sperm morphology and forward motility and morphology. There were no statistically significant ($p < 0.05$) changes in any of the study endpoints at 0.7 mg/kg-day. Effects observed at higher doses included dose-related reductions in numbers of all germ cell types within Stage I seminiferous tubular cross sections (significantly reduced numbers of spermatogonia and preleptotene spermatocytes at >1.3 mg/kg-day, pachytene spermatocytes at >2.7 mg/kg-day, and round spermatids at >5.4 mg/kg-day) (Table 1 [in U.S. EPA 2006]*). Other effects included dose-related significantly reduced numbers of leptotene primary spermatocytes per Sertoli cell at >2.7 mg/kg-day, and significantly reduced mean diameter of seminiferous tubules and increased percentage of sperm with abnormal tails at >5.4 mg/kg-day (Table 2* [in U.S. EPA 2006]*). Testis weight and volume, and sperm production (number of seminiferous tubules with round or elongating spermatids), output (ejaculate volume times sperm concentration) and motility were reduced, and serum FSH level was increased, at 10.7 mg/kg-day (Table 3* [in U.S. EPA 2006].*). Fertility was not affected at any dose level, as assessed by number of males producing young, number or percentage of live births, total number of young, average litter size, and gestation length. The results summarized above are based on comparisons of mean data from the treated and control groups. Regression analyses showed highly significant correlations between DBCP dosage and essentially all of the testicular responses. The findings of this study indicate that rabbits are more sensitive than rats to testicular effects of DBCP. This study identified a NOAEL of 0.7 mg/kg-day and LOAEL of 1.3 mg/kg-day for reproductive toxicity in male rabbits.*

The critical effect in this study was testicular toxicity in male rabbits; the no-observed-adverse-effect level (NOAEL) of 0.7 mg/kg-day was used as the point of departure (POD) for 1,2-dibromo-3-chloropropane (U.S. EPA, 2006) and is adopted as the analogue POD for the current assessment of 1-bromo-2-chloroethane.

For the current assessment, the NOAEL of 0.7 mg/kg-day was converted to a human equivalent dose (HED) according to current (U.S. EPA, 2011c) guidance. In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011c), the Agency endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD from effects that are not portal-of-entry effects.

Following U.S. EPA (2011c) guidance, the POD for testicular effects in male rabbits is converted to an HED by applying a dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a reference BW_a of 2.86 kg for rabbits and a reference BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.45. Applying this DAF to the NOAEL of 0.7 mg/kg-day yields a POD (HED) as follows:

$$\begin{aligned} \text{POD (HED)} &= \text{NOAEL (mg/kg-day)} \times \text{DAF} \\ &= 0.7 \text{ mg/kg-day} \times 0.45 \\ &= 0.3 \text{ mg/kg-day} \end{aligned}$$

The U.S. EPA (2006) subchronic p-RfD for 1,2-dibromo-3-chloropropane was derived using a composite uncertainty factor (UF_C) of 300, reflecting 10-fold uncertainty factors for interspecies extrapolation and intraspecies variability and a 3-fold uncertainty factor for database uncertainties (UF_A, UF_H, and UF_D, respectively). Wang et al. (2012) indicated that the uncertainty factors typically applied in deriving a toxicity value for the selected analogue are the same as those applied to the chemical of concern unless additional information is available. For 1-bromo-2-chloroethane, a UF_A of 3 is applied because cross-species dosimetric adjustment was performed, and a UF_D of 10 was used to reflect the lack of repeated-dose toxicity data; the UF_H remained the same as for 1,2-dibromo-3-chloropropane. Thus, the screening subchronic p-RfD for 1-bromo-2-chloroethane is derived using a UF_C of 300.

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= \text{Analogue POD (HED)} \div UF_C \\ &= 0.3 \text{ mg/kg-day} \div 300 \\ &= \mathbf{1 \times 10^{-3} \text{ mg/kg-day}} \end{aligned}$$

Table A-5 summarizes the uncertainty factors for the screening subchronic p-RfD for 1-bromo-2-chloroethane.

Table A-5. Uncertainty Factors for the Screening Subchronic p-RfD for 1-Bromo-2-Chloroethane (CASRN 107-04-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rabbits and humans following 1-bromo-2-chloroethane exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011c). Dosimetric adjustment calculations were performed on the POD for the selected analogue, 1,2-dibromo-3-chloropropane.
UF_D	10	A UF_D of 10 is applied to reflect database limitations for 1,2-dibromo-3-chloropropane and the absence of repeated-dose toxicity data for 1-bromo-2-chloroethane.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1-bromo-2-chloroethane in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic study was selected as the principal study for the subchronic assessment.
UF_C	300	Composite uncertainty factor = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Dose

1,2-Dibromo-3-chloropropane is also selected as the analogue for 1-bromo-2-chloroethane for deriving a screening chronic p-RfD. The key study and calculation of the POD (HED) are described above for the subchronic p-RfD. The uncertainty factors used for the screening subchronic p-RfD (UF_A of 3, UF_H of 10, and UF_D of 10) are applied, and a UF_S of 10 is applied to account for extrapolation from a subchronic to a chronic duration (consistent with the UF_S applied during the derivation of the chronic p-RfD for 1,2-dibromo-3-chloropropane). Thus, the screening chronic p-RfD for 1-bromo-2-chloroethane is derived using a UF_C of 3,000.

Screening Chronic p-RfD = Analogue POD (HED) ÷ UF_C
= 0.3 mg/kg-day ÷ 3,000
= **1×10^{-4} mg/kg-day**

Table A-6 summarizes the uncertainty factors for the screening chronic p-RfD for 1-bromo-2-chloroethane.

Table A-6. Uncertainty Factors for the Screening Chronic p-RfD for 1-Bromo-2-Chloroethane (CASRN 107-04-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rabbits and humans following 1-bromo-2-chloroethane exposure. The toxicokinetic uncertainty has been accounted for by calculating an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011c). Dosimetric adjustment calculations were performed on the POD for the selected analogue, 1,2-dibromo-3-chloropropane.
UF_D	10	A UF_D of 10 is applied to reflect database limitations for 1,2-dibromo-3-chloropropane and the absence of repeated-dose toxicity data for 1-bromo-2-chloroethane.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1-bromo-2-chloroethane in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	10	A UF_S of 10 is applied because a subchronic study was selected as the principal study for the chronic assessment.
UF_C	3,000	Composite uncertainty factor = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

NONCANCER INHALATION TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Concentration

Based on the overall analogue approach presented in this PPRTV assessment, 1,2-dibromo-3-chloropropane is selected as the most appropriate analogue for 1-bromo-2-chloroethane for deriving a screening subchronic p-RfC. The study used for the subchronic p-RfC for 1,2-dibromo-3-chloropropane was a 14-week study in rabbits [Rao et al. (1982) as cited in U.S. EPA (2006)]. U.S. EPA (2006) described the study as follows:

> *In rabbits, reproductive toxicity was evaluated in groups of 10 New Zealand white males (age 6 months) that were exposed to 0, 0.1, 1 or 10 ppm (0, 0.94, 9.4 or 94 mg/m^3) vapor for 6 hours/day, 5 days/week for 14 weeks, and observed for the following 32 weeks (0, 0.1 and 1 ppm groups) or 38 weeks (10 ppm group) (Rao et al., 1982). The 10 ppm rabbits were exposed for only 8 weeks due to high mortality (apparently from pneumonia). Body weight and hematological and clinical chemistry parameters were evaluated, but no exposure related changes were found. No gross lesions were found in the lungs or upper respiratory tract, but these tissues were not examined histologically. Semen was collected during the exposure and recovery periods to assess sperm motility, viability and counts. The average sperm count of the 10-ppm rabbits was significantly less than that of the controls after 7 weeks of exposure, and remained*

decreased for the duration of the exposure and observation periods. At 1 ppm (9.4 mg/m^3), sperm counts were significantly reduced, compared with controls, from weeks 11 to 13 of exposure. At 0.1 ppm (0.94 mg/m^3), sperm counts were sporadically lower than control values (significantly reduced at only one interim time point). The percentage of live sperm in the semen of the 10 ppm (94 mg/m^3) rabbits was also significantly reduced compared to controls during weeks 8−26. Rabbits exposed to 1 ppm (9.4 mg/m^3), but not those exposed to 0.1 ppm (0.94 mg/m^3), exhibited significant decreases in the percentage of live sperm during weeks 6, 12 and 13. From the 8th week of exposure onward, the 10-ppm (94 mg/m^3) rabbits had a marked decrease in the percentage of progressively motile sperm; no consistent statistically significant decreases in this endpoint were found at <1 ppm (9.4 mg/m^3) (Table 4 [in U.S. EPA 2006]*). Abnormal spermatozoa within the seminiferous tubules were counted in 3−4 rabbits per group; the percentage of abnormal sperm at 14 weeks was 5% in controls, 10% at 0.1 ppm (0.94 mg/m^3), and 18% at 1 ppm (9.4 mg/m^3).*

To assess the effects of DBCP on fertility in the rabbits, exposed males were mated to unexposed females at study weeks 14 and 41 (Rao et al., 1982) (Tables 5, 6 [in U.S. EPA 2006]*). There were no effects on the libido of the exposed male rabbits during week 14, based on percentages of males (78−100%) that copulated with unexposed females. Five of the 10 males exposed to 10 ppm were infertile (none of the females that they were mated with became pregnant). The mean number of implantations/litter in the 1 ppm (9.4 mg/m^3) group was significantly less than that of the control group. During week 41 (27 weeks post-exposure), all rabbits exposed to 0.1 or 1 ppm (0.94 or 9.4 mg/m^3) DBCP produced normal litters, and 2 of the 5 infertile males exposed to 10 ppm (94 mg/m^3) recovered (sperm counts increased) and produced normal litters. Serum levels of follicle stimulating hormone (FSH) were significantly elevated at 14 weeks in the males exposed to 1 ppm (9.4 mg/m^3) and at 46 weeks in the males exposed to 10 ppm (94 mg/m^3), but serum levels of testosterone were unchanged (Table 7* [in U.S. EPA 2006]*). The increases in serum FSH were consistent with the decreases in sperm count. Gross pathologic examinations showed small testes size in rabbits exposed to 1 or 10 ppm. Testes weight was significantly decreased to 50% of control values (week 14) in the group exposed to 1 ppm (9.4 mg/m^3) and to 75% of control values (week 8) in the group exposed to 10 ppm. Histological examinations showed reproductive system effects that included atrophy of the testes, epididymides, and accessory sex glands, including the prostate. The testicular atrophy was severe, as characterized by nearly complete or complete loss of spermatogenic elements in nearly all seminiferous tubules. Following the recovery period, tubular regeneration was observed in the testes of some 10 ppm (94 mg/m^3) rabbits (3/5 had regeneration such that 25% of the seminiferous tubules appeared normal). At 1 ppm, testicular recovery was reported to be nearly complete in some rabbits (incidences not given). The testes of the 0.1 ppm rabbits appeared normal. The lack of exposure-related adverse testicular and fertility effects at 0.1 ppm indicates that this study identified a*

NOAEL of 0.1 ppm (0.94 mg/m^3) and LOAEL of 1 ppm (9.4 mg/m^3) for reproductive effects in rabbits.

The critical effect in this study was testicular toxicity in male rabbits; the NOAEL of 0.94 mg/m^3 was used as the POD for 1,2-dibromo-3-chloropropane. The U.S. EPA (2006) calculated a POD (human equivalent concentration [HEC]) according to U.S. EPA (1994) guidance for Category 3 gases by adjusting intermittent exposure levels to a continuous exposure basis (U.S. EPA, 2002) and multiplying the result by a ratio of the animal blood-gas partition coefficient (concentration ÷ concentration) for 1,2-dibromo-3-chloropropane to the human blood-gas partition coefficient (concentration ÷ concentration) for 1,2-dibromo-3-chloropropane. Because blood-air partition coefficients for 1,2-dibromo-3-chloropropane are unknown, a default value of 1 was assigned.

$$\begin{aligned}\text{POD (HEC)} &= \text{NOAEL (mg/m}^3\text{)} \times \text{(hours exposed/24 hours)} \times \\ &\quad \text{(days/week exposed/7 days)} \times \text{(animal blood-gas partition} \\ &\quad \text{coefficient} \div \text{human blood-gas partition coefficient)} \\ &= 0.94 \text{ mg/m}^3 \times (6/24) \times (5/7) \times 1 \\ &= 0.17 \text{ mg/m}^3\end{aligned}$$

The POD (HEC) of 0.17 mg/m^3 derived for 1,2-dibromo-3-chloropropane by U.S. EPA (2006) is adopted as the analogue POD (HEC) for the current assessment of 1-bromo-2-chloroethane.

The U.S. EPA (2006) subchronic p-RfC for 1,2-dibromo-3-chloropropane was derived using a UF_C of 100 to account for uncertainties due to interspecies extrapolation (UF_A = 3), intraspecies variability (UF_H = 10), and database uncertainties (UF_D = 3) (U.S. EPA, 2006). Wang et al. (2012) indicated that the uncertainty factors typically applied in deriving a toxicity value for the chemical of concern are the same as those applied to the analogue unless additional information is available. Because no repeated-exposure inhalation toxicity data are available for 1-bromo-2-chloroethane, a UF_D of 10 is used; other UF values remain the same as for 1,2-dibromo-3-chloropropane. Thus, the screening subchronic p-RfC for 1-bromo-2-chloroethane is derived using a UF_C of 300, reflecting a UF_A of 3, a UF_H of 10, and a UF_D of 10.

$$\begin{aligned}\textbf{Screening Subchronic p-RfC} &= \text{Analogue POD (HEC)} \div UF_C \\ &= 0.17 \text{ mg/m}^3 \div 300 \\ &= \mathbf{6 \times 10^{-4} \text{ mg/m}^3}\end{aligned}$$

Table A-7 summarizes the uncertainty factors for the screening subchronic p-RfC for 1-bromo-2-chloroethane.

Table A-7. Uncertainty Factors for the Screening Subchronic p-RfC for 1-Bromo-2-Chloroethane (CASRN 107-04-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed. Dosimetric adjustment calculations were performed on the POD for the selected analogue, 1,2-dibromo-3-chloropropane.
UF_D	10	A UF_D of 10 is applied to reflect database limitations for 1,2-dibromo-3-chloropropane and the absence of repeated-exposure toxicity data for 1-bromo-2-chloroethane.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1-bromo-2-chloroethane in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic study was selected as the principal study for the subchronic assessment.
UF_C	300	Composite uncertainty factor = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Concentration

1,2-Dibromo-3-chloropropane is also selected as the analogue for 1-bromo-2-chloroethane for deriving a screening chronic p-RfC. The key study and calculation of the POD (HEC) are described above for the subchronic p-RfC. The uncertainty factor values used for the screening subchronic p-RfC (UF_A of 3, UF_H of 10, and UF_D of 10) are applied, and a UF_S of 10 is applied to account for extrapolation from a subchronic to a chronic duration (consistent with the UF_S applied during the derivation of the chronic RfC for 1,2-dibromo-3-chloropropane) (U.S. EPA, 2003). Thus, the screening chronic p-RfC for 1-bromo-2-chloroethane is derived using a UF_C of 3,000.

$$\begin{aligned} \textbf{Screening Chronic p-RfC} &= \text{Analogue POD (HEC)} \div UF_C \\ &= 0.17\ \text{mg/m3} \div 3{,}000 \\ &= \mathbf{6 \times 10^{-5}\ mg/m^3} \end{aligned}$$

Table A-8 summarizes the uncertainty factors for the screening chronic p-RfC for 1-bromo-2-chloroethane.

Table A-8. Uncertainty Factors for the Screening Chronic p-RfC for 1-Bromo-2-Chloroethane (CASRN 107-04-0)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed. Dosimetric adjustment calculations were performed on the POD for the selected analogue, 1,2-dibromo-3-chloropropane.
UF_D	10	A UF_D of 10 is applied to reflect database limitations for 1,2-dibromo-3-chloropropane and the absence of repeated-exposure toxicity data for 1-bromo-2-chloroethane.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1-bromo-2-chloroethane in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	10	A UF_S of 10 is applied because a subchronic study was selected as the principal study for the chronic assessment.
UF_C	3,000	Composite uncertainty factor = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor(s); UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

APPENDIX B. BACKGROUND AND METHODOLOGY FOR THE SCREENING EVALUATION OF POTENTIAL CARCINOGENICITY

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, there is inadequate information to assess the carcinogenic potential of 1-bromo-2-chloroethane. However, information is available for this chemical which, although insufficient to support a weight-of-evidence (WOE) descriptor and derivation of provisional cancer risk estimates under current guidelines, may be of limited use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a "screening evaluation of potential carcinogenicity." Appendices receive the same level of internal and external scientific peer review as the provisional cancer assessments in PPRTVs to ensure their appropriateness within the limitations detailed in the document. Users of the information regarding potential carcinogenicity in this appendix should understand that there could be more uncertainty associated with this evaluation than for the cancer WOE descriptors presented in the body of the assessment. Questions or concerns about the appropriate use of the screening evaluation of potential carcinogenicity should be directed to the CPHEA.

The screening evaluation of potential carcinogenicity includes the general steps shown in Figure B-1. The methods for Steps 1 through 8 apply to any target chemical and are described in this appendix. Chemical-specific data for all steps in this process are summarized in Appendix C.

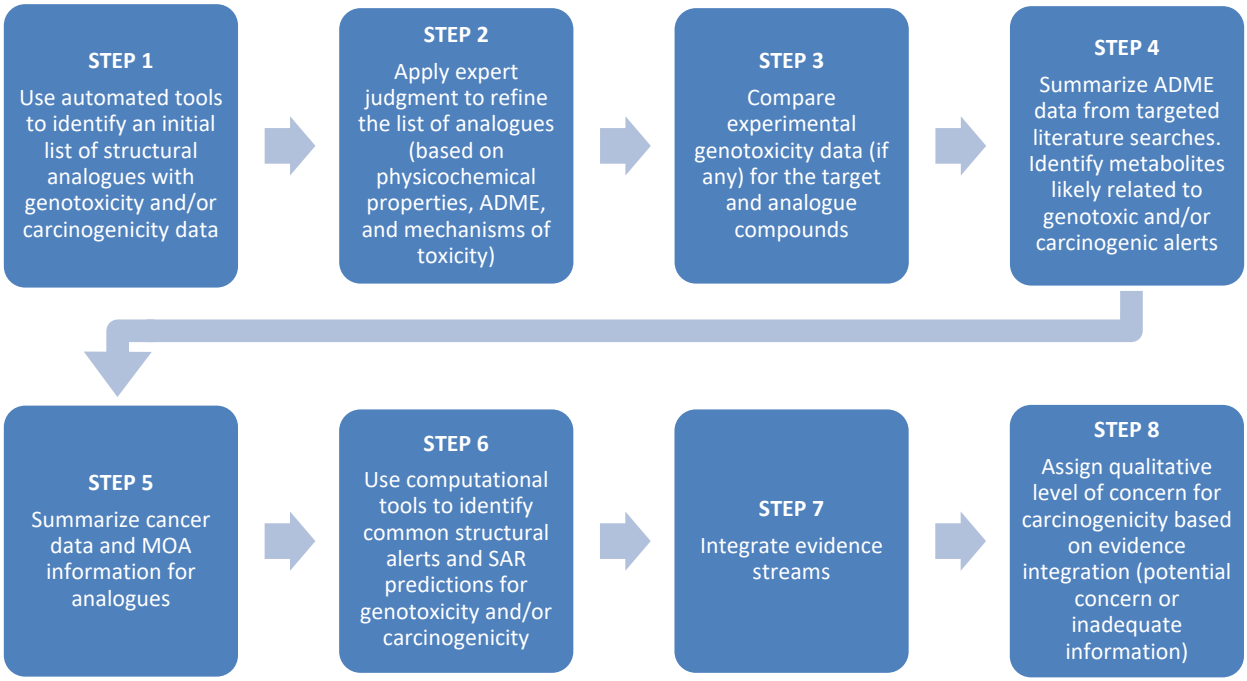


Figure B-1. Steps Used in the Screening Evaluation of Potential Carcinogenicity

STEP 1. USE OF AUTOMATED TOOLS TO IDENTIFY STRUCTURAL ANALOGUES WITH CARCINOGENICITY AND/OR GENOTOXICITY DATA

ChemACE Clustering

The U.S. EPA's Chemical Assessment Clustering Engine [ChemACE; U.S. EPA (2011a)] is an automated tool that groups (or clusters) a user-defined list of chemicals based on chemical structure fragments. The methodology used to develop ChemACE was derived from U.S. EPA's Analog Identification Methodology (AIM) tool, which identifies structural analogues for a chemical based on common structural fragments. ChemACE uses the AIM structural fragment recognition approach for analogue identification and applies advanced queries and user-defined rules to create the chemical clusters. The ChemACE cluster outputs are available in several formats and layouts (i.e., Microsoft Excel, Adobe PDF) to allow rapid evaluation of structures, properties, mechanisms, and other parameters, which are customizable based on an individual user's needs. ChemACE clustering has been successfully used with chemical inventories for identifying trends within a series of structurally similar chemicals, demonstrating structural diversity in a chemical inventory, and detecting structural analogues to fill data gaps and/or perform read-across.

For this project, ChemACE is used to identify potential structural analogues of the target compound that have available carcinogenicity assessments and/or carcinogenicity data. An overview of the ChemACE process is shown in Figure B-2.

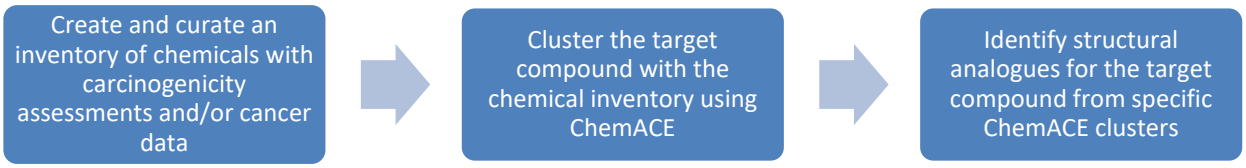


Figure B-2. Overview of ChemACE Process

The chemical inventory was populated with chemicals from the following databases and lists:

- Carcinogenic Potency Database [CPDB; CPDB (2011)]
- Agents classified by the International Agency for Research on Cancer (IARC) monographs (IARC, 2018)
- National Toxicology Program (NTP) Report on Carcinogens [ROC; NTP (2016a)]
- NTP technical reports (NTP, 2017)
- Integrated Risk Information (IRIS) carcinogens (U.S. EPA, 2017)
- California EPA Prop 65 list (CalEPA, 2020)
- European Chemicals Agency (ECHA) carcinogenicity data available in the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox (OECD, 2018)
- PPRTVs for Superfund (U.S. EPA, 2020d)

In total, 2,123 distinct substances were identified from the sources above. For the purpose of ChemACE clustering, each individual substance needed to meet the following criteria:

1) Substance is not a polymer, metal, inorganic, or complex salt because ChemACE is not designed to accommodate these substances;
2) Substance has a CASRN or unambiguous chemical identification; and
3) Substance has a unique Simplified Molecular Input Line Entry System (SMILES) notation (encoded molecular structure format used in ChemACE) that can be identified from one of these sources:
    a. Syracuse Research Corporation (SRC) and Distributed Structure-Searchable Toxicity (DSSTox) database lists of known SMILES associated with unique CASRNs (the combined lists contained >200,000 SMILES) or
    b. ChemIDplus, U.S. EPA Chemicals Dashboard, or internet searches.

Of the initial list of 2,123 substances, 201 were removed because they did not meet one of the first two criteria, and 155 were removed because they did not meet the third. The final inventory of substances contained 1,767 unique compounds.

Two separate ChemACE approaches were compared for clustering of the chemical inventory. The restrictive clustering approach, in which all compounds in a cluster contain all of the same fragments and no different fragments, resulted in 208 clusters. The less restrictive approach employed the following rules for remapping the chemical inventory:

- treat adjacent halogens as equivalent, allowing fluorine (F) to be substituted for chlorine (Cl), Cl for bromine (Br), Br for iodine (I);
- allow methyl, methylene, and methane to be equivalent;
- allow primary, secondary, and tertiary amines to be equivalent; and
- exclude aromatic thiols (removes thiols from consideration).

Clustering using the less restrictive approach (Pass 2) resulted in 284 clusters. ChemACE results for clustering of the target chemical within the clusters of the chemical inventory are described in Appendix C.

Analogue Searches in the OECD QSAR Toolbox (Dice Method)

The OECD QSAR Toolbox (Version 4.1) is used to search for additional structural analogues of the target compound. There are several structural similarity score equations available in the toolbox (Dice, Tanimoto, Kulczynski-2, Ochiai/Cosine, and Yule). Dice is considered the default equation. The specific options that are selected for the performance of this search include a comparison of molecular features (atom-centered fragments) and atom characteristics (atom type, count hydrogens attached, and hybridization). Chemicals identified in these similarity searches are selected if their similarity scores exceeded 50%.

The OECD QSAR Toolbox Profiler is used to identify those structural analogues from the Dice search that have carcinogenicity and/or genotoxicity data. Nine databases in the OECD QSAR Toolbox (Version 4.1) provide data for carcinogenicity or genotoxicity (see Table B-1).

Analogue search results for the target chemical are described in Appendix C.

Table B-1. Databases Providing Carcinogenicity and Genotoxicity Data in the OECD QSAR Toolbox (Version 4.1)

Database Name	Toolbox Database Description[a]
CPDB	The CPDB provides access to bioassay literature with qualitative and quantitative analysis of published experiments from the general literature (through 2001) and from the NCI/NTP (through 2004). Reported results include bioassays in rats, mice, hamsters, dogs, and nonhuman primates. A calculated carcinogenic potency (TD_{50}) is provided to standardize quantitative measures for comparison across chemicals. The CPDB contains 1,531 chemicals and 3,501 data points.
ISSCAN	The ISSCAN database provides information on carcinogenicity bioassays in rats and mice reported in sources including NTP, CPDB, CCRIS, and IARC. This database reports a carcinogenicity TD_{50}. There are 1,149 chemicals and 4,518 data points included in the ISSCAN database.
ECHA CHEM	The ECHA CHEM database provides information on chemicals manufactured or imported in Europe from registration dossiers submitted by companies to ECHA to comply with the REACH Regulation framework. The ECHA database includes 9,229 chemicals with almost 430,000 data points for a variety of endpoints including carcinogenicity and genotoxicity. ECHA does not verify the information provided by the submitters.
ECVAM Genotoxicity and Carcinogenicity	The ECVAM Genotoxicity and Carcinogenicity database provides genotoxicity and carcinogenicity data for Ames positive chemicals in a harmonized format. ECVAM contains in vitro and in vivo bacteria mutagenicity, carcinogenicity, CA, CA/aneuploidy, DNA damage, DNA damage and repair, mammalian culture cell mutagenicity, and rodent gene mutation data for 744 chemicals and 9,186 data points.
ISSCTA	ISSCTA provides results of four types of in vitro cell transformation assays including Syrian hamster embryo cells, mouse BALB/c 3T3, mouse C3H/10T1/2, and mouse Bhas 42 assays that inform nongenotoxic carcinogenicity. ISSCTA consists of 352 chemicals and 760 data points.
Bacterial mutagenicity ISSSTY	The ISSSTY database provides data on in vitro *Salmonella typhimurium* Ames test mutagenicity (positive and negative) taken from the CCRIS database in TOXNET. The ISSSTY database provides data for 7,367 chemicals and 41,634 data points.
Genotoxicity OASIS	The Genotoxicity OASIS database provides experimental results for mutagenicity results from "Ames tests (with and without metabolic activation), in vitro chromosomal aberrations and MN and MLA evaluated in vivo and in vitro, respectively." The Genotoxicity OASIS database consists of 7,920 chemicals with 29,940 data points from 7 sources.
Micronucleus OASIS	The Micronucleus OASIS database provides experimental results for in vivo bone marrow and peripheral blood MNT CA studies in blood erythrocytes, bone marrow cells, and polychromatic erythrocytes of humans, mice, rabbits, and rats for 557 chemicals.

Table B-1. Databases Providing Carcinogenicity and Genotoxicity Data in the OECD QSAR Toolbox (Version 4.1)

Database Name	Toolbox Database Description[a]
ISSMIC	The ISSMIC database provides data on the results of in vivo MN mutagenicity assays to detect CAs in bone marrow cells, peripheral blood cells, and splenocytes in mice and rats. Sources include TOXNET, NTP, and the Leadscope FDA CRADA Toxicity Database. The ISSMIC database includes data for 563 chemicals and 1,022 data points.

[a]Descriptions were obtained from the OECD QSAR Toolbox documentation [Version 4.1; OECD (2018)].

CA = chromosomal aberration; CCRIS = Chemical Carcinogenesis Research Information System; CPBD = Carcinogenic Potency Database; CRADA = Cooperative Research and Development Agreement; DNA = deoxyribonucleic acid; ECHA = European Chemicals Agency; ECVAM = European Centre for the Validation of Alternative Methods; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; ISSCAN = Istituto Superiore di Sanità Chemical Carcinogen; ISSCTA = Istituto Superiore di Sanità Cell Transformation Assay; ISSMIC = Istituto Superiore di Sanità Micronucleus; ISSSTY = Istituto Superiore di Sanità *Salmonella typhimurium*; MLA = mouse lymphoma gene mutation assay; MN = micronuclei; MNT = micronucleus test; NCI = National Cancer Institute; NTP = National Toxicology Program; OECD = Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship; REACH = Registration, Evaluation, Authorisation and Restriction of Chemicals; TD_{50} = median toxic dose.

STEPS 2−5. ANALOGUE REFINEMENT AND SUMMARY OF EXPERIMENTAL DATA FOR GENOTOXICITY, TOXICOKINETICS, CARCINOGENICITY, AND MODE OF ACTION

The outcome of the Step 1 analogue identification process using ChemACE and the OECD QSAR Toolbox is an initial list of structural analogues with genotoxicity and/or carcinogenicity data. Expert judgment is applied in Step 2 to refine the list of analogues based on physicochemical properties; absorption, distribution, metabolism, and excretion (ADME); and mechanisms of toxicity. The analogue refinement process is chemical specific and is described in Appendix C. Steps 3, 4, and 5 (summary of experimental data for genotoxicity, toxicokinetics, carcinogenicity, and mode of action [MOA]) are also chemical specific (see Appendix C for further details).

STEP 6. STRUCTURAL ALERTS AND STRUCTURE-ACTIVITY RELATIONSHIP PREDICTIONS FOR 1-BROMO-2-CHLOROETHANE AND ANALOGUES

Structural alerts (SAs) and predictions for genotoxicity and carcinogenicity are identified using six freely available structure-based tools (described in Table B-2).

Table B-2. Tools Used to Identify Structural Alerts and Prediction of Carcinogenicity and Genotoxicity

Name	Description[a]
OECD QSAR Toolbox (Version 4.1)	Seven OECD QSAR Toolbox profiling methods were used, including: • Carcinogenicity (genotox and nongenotox) alerts by ISS (Version 2.3); updated version of the module originally implemented in Toxtree. It is a decision tree for estimating carcinogenicity, based on 55 SAs (35 from the Toxtree module and 20 newly derived). • DNA alerts for Ames by OASIS (Version 1.4); based on the Ames mutagenicity TIMES model, uses 85 SAs responsible for interaction of chemicals with DNA. • DNA alerts for CA and MNT by OASIS (Version 1.1); based on the DNA reactivity of the CAs TIMES model, uses 85 SAs for interaction of chemicals with DNA. • In vitro mutagenicity (Ames test) alerts by ISS (Version 2.3); based on the Mutagenicity module in Toxtree. It is a decision tree for estimating in vitro (Ames test) mutagenicity, based on a list of 43 SAs relevant for the investigation of chemical genotoxicity via DNA adduct formation. • In vivo mutagenicity (MN) alerts by ISS (Version 2.3); based on the ToxMic rulebase in Toxtree. The rule base has 35 SAs for in vivo MN assay in rodents. • OncoLogic Primary Classification (Version 4.0); "developed by LMC and OECD to mimic the structural criteria of chemical classes of potential carcinogens covered by the U.S. EPA's OncoLogic Cancer Expert System for Predicting the Carcinogenicity Potential" for categorization purposes only, not for predicting carcinogenicity. It is applicable to organic chemicals with at least one of the 48 alerts specified. • Protein binding alerts for CAs by OASIS (Version 1.3); based on 33 SAs for interactions with specific proteins including topoisomerases, cellular protein adducts, etc.
OncoLogic (Version 7)	OncoLogic is a tool for predicting the potential carcinogenicity of chemicals based on the application of rules for SAR analysis, developed by experts. Results may range from "low" to "high" concern level.

ToxAlerts	ToxAlerts is a platform for screening chemical compounds against SAs, developed as an extension to the OCHEM system (https://ochem.eu). Only "approved alerts" were selected, which corresponds to a moderator approved the submitted data. A list of the ToxAlerts found for the chemicals screened in the preliminary batch is below:
	• Genotoxic carcinogenicity, mutagenicity
	  ○ Aliphatic halide (general)
	  ○ Aliphatic halide (specific)
	  ○ Aliphatic halogens
	  ○ Aromatic amine (general)
	  ○ Aromatic amine (specific)
	  ○ Aromatic amines
	  ○ Aromatic and aliphatic substituted primary alkyl halides
	  ○ Aromatic nitro (general)
	  ○ Aromatic nitro (specific)
	  ○ Aromatic nitro groups
	  ○ Nitroarenes
	  ○ Nitro-aromatic
	  ○ Primary and secondary aromatic amines
	  ○ Primary aromatic amine, hydroxyl amine and its derived esters or amine-generating group
	• Nongenotoxic carcinogenicity
	  ○ Aliphatic halogens

Table B-2. Tools Used to Identify Structural Alerts and Prediction of Carcinogenicity and Genotoxicity

Name	Description[a]
ToxRead (Version 0.9)	ToxRead is a tool designed to assist in making read-across evaluations reproducible. SAs for mutagenicity are extracted from similar molecules with available experimental data in its database. Five similar compounds were selected for this project. The rule sets included: • Benigni/Bossa as available in Toxtree (Version 1) • SARpy rules extracted by Politecnico di Milano, with the automatic tool SARpy • IRFMN rules extracted by human experts • CRS4 rules extracted by CRS4 with automatic tools
Toxtree (Version 2.6.13)	Toxtree estimates toxic hazard by applying a decision tree approach. Chemicals were queried in Toxtree using the Benigni/Bossa rulebase for mutagenicity and carcinogenicity. If a potential carcinogenic alert based on any QSAR model or if any SA for genotoxic and nongenotoxic carcinogenicity was reported, then the prediction was recorded as a positive carcinogenicity prediction for the test chemical. The output definitions from the tool manual are listed below: • SA for genotoxic carcinogenicity (recognizes the presence of one of more SAs and specifies a genotoxic mechanism) • SA for nongenotoxic carcinogenicity (recognizes the presence of one or more SAs, and specifies a nongenotoxic mechanism) • Potential *Salmonella typhimurium* TA100 mutagen based on QSAR • Unlikely to be a *S. typhimurium* TA100 mutagen based on QSAR • Potential carcinogen based on QSAR (assigned according to the output of QSAR8 aromatic amines) • Unlikely to be a carcinogen based on QSAR (assigned according to the output of QSAR8 aromatic amines) • Negative for genotoxic carcinogenicity (no alert for genotoxic carcinogenicity) • Negative for nongenotoxic carcinogenicity (no alert for nongenotoxic carcinogenicity)

Table B-2. Tools Used to Identify Structural Alerts and Prediction of Carcinogenicity and Genotoxicity

Name	Description[a]
VEGA	VEGA applies several QSARs to a given chemical, as described below: • Mutagenicity (Ames test) CONSENSUS model: a consensus assessment is performed based on predictions of the VEGA mutagenicity models (CAESAR, SARpy, ISS, and *k*-NN) • Mutagenicity (Ames test) model (CAESAR): integrates two models, one is a trained SVM classifier, and the other is for FN removal based on SAs matching • Mutagenicity (Ames test) model (SARpy/IRFMN): rule-based approach with 112 rules for mutagenicity and 93 for nonmutagenicity, extracted with SARpy software from the original training set from the Caesar model; includes rules for both mutagenicity and nonmutagenicity • Mutagenicity (Ames test) model (ISS): rule-based approach based on the work of Benigni and Bossa (ISS) as implemented in the software Toxtree Version 2.6 • Mutagenicity (Ames test) model (*k*-NN/read-across): performs a read-across and provides a qualitative prediction of mutagenicity on *S. typhimurium* (Ames test) • Carcinogenicity model (CAESAR): Counter Propagation Artificial neural network developed using data for carcinogenicity in rats extracted from the CPDB database • Carcinogenicity model (ISS): built implementing the same alerts Benigni and Bossa (ISS) implemented in the software Toxtree 2.6 • Carcinogenicity model (IRFMN/Alternative Non-Testing Methods Assessed for REACH Substances [ANTARES]): a set of rules (127 SAs), extracted with the SARpy software from a data set of 1,543 chemicals obtained from the carcinogenicity database of European Union-funded project ANTARES • Carcinogenicity model (IRFMN/ISSCAN-CGX): based on a set of rules (43 SAs) extracted with the SARpy software from a data set of 986 compounds; the data set of carcinogenicity of different species was provided by Kirkland et al. (2005)

[a]There is some overlap between the tools. For example, OncoLogic classification is provided by the QSAR Toolbox, but the prediction is available only through OncoLogic, and alerts or decision trees were used in or adapted from several models (e.g., Benigni and Bossa alerts and Toxtree decision tree).

ANTARES = Alternative Non-Testing Methods Assessed for REACH Substances; CA = chromosomal aberration; CAESAR = Computer-Assisted Evaluation of industrial chemical Substances According to Regulations; CONSENSUS = consensus assessment based on multiple models (CAESAR, SARpy, ISS, and *k*-NN); CPDB = Carcinogenic Potency Database; CRS4 = Center for Advanced Studies, Research and Development in Sardinia; DNA = deoxyribonucleic acid; FN = false negative; IRFMN = Istituto di Ricerche Farmacologiche Mario Negri; ISS = Istituto Superiore di Sanità; ISSCAN-CGX = Istituto Superiore di Sanità Chemical Carcinogen; *k*-NN = *k*-nearest neighbor; LMC = Laboratory for Mathematical Chemistry; MN = micronucleus; MNT = micronucleus test; OCHEM = Online Chemical Monitoring Environment; OECD = Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship; REACH = Registration, Evaluation, Authorisation and Restriction of Chemicals; SA = structural alert; SAR = structure-activity relationship; SVM = support vector machine; TIMES = The Integrated MARKEL-EFOM System; VEGA = Virtual models for property Evaluation of chemicals within a Global Architecture.

The tool results for the target and analogue compounds are provided in Appendix C.

STEP 7. EVIDENCE INTEGRATION FOR SCREENING EVALUATION OF 1-BROMO-2-CHLOROETHANE CARCINOGENICITY

Available data across multiple lines of evidence from Steps 1−6 (outlined above) are integrated to determine the qualitative level of *concern for potential carcinogenicity* of the target compound (Step 8). In the absence of information supporting carcinogenic portal-of-entry effects, the qualitative level of concern for the target chemical should be considered applicable to all routes of exposure.

Evidence integration for the target compound is provided in Appendix C.

APPENDIX C. RESULTS OF THE SCREENING EVALUATION OF POTENTIAL CARCINOGENICITY

STEP 1. USE OF AUTOMATED TOOLS TO IDENTIFY STRUCTURAL ANALOGUES WITH CARCINOGENICITY AND/OR GENOTOXICITY DATA

U.S. EPA's Chemical Assessment Clustering Engine (ChemACE) clustering was performed as described in Appendix B. Using the most restrictive clustering rules (where ChemACE assigns a unique definition for each fragment, ensuring that each chemical submitted for clustering appears in only one ChemACE cluster), 1-bromo-2-chloroethane appeared in Cluster 67, which did not contain any other compounds. Using the less restrictive clustering option, ChemACE treats adjacent halogens as equivalent fragments, resulting in the inclusion of 1-bromo-2-chloroethane in multiple clusters. Using the more permissive fragment definition, halogens (i.e., bromine [Br] and chlorine [Cl]) in the structures could be swapped in the clustering scheme and appear in more than one cluster. Five clusters (15, 31, 34, 49, and 152) contain 1-bromo-2-chloroethane and a total of 38 other halogenated chemicals (see Table C-1 below). All of these clusters contain halogenated alkanes with chain lengths of 1−3 carbon atoms and 1−6 halogen substituents.

Table C-1. Clusters Containing 1-Bromo-2-Chloroethane (CASRN 107-04-0) and the Associated Fragments

Cluster	Fragments
15	Cl-R or F-R or Br-R
31	Cl-R or F-R or Br-R (but not Br-R only structures)
34	Cl-R or F-R or Br-R (but not F-R only structures)
49	Cl-R or F-R or Br-R or I-R
152	Cl-R or F-R or Br-R (but not Br-R or F-R only structures)

Br = bromine; Cl = chlorine; F = fluorine; I = iodine; R = functional group (must be an aliphatic carbon attachment).

The Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox Profiler was used to identify structural analogues from the Dice analogue search with carcinogenicity and/or genotoxicity data (see Step 1 methods in Appendix B). Only one analogue was identified in the Dice analogue search (1-bromo-3-chloropropane); this compound was also identified by ChemACE. Refinement of selection of final analogues is described below.

STEP 2. ANALOGUE REFINEMENT USING EXPERT JUDGMENT

Expert judgment was applied to refine the initial list of 38 potential analogues based on physicochemical properties; absorption, distribution, metabolism, and excretion (ADME); and mechanisms of toxicity.

1-Bromo-2-chloroethane contains two halogen substituents with the following attributes: (1) they are labile (easily displaced) leaving groups that can undergo nucleophilic substitution; (2) they are attached to adjacent carbon atoms (1,2-substitution pattern); and (3) they are both attached at primary carbon atoms ($R\text{-}CH_2\text{-}X$). Each of these attributes influences the reactivity of the molecule, its available metabolic pathways, and its potential bioactivity. Therefore, compounds were considered potential analogues if they contain (1) two or more labile halogen substituents; (2) halogens attached to adjacent, primary carbon atoms; and (3) no more than one halogen per carbon atom.

Of the 38 chemicals identified as potential analogues by ChemACE clustering and the OECD Toolbox analogue selection tool (Dice), 32 were not selected for further review, including halogenated methanes, monohalogenated compounds, and compounds with more than one halogen per carbon atom. Each of these attributes introduce significant differences in bioavailability, reactivity, and applicable metabolic pathways relative to 1-bromo-2-chloroethane.

The remaining six possible analogues for 1-bromo-2-chloroethane are listed in Table C-2. The existence of a cancer risk estimate and/or a weight-of-evidence (WOE) determination for cancer is indicated for each analogue. All of the potential analogues were included in each of the five clusters, except for 1,2-dibromoethane, which was excluded from Clusters 31 and 152.

Table C-2. Summary of Cancer Assessment Information for Analogues of 1-Bromo-2-Chloroethane (CASRN 107-04-0)[a]

Analogue Name (CASRN)	Cancer Risk Estimates (if available)	WOE Determinations
1,2-Dibromoethane (106-93-4)[b]	U.S. EPA (2004)—OSF, IUR CalEPA (2011)—OSF, IUR	U.S. EPA (2004)—*likely* IARC (1999)—*probably (Group 2A)* NTP (2016c)—*reasonably anticipated* CalEPA (2018)—*known*
1,2-Dichloroethane (107-06-2)[b]	U.S. EPA (1993)—OSF, IUR CalEPA (1999b)—OSF	U.S. EPA (1993)—*probable* IARC (1999)—*possibly (Group 2B)* NTP (2016d)—*reasonably anticipated* CalEPA (2018)—*known*
1-Bromo-3-chloropropane (109-70-6)[b, c]	None[d]	None
1,2-Dichloropropane (78-87-5)[b]	U.S. EPA (2020c)—p-OSF, p-IUR CalEPA (2004); CalEPA (1999b)—OSF	U.S. EPA (2020c)—*likely* IARC (2017)—*carcinogenic (Group 1)* CalEPA (2018)—*known*
1,2-Dibromo-3-chloropropane (96-12-8)[b]	U.S. EPA (2006)—p-OSF, p-IUR CalEPA (2020)—OSF, IUR	U.S. EPA (2006)—*likely* IARC (1999)—*possibly (Group 2B)* NTP (2016b)—*reasonably anticipated* CalEPA (2018)—*known*
1,2,3-Trichloropropane (96-18-4)[b]	U.S. EPA (2009)—OSF CalEPA (2009)—OSF	U.S. EPA (2009)—*likely* IARC (1995)—*probably (Group 2A)* NTP (2016b)—*reasonably anticipated* CalEPA (2018)—*known*

[a]Gray shading indicates that there was not a cancer risk estimate and/or a WOE determination for cancer for that analogue.
[b]Found by ChemACE.
[c]Found by Dice.
[d]No cancer toxicity values are available; however, a 2-year inhalation bioassay in rats and mice with clear evidence of carcinogenicity is available from the Japanese Industrial Safety and Health Association (Japan Industrial Safety and Health Association, 2005a, b).

ChemACE = Chemical Assessment Clustering Engine; IUR = inhalation unit risk; OSF = oral slope factor; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor; WOE = weight of evidence.

1-Bromo-3-chloropropane, which lacks a cancer risk estimate or a WOE determination for cancer (highlighted in gray in Table C-2), was not further considered as a potential analogue for the screening evaluation of potential carcinogenicity of 1-bromo-2-chloroethane. Compounds selected for further consideration were 1,2-dibromoethane (1,2-DBE), 1,2-dichloroethane (1,2-DCE), 1,2-dichloropropane (1,2-DCP), 1,2-dibromo-3-chloropropane (1,2-DB-3-CP), and 1,2,3-trichloropropane (TCP).

STEP 3. COMPARISON OF THE EXPERIMENTAL GENOTOXICITY DATA FOR 1-BROMO-2-CHLOROETHANE AND ANALOGUES

The genotoxicity data available for 1-bromo-2-chloroethane are described in the "Other Data" section in the main body of this report. Available data indicate that 1-bromo-2-chloroethane and/or its metabolites display genotoxic, mutagenic, clastogenic, and deoxyribonucleic acid (DNA)-damaging activity. Genotoxicity data for the analogue compounds have been extensively reviewed. A summary of the genotoxicity data for analogue halogenated alkanes is provided in Table C-3. Overall data indicate that these analogues are mutagenic and clastogenic, and capable of binding DNA and causing DNA damage.

Table C-3. Comparison of Available Genotoxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Parameter	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloropropane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloropropane CASRN 96-18-4
Mutagenicity	• Mutagenic in *Salmonella typhimurium* • Mutagenic in mammalian cells in vitro	• Mutagenic in *S. typhimurium* and *Streptomyces coelicolor*; mixed results in *Escherichia coli* • Mutagenic in *Aspergillus nidulans* • Induced somatic and sex-linked recessive mutations in *Drosophila melanogaster* • Mutagenic in mammalian cells in vitro • Did not induce dominant lethal mutations in mice	• Mutagenic in *S. typhimurium*; mixed results in E. coli; not mutagenic in *S. coelicolor* or *Bacillus subtilis* • Not mutagenic in *A. nidulans* • Induced somatic and sex-linked recessive mutations • Mutagenic in mammalian cells in vitro • Induced somatic mutations in mice • Did not induce dominant lethal mutations in mice	• Mixed results in *S. typhimurium*; not mutagenic in *E. coli* or *S. coelicolor* • Mutagenic in *A. nidulans* • Induced somatic mutations in *D. melanogaster*, but not sex-linked recessive mutations • Mutagenic in mammalian cells in vitro • Did not induce dominant lethal mutations in rats • Did not induce *Pig-a* or *Gpt* mutations in mice	• Mutagenic in *S. typhimurium* with and without metabolic activation • Induced sex-linked recessive mutations in *D. melanogaster* • Mutagenic in mammalian cells with and without metabolic activation • Induced somatic mutations in mice (spot test) • Induced dominant lethal mutations in rats, but not mice	• Mutagenic in *S. typhimurium* with metabolic activation; not mutagenic in *E. coli* • Not mutagenic in *A. nidulans* • Induced somatic mutations in *D. melanogaster* • Mutagenic in mammalian cells with metabolic activation • Did not induce dominant lethal mutations in rats

Table C-3. Comparison of Available Genotoxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Parameter	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloropropane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloropropane CASRN 96-18-4
Clastogenicity	• Induced CAs in mammalian cells in vitro • Induced mitotic malsegregation/ aneuploidy in *A. nidulans* • Induced mitotic recombination in *D. melanogaster*	• Induced SCEs in mammalian cells in vitro and in vivo • Induced CAs and MNs in mammalian cells in vitro, but not in vivo	• Induced SCEs in mammalian cells in vivo • Induced MNs in mammalian cells in vitro • Induced chromosomal loss and mitotic recombination in *D. melanogaster* • Induced aneuploidy and mitotic segregation aberrations in *A. nidulans*; no clear evidence of aneuploidy in mammalian cells in vitro	• Induced CAs and SCEs in mammalian cells in vitro • Did not induce MNs in mammalian cells in vivo • Induced mitotic recombination in *D. melanogaster*, but not *Saccharomyces cerevisiae* • Did not induce chromosomal abnormalities in *A. nidulans*	• Induced CAs in mammalian cells in vitro and in vivo • Induced MNs in mammalian cells in vivo • Induced SCEs in mammalian cells in vitro • Induced heritable translocation and mitotic recombination in *D. melanogaster*	• Induced polyploidy in mammalian cells in vivo • Induced MNs in mammalian cells in vitro, but not in vivo • Induced CAs and SCEs in mammalian cells in vitro • Induced MN without metabolic activation • Induced mitotic gene conversion in *S. cerevisiae* • Did not induce chromosomal abnormalities in *A. nidulans*
DNA damage and adducts	• Induced DNA damage in mammalian cells in vivo • Induced DNA damage in *S. typhimurium*	• Induced DNA damage/repair in mammalian cells in vitro and in vivo • Forms DNA adducts	• Induced DNA damage/repair in mammalian cells in vitro and in vivo • Equivocal DNA damage detected via comet assay in rodent liver cells. • Forms DNA adducts	• Induced DNA damage/repair in mammalian cells in vitro and in vivo	• Induced DNA damage/repair in mammalian cells in vitro and in vivo • Forms DNA adducts	• Induced DNA damage/repair in mammalian cells in vitro and in vivo • Forms DNA adducts

Table C-3. Comparison of Available Genotoxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Parameter	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloropropane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloropropane CASRN 96-18-4
Cell transformation	ND	• Induced neoplastic transformation in mammalian cells	• Mixed results for cell transformation	ND	• Induced neoplastic transformation in mammalian cells	• Induced neoplastic transformation in mammalian cells
References	See "Genotoxicity" section in main document for references	U.S. EPA (2004); IARC (1999)	Gwinn et al. (2011); ATSDR (2001); CalEPA (1999a); IARC (1999); U.S. EPA (1993); Lebaron et al. (2021)	IARC (2017); U.S. EPA (2020c); CalEPA (1999b)	U.S. EPA (2006); Clark and Snedeker (2005); IARC (1999)	U.S. EPA (2009); IARC (1995)

CA = chromosomal aberration; DNA = deoxyribonucleic acid; MN = micronuclei; ND = no data; SCE = sister chromatid exchange.

STEP 4. TOXICOKINETICS OF 1-BROMO-2-CHLOROETHANE AND ANALOGUES

The toxicokinetics of 1-bromo-2-chloroethane and potential analogues are briefly described in Table C-4. Each of the candidate analogue compounds is metabolized by a CYP450 oxidation pathway and a direct glutathione (GSH) conjugation pathway (U.S. EPA, 2020c; IARC, 2017; CalEPA, 2009; U.S. EPA, 2009, 2006, 2004; ATSDR, 2001; IARC, 1999, 1995). Contributions from both pathways are presumed by analogy for 1-bromo-2-chloroethane as well, although experimental data for the target compound are available for the GSH conjugation pathway only (Jean and Reed, 1992; Marchand and Reed, 1989).

Experimental data show that GSH conjugation leads to the formation of episulfonium ions via cyclization of GSH adducts for 1,2-DBE, 1,2-DCE, 1,2-DB-3-CP, and TCP (CalEPA, 2009; U.S. EPA, 2009, 2004; ATSDR, 2001; IARC, 1995; Guengerich, 1994; van Beerendonk et al., 1994; Dekant and Vamvakas, 1993; Pearson et al., 1990; Dohn et al., 1988; Omichinski et al., 1988b; Omichinski et al., 1988a; Guengerich et al., 1987). Based on analogy and identified glutathione-conjugated metabolites, episulfonium ion generation is also expected following GSH conjugation of 1-bromo-2-chloroethane (based on formation of *S*-[2-chloroethyl]glutathione [CEG]) (Jean and Reed, 1992; Marchand and Reed, 1989) and 1,2-DCP (based on the formation of *S*-[2-hydroxypropyl]glutathione) (IARC, 2017).

No data are available for absorption, distribution, or excretion of 1-bromo-2-chloroethane. Experimental data indicate that all candidate analogues show rapid and extensive absorption, wide distribution, and primary excretion in urine (U.S. EPA, 2020c; IARC, 2017; CalEPA, 2009; U.S. EPA, 2009, 2006, 2004; ATSDR, 2001; IARC, 1999, 1995).

Table C-4. Summary of Toxicokinetic Data for 1-Bromo-2-Chloroethane and Analogues

Compound (CASRN)	Absorption, Distribution, Excretion	Metabolism	References
1-Bromo-2-chloroethane (107-04-0)	ND	Primary metabolic pathways are oxidation by CYP450 (by analogy to other dihaloalkanes) and GSH conjugation (demonstrated) 1. Primary metabolites formed via oxidation expected to be: • 2-bromoacetaldehyde • 2-chloroacetaldehyde • HBr • HCl 2. Primary metabolites formed via GSH conjugation: • CEG, with HBr release (minor HCl release) • Inferred from other dihaloalkanes: CEG will cyclize to form episulfonium ion	Guengerich (1994); Dekant and Vamvakas (1993); Jean and Reed (1992); Gargas et al. (1989); Marchand and Reed (1989); Guengerich et al. (1987)
1,2-Dibromoethane (106-93-4)	• Rapid and extensive absorption (oral and inhalation) • Wide distribution • Primary excretion in urine, small amounts in feces and exhaled air	Primary metabolic pathways are oxidation by CYP450 and GSH conjugation 1. Primary metabolites formed via oxidation: • 2-bromoacetaldehyde • HBr 2. Primary metabolites formed via GSH conjugation: • BEG, with HBr release • Episulfonium ion (from cyclization of GSH adduct in BEG)	U.S. EPA (2004); Gargas et al. (1989); Guengerich et al. (1987)
1,2-Dichloroethane (107-06-2)	• Rapid and extensive absorption (oral and inhalation) • Wide distribution • Primary excretion in urine, small amounts in feces and exhaled air	Primary metabolic pathways are oxidation by CYP450 and GSH conjugation 1. Primary metabolites formed via oxidation: • 2-chloroacetaldehyde • HCl 2. Primary metabolites formed via GSH conjugation: • CEG, with HCl release • Episulfonium ion (from cyclization of GSH adduct in CEG)	ATSDR (2001); Gargas et al. (1989); Guengerich et al. (1987)

Table C-4. Summary of Toxicokinetic Data for 1-Bromo-2-Chloroethane and Analogues

Compound (CASRN)	Absorption, Distribution, Excretion	Metabolism	References
1,2-Dichloropropane (78-87-5)	• Readily absorbed (oral, inhalation, dermal) • Wide distribution, with preferential disposition in body fat at high exposures • Rapid elimination, primarily via urine with small amounts via exhaled breath (proportion increases with increased exposure)	Primary metabolic pathway is oxidation by CYP2E1 followed by GSH conjugation (or vice versa) to form: • *S*-(2-oxopropyl)glutathione (identified) • *S*-(1-carboxyethyl)glutathione (identified) • *S*-(2-hydroxypropyl)glutathione (presumed based on cysteine-conjugated urinary metabolite) Presumed secondary pathways (based on identified metabolites and known metabolism of similar haloalkanes) • Formation of episulfonium ions from cyclization of GSH adduct in *S*-(2-hydroxypropyl)glutathione • Oxidative dechlorination, leading to formation of lactate and release of carbon dioxide	IARC (2017); U.S. EPA (2020c)
1,2-Dibromo-3-chloropropane (96-12-8)	• Rapid and extensive absorption (oral; no inhalation data) • Wide distribution • Most excretion in urine, some in exhaled air, small amounts in feces	Primary metabolic pathways are oxidation by CYP450 and GSH conjugation 1. Primary metabolites formed via oxidation: • 2-chloro-3-(bromomethyl)oxirane • 1-bromo-3-chloroacetone • HBr • HCl 2. Primary metabolites formed via GSH conjugation: • CBPG, with HBr release (minor HCl release) • Episulfonium ion (from cyclization of GSH adduct in CBPG)	Guengerich (1994); van Beerendonk et al. (1994); Dekant and Vamvakas (1993); Humphreys et al. (1991); Pearson et al. (1990); Dohn et al. (1988); Omichinski et al. (1988a); Omichinski et al. (1988b); Gingell et al. (1987); Guengerich et al. (1987)

Table C-4. Summary of Toxicokinetic Data for 1-Bromo-2-Chloroethane and Analogues

Compound (CASRN)	Absorption, Distribution, Excretion	Metabolism	References
1,2,3-Trichloropropane (96-18-4)	• Rapid and extensive absorption (oral; no inhalation data) • Rapid distribution, initially to adipose tissue, liver, and kidney • Primary excretion in urine, smaller amounts in feces and exhaled air	Primary metabolic pathways are oxidation by CYP450 and GSH conjugation 1. Primary metabolites formed via oxidation: • 1,3-dichloroacetone • 2,3-dichloropropanal • Chloroacrolein • HCl 2. Primary metabolites formed via GSH conjugation: • B-chlorothioether with HCl release • Episulfonium ion (from cyclization of GSH adduct in thioether)	CalEPA (2009); U.S. EPA (2009); IARC (1995)

BEG = *S*-(2-bromoethyl)glutathione; CBPG = *S*-(3-chloro-2-bromopropyl) glutathione; CEG = *S*-(2-chloroethyl)glutathione; CYP450 = cytochrome P450; GSH = glutathione; HBr = hydrogen bromide; HCl = hydrogen chloride; ND = no data.

STEP 5. CARCINOGENICITY OF 1-BROMO-2-CHLOROETHANE ANALOGUES AND MODE-OF-ACTION DISCUSSION

U.S. EPA cancer WOE descriptors for 1-bromo-2-chloroethane and analogue compounds are shown in Tables C-5 (oral) and C-6 (inhalation). As noted in the PPRTV document, there is *"Inadequate Information to Assess the Carcinogenic Potential"* of 1-bromo-2-chloroethane. All analogues are characterized as having evidence of carcinogenic potential. 1,2-DBE, 1,2-DCP, 1,2-DB-3-CP, and TCP were all classified as *"Likely to be Carcinogenic to Humans"* (U.S. EPA, 2020c, 2009, 2006, 2004) under the 2005 or 1999 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). 1,2-DCE is considered a *"Probable Human Carcinogen"* (U.S. EPA, 1993) under the 1986 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986). OSF values varied by several orders of magnitude, with the highest potency value calculated for TCP and the lowest (provisional) potency value for 1,2-DCP. IUR values also varied by several orders of magnitude, with the highest potency value calculated for 1,2-DB-3-CP (provisional) and the lowest potency value for 1,2-DCP (provisional).

Several epidemiology studies in print shop workers in Japan reported a potential correlation between exposure to 1,2-DCP (and other solvents) and cholangiocarcinoma, a rare cancer of the bile duct (U.S. EPA, 2020c; IARC, 2017). However, the population size is small in most of these studies, and the workers were exposed to numerous other solvents, including dichloromethane and 1,1,1-trichloroethane, as well as kerosene and printing ink, confounding interpretation of the results. Some human epidemiology studies for 1,2-DCE, 1,2-DBE, and 1,2-DB-3-CP have found limited evidence of increased risk of certain cancers (e.g., lymphatic, hematopoietic, pancreatic, and stomach cancer); however, due to multiple exposures in the available studies, these data are inadequate to evaluate a relationship between human cancer and exposure to a specific compound (NTP, 2016b, c, d; U.S. EPA, 2006, 2004; IARC, 1999). No human cancer data are available for TCP (NTP, 2016e; U.S. EPA, 2009).

All analogues are associated with tumor induction in animal bioassays (U.S. EPA, 2020c; IARC, 2017; NTP, 2016b, c, d, e; U.S. EPA, 2006, 2004; IARC, 1999, 1995; U.S. EPA, 1993). These are briefly summarized below and in Table C-5 (oral) and Table C-6 (inhalation).

Common target organs and systems in rats and/or mice following exposure to analogues include the liver, respiratory system, and mammary gland. All analogues induced hepatocellular neoplasms (adenomas and/or carcinomas) following chronic oral exposure; liver tumors were also increased following chronic inhalation exposure to 1,2-DCE. All analogues tested via the inhalation route also induced respiratory tract tumors, including nasal cavity tumors (1,2-DBE, 1,2-DCP, 1,2-DB-3-CP) and lung tumors (1,2-DBE, 1,2-DCE, 1,2-DCP, 1,2-DB-3-CP). Lung tumors were also observed following oral exposure to 1,2-DBE and 1,2-DCE. Mammary gland tumors were increased following exposure to analogues via the oral route (1,2-DCE, 1,2-DCP, 1,2-DB-3-CP, TCP) and/or the inhalation route (1,2-DBE, 1,2-DCE, 1,2-DB-3-CP).

The gastrointestinal, endocrine, and circulatory systems were also identified as cancer targets for the majority of analogues. Most analogues induced tumors of the gastrointestinal system following chronic oral exposure, including forestomach tumors (1,2-DBE, 1,2-DCE, 1,2-DB-3-CP, TCP); tongue, pharynx, and stomach tumors (1,2-DB-3-CP); oral cavity and alimentary system tumors (TCP); and esophageal papillomas (1,2-DBE). Endocrine tumors observed included thyroid tumors (1,2-DBE, 1,2-DCP) and pancreatic tumors (TCP) following

oral exposure and adrenal tumors (1,2-DBE and 1,2-DB-3-CP) following inhalation exposure. Hemangiosarcoma, most notably in the spleen, was observed following oral or inhalation exposure to 1,2-DBE, oral exposure to 1,2-DCE, and inhalation exposure to 1,2-DCP.

Other tumor types were identified in only one or two of the analogues and therefore do not represent common targets of the identified analogue chemicals (see Tables C-5 and C-6 for more details). Observed tumors included female reproductive tumors (1,2-DCE, TCP), renal tumors (TCP, 1,2-DB-3-CP), malignant lymphoma (1,2-DCE), Harderian gland tumors (TCP, 1,2-DCP), Zymbal gland tumors (TCP), preputial gland tumors (TCP), mesothelioma of the peritoneum (1,2-DCE), mesothelioma of the tunica vaginalis (1,2-DBA, 1,2-DB-3-CP), and subcutaneous tumors (1,2-DBE, 1,2-DCE).

U.S. EPA (2009) and U.S. EPA (2006) concluded that 1,2-DB-3-CP and TCP are carcinogenic through a mutagenic MOA, supported by experimental evidence of mutagenicity. The U.S. EPA (2004) report did not make a formal determination regarding a carcinogenic MOA for 1,2-DBE; however, available evidence suggested potential mutagenicity and/or DNA damage as potential MOAs. Available data for 1,2-DCP were considered inadequate for a formal MOA analysis by U.S. EPA (2020c); however, DNA damage has been proposed as a potential mechanism. The U.S. EPA (1993) report did not evaluate potential carcinogenic MOAs for 1,2-DCE, but experimental data indicate that the chemical is both DNA damaging and mutagenic (see Step 3). Taken together, all analogues except 1,2-DCP have sufficient evidence of mutagenicity (see Step 3) to indicate a potential common mutagenic MOA for halogenated alkanes. Specifically, experimental data show that 1,2-DBE, 1,2-DCE, 1,2-DB-3-CP, and TCP form DNA-reactive episulfonium ions via cyclization of GSH adducts during metabolism. By analogy, both 1,2-DCP and the target compound, 1-bromo-2-chloroethane, are expected to form episulfonium ions as well (see Table C-4). Data for 1,2-DCE indicate that although oxidative metabolites appear to influence CAs, the formation of the episulfonium ion is likely the primary mutagen (Gwinn et al., 2011). However, 1,2-DCP is not considered a potent mutagen, and experimental data do not support the potential for GSH-mediated mutagenicity (U.S. EPA, 2020c; Akiba et al., 2017; IARC, 2017).

Table C-5. Comparison of Available Oral Carcinogenicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

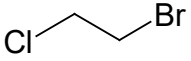
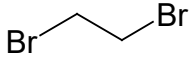
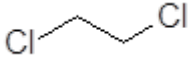
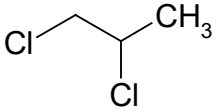
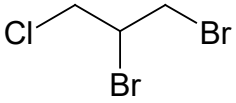
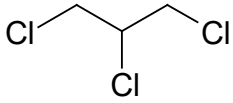
Type of Data	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloropropane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
Structure						
U.S. EPA WOE characterization	*"Inadequate Information to Assess Carcinogenic Potential"* (see Table 6)	"*Likely to Be Carcinogenic to Humans"*	*"Probable Human Carcinogen"*	"*Likely to Be Carcinogenic to Humans"*	"*Likely to Be Carcinogenic to Humans"*	"*Likely to Be Carcinogenic to Humans"*
OSF $(mg/kg\text{-}d)^{-1}$	NDr	2 (upper bound)[a]	9.1×10^{-2}	3.7×10^{-2} (provisional)	8×10^{-1} (provisional)	3×10^{1} (upper bound)[b]
Data set(s) used for slope factor derivation	NA	Forestomach tumors, hemangiosarcomas, and thyroid follicular cell adenomas or carcinomas in male rats	Hemangiosarcoma in male rats	Hepatocellular adenoma or carcinoma in male mice	Renal adenoma or carcinoma in male rat	Alimentary system, liver, Harderian gland, and uterine tumors in female mice

Table C-5. Comparison of Available Oral Carcinogenicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Type of Data	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloropropane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
Other tumors observed in animal oral bioassays	ND	Rat: forestomach, thyroid, or liver tumors and hemangiosarcomas (females) Mouse: forestomach and lung tumors, esophageal papilloma (female)	Rat: forestomach and mammary gland tumors Mouse: lung, liver, and uterus tumors; malignant lymphoma	Rat: mammary gland tumors (marginal increase in females) Mouse: liver tumors (female), thyroid tumors (female)	Rat: mammary gland and kidney tumors (female), liver tumors (male), forestomach and stomach tumors (both) Mouse: forestomach and stomach tumors	Rat: alimentary system and Zymbal gland tumors (both); pancreatic, preputial gland, and kidney tumors (males); clitoral and mammary gland tumors (females) Mouse: alimentary system, Harderian gland, and liver tumors (males)
Study doses (mg/kg-d)	NA	TWA: 0, 38, 41 HED[b]: 0, 11, 22	TWA: 0, 47, 95 HED: 0, 4.46, 8.23	TWA: 0, 89.3, 179 HED: 0, 12.5, 25.1	TWA: 0, 0.24, 0.80, 2.39 HED: not reported per dose (HED conversion done after OSF calculation)	0, 6, 20, 60 HED: not reported per dose (HED conversion done after BMD modeling)
Route (method)	NA	Gavage in corn oil (5 d/wk)	Gavage in corn oil (5 d/wk)	Gavage in corn oil (5 d/wk)	Diet	Gavage
Duration	NA	49 wk	78 wk, followed by untreated observation period up to 32 wk	103 wk	104 wk	2 yr; all high-dose females sacrificed after 73 wk
POD type	NA	$BMDL_{10}$ (HED)	BMDL (linearized multistage with time-to-death analysis, extra risk)	$BMDL_{10}$ (HED)	$BMDL_{10}$ (HED)	$BMDL_{10}$ (HED)

Table C-5. Comparison of Available Oral Carcinogenicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Type of Data	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloropropane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
Source	NA	NTP (2016c); U.S. EPA (2004)	NTP (2016d); U.S. EPA (2020c); U.S. EPA (2010)	U.S. EPA (2020c)	U.S. EPA (2006)	U.S. EPA (2009)

[a]An upper bound on cancer risk was estimated by adding the central tendency risk estimates for the three tumor types and calculating an upper confidence limit on the sum, using an estimate of the variance pooled across the three slope factors. The resulting (upper bound) slope factor was adjusted for daily exposure by multiplying by 5 days/7 days and for lifetime exposure by dividing by (49 weeks/104 weeks).
[b]HED values were reported in the modeling section of U.S. EPA (2004) and appear to correlate with initial doses of 40 and 80 mg/kg-day, not TWA doses that reflect lowered dose in the high-dose group.

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; HED = human equivalent dose; NA = not applicable; ND = no data; NDr = not determined; OSF = oral slope factor; POD = point of departure; TWA = time-weighted average; WOE = weight of evidence.

Table C-6. Comparison of Available Inhalation Carcinogenicity Toxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

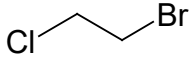
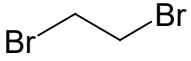
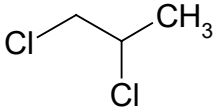
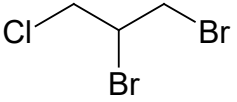
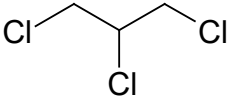
Type of Data	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloro-propane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
Structure						
WOE characterization	*"Inadequate Information to Assess Carcinogenic Potential"* (see Table 6)	*"Likely to Be Carcinogenic to Humans"*	*"Probable Human Carcinogen"*	*"Likely to Be Carcinogenic to Humans"*	*"Likely to Be Carcinogenic to Humans"*	"*Likely to Be Carcinogenic to Humans"*
IUR $(\mu g/m^3)^{-1}$	NDr	6×10^{-4} (upper bound)[a]	2.6×10^{-5} [b] 1.0×10^{-6} (95% upper bound)[c]	3.7×10^{-6} (provisional)	6×10^{0} (provisional)	NDr
Data set(s) used for slope factor derivation	NA	Nasal tumors (male and female rats, female mice), hemangiosarcomas (male and female rats, female mice), mesothelioma (male rats), lung tumors (female rats and mice), mammary tumors (female rats and mice), fibrosarcoma (female mice)	Hemangiosarcoma (oral study)[a]	Nasal cavity tumors in male rats	Nasal cavity tumors in male rats	NA

Table C-6. Comparison of Available Inhalation Carcinogenicity Toxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Type of Data	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloro-propane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
Human carcinogenicity data	ND	Available occupational data inadequate to evaluate relationship between 1,2-DBE and cancer	Available occupational data inadequate to evaluate relationship between 1,2-DCE and cancer	Elevated risk of cholangiocarcinoma in print shop workers from several cohorts exposed to 1,2-DCP (and other chlorinated solvents)	Available occupational data inadequate to evaluate relationship between 1,2-DB-3-CP and cancer; no associations between gastric cancer or leukemia and 1,2-DB-3-CP in drinking water (case-control)	ND
Other tumors observed in animal inhalation bioassays	ND	Rat: splenic hemangiosarcoma, adrenal tumors, subcutaneous mesenchymal tumor	Inhalation study published since derivation of IUR: Rat: mammary gland tumors, peritoneal mesothelioma, subcutaneous fibroma Mouse: lung, liver, and mammary gland tumors (females)	Rats: nasal cavity tumors (female) Mice: Harderian gland tumors (male), lung tumors (female), hemangiocarcinoma (male)	Rats: nasal cavity, pharynx, adrenal gland, and mammary gland tumors (females), tongue tumors (both), mesothelioma (males) Mice: nasal and lung tumor (both)	ND

Table C-6. Comparison of Available Inhalation Carcinogenicity Toxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Type of Data	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloro-propane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
Study concentrations	NA	Reported (ppm): 0, 10, 40 HEC_{ER} (ppm): 0, 1.8, 7.1 (rat, mouse) HEC_{ET} (ppm): 0, 0.36, 1.42 (male rat, female mouse); 0, 0.25, 0.99 (female rat) HEC_{PU} (ppm) 0, 3.1, 12.3 (female rat); 0, 5.8, 22.7 (female mouse) HEC_{TB} (ppm) 0, 4.86, 19.2 (female mouse)	TWA (mg/kg-d): 0, 47, 95 HED (mg/kg-d): 0, 4.46, 8.23	Analytical (ppm): 0, 80.2, 200.5, 500.2 HEC_{ET} (mg/m^3): 0, 16.2, 40.54, 101.1	Reported (ppm): 0, 0.6, 3 HEC_{ET} (mg/m^3): 0, 0.23, 1.13	NA
Route (method)	NA	Inhalation (6 h/d; 5 d/wk)	Gavage in corn oil (5 d/wk)[b]	Inhalation (6 h/d; 5 d/wk)	Inhalation (6 h/d; 5 d/wk)	NA
Duration	NA	79−104 wk	78 wk, plus untreated observation period up to 32 wk	104 wk	Control: 105−107 wk; 0.6 ppm: 103 wk plus 1-wk observation; 3 ppm: 84 wk plus 0−1-wk observation	NA

Table C-6. Comparison of Available Inhalation Carcinogenicity Toxicity Data for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Candidate Analogues

Type of Data	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloro-propane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
POD type	NA	$BMCL_{10}$ (HEC)	BMDL (linearized multistage with time-to-death analysis, extra risk)	$BMCL_{10}$ (HEC)	$BMCL_{10}$ (HEC)	NA
Source	NA	NTP (2016c); U.S. EPA (2004)	NTP (2016d); U.S. EPA (2010); U.S. EPA (1993)	IARC (2017); U.S. EPA (2020c)	NTP (2016b); U.S. EPA (2006); IARC (1995)	NTP (2016e); U.S. EPA (2009)

[a]An upper bound on cancer risk was estimated by using the multistage model with Poly-3 adjusted incidence data central tendency estimate for tumors at six sites in two species.
[b]Available inhalation data in 1987 was inadequate to derive an IUR (no induction of tumors); therefore, data from oral studies used to derive IUR in 1987 (the same major urinary metabolites and concentration from both oral and inhalation exposure) (Reitz et al., 1982). The IUR was calculated from oral data, assuming 100% absorption and metabolism at the low dose. See findings from oral study in Table C-5.
[c]Inferred unit risk from negative inhalation study (Maltoni et al., 1980).

1,2-DB-3-CP = 1,2-dibromo-3-chloropropane; 1,2-DBE = 1,2-dibromoethane; 1,2-DCE = 1,2-dichloroethane; 1,2-DCP = 1,2-dichloropropane; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; ER = extrarespiratory; ET = extrathoracic; HEC = human equivalent concentration; HED = human equivalent dose; IUR = inhalation unit risk; NA = not applicable; ND = no data; NDr = not determined; POD = point of departure; PU = pulmonary; TB = tracheobronchial; TWA = time-weighted average; WOE = weight of evidence.

STEP 6. STRUCTURAL ALERTS AND STRUCTURE-ACTIVITY RELATIONSHIP PREDICTIONS FOR 1-BROMO-2-CHLOROETHANE AND ANALOGUES

Structural alerts (SAs) and predictions for genotoxicity and carcinogenicity were identified using computational tools as described in Appendix B. The model results for 1-bromo-2-chloroethane and its analogue compounds are shown in Table C-7. Concerns for carcinogenicity and/or mutagenicity of 1-bromo-2-chloroethane and its analogues were indicated by several models within each predictive tool (see Table C-7). Table C-8 provides a list of the specific SAs that underlie the findings of a concern for carcinogenicity or mutagenicity in Table C-7.

OECD QSAR Toolbox models showed a concern for in vitro and in vivo mutagenicity for 1-bromo-2-chloroethane and all analogues based on structural alerts, a concern for CAs for 1-bromo-2-chloroethane, and concerns for all analogues based on protein binding alerts (see Table C-7). OECD QSAR Toolbox models also showed a concern for mutagenicity, CAs, and MN induction for 1-bromo-2-chloroethane, 1,2-DBE, 1,2-DCE, and 1,2-DCP; no results were reported for 1,2-DB-3-CP or TCP. The ToxRead and VEGA models also indicated a concern for mutagenicity for 1-bromo-2-chloroethane and all analogues.

OECD QSAR Toolbox models showed a concern for carcinogenicity for 1-bromo-2-chloroethane and all analogues based on structural alerts (see Table C-8). The level of carcinogenicity concern in OncoLogic was “moderate” for 1-bromo-2-chloroethane and 1,2-DCE based on SAR analysis only (haloalkanes and haloalkenes structural alert) and 1,2-dichloropropane based on experimental data and SAR analysis (haloalkanes and haloalkenes structural alert). The level of carcinogenicity concern in OncoLogic was “high-moderate” for 1,2-DBE, 1,2-DB-3-CP, and TCP based on experimental data and SAR analysis (haloalkanes and haloalkenes structural alert). Two carcinogenicity models in VEGA showed concern for carcinogenicity for 1-bromo-2-chloroethane (ISS and IFRMN/ANTARES). The CAESAR and IRFMN/ISSCAN-CGX models did not have reliable data for 1-bromo-2-chloroethane. For analogues, all four carcinogenicity models in VEGA showed concern for carcinogenicity for 1,2-DBE, 1,2-DCE, 1,2-DB-3-CP, and TCP. For 1,2-DCP, the ISS and IRFMN/ISSCAN-CGX models in VEGA showed concern for carcinogenicity, but the CAESAR and IRFMN/ANTARES models showed no concern for carcinogenicity. The ToxAlerts tool showed concern for nongenotoxic carcinogenicity for 1-bromo-2-chloroethane and all analogues based on structural alerts (aliphatic halogens). In contrast, the Toxtree tool indicated that there was no concern for nongenotoxic carcinogenicity for 1-bromo-2-chloroethane or any of its analogues.

The ToxAlerts and Toxtree tools showed a concern for genotoxic carcinogenicity for 1-bromo-2-chloroethane and all analogues based on various structural alerts (see Table C-8).

Table C-7. Heat Map Illustrating the Structural Alert and SAR Prediction Results for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Analogues

Tool	Model[a]	1-Bromo-2-chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dichloropropane	1,2-Dibromo-3-chloropropane	1,2,3-Trichloropropane
Mutagenicity/genotoxicity alerts							
OECD QSAR Toolbox	DNA alerts for Ames by OASIS						
	DNA alerts for CA and MNT by OASIS						
	In vitro mutagenicity (Ames test) alerts by ISS						
	In vivo mutagenicity (micronucleus) alerts by ISS						
	Protein binding alerts for CA by OASIS						
ToxRead	ToxRead (mutagenicity)						
VEGA	Mutagenicity (Ames test) CONSENSUS model—assessment						
	Mutagenicity (Ames test) model (CAESAR)—assessment						
	Mutagenicity (Ames test) model (SARpy/IRFMN)—assessment						
	Mutagenicity (Ames test) model (ISS)—assessment						
	Mutagenicity (Ames test) model (*k*-NN/read-across)—assessment						
Carcinogenicity alerts							
OECD QSAR Toolbox	Carcinogenicity (genotoxicity and nongenotoxicity) alerts by ISS						
OncoLogic	OncoLogic (prediction of the carcinogenic potential of the chemical)						
VEGA	Carcinogenicity model (CAESAR)—assessment						
	Carcinogenicity model (ISS)—assessment						
	Carcinogenicity model (IRFMN/ANTARES)—assessment						
	Carcinogenicity model (IRFMN/ISSCAN-CGX)—assessment						
ToxAlerts	Aliphatic halogens (for nongenotoxic carcinogenicity)						
Toxtree	Nongenotoxic carcinogenicity						

Table C-7. Heat Map Illustrating the Structural Alert and SAR Prediction Results for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Analogues

Tool	Model[a]	1-Bromo-2-chloroethane	1,2-Dibromoethane	1,2-Dichloroethane	1,2-Dichloropropane	1,2-Dibromo-3-chloropropane	1,2,3-Trichloropropane
Combined alerts							
ToxAlerts	Aliphatic halide (general) (for genotoxic carcinogenicity, mutagenicity)						
	Aliphatic halide (specific) (for genotoxic carcinogenicity, mutagenicity)						
	Aliphatic halogens (for genotoxic carcinogenicity, mutagenicity)						
	Aromatic and aliphatic substituted primary alkyl halides (for genotoxic carcinogenicity, mutagenicity)						
	Structural alert for genotoxic carcinogenicity						
Toxtree	Model results outside the applicability domain for carcinogenicity/mutagenicity.						

	Model results or alerts indicating no concern for carcinogenicity/mutagenicity.
	Model results outside the applicability domain for carcinogenicity/mutagenicity.
	Model results or alerts indicating concern for carcinogenicity/mutagenicity.

[a]All tools and models described in Appendix B were used. Models with results or alerts are presented in the heat map (models without results were omitted).

ANTARES = Alternative Non-Testing Methods Assessed for REACH Substances; CA = chromosomal aberration; CAESAR = Computer-Assisted Evaluation of industrial chemical Substances According to Regulations; CONSENSUS = consensus assessment based on multiple models (CAESAR, SARpy, ISS, and *k*-NN); DNA = deoxyribonucleic acid; IRFMN = Istituto di Ricerche Farmacologiche Mario Negri; ISS = Istituto Superiore di Sanità; ISSCAN-CGX = Istituto Superiore di Sanità Chemical Carcinogen; *k*-NN = *k*-nearest neighbor; MNT = micronucleus test; OECD = Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship; REACH = Registration, Evaluation, Authorisation and Restriction of Chemicals; SAR = structure-activity relationship; VEGA = Virtual models for property Evaluation of chemicals within a Global Architecture.

Table C-8. Structural Alerts for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Analogues

SA	Tool	Compounds
Haloalkanes and haloalkenes	OncoLogic	1-Bromo-2-chloroethane[a],1,2-DBE[b], 1,2-DCE,[a] 1,2-DCP[c], 1,2-DB-3-CP[b], TCP[b]
Aliphatic halogens	ToxAlerts	1-Bromo-2-chloroethane, 1,2-DBE, 1,2-DCE, 1,2-DCP, 1,2-DB-3-CP, TCP
	Toxtree	
	OECD QSAR Toolbox	
Aliphatic halide	ToxAlerts	1-Bromo-2-chloroethane, 1,2-DBE, 1,2-DCE, 1,2-DCP, 1,2-DB-3-CP, TCP
Aromatic and aliphatic substituted primary alkyl halides		
Vicinal dihaloalkanes	OECD QSAR Toolbox	1-Bromo-2-chloroethane, 1,2-DBE, 1,2-DCE, 1,2-DCP
Halogenated vicinal hydrocarbons		1-Bromo-2-chloroethane, 1,2-DBE, 1,2-DCE, 1,2-DCP, 1,2-DB-3-CP, TCP

[a]Identified as moderate alert based on SAR analysis only.
[b]Identified as high-moderate alert based on experimental data and SAR analysis.
[c]Identified as moderate alert based on experimental data and SAR analysis.

1,2-DB-3-CP = 1,2-dibromo-3-chloropropane; 1,2-DBE = 1,2-dibromoethane; 1,2-DCE = 1,2-dichloroethane; 1,2-DCP = 1,2-dichloropropane; OECD = Organisation for Economic Co-operation and Development; QSAR = quantitative structure-activity relationship; SA = structural alert; SAR = structure-activity relationship; TCP = 1,2,3-trichloropropane.

STEP 7. EVIDENCE INTEGRATION FOR SCREENING EVALUATION OF 1-BROMO-2-CHLOROETHANE CARCINOGENICITY

Table C-9 presents the data for multiple lines of evidence pertinent to the screening evaluation of the carcinogenic potential of 1-bromo-2-chloroethane.

Table C-9. Integration of Evidence for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Analogues

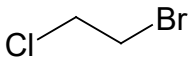
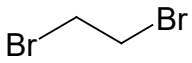
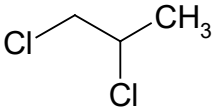
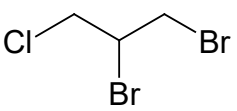
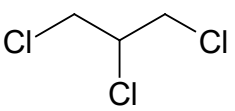
Evidence Streams	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloropropane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
Structure						
Analogue selection and evaluation (see Steps 1 and 2)	Target compound Contains: (1) two labile halogen substituents; (2) halogens attached to adjacent, primary carbon atoms; and (3) no more than one halogen per carbon atom	Contains: (1) two labile halogen substituents; (2) halogens attached to adjacent, primary carbon atoms; and (3) no more than one halogen per carbon atom	Contains: (1) two labile halogen substituents; (2) halogens attached to adjacent, primary carbon atoms; and (3) no more than one halogen per carbon atom	Contains: (1) two labile halogen substituents; (2) halogens attached to adjacent, primary carbon atoms; and (3) no more than one halogen per carbon atom	Contains: (1) three labile halogen substituents; (2) halogens attached to adjacent, primary carbon atoms; and (3) no more than one halogen per carbon atom	Contains: (1) three labile halogen substituents; (2) halogens attached to adjacent, primary carbon atoms; and (3) no more than one halogen per carbon atom
Experimental genotoxicity data (see Step 3)	Mutagenic Clastogenic DNA damaging Forms DNA adducts	Mutagenic Clastogenic DNA damaging Forms DNA adducts Induces cell transformation	Mutagenic Clastogenic DNA damaging Forms DNA adducts	Not a potent mutagen Clastogenic DNA damaging	Mutagenic Clastogenic DNA damaging Forms DNA adducts Induces cell transformation	Mutagenic Clastogenic DNA damaging Forms DNA adducts Induces cell transformation
ADME evaluation (see Step 4)	Oxidation (based on analogy to other dihaloalkanes) and GSH conjugation (demonstrated) Expected to form episulfonium ion	Common metabolic pathways with other haloalkanes (oxidation and GSH conjugation) Forms episulfonium ion	Common metabolic pathways with other haloalkanes (oxidation and GSH conjugation) Forms episulfonium ion	Common metabolic pathways with other haloalkanes (oxidation and GSH conjugation) Expected to form episulfonium ion	Common metabolic pathways with other haloalkanes (oxidation and GSH conjugation) Forms episulfonium ion	Common metabolic pathways with other haloalkanes (oxidation and GSH conjugation) Forms episulfonium ion

Table C-9. Integration of Evidence for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Analogues						
Evidence Streams	**1-Bromo-2-Chloroethane CASRN 107-04-0**	**1,2-Dibromoethane CASRN 106-93-4**	**1,2-Dichloroethane CASRN 107-06-2**	**1,2-Dichloropropane CASRN 78-87-5**	**1,2-Dibromo-3-Chloropropane CASRN 96-12-8**	**1,2,3-Trichloro-propane CASRN 96-18-4**
Cancer data and MOA[a] (see Step 5)	No data	Multisite carcinogen in rats and mice following oral or inhalation exposure Proposed MOA: Mutagenicity and/or DNA damage	Multisite carcinogen in rats and mice following oral or inhalation exposure Potential MOA: Mutagenicity and/or DNA damage	Liver tumors (mice) and marginal increase in mammary gland tumors (rats) following oral exposure; nasal tumors (rats) and lung and Harderian gland tumors (mice) following inhalation exposure Proposed MOA: DNA damage	Multisite carcinogen in rats and mice following oral exposure; primarily respiratory tract cancer (nasal, pharynx, lung) following inhalation exposure MOA: mutagenicity	Multisite carcinogen in rats and mice following oral exposure; no inhalation data MOA: mutagenicity

Table C-9. Integration of Evidence for 1-Bromo-2-Chloroethane (CASRN 107-04-0) and Analogues

Evidence Streams	1-Bromo-2-Chloroethane CASRN 107-04-0	1,2-Dibromoethane CASRN 106-93-4	1,2-Dichloroethane CASRN 107-06-2	1,2-Dichloropropane CASRN 78-87-5	1,2-Dibromo-3-Chloropropane CASRN 96-12-8	1,2,3-Trichloro-propane CASRN 96-18-4
Common structural alerts and SAR predictions (see Step 6)	ALERTS • Haloalkanes and haloalkenes • Aliphatic halogens • Aliphatic halide • Vicinal dihaloalkanes • Halogenated vicinal hydrocarbons SAR PREDICTIONS: Concerns for mutagenicity and carcinogenicity in most models; no concern for nongenotoxic carcinogenicity in Toxtree	ALERTS • Haloalkanes and haloalkenes • Aliphatic halogens • Aliphatic halide • Vicinal dihaloalkanes • Halogenated vicinal hydrocarbons SAR PREDICTIONS: Concerns for mutagenicity and carcinogenicity in most models; no concern for nongenotoxic carcinogenicity in Toxtree	ALERTS • Haloalkanes and haloalkenes • Aliphatic halogens • Aliphatic halide • Vicinal dihaloalkanes • Halogenated vicinal hydrocarbons SAR PREDICTIONS: Concerns for mutagenicity and carcinogenicity in most models; no concern for nongenotoxic carcinogenicity in Toxtree	ALERTS • Haloalkanes and haloalkenes • Aliphatic halogens • Aliphatic halide • Vicinal dihaloalkanes • Halogenated vicinal hydrocarbons SAR PREDICTIONS: Concerns for mutagenicity and carcinogenicity in most models; no concern for carcinogenicity in two of four VEGA models and no concern for nongenotoxic carcinogenicity in Toxtree	ALERTS • Haloalkanes and haloalkenes • Aliphatic halogens • Aliphatic halide • Halogenated vicinal hydrocarbons SAR PREDICTIONS: Concerns for mutagenicity and carcinogenicity in most models; no concern for nongenotoxic carcinogenicity in Toxtree	ALERTS • Haloalkanes and haloalkenes • Aliphatic halogens • Aliphatic halide • Halogenated vicinal hydrocarbons SAR PREDICTIONS: Concerns for mutagenicity and carcinogenicity in most models; no concern for nongenotoxic carcinogenicity in Toxtree

[a]For MOA descriptions, "MOA" was used if the U.S. EPA did a formal MOA evaluation and made a conclusion regarding cancer MOA(s); "proposed MOA" was used if the U.S. EPA did not do formal MOA evaluation, but proposed possible MOAs; and "potential MOA" was used if the U.S. EPA did not discuss potential MOAs but available experimental data suggest an MOA.

ADME = absorption, distribution, metabolism, excretion; DNA = deoxyribonucleic acid; GSH = glutathione; MOA = mode of action; SAR = structure-activity relationship; VEGA = Virtual models for property Evaluation of chemicals within a Global Architecture.

STEP 8. QUALITATIVE LEVEL OF CONCERN FOR 1-BROMO-2-CHLOROETHANE POTENTIAL CARCINOGENICITY

Table C-10 identifies the qualitative level of concern for potential carcinogenicity of 1-bromo-2-chloroethane based on the multiple lines of evidence described above. Due to lack of information supporting carcinogenic portal-of-entry effects, the qualitative level of concern for this chemical is considered to be applicable to all routes of exposure.

Table C-10. Qualitative Level of Concern for Carcinogenicity of 1-Bromo-2-Chloroethane (CASRN 107-04-0)

Level of Concern	Designation	Comments
Concern for potential carcinogenicity	**Selected**	**All analogues of 1-bromo-2-chloroethane have carcinogenic potential based on tumors observed in rodent studies. The U.S. EPA identified a mutagenic MOA for 1,2-DB-3-CP and TCP, and all analogues except 1,2-DCP are mutagenic (evidence is limited for 1,2-DCP). DNA damage is also a potential MOA suggested for 1,2-DBE and 1,2-DCP, and experimental evidence indicates that all analogues are DNA damaging and all except 1,2-DCP form DNA adducts (no data for 1,2-DCP). Common metabolic pathways exist between 1-bromo-2-chloroethane and the analogue compounds. 1-Bromo-2-chloroethane and its analogues have similar structural alerts (e.g., haloalkanes and haloalkenes, aliphatic halogens, aliphatic halide, halogenated vicinal hydrocarbons) and similar SAR predictions showing concern for carcinogenicity and/ or genotoxicity.**
Inadequate information for assigning qualitative level of concern	Not selected	NA

1,2-DB-3-CP = 1,2-dibromo-3-chloropropane; 1,2-DBE = 1,2-dibromoethane; 1,2-DCP = 1,2-dichloropropane; DNA = deoxyribonucleic acid; MOA = mode of action; NA = not applicable; SAR = structure-activity relationship; TCP = 1,2,3-trichloropropane.

APPENDIX D. REFERENCES

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