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Provisional Peer-Reviewed Toxicity Values for

1,3-Dibromobenzene
(CASRN 108-36-1)

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TABLE OF CONTENTS

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
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
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV1	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
NCEA	National Center for Environmental Assessment
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	glutamic oxaloacetic transaminase, also known as AST
SGPT	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_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,3-DIBROMOBENZENE (CASRN 108-36-1)

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 Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

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.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

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. Environmental Protection Agency (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.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

1,3-Dibromobenzene (CASRN 108-36-1), also known as meta-dibromobenzene (*m*-dibromobenzene), appears as a clear, colorless to light-yellow liquid. It is used in various organic syntheses. 1,3-Dibromobenzene is an irritant that can cause inflammation and burns to the eyes and skin. It is stable but flammable and its combustion can lead to irritating, corrosive, and/or toxic fumes. The molecular formula of 1,3-dibromobenzene is $C_6H_4Br_2$ (see Figure 1). Table 1 provides a list of its physicochemical properties.

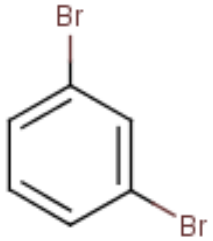


Figure 1. Structure of 1,3-Dibromobenzene

Table 1. Physicochemical Properties of 1,3-Dibromobenzene (CASRN 108-36-1)

Property (unit)	Value
Boiling point (°C)	218−219[a]
Melting point (°C)	−7[a]
Density at 25°C (g/mL)	1.952[a]
Log P (unitless)	3.75[b]
Vapor pressure (mm Hg at 25°C)	0.269[b]
pH (unitless)	Not available
Solubility in water (mg/L at 35°C)	67.5[b]
Relative vapor density (air = 1)	8.16[a]
Molecular weight (g/mol)	235.9[a]

[a]ChemicalBook (accessed on 7-22-2013).
[b]NLM (accessed on 7-22-2013).

A summary of available toxicity values for 1,3-dibromobenzene from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for 1,3-Dibromobenzene (CASRN 108-36-1)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	NV	NA	ACGIH (2013)	N/A
ATSDR	NV	NA	ATSDR (2013)	N/A
Cal/EPA	NV	NA	Cal/EPA (2014, 2013)	4-17-2014[b]
NIOSH	NV	NA	NIOSH (2010)	NA
OSHA	NV	NA	OSHA (2011, 2006)	NA
IRIS	NV	NA	U.S. EPA	4-17-2014
Drinking water	NV	NA	U.S. EPA (2012a)	NA
HEAST	NV	NA	U.S. EPA (2011a)	NA
CARA HEEP	NV	Noncancer toxicity values were not derived due to inadequate noncancer data and lack of carcinogenicity studies on the chemical.	U.S. EPA (1994)	NA
WHO	NV	NA	WHO	4-14-2014
Cancer				
IRIS	NV	NA	U.S. EPA	4-14-2014
HEAST	NV	NA	U.S. EPA (2011a)	NA
IARC	NV	NA	IARC (2013)	NA
NTP	NV	NA	NTP (2011)	NA
Cal/EPA	NV	NA	Cal/EPA (2013, 2011)	NA

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA Occupational Safety and Health Administration; WHO = World Health Organization.

[b]The Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database (http://oehha.ca.gov/tcdb/index.asp) was also reviewed and found to contain no information on 1,3-Dibromobenzene.

NA = not applicable; NV = not available.

Literature searches were conducted on sources published from 1900 through April 2014 for studies relevant to the derivation of provisional toxicity values for 1,3-dibromobenzene (CASRN 108-36-1). The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for toxicity values or exposure limits: ACGIH, ATSDR, Cal EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Table 3 provides an overview of the relevant databases for studies on 1,3-dibromobenzene and includes all potentially relevant, repeated-dose, short-term-duration studies (no subchronic-duration or longer-term-duration studies have been located). All statistical comparisons were made at the 5% level of statistical significance ($p < 0.05$), unless noted otherwise.

Table 3. Summary of Potentially Relevant Data for 1,3-Dibromobenzene (CASRN 108-36-1)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL	Reference	Comments
Human								
1. Oral								
No data								
2. Inhalation								
No data								
Animal								
1. Oral								
Short-term	4−6 female Wistar rats, gavage, 7 days	0, 70, 135, 270, or 400 mg/kg	Increased ALA-D (135- and 270-mg/kg dose groups only) and increased ALA-S (all dose groups except for 70 mg/kg) activities	ND	NC	ND	Szymańska (1996)	No hepatic lesions were found.
Short-term	4−6 female Wistar rats, gavage, 28 days	0, 5, 25, or 125 mg/kg	Increased serum GGT activity (25- and 125-mg/kg dose groups only), and porphyrinuria	ND	NC	ND	Szymańska (1996)	Increased GSH level as a compensatory effect. No hepatic lesions were observed.
Subchronic	No data							
Chronic	No data							
Developmental	No data							
Reproductive	No data							
Carcinogenic	No data							

Table 3. Summary of Potentially Relevant Data for 1,3-Dibromobenzene (CASRN 108-36-1)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry	Critical Effects	NOAEL	BMDL/ BMCL	LOAEL	Reference	Comments
2. Inhalation								
No data								

ALA-D = delta-aminolevulinate dehydratase; ALA-S = delta-aminolevulinate synthase; GGT = L-γ-glutamyltransferase; GSH = glutathione; NC = not calculated; ND = not determined.

HUMAN STUDIES

No studies have been identified.

ANIMAL STUDIES

No subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on 1,3-dibromobenzene exposure (via the oral or inhalation route) were identified. A few short-term-duration gavage studies were located and are discussed below.

Oral Exposures

The effects of oral exposure of animals to 1,3-dibromobenzene via gavage have been evaluated in two short-term-duration, repeated-dose toxicity studies (Szymańska, 1996).

Inhalation Exposures

No studies have been identified.

Short-Term-Duration Studies

Szymańska (1996)

In a 7-day repeated-dose study, Szymańska (1996) administered daily doses of 1,3-dibromobenzene via gavage. Female Wistar rats (4–6 per dose group) were treated with 0, 70, 135, 270, or 400 mg/kg of 1,3-dibromobenzene or 1,3-dibromo[^{3}H]-benzene (purity not specified) in sunflower oil. The control group received either sunflower oil or no gavage. Animals were sacrificed 24 hours after the administration of the seventh dose and the liver was excised for histological examination as well as to determine enzyme levels. The activity of alanine aminotransaminase (ALT) and L-γ-glutamyltransferase (GGT) were determined in serum. The levels of glutathione (GSH) and malondialdehyde (MDA) as well as the activity of 5-aminolevulinate dehydratase (ALA-D) and synthase (ALA-S) were determined in liver. The study author reported a 50% increase in liver GSH for the 70-mg/kg dose group. In addition, ALT activity did not correlate with the change in GSH levels. There was a statistically significant increase of ALT in the 270-mg/kg dose group only. The activities of ALA-D (135- and 270-mg/kg dose groups only) and ALA-S (all dose groups except for 70 mg/kg) also increased. There were no statistically significant changes in GGT activity or MDA levels. No hepatic lesions were observed.

In another short-term-duration (28-day repeated-dose) study, Szymańska (1996) administered daily doses of 1,3-dibromobenzene via gavage. Female Wistar rats (4–6 per dose group) were treated with 0, 5, 25, or 125 mg/kg of 1,3-dibromobenzene (purity not specified) in each dose group. The control group received either sunflower oil alone or no gavage. Control animals were kept in two types of cages: (1) metabolic cages (n = 14; Control Group 1) and (2) normal breeding cages (n = 21; Control Group 2). Treated animals were kept in metabolic cages beginning at 24 hours before the start of the investigation. Animals were sacrificed 24 hours after the administration of 7, 14, 21, or 28 doses. Livers were excised for histological examination and to determine enzyme levels. Increased GSH levels were observed in the 125-mg/kg dose group starting on Day 7. There was also a statistically significant increase in GGT activity for the mid- and high-dose groups. ALT activity did not change significantly in any of the dose groups. There was no statistically significant change in ALA-D in any of the dose groups on Day 28 (some statistically significant changes on Day 7 only). For ALA-S, a statistically significant decrease was observed in the 5-mg/kg dose group only. For liver MDA

concentrations, the results were ambiguous in terms of the types of control groups used. Control Group 1 had much higher MDA levels than Control Group 2. All test groups had lower MDA concentrations than Control Group 1 and higher MDA concentrations than Control Group 2. The study author concluded that the change in MDA concentrations was likely a stress-induced effect due to the changing of cages rather than treatment related. No hepatic lesions were observed.

In addition to the liver parameters mentioned above, Szymańska (1996) also examined liver iron levels and concentrations of 5-animolevulinic acid (ALA-U) and porphyrins in urine. There were no significant changes in iron concentrations in the rat liver in any of the dose groups. At the end of Week 4, however, there was a statistically significant decrease of excreted ALA-U in urine for the 25-mg/kg dose group. The study author also observed that several urinary porphyrins (i.e., tetracarboxy-, pentacarboxy-, and heptacarboxyporphyrins) were increased following repeated exposure to 1,3-dibromobenzene (Day 28), mostly at the higher doses. Because increased porphyrins were not accompanied by an increased excretion of ALA-U, the study author concluded that short-term exposure to 1,3-dibromobenzene produced porphyrinuria only and not porphyria in rats. Due to the short duration and differences observed between the two control groups, the 7-day and 28-day studies by Szymańska (1996) are not suitable for the derivation of a provisional reference dose (p-RfD). The study author did not identify any effect levels or median lethal dose (LD_{50}) values, and neither a NOAEL nor a LOAEL are determined for this PPRTV assessment.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Other studies that examined 1,3-dibromobenzene but are not appropriate for the selection of a point of departure (POD) are described here. These studies are not adequate for the determination of p-RfD, provisional reference concentration (p-RfC), provisional oral slope factor (p-OSF), or provisional inhalation unit risk (p-IUR) values but provide supportive data supplementing a weight-of-evidence (WOE) approach. These may include genotoxicity, metabolism/toxicokinetic, and studies using routes of exposure other than the oral or inhalation route (see Table 4).

Table 4. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Other toxicity studies (exposures other than oral or inhalation)	Male BALB/c mice (4−12 per dose group); single i.p. injection (0, 150, 300, or 600 mg/kg) of 1,2-, 1,3- ,or 1,4-dibromobenzene.	Decreased glutathione (GSH) and increased malondialdehyde (MDA) levels in liver; increased gamma-glutamyltransferase (GGT) activities with all three isomers. Increased serum glutamate pyruvate transaminase (GPT) and hepatic necrosis in the central lobular zone with 1,2- and 1,3-dibromobenzene but not 1,4-dibromobenzene.	1,2- and 1,3-Dibromobenzene appear to have more pronounced effects on the liver than 1,4-dibromobenzene.	Szymańska et al. (1996)
	Female Wistar rats (4−6 per dose group); single i.p. injection (0, 40, 100, 300, or 600 mg/kg) of 1,3-dibromobenzene.	Reduced GSH levels, increased alanine aminotransferase (ALT) and GGT activities, and increased MDA concentration (two highest dose groups only). This study did not indicate whether the liver was histologically examined.	1,3-Dibromobenzene induces liver enzyme changes in rats.	Szymańska (1996)
	Male Outbred Imp BALB/c mice (4−12 per dose group); single i.p. injection (0, 150, 300, or 600 mg/kg) of 1,2,4- or 1,3,5-tribromobenzene, 1,2,4,5-tetrabromobenzene, bromobenzene, or hexabromobenzene.	Results from this study were compared to those from a previous study with dibromobenzenes (Szymańska et al., 1996). All brominated compounds decreased liver GSH levels and increased GGT activity as well as MDA levels in the liver, but these effects were more pronounced with dibromobenzenes and bromobenzene.	The acute hepatotoxicity of bromobenzenes decreases with the increase in the number of bromine atoms.	Szymańska (1998)
	Male BALB/c mice (4–5 per dose group); i.p. injection (0, 30, 60, 80, or 140 mg/kg) of 1,3-dibromobenzene or seven other brominated benzenes for 7 days.	Increased relative liver weight (liver-to-body weight ratio) and increased MDA concentration in all brominated benzenes. Steatosis was observed for some brominated benzenes but not for 1,3-dibromobenzene.	Liver effects were observed following repeated exposure to brominated benzenes.	Szymańska et al. (1998)
Metabolism/ Toxicokinetic	Female Outbred IMP:Wist rats (4 per dose group);single i.p. injection (100 or 300 mg/kg) of 1,3-dibromobenzene (no controls identified).	An average of 79.3% of 1,3-dibromobenzene and its metabolites was excreted in urine. The highest concentration of 1,3-dibromobenzene was found in the liver, kidneys, and fat tissue.	Urine is the main route of excretion for 1,3-dibromobenzene.	Sapota et al. (1999)

Other Toxicity Studies (Exposures Other than Oral or Inhalation)

The effects of intraperitoneal (i.p.) exposure of animals to 1,3-dibromobenzene have been evaluated in three acute, single-injection studies (Szymańska, 1998, 1996; Szymańska et al., 1996) and one short-term-duration, repeated-injection study. The results are reported in Szymańska et al. (1998) and Szymańska (1996).

Acute Studies

Szymańska et al. (1996)

Szymańska et al. (1996) conducted an acute toxicity study of 1,2-, 1,3-, and 1,4-dibromobenzene isomers in male BALB/c mice. Single doses of 0, 150, 300, or 600 mg/kg in sunflower oil (purity not reported) were administered to 4−12 male mice per dose group by i.p. injection. The control group (n = 28−30) received no injections or were injected with sunflower oil only. Livers were removed and blood was collected at different time intervals: 2, 4, 12, 24, 48, 72, and 120 hours after injection. Treatment-related effects included decreased GSH levels in the first 24 hours after administration at the two highest doses (up to 90% decrease), a statistically significant increase in MDA in the liver, and increases in GGT in all three isomers. Increased GPT activities and an increase in the incidence of hepatic necrosis (as determined in histopathology) were observed with 1,2- and 1,3-dibromobenzene but not 1,4-dibromobenzene. The results of this study indicated that all three isomers are acutely hepatotoxic, with 1,3- and 1,2-dibromobenzene being more toxic (based on more pronounced incidences of hepatic necrosis in the central lobular zone) than 1,4-dibromobenzene (no statistically significant change from the control group; caused necrosis only in individual hepatocytes). Neither effect levels nor LD_{50}s were determined by the study authors.

Szymańska (1996)

In addition to the short-term-duration oral studies in rats, Szymańska (1996) conducted an acute single-dose study. Female Wistar rats (4−6 per dose group) were administered 0, 40, 100, 300, or 600 mg/kg of 1,3-dibromobenzene (purity not specified) in sunflower oil by i.p. injection. The control rats (n = 21−22) received either sunflower oil alone or no injection. Heavy depletion of liver GSH was observed at the high doses. Even at the low doses, there was a statistically significant decrease in GSH levels. However, GSH levels eventually went up in all dose groups, and in some cases, increased above control levels after 24 hours of administration. The study author stated that these increases in GSH may indicate either an adaptation or compensatory effect. Serum ALT increased slightly within a short time after the administration of 1,3-dibromobenzene but then fluctuated above and below control levels between 4 and 72 hours after administration. There was a statistically significant increase in GGT activity within 4 hours. A statistically significant increase in liver MDA concentration was observed in the highest dose group only (up to 12 hours after administration). The study author did not indicate whether morphological examinations were conducted to detect hepatic lesions (necrosis), as previously observed in the mouse study (Szymańska et al., 1996). In terms of acute hepatotoxicity, a species-specific difference (rats vs. mice) could exist; however, the study author did not speculate on reasons for this possible difference.

Szymańska (1998)

Szymańska (1998) conducted another acute single-dose hepatotoxicity study for multiple brominated benzenes (bromobenzene, 1,2,4-tribromobenzene, 1,3,5-tribromobenzene, 1,2,4,5-tetrabromobenzene, and hexabromobenzene) in male Outbred Imp BALB/cJ mice in an

attempt to find a relationship between chemical structure and hepatotoxic effects. Single doses of 0, 150, 300, or 600 mg/kg in sunflower oil (purity not reported) were administered to 4−12 male mice per dose group by i.p. injection. The control mice received either sunflower oil alone or no injection. Similar to the other acute single-dose i.p. studies (Szymańska, 1996; Szymańska et al., 1996), Szymańska (1998) found that all examined compounds (i.e., bromobenzene, 1,2,4-tribromobenzene, 1,3,5-tribromobenzene, 1,2,4,5-tetrabromobenzene, and hexabromobenzene) lowered liver GSH levels shortly after the administration. The results were compared with data for dibromobenzenes (1,2-, 1,3-, and 1,4-dibromobenzene) obtained from an earlier study (Szymańska et al., 1996). Statistically significant changes (30- to 120-fold increases) in ALT activity were observed for bromobenzene, 1,2-dibromobenzene, 1,3-dibromobenzene, and 1,2,4-tribromobenzene. All brominated compounds produced an increase in GGT activity in serum and MDA concentration in the liver. As stated in the Szymańska et al. (1996) study and summarized in Szymańska (1998), increased incidence of hemorrhagic necrosis in the liver central lobular zone was observed for 1,3-dibromobenzene. Finally, Szymańska (1998) concluded that in mice "…acute toxicity of bromobenzenes decreases with the increase of the number of bromine atoms in the molecule" (p. 97). Neither effect levels nor LD_{50}s were determined.

Short-Term-Duration Studies

Szymańska et al. (1998)

In a follow-up study, Szymańska et al. (1998) conducted another short-term-duration (7-day repeated dose) study in male BALB/c mice. Szymańska et al. (1998) reported the effects on selected indicators of liver impairment after repeated administration of mono- and polybromobenzenes. Szymańska et al. (1998) administered 1,3-dibromobenzene along with seven other brominated benzenes (i.e., bromobenzene, 1,2-dibromobenzene, 1,4-dibromobenzene, 1,2,4-tribromobenzene, 1,3,5-tribromobenzene, 1,2,4,5-tetrabromobenzene, and hexabromobenzene; purity not specified) daily via i.p. injection in sunflower oil in volumes of 0.2 ml per 20 g body weight of mice. The mice (4−5/group) were exposed to 0, 30, 60, 80, or 140 mg/kg in each dose group. The control mice received either sunflower oil only or no injection. Because the study authors found no difference between the control groups, they chose the pooled controls that received no injection for comparison with other treatment groups. Changes in relative liver weight (liver-to-body weight ratio) were observed for all brominated benzenes.

For exposure to 1,3-dibromobenzene, relative liver weight increased in the 60-, 80-, and 140-mg/kg dose groups, but these changes were not dose dependent. For histopathological changes, distinct steatosis in the peripheral lobular zone was observed for 1,4-dibromobenzene, 1,2,4-tribromobenzene, 1,3,5-tribromobenzene, 1,2,4,5-tetrabromobenzene, and hexabromobenzene but not 1,3-dibromobenzene. For exposure to 1,3-dibromobenzene, the GSH level was statistically significantly increased in the 80-mg/kg dose group only; no depletion of the GSH level was observed in any of the dose groups (the study authors stated that this may explain the lack of hepatic necrosis). There was also a statistically significant increase in liver MDA level at the highest dose of 1,3-dibromobenzene (140 mg/kg). ALA-S was significantly decreased after exposure to 1,2-dibromobenzene and 1,3-dibromobenzene. 1,4-Dibromobenzene decreased ALA-S in the lower doses and increased ALA-S in the higher doses. For ALA-D, the study authors claimed there were no statistically significant changes for any of the brominated benzenes. The activity of ALT—another key indicator for necrotic changes of hepatocytes—was not affected by any of the brominated benzenes.

Szymańska et al. (1998) stated that there was an apparent "shift" from single exposure to repeated exposure in terms of hepatotoxic effects, with necrosis occurring after single-dose exposure and the less severe steatosis occurring after repeated exposure (observed for other brominated benzenes but not observed for 1,3-dibromobenzene directly). These findings are consistent with the interpretation by Chakrabarti (1991) that, "…repeated doses of bromobenzene may by means of inducing microsomal enzymes and GSH levels accelerate the process of bromobenzene metabolism and/or may intensify repair/regeneration processes in the cell" (as cited in Szymańska et al., 1998, p. 28). In addition, instead of necrosis in the liver and associated increases in ALT and GGT activities in the serum observed in the acute single-dose studies in mice, the study authors found changes in heme synthesis and subsequent porphyrogenic effects in the repeated dose studies.

Neither effect levels nor LD_{50}s have been identified or determined in any of the studies in this section, and none of the studies are suitable for the derivation of a p-RfD due to the route of administration (i.p.), study duration (<90 days), and study design (e.g., metabolic cage vs. normal breeding cage).

Toxicokinetics Studies

Sapota et al. (1999) investigated the toxicokinetic (distribution and excretion) properties of 1,3-dibromobenzene in rats by radiotracing. Four female Outbred IMP:Wist rats per group were administered 100 or 300 mg/kg of 1,3-dibromobenzene-[^{3}H] (purity not specified) dissolved in olive oil via a single i.p. injection. The use of a control group was not reported. Metabolites were identified and quantified by gas chromatography-mass spectrometry (GC-MS) technique. Urine was the main route of excretion, where an average of 79.3% was excreted in urine after 72 hours at a dose of 300 mg/kg, with 10% in feces. Similar (slightly lower) absorption and excretion rates were also found at a dose of 100 mg/kg. Tissues examined included the liver, kidneys, lung, adrenals, sciatic nerve, spleen, heart, brain, and fat. The highest concentrations (radioactivity) of 1,3-dibromobenzene-[^{3}H] after administration at a dose of 100 mg/kg were found in the liver, kidneys, and fat tissue. A similar pattern was observed for the 300-mg/kg dose group. Several metabolites isolated from urine were identified by GC-MS: unchanged (unconjugated) 1,3-dibromobenzene (18%), dibromophenols (34%), dibromothiophenols (28%), dibromothioanisole (1.8%), bromophenol (5.5%), bromohydroxythiophenols (5%), and bromohydroxythioanisole (7.5%). The study authors concluded that there are three different metabolic pathways of 1,3-dibromobenzene: (1) ring hydroxylation (dibromophenols), (2) glutathione conjugation (dibromothiophenols and dibromothioanisole), and (3) hydrolytic dehalogenation (bromophenol, bromohydroxythiophenol and bromohydroxythioanisole).

The study authors observed that approximately half of the metabolism products contain sulfur, and this finding is consistent with earlier observations (Szymańska et al., 1996) in which the hepatic necrotic action of 1,3-dibromobenzene was accompanied by decreased hepatic GSH levels. The study authors also concluded that 1,3-dibromobenzene has a relatively high turnover rate (e.g., high level of excretion in urine) with minor levels of radiotracer ^{3}H in the tissues for longer time periods. Finally, they stated that 1,3-dibromobenzene is an acute hepatotoxicant in rats and is also a potential nephrotoxicant (Sapota et al., 1999).

In a follow-up toxicokinetic study, Szymańska et al. (2002) compared the metabolism and tissue distribution of 1,2- and 1,4-dibromobenzene isomers in female Outbred IMP:Wist rats. The study used a similar protocol as detailed in Sapota et al. (1999). As with 1,3-dibromobenzene, urine is also the main route of excretion for both the 1,2- and 1,4-dibromobenzene isomers. Several metabolites isolated from urine were identified by GC-MS for the 1,2- and 1,4-dibromobenzene isomers; they included unchanged (unconjugated) parent compound (11 and 5%), dibromophenols (73 and 84%), dibromothiophenols (10 and 5%), and bromophenols (0.7 and 1.9%). The study authors concluded that 1,2-dibromobenzene (82.0% excreted in urine after 72 hours for the 100-mg/kg dose group) was similar to 1,3-dibromobenzene (66.5% excreted in urine for the 100-mg/kg dose group) (Sapota et al., 1999) in having a higher turnover rate than 1,4-dibromobenzene, which had a longer retention time in the body (29.6% excreted in urine for the 70-mg/kg dose group).

Genotoxicity Studies

No studies investigating the genotoxic effects of 1,3-dibromobenzene have been identified.

DERIVATION OF PROVISIONAL VALUES

Table 5 below presents a summary of noncancer screening oral provisional reference values derived using a surrogate approach (see Appendix A for details). Table 6 presents a summary of cancer values. The toxicity values have been converted to human equivalent dose (HED) units where appropriate.

Table 5. Summary of Noncancer Reference Values for 1,3-Dibromobenzene (CASRN 108-36-1)

Toxicity Type (units)	Species/Sex	Critical Effect	Screening p-Reference Value	POD Method	POD_{HED}	UFc	Principal Study
Screening subchronic p-RfD (mg/kg-day)[a]	Rat/Male	Increased relative liver weight and hepatic microsomal enzyme induction	4×10^{-3}	NOAEL	1.2	300	Carlson and Tardiff (1977)
Screening chronic p-RfD (mg/kg-day)[a]	Rat/Male	Increased relative liver weight and hepatic microsomal enzyme induction	4×10^{-4}	NOAEL	1.2	3,000	Carlson and Tardiff (1977)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

[a]A surrogate approach was applied. See Appendix A.

NDr = not determined

Table 6. Summary of Cancer Values for 1,3-Dibromobenzene (CASRN 108-36-1)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None			
p-IUR	None			

DERIVATION OF ORAL REFERENCE DOSES

Feasibility of Deriving Subchronic and Chronic p-RfDs

No subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on 1,3-dibromobenzene exposure via the oral route were identified. However, Appendix A of this document contains screening values (screening subchronic and chronic p-RfDs) using a surrogate (e.g., structural and metabolic) approach, which may be of use under certain circumstances. Please see Appendix A for details regarding the screening values.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Feasibility of Deriving Subchronic and Chronic p-RfCs

No subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on 1,3-dibromobenzene exposure via the inhalation route were identified. No inhalation toxicity data have been identified for the derivation of a p-RfC for 1,3-dibromobenzene. Furthermore, no inhalation toxicity data were identified for any of the

potential surrogates for 1,3-dibromobenzene, thus precluding derivation of screening subchronic and chronic p-RfCs.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 7 identifies the cancer WOE descriptor for 1,3-dibromobenzene (in bold).

Table 7. Cancer WOE Descriptor for 1,3-Dibromobenzene (CASRN 108-36-1)

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	NA	NA	No studies pertaining to the carcinogenicity of 1,3-dibromobenzene in humans are available.
"Likely to be Carcinogenic to Humans"	NA	NA	No studies pertaining to the carcinogenicity of 1,3-dibromobenzene in multiple species of animals are available.
"Suggestive Evidence of Carcinogenic Potential"	NA	NA	No data are available regarding the carcinogenic potential of 1,3-dibromobenzene even in a single animal species.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**There is no pertinent information available to assess the carcinogenic potential of 1,3-dibromobenzene.**
"Not Likely to be Carcinogenic to Humans"	NA	NA	No data are available to suggest that 1,3-dibromobenzene is not likely to be a carcinogen in humans following oral or inhalation exposure.

NA= not applicable.

DERIVATION OF PROVISIONAL CANCER RISK VALUES

The lack of quantitative data on the carcinogenicity of 1,3-dibromobenzene precludes the derivation of a quantitative estimate of cancer risk for either oral (p-OSF) or inhalation (p-IUR) exposures.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main provisional peer-reviewed toxicity value (PPRTV) document, it is inappropriate to derive provisional toxicity values for 1,3-dibromobenzene. However, information is available for a related 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 Superfund Health Risk Technical Support Center 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 PPRTV documents 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 is considerably more uncertainty associated with the derivation of 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 Superfund Health Risk Technical Support Center.

APPLICATION OF AN ALTERNATIVE SURROGATE APPROACH

The surrogate 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 surrogate analysis are presented in Wang et al. (2012). Three types of potential surrogates (structural, metabolic, and toxicity-like) are identified to facilitate the final surrogate chemical selection. The surrogate approach may or may not be route-specific or applicable to multiple routes of exposure. In this document, it is limited to the oral noncancer effects only, based on the available toxicity data. All information was considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable surrogate both toxicologically and chemically.

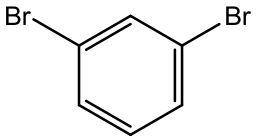
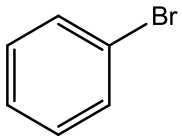
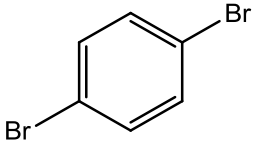
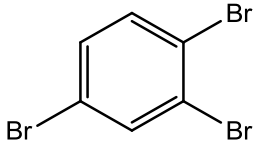
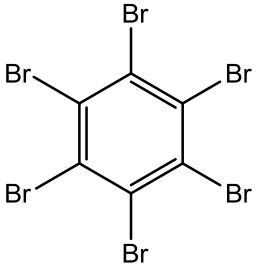
Structural Surrogates (Structural Analogs)

1,3-Dibromobenzene is a halogenated compound belonging to the brominated benzene class. Thus, an initial surrogate search focused on the identification of brominated benzenes with toxicity values from the Integrated Risk Information System (IRIS), PPRTV, and Health Effects Assessment Summary Tables (HEAST) databases to take advantage of the well-characterized chemical-class information. Four brominated benzenes were found to have oral toxicity values listed on IRIS: bromobenzene (U.S. EPA, 2009); 1,4-dibromobenzene (U.S. EPA, 1988a); 1,2,4-tribromobenzene (U.S. EPA, 1993); and hexabromobenzene (U.S. EPA, 1988b) (see Tables A-1 and A-3). Similarity scores for these chemicals were identified by searching for structural analogs at least 50% similar to 1,3-dibromobenzene using the National Library of Medicine's ChemIDplus database (NLM). Out of the four brominated benzenes initially obtained from IRIS, only 1,2,4-tribromobenzene had a similarity match of >50% to 1,3-dibromobenzene (55.92%, see Table A-1). The remaining three potential surrogates had a similarity score less than 50%. However, all four brominated benzenes were retained because of the chemical-class specific information (e.g., common target organ and effect[s]). Table A-1 summarizes their physicochemical properties and structural similarity.

Although 1,2,4-tribromobenzene was found to be the most structurally similar to 1,3-dibromobenzene based on the ChemIDplus similarity score, 1,2,4-tribromobenzene was not as similar to 1,3-dibromobenzene with regard to physicochemical properties. Instead, 1,4-dibromobenzene displayed the most similarity to 1,3-dibromobenzene with regard to

physicochemical properties, followed by bromobenzene and 1,2,4-dibromobenzene (see Table A-1). Hexabromobenzene displayed physicochemical properties that were the least similar to 1,3-dibromobenzene (see Table A-1). Based on this information, the top three chemicals considered as structural surrogates are bromobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene (see details below).

Table A-1. Structural Similarity and Physicochemical Properties of 1,3-Dibromobenzene and Potential Surrogates[a]

Characteristic	1,3-Dibromobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene	Hexabromobenzene
Structure					
CASRN	108-36-1	108-86-1	106-37-6	615-54-3	87-82-1
Similarity score (%)	100	<50	<50	55.92	<50
Molecular formula	$C_6H_4Br_2$	C_6H_5Br	$C_6H_4Br_2$	$C_6H_3Br_3$	C_6Br_6
Molecular weight	235.9	157	235.9	314.8	551.5
Melting point (°C)	−7.00	−30.6	87.3	44.5	326
Boiling point (°C)	218	156	219	275	-
Vapor pressure (mm Hg at 25°C)	0.269	4.18	0.058	5.48×10^{-3}	1.63×10^{-8}
Henry's law constant (atm-m^3/mole at 25°C)	1.24×10^{-3}	2.47×10^{-3}	8.93×10^{-4}	3.41×10^{-4}	2.81×10^{-5}
Water solubility (mg/L)	67.5	446	20	4.9	1.60×10^{-4}
Log K_{ow}[b]	3.78	2.99	3.89	4.54	6.07

[a]NLM (accessed 7-22-2013).
[b]Lu et al. (2000).

Metabolic Surrogates

Toxicokinetic Data

The specific metabolism information for 1,3-dibromobenzene and the four potential metabolic surrogates was based on the available metabolic information in the form of metabolites detected in urine; Table A-2 displays a summary of these excretion data. Similar to the analysis of physicochemical properties, hexabromobenzene was the least similar to 1,3-dibromobenzene in terms of metabolite profile; hence, it was concluded that hexabromobenzene is not a suitable candidate to serve as a metabolic surrogate for 1,3-dibromobenzene. Bromobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene had the same common metabolites as 1,3-dibromobenzene (i.e., bromophenols), and they were considered as metabolic surrogates.

In a related but indirect metabolism study, Lupton et al. (2009) analyzed brominated diphenyl ethers (BDEs) 47, 99, and 153 and identified their metabolites using human liver microsomes. The study authors found that BDE 99 was metabolized primarily to dihydroxylated BDE 99, but it was also metabolized to 2,4,5-tribromophenol, and 1,3-dibromobenzene to a lesser extent (<2−8%). Because 1,3-dibromobenzene only accounts for a small amount of the metabolites of BDE 99, BDE 99 was not considered as a potential metabolic surrogate for 1,3-dibromobenzene (BDE 99 also has a different toxic endpoint: neurotoxicity).

Table A-2. Summary of Brominated Benzene Metabolites Detected in Urine

Chemical	Route	Species	Metabolites	Reference
Bromobenzene	i.p.	Rabbit	Bromophenols	Ruzo et al. (1976)
	i.p.	Rat	Bromophenols and dihydrodiols	Miller et al. (1990) and Lertratanangkoon and Horning (1987)
1,4-Dibromobenzene	i.p.	Rabbit	Bromophenols	Ruzo et al. (1976)
	i.p.	Rat	Bromophenols	Szymańska et al. (2002)
1,2,4-Tribromobenzene	i.p.	Rabbit	Bromophenols	Ruzo et al. (1976)
Hexabromobenzene	oral	Rat	Bromobenzenes	Yamaguchi et al. (1988)
1,3-Dibromobenzene	i.p.	Rabbit	Three phenolic products—Due to small amounts of metabolites and unavailability of authentic standards, these metabolites could not be identified.	Ruzo et al. (1976)
	i.p.	Rat	Bromophenols	Sapota et al. (1999)

i.p. = intraperitoneal.

Toxicity-Like Surrogates

Table A-3 summarizes available toxicity data for 1,3-dibromobenzene and the four brominated benzenes identified as potential surrogates. All of the four brominated benzenes induced liver effects (e.g., hepatocellular cytomegaly, increased liver-to-body-weight ratio, hepatic microsomal enzyme induction, etc.). Furthermore, three of the brominated benzenes (bromobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene) had critical effects involving the liver. For hexabromobenzene, liver changes were observed (i.e., increased liver-to-body-weight ratio and increased liver porphyrins at higher doses) but these were not the most sensitive endpoints. From these long-term toxicity data, it is clear that the liver is a common target organ, and liver effects are often times the most sensitive endpoint for the brominated benzene chemical class. Also, the available acute and short-term toxicity studies similarly point to the liver as a target organ for 1,3-dibromobenzene (Szymańska et al., 1998; Szymańska, 1998, 1996; Szymańska et al., 1996). Hence, with respect to 1,3-dibromobenzene, the liver is likely to be the target organ and liver effects the most sensitive endpoint for long-term toxicity.

Although Szymańska (1998) demonstrated that the acute toxicity of bromobenzenes in mice is reduced when the number of bromine atoms is increased, comparison of median lethal dose (LD_{50}) values among bromobenzenes was inconclusive. The mouse LD_{50} values for bromobenzene and 1,4-dibromobenzene were slightly higher than the mouse LD_{50} for 1,3-dibromobenzene, but there were no mouse LD_{50} data for 1,2,4-tribromobenzene or hexabromobenzene to make a direct comparison (see Table A-3). Furthermore, an opposite trend in the long-term toxicity of brominated benzenes in terms of their effect levels was observed (see Table A-3) (i.e., the higher the number of bromine atoms, the more toxic the chemical is chronically). This trend is consistent with later findings by Szymańska et al. (1998) that there is an apparent "shift" from single exposure to repeated exposure in terms of hepatotoxic effects from necrosis to less severe steatosis and porphyrogenic effects (Szymańska et al., 1998). This shift may occur because repeated doses of brominated benzenes could accelerate the process of metabolism towards the formation of less toxic metabolites and/or may intensify the repair/regeneration processes in cells (Szymańska et al., 1998).

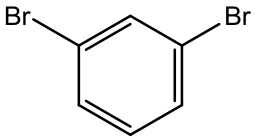
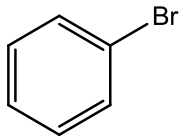
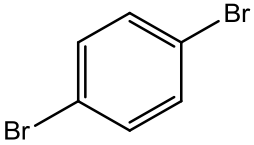
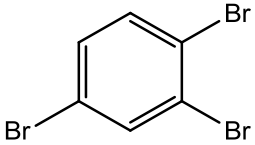
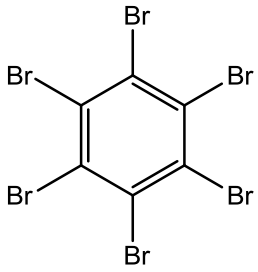
In vitro Hepatotoxicity Data

In addition to the in vivo data on the potential surrogates, in vitro measurements of toxicity such as median lethal concentration (LC_{50}) were also available. The human hepatocyte LC_{50} of 1,3-dibromobenzene was most similar to the human hepatocyte LC_{50} of 1,2,4-tribromobenzene (488 vs. 475 µM; see Table A-3). The rat hepatocyte toxicity data LC_{50} of 1,3-dibromobenzene was most similar to the rat hepatocyte LC_{50} of 1,4-dibromobenzene (355 vs. 371 µM; see Table A-3). The human and rat LC_{50}s of bromobenzene were 2−3 times higher than the LC_{50}s of 1,3-dibromobenzene; these data suggest that 1,3-dibromobenzene could be 2 to 3 times more toxic than bromobenzene in terms of in vitro toxicity. No comparison was possible between hexabromobenzene and 1,3-dibromobenzene because there were no in vitro human or rat hepatocyte toxicity data. Therefore, based on the similarities in in vitro toxicity levels as well as critical effects involving the liver, 1,4-dibromobenzene and 1,2,4-tribromobenzene were considered toxicity-like surrogates.

In conclusion, an attempt was made to identify a suitable surrogate to derive toxicity values for 1,3-dibromobenzene. Comparison of the potential surrogates (bromobenzene, 1,4-dibromobenzene, 1,2,4-tribromobenzene, and hexabromobenzene) was made based on their

profiles of structural similarity, toxicokinetics, and tissue-specific toxicity. The chronic reference doses (RfDs) for the four potential surrogates range from 2×10^{-3} to 1×10^{-2} mg/kg-day, and therefore, use of any of these candidates would have resulted in a comparable screening chronic provisional reference dose (p-RfD) for 1,3-dibromobenzene (see Table A-3). The common target organ among the potential surrogates appears to be the liver, with the kidneys as a likely secondary target organ for some brominated benzenes (e.g., bromobenzene).

Table A-3. Comparison of Available Toxicity Data for 1,3-Dibromobenzene and Potential Surrogates

Characteristic	1,3-Dibromobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene	Hexabromobenzene
Structure					
Human hepatocyte toxicity LC_{50} (µM)[a]	488 ± 48.8	1,150 ± 115	560 ± 56	475 ± 37.5	NA
Rat hepatocyte toxicity LC_{50} (µM)[a]	355 ± 35.5	750 ± 75	371 ± 37.1	214 ± 21.4	NA
Mouse LD_{50} (mg/kg)[b]	2,250	2,700	3,120	NA	NA
Chronic RfD (mg/kg-day)	NA	8×10^{-3}	1×10^{-2}	5×10^{-3}	2×10^{-3}
Critical effect	NA	Hepatocellular cytomegaly	Increased liver-to-body-weight ratio and hepatic microsomal enzyme induction	Increased liver-to-body-weight ratio and hepatic microsomal enzyme induction	Induced serum carboxylesterase activity
POD (mg/kg-day)	NA	$BMDL_{10}$: 24.1	NOAEL: 10	NOAEL: 5	NOAEL: 2
UF_C	NA	3,000	1,000	1,000	1,000
Source	NA	U.S. EPA (2009)	U.S. EPA (1988a)	U.S. EPA (1993)	U.S. EPA (1988b)

[a]Chan et al. (2007).
[b]NLM (accessed on 7-22-2013).

BMDL = benchmark dose lower confidence limit; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; NA = not available; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF_C = composite uncertainty factor.

Weight-of-Evidence (WOE) Approach

To select the best surrogate chemical based on all of the information from the three surrogate types, the following considerations were used in a WOE approach: (1) biological and toxicokinetic data are preferred over the structural data, (2) lines of evidence that indicate pertinence to humans are preferred, (3) chemicals with more conservative/health protective toxicity values may be favored, and (4) if there are no clear indications as to the best surrogate chemical based on the first three considerations, then the candidate surrogate with the highest structural similarity may be preferred.

In summary, bromobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene were identified as structural surrogates; bromobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene were identified as metabolic surrogates; and 1,4-dibromobenzene and 1,2,4-tribromobenzene were identified as toxicity-like surrogates. Overall, based on the WOE of all the information presented above, 1,2,4-tribromobenzene appears to be the most appropriate surrogate for 1,3-dibromobenzene because of the following factors:

- More similar structurally
  - Structural similarity of 55.92% (highest similarity score) using the National Library of Medicine's ChemIDplus database (NLM)
- Similar toxicokinetic profile and target organ (see Table A-2 and A-3)
- Similar in vitro hepatotoxicity data (see Table A-3) (Chan et al., 2007)
- More sensitive effect level (see Table A-3)

The *1,2,4-Tribromobenzene IRIS Summary* (U.S. EPA, 1993) cited Carlson and Tardiff (1977) as the principal study for the RfD.

> *Six male rats/group were dosed daily with 0, 2.5, 5 or 10 mg 1,2,4-tribromobenzene (TBB)/kg bw for 45 or 90 days. TBB was administered in corn oil p.o. as 0.1% of body weight. Controls received corn oil only. Animals were sacrificed at 45 or 90 days or after an additional 30-day recovery period after 90 days of treatment. Body weight, liver weight, and hepatic microsomal enzyme activity were measured. Liver-to-body weight ratios were increased 12−16% over controls for the rats treated at 10 mg/kg/day. Liver enzyme activities were 1.4- to 3-fold that of controls for the same group. Full recovery to baseline enzyme activity was observed after the 30-day recovery period; liver-to-body weight ratios were only 7% greater than the control values. Similar results were reported by Carlson (1979) in a follow-up study.*
>
> *Although no overt liver toxicity was demonstrated for TBB, bromobenzene mixtures at higher doses cause acute hepatic necrosis. The mechanism of bromobenzene toxicity has been studied in detail and involves conversion of the parent compound to toxic intermediates by hepatic microsomal enzymes. Induction of these enzymes can potentiate the toxicity of bromobenzenes and other similarly-activated compounds.*
>
> *The uncertainty factor includes factors for interspecies variability, subchronic-to-chronic exposure duration extrapolation, and intrahuman variability.*

Low confidence levels were assigned to both the study and the database because of the lack of adequate toxicity parameters in the critical study, the lack of chronic toxicity data in general, and a degree of uncertainty about the significance of the effects. Low confidence in the RfD follows.

An updated literature search from 2004 to 2013 was performed for 1,2,4-tribromobenzene and one additional subchronic study was identified. Dodd et al. (2012) treated 10 male Sprague-Dawley rats/dose with 1,2,4-tribromobenzene via gavage for either 5 days, 2, 4, or 13 weeks at 0, 2.5, 5, 10, 25, or 75 mg/kg-day. This study only focused on liver effects and did not evaluate any other possible endpoints of toxicity. The study authors identified a no-observed-adverse-effect level (NOAEL) of 5 mg/kg-day based on increased liver weight and increased incidence of hepatocyte hypertrophy. This coincides with the NOAEL of 5 mg/kg-day identified from Carlson and Tardiff (1977) which is used as the point of departure (POD) in the IRIS assessment of 1,2,4-tribromobenzene.

ORAL TOXICITY VALUES

Derivation of Screening Subchronic Provisional Reference Dose (Screening Subchronic p-RfD)

Based on the overall surrogate approach presented in this PPRTV assessment, the Integrated Risk Information System (IRIS) POD for 1,2,4-tribromobenzene (a NOAEL of 5 mg/kg-day) established in 1993 and based on increased relative liver weight (liver-to-body-weight ratio) and hepatic microsomal enzyme induction in male Sprague-Dawley rats from a 90-day study (Carlson and Tardiff, 1977) is recommended as the surrogate POD for 1,3-dibromobenzene. No duration adjustment was performed for the doses reported in the principal study because Carlson and Tardiff (1977) did not report the treatment schedule used. The data are not amenable to BMD modeling; thus, calculation of a BMDL is precluded.

As described in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the POD from the 90-day 1,2,4-tribromobenzene study by Carlson and Tardiff (1977) in rats is converted to a human equivalent dose (HED) through an application of 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 BW_a of 0.25 kg for rats and a default BW_h of 70 kg for humans (U.S. EPA, 1988c), the resulting DAF is 0.24. Applying this DAF to the NOAEL identified in the rat study yields a surrogate POD_{HED} as follows:

$$\begin{aligned} \text{Surrogate POD}_{HED} &= \text{NOAEL (mg/kg-day)} \times \text{DAF} \\ &= \text{NOAEL (mg/kg-day)} \times 0.24 \\ &= 5 \text{ mg/kg-day} \times 0.24 \\ &= 1.2 \text{ mg/kg-day} \end{aligned}$$

As described by Wang et al. (2012), the uncertainty factors typically applied to the chemical of concern are the same as those applied to the surrogate unless additional information is available. The IRIS assessment for the 1,2,4-tribromobenzene surrogate was performed prior to the recommended use of $BW^{3/4}$ scaling for noncancer effects (U.S. EPA, 2011b) and prior to the application of a database uncertainty factor (UF_D). Thus, the composite UF (UF_C) for 1,3-dibromobenzene has been adjusted and differs from that of the surrogate. To derive a screening subchronic p-RfD for 1,3-dibromobenzene, a UF_C of 300 has been applied to the surrogate POD_{HED}. The screening subchronic p-RfD for 1,3-dibromobenzene is derived as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= \text{Surrogate POD}_{HED} \div UF_C \\ &= 1.2 \text{ mg/kg-day} \div 300 \\ &= \mathbf{4 \times 10^{-3} \text{ mg/kg-day}} \end{aligned}$$

Table A.4 summarizes the uncertainty factors for the screening subchronic p-RfD for 1,3-dibromobenzene.

Table A-4. Uncertainty Factors for the Screening Subchronic p-RfD for 1,3-Dibromobenzene

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following oral 1,3-dibromobenzene exposure. The toxicokinetic uncertainty has been accounted for by calculation of a HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies via the oral route.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1,3-dibromobenzene in humans.
UF_L	1	A UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 has been applied because a subchronic-duration study was selected as the principal study.
UF_C	300	Composite UF.

Derivation of Screening Chronic Provisional Reference Dose (Screening Chronic p-RfD)

The surrogate POD used to derive a screening chronic p-RfD is the same as the surrogate POD (POD_{HED} = 1.2 mg/kg-day) used to derive the screening subchronic p-RfD above. To

derive a screening chronic p-RfD, a UF_C of 3,000 has been applied to the surrogate POD_{HED}. The screening chronic p-RfD for 1,3-dibromobenzene is derived as follows:

Screening Chronic p-RfD = Surrogate $POD_{HED} \div UF_C$
= 1.2 mg/kg-day ÷ 3,000
= **4×10^{-4} mg/kg-day**

Table A.5 summarizes the uncertainty factors for the screening chronic p-RfD for 1,3-dibromobenzene.

Table A.5. Uncertainty Factors for the Screening Chronic p-RfD for 1,3-Dibromobenzene

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) has been applied to account for uncertainty in characterizing the toxicodynamic differences between rats and humans following oral 1,3-dibromobenzene exposure. The toxicokinetic uncertainty has been accounted for by calculation of a HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 has been applied because there are no acceptable two-generation reproductive toxicity or developmental toxicity studies via the oral route.
UF_H	10	A UF_H of 10 has been applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1,3-dibromobenzene in humans.
UF_L	1	A UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	10	A UF_S of 10 has been applied to account for the extrapolation from less than chronic exposure because no chronic-duration toxicity studies are available to evaluate chronic systemic toxicity.
UF_C	3,000	Composite UF.

APPENDIX B. DATA TABLES

No data tables are presented.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

There are no BMD modeling outputs.

APPENDIX D. REFERENCES

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