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Provisional Peer-Reviewed Toxicity Values for

1-Bromo-3-fluorobenzene
(CASRN 1073-06-9)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

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
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
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	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

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1-BROMO-3-FLUOROBENZENE (CASRN 1073-06-9)

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 at least two National Center for Environment Assessment (NCEA) scientists and an independent external peer review by at least 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.

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

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 EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

1-Bromo-3-fluorobenzene, CASRN 1073-06-9, belongs to the class of compounds known as aryl halides. 1-Bromo-3-fluorobenzene is used as an intermediate in agrochemical production (PTG, 2013). It is listed on U.S. EPA's Toxic Substances Control Act's public inventory (U.S. EPA, 2017b) and Canada's Non-Domestic Substances List (NDSL) (Environment Canada, 2015) but it is not registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2017).

1-Bromo-3-fluorobenzene can be produced in a stepwise process. First, an isomeric mixture of bromofluorobenzenes is produced by the bromination of fluorobenzene. The isomers are then reacted with benzene in the presence of a Friedel-Crafts catalyst to isolate the meta-substituted 1-bromo-3-fluorobenzene (Tolgyesi and Ontario, 1967).

The empirical formula for 1-bromo-3-fluorobenzene is C_6H_4BrF. The chemical structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of 1-bromo-3-fluorobenzene. The compound is a flammable, colorless liquid at room temperature (NOAA, 2015) with an estimated high vapor pressure that indicates it is likely to exist as a vapor in the atmosphere. Given its vapor pressure and estimated Henry's law constant, it is likely to volatilize from either dry or moist soil surfaces, and from water surfaces. The estimated low water solubility and moderate soil adsorption coefficient for 1-bromo-3-fluorobenzene indicate that it will have low to moderate potential to leach to groundwater or undergo runoff after a rain event. Volatilization to the atmosphere is likely to be the main transport pathway. 1-Bromo-3-fluorobenzene was shown to undergo photohydrolysis in dilute aqueous solution with a measured rate constant of 0.016/minute, which corresponds to a half-life of 44 minutes, when irradiated with ultraviolet light at wavelengths ranging from 250−350 nm (Peljnenburg et al., 1992).

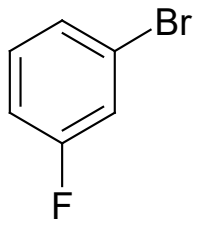


Figure 1. 1-Bromo-3-fluorobenzene Structure

Table 1. Physicochemical Properties of 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	150[a]
Melting point (°C)	−8[b]
Density (g/cm^3)	1.594[c]
Vapor pressure (mm Hg at 25°C)	4.0 (estimated)[a]
pH (unitless)	NV
pKa (unitless)	NV
Solubility in water (mg/L at 25°C)	378[a]
Octanol-water partition coefficient (log K_{ow})	2.92[a]
Henry's law constant (atm-m^3/mol at 25°C)	6.3×10^{-3} (estimated)[a]
Soil adsorption coefficient K_{oc} (L/kg)	380 (estimated)[a]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	1.5×10^{-12} (estimated)[a]
Atmospheric half-life (d)	7 (estimated)[a]
Relative vapor density (air = 1)	6.03[d]
Molecular weight (g/mol)	175[a]
Flash point (°C)	46[c]

[a]U.S. EPA (2012b).
[b]Alfa Aesar (2017).
[c]Sigma-Aldrich (2017).
[d]Fisher Scientific (2008).

NV = not available.

No toxicity values for 1-bromo-3-fluorobenzene are available from U.S. EPA or other agencies/organizations, as shown in Table 2.

Table 2. Summary of Available Toxicity Values for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)

Source[a]	Value	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2017a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2017)
IPCS	NV	NA	IPCS (2017); WHO (2017)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2017a); Cal/EPA (2017b)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2016)
Cancer			
IRIS	NV	NA	U.S. EPA (2017a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2017)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2017a); Cal/EPA (2017b)
ACGIH	NV	NA	ACGIH (2016)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; 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.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in November 2015 and updated in June 2017 for studies relevant to the derivation of provisional toxicity values for 1-bromo-3-fluorobenzene (CASRN 1073-06-9). 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 (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related data: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (Cal/EPA), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), and Occupational Safety and Health Administration (OSHA).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

As shown in Tables 3A and 3B, there are no potentially relevant short-term-, subchronic-, or chronic-duration studies or developmental or reproductive toxicity studies of 1-bromo-3-fluorobenzene in humans or animals exposed by oral or inhalation routes. In addition, no data on acute toxicity or genotoxicity were identified for this compound.

Table 3A. Summary of Potentially Relevant Noncancer Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)							
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**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							

LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level.

Table 3B. Summary of Potentially Relevant Cancer Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)					
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.

A single study examining the Phase II metabolism of 1-bromo-3-fluorobenzene (as part of a series of 3-halofluorobenzenes) was identified. Soffers et al. (1994) administered a single gavage dose of 500 µmol/kg 1-bromo-3-fluorobenzene (purity not reported) in olive oil to male Wistar rats and collected urine for the first 24 hours after dosing. Urine samples were enzymatically treated to hydrolyze sulfate and glucuronide conjugates, and then analyzed by ^{19}F nuclear magnetic resonance (NMR). Urinary recovery of fluorine was 78% of the administered dose after exposure to 1-bromo-3-fluorobenzene. Metabolites identified in the urine included the sulfate and glucuronide conjugates of 4-bromo-2-fluorophenol; the sulfate conjugate represented ~8% of the total fluorine intensity in the urine, while the glucuronide represented <2%. The primary metabolites in the urine (which apparently represented ~90% of the excreted fluorine) were not identified, but the authors suggested that these most likely were products of glutathione (GSH) conjugation pathways (Soffers et al., 1994). In vitro experiments in which rat liver microsomes were incubated with 1-bromo-3-fluorobenzene (0.5, 1.0, or 2.0 mM) showed dose-dependent formation of 4-bromo-2-fluorophenol (Soffers et al., 1994).

DERIVATION OF PROVISIONAL VALUES

The lack of repeated-dose toxicity data in humans or animals precludes derivation of subchronic or chronic provisional reference doses (p-RfDs) or provisional reference concentrations (p-RfCs) for 1-bromo-3-fluorobenzene. However, screening subchronic and chronic p-RfDs and a screening subchronic p-RfC are derived based on data for structurally similar compounds (see Appendix A).

Tables 4 and 5 present summaries of noncancer and cancer references values, respectively.

Table 4. Summary of Noncancer Reference Values for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)

Toxicity Type (units)	Species/Sex	Critical Effects	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat/M	Increased relative liver weight (liver:body-weight ratio) and hepatic microsomal enzyme induction	3×10^{-3}	NOAEL (HED)	1 (based on surrogate)	300	Carlson and Tardiff (1977)
Screening chronic p-RfD (mg/kg-d)	Rat/M	Increased relative liver weight (liver:body-weight ratio) and hepatic microsomal enzyme induction	3×10^{-4}	NOAEL (HED)	1 (based on surrogate)	3,000	Carlson and Tardiff (1977)
Screening subchronic p-RfC (mg/m^3)	Rat/M	Centrilobular hepatocyte enlargement	3×10^{-2}	$BMCL_{10}$ (HEC)	8.9 (based on surrogate)	300	Safepharm Labs, Ltd. (1993) as cited in U.S. EPA (2011b)
Chronic p-RfC (mg/m^3)	NDr						

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; HED = human equivalent dose; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; POD = point of departure; UF_C = composite uncertainty factor.

Table 5. Summary of Cancer Reference Values for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)

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

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

DERIVATION OF ORAL REFERENCE DOSES

There are no relevant data on the effects of 1-bromo-3-fluorobenzene in humans or animals exposed orally. However, screening subchronic and chronic p-RfD values are derived based on data for structurally similar compounds (see Appendix A).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

There are no relevant data on the effects of 1-bromo-3-fluorobenzene in humans or animals exposed by inhalation. However, a screening subchronic p-RfC value is derived based on data for structurally similar compounds (see Appendix A).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No relevant data are available. Under the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is *"Inadequate Information to Assess the Carcinogenic Potential"* of 1-bromo-3-fluorobenzene following both oral and inhalation exposure as shown in Table 6.

Table 6. Cancer WOE Descriptor for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human carcinogenicity data identified to support this descriptor.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no animal carcinogenicity studies identified to support this descriptor.
"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-3-fluorobenzene in humans or animals following oral or inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

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

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of quantitative estimates of cancer risk for 1-bromo-3-fluorobenzene is precluded by the absence of carcinogenicity data.

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-bromo-3-fluorobenzene. However, 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 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.

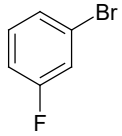
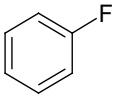
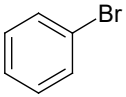
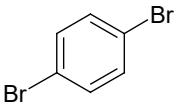
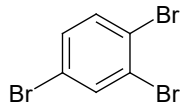
APPLICATION OF AN ALTERNATIVE SURROGATE APPROACH

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. 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)

Initial surrogate searches focused on identifying structurally similar chemicals with oral and/or inhalation toxicity values from the Integrated Risk Information System (IRIS), PPRTV, Agency for Toxic Substances and Disease Registry (ATSDR), or California Environmental Protection Agency (Cal/EPA) databases to take advantage of the well-characterized chemical-class information. This search did not identify any candidate analogs containing both fluorine and bromine substituents on a benzene ring, as in the case of the target chemical (including potential surrogates containing other substituents on the ring such as a methyl group); the available analogs contain either fluorine or bromine. Under Wang et al. (2012), structural similarity for analogs is typically evaluated using U.S. EPA's DSSTox database (DSSTox, 2016) and the National Library of Medicine's (NLM's) ChemIDplus database (ChemIDplus, 2017). At the time this PPRTV assessment was developed, however, DSSTox was not available to the public. In lieu of DSSTox scores, the Organisation for Economic Co-operation and Development (OECD) toolbox was used to calculate structural similarity using the Tanimoto method (the same quantitative method used by ChemIDplus and DSSTox). Table A-1 summarizes the analogs' physicochemical properties and similarity scores.

Table A-1. Comparison of Physicochemical Properties for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Analogs[a]

	1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
Structure					
CASRN	1073-06-9	462-06-6	108-86-1	106-37-6	615-54-3
Molecular weight	175	96	157	236	315
DSSTox similarity score (%)[b]	100	NV	NV	NV	NV
ChemIDplus similarity score (%)[c]	100	<50	<50	<50	52
OECD toolbox similarity score (%)[d]	100	33	33	26	26
Melting point (°C)	−8	−42.2	−30.6	87.3	44.5
Boiling point (°C)	150	84.7	156	218.5	275
Vapor pressure (mm Hg at 25°C)	4.0 (estimated)[b]	7.72×10^{1}	4.18	5.75×10^{-2}	4.8×10^{-3} (estimated)
Henry's law constant (atm-m^3/mole at 25°C)	6.3×10^{-3} (estimated)[b]	6.25×10^{-3}	2.47×10^{-3}	8.9×10^{-4}	3.9×10^{-4} (estimated)
Water solubility (mg/L)	378	1,540 (at 30°C)	446 (at 30°C)	20	4.9
Log K_{ow}	2.92	2.27	2.99	3.79	4.66 (estimated)
pKa	NA	NA	NA	NA	NA

[a]Data were gathered from PHYSPROP for each respective compound unless otherwise specified (U.S. EPA, 2012b).
[b]DSSTox (2016).
[c]ChemIDplus Advanced, similarity scores (ChemIDplus, 2017).
[d]OECD (2016).

NA = not applicable; NV = not available; OECD = Organisation for Economic Co-operation and Development.

Physicochemical properties indicate that 1-bromo-3-fluorobenzene and all candidate surrogates are likely to be bioavailable by oral and inhalation routes (based on water solubility and vapor pressure). In addition, relatively high octanol-water partition coefficient (log K_{ow}) values suggest that, after systemic absorption, these compounds will exhibit an affinity for adipose tissue. The target and candidate surrogate compounds are all neutral compounds and will not ionize. Although the di- and tribromobenzenes are solids at room temperature, the relatively minor differences in physicochemical properties between the candidate surrogates and the target compound does not preclude any of the surrogates from further consideration.

ChemIDplus similarity scores for the candidate surrogates were <50%, except for 1,2,4-tribromobenzene (52%). Low similarity scores (26−33%) were obtained using the OECD toolbox. The low similarity scores for the candidate surrogates are likely related to the limited number of structural descriptors available for these compounds. Structural similarity metrics use a variety of structural descriptors to calculate similarity (although the nature of the descriptors may vary across different tools). Similarity scores calculated for compounds with few structural descriptors will be disproportionately influenced by changes in, or absence of, a single descriptor, while these same changes have relatively lower impact on similarity scores for compounds with many descriptors. Thus, similarity scores may be of limited use when comparing surrogates with relatively simple structures such as those evaluated in this assessment.

Despite the low similarity scores, examination of the structural features demonstrates that the available candidate surrogates all share a benzene ring with one or more bromine or fluorine substituents. Moreover, they all contain at least one set of adjacent hydrogen atoms on the aromatic ring which, as indicated in the subsequent section, suggests that they all have the potential to follow the same first step in their metabolic transformation. Thus, all of these analogs may be considered potential structural surrogates.

Metabolic Surrogates

Oral toxicokinetic data are available for 1-bromo-3-fluorobenzene and the candidate surrogates (see Table A-2). There were no data on inhalation toxicokinetics of 1-bromo-3-fluorobenzene or the candidate surrogate compounds.

Table A-2. Comparison of Available ADME Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

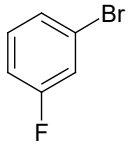
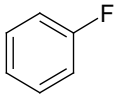
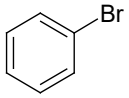
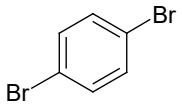
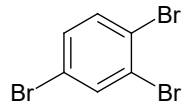
1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
CASRN 1073-06-9	CASRN 462-06-6	CASRN 108-86-1	CASRN 106-37-6	CASRN 615-54-3
				
Absorption				
78% in rats exposed orally based on urinary excretion in the first 24 hr postdosing	83% in rats exposed orally based on urinary excretion in the first 24 hr postdosing	60−70% in rats, mice, and rabbits exposed orally (based on elimination of metabolites via urine)	24−40% in rats, mice, and rabbits exposed orally (based on elimination of metabolites via urine)	ND
Distribution				
ND	ND	In rats exposed i.p., highest bromobenzene concentrations in: • Fat • Liver, kidney, brain, muscle, heart, blood, seminal fluid Bromophenol metabolites highest in kidney, lungs, and blood	In rats exposed i.p., highest 1,4-dibromobenzene concentrations in: • Fat • Muscle • Adrenals • Sciatic nerve	ND

Table A-2. Comparison of Available ADME Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
Metabolites				
Rats exposed orally Urinary (% of urinary fluorine): • Unidentified metabolites (~90%) • 4-Bromo-2-fluorophenyl-sulfate (~8%) • 4-Bromo-2-fluorophenyl-glucuronide (<2%) Study authors suggested that the unidentified metabolites may be products of GSH conjugation pathways. Rat liver microsomes • 4-Bromo-2-fluorophenol	Rats exposed orally Urinary (as sulfate and glucuronide conjugates, in descending order of abundance): • Phenol, 4-fluoro- • Phenol, 2-fluoro- • Phenol, 3-fluoro- • Unidentified metabolites • 1,2-Benzenediol, 4-fluoro- • 1,2-Benzenediol, 3-fluoro- Study authors suggested that the unidentified metabolites may be mercapturic acids or other sulfur-containing metabolites Rabbits exposed orally Urinary (% dose): • Sulfate conjugate (21%) • Glucuronide conjugate (10%) • Mercapturic acid (1.6%)	Rats, mice, and rabbits exposed orally Urinary (% dose): • 4-Bromophenyl mercapturic acid (35−38%) • Phenol, 3-bromo- (9−23%) • Phenol, 4-bromo- (3−13%) • Phenol, 2-bromo- (3−12%) • Bromobenzene (1.2%) Similar in rabbits; higher 2-bromophenol (12.1%) and lower 3- and 4-bromophenol (8.8 and 3.1%, respectively) in mice Rabbits exposed orally Urinary (% dose): • Sulfate conjugate (37%) • Glucuronide conjugate (40%) • Mercapturic acid (21%) 28% of the sulfate and glucuronide conjugates consisted of catechol derivatives Rabbits exposed i.p. Urinary (ether extractable metabolites): • Phenol, 4-bromo- • Phenol, 3-bromo- Rats exposed i.v. or i.p. Urinary (% urinary radioactivity): • Bromophenyl mercapturic acid (48−70%) • Phenol, 4-bromo- (18−37%) • 1,2-Benzenediol, bromo- (4−6%)	Rats and mice exposed orally Urinary (% dose): • Phenol, 2,5-dibromo- (23−39%) • Phenol, 3-bromo- (0.6−1.0%) • Phenol, 2-bromo- (0.2−0.3%) Rabbits exposed i.p. Urinary (ether extractable metabolites): • Phenol, 2,4-dibromo- • Phenol, 2,5-dibromo- Rats exposed i.p. Urinary (% urinary radioactivity): • Phenol, 2,5-dibromo- (84%) • 1,4-dibromobenzene (5.3%) • Benzenethiol, 2,5-dibromo- (4.6%) • Bromophenol (isomer not identified; 1.9%) • Methylated benzenethiol, 2,5-dibromo- (0.8%) Two additional metabolites containing ethylmercapto groups and free mercapto groups in addition to methyl mercapto group already on ring (2.6 and 0.5%)	Rats exposed orally ND Rabbits exposed i.p. Urinary (ether extractable metabolites): • Phenol, 2,4,5-tribromo- • Phenol, 2,4,6-tribromo- Third tribromophenol not identified

Table A-2. Comparison of Available ADME Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
Continued:	Continued: 12% of the sulfate and glucuronide conjugates consisted of catechol derivatives	Continued: • Bromophenyldihydrodiol (4%) • Phenol, 2-bromo- (3−4%) PB-induced rats exposed i.p. Urinary (% ether extractable metabolites): • Phenol, 3-bromo- (44%) • Phenol, 4-bromo- (38%) • 1,2-Benzenediol, 4-bromo- (18%) • Dihydrodiol (4%) ~57% of the urinary radioactivity was not ether extractable; the study authors indicated that this fraction likely consisted of mercapturic acids and premercapturic acids. PB-induced rat liver microsomes (% total) • Phenol, 4-bromo- (58%) • 1,2-Benzenendiol, 4-bromo- (24%) • 3,5-Cyclohexadiene-1,2-diol, 4-bromo- (17%) PB-induced rat hepatocytes (% total) • 3,5-Cyclohexadiene-1,2-diol, 4-bromo- (25−55%) • Phenol, 4-bromo- (12−60%) • 1,2-Benzenediol, 4-bromo- (8−22%) • 3,5-Cyclohexadiene-1,2-diol, 3-bromo- (3−12%) • Phenol, 3-bromo- (3−4%)	Continued:	Continued:

Table A-2. Comparison of Available ADME Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
Excretory pattern				
Rats exposed orally (% dose in 24 hr): • Urine: 78% • Feces: ND	Rats exposed orally (% dose in 24 hr): • Urine: 83% • Feces: ND	Rats, rabbits, and mice exposed orally (% dose): • Urine: 60−71% • Feces: ND	Rats and mice exposed orally (% dose): • Urine: 24−40% • Feces: ND Rats exposed i.p. (% dose in 72 hr): • Urine: 30% • Feces: 3.6%	ND
Sources				
Soffers et al. (1994)	Koerts et al. (1997); Azouz et al. (1953, 1952)	Miller et al. (1990); Ogino (1984); Ruzo et al. (1976); Zampaglione et al. (1973); Azouz et al. (1953, 1952)	Szymańska et al. (2002); Ogino (1984); Ruzo et al. (1976)	Ruzo et al. (1976)

ADME = absorption, distribution, metabolism, and excretion; GSH = glutathione; i.p. = intraperitoneal; i.v. = intravenous; ND = no data; PB = phenobarbital.

After oral exposure, 78% of 1-bromo-3-fluorobenzene, 60−70% of bromobenzene, and 24−40% of 1,4-dibromobenzene is absorbed (Soffers et al., 1994; Ogino, 1984; Ruzo et al., 1976); no data are available on the other candidates. Studies examining systemic distribution in rats after intraperitoneal (i.p.) exposure indicate that bromobenzene and 1,4-dibromobenzene are both deposited at highest concentrations in the fat (Ruzo et al., 1976). No information on the distribution of 1-bromo-3-fluorobenzene or the other candidate surrogates was located; however, given that 1-bromo-3-fluorobenzene has a lower log K_{ow} value and higher water solubility than the di- and tribromobenzenes, its partitioning to fat is expected to be lower.

After oral exposure, 1-bromo-3-fluorobenzene, fluorobenzene, and bromobenzene are primarily excreted via the urine; urinary excretion is also the primary pathway after i.p. exposure to 1,4-dibromobenzene. Excretion information is not available for 1,2,4-tribromobenzene.

1-Bromo-3-fluorobenzene and all of the candidate surrogates are initially metabolized via cytochrome P450 (CYP450) isozymes to phenolic derivatives. The phenolic compounds may be excreted unchanged, further hydroxylated to yield benzenediols (catechols) and/or quinones, or conjugated with sulfate or glucuronide. Available data suggest that, for fluorobenzene, sulfate and glucuronide conjugation play major roles in the Phase II metabolism (Koerts et al., 1997), while glutathione (GSH) conjugation of electrophilic intermediates appears to play a minor role (Azouz et al., 1953, 1952). In contrast, GSH conjugation represents a significant pathway for bromobenzene [reviewed by Lau and Monks (1997)]. Soffers et al. (1994) hypothesized that products of GSH conjugates might account for the unidentified metabolites (representing ~90% of total urinary fluorine) in their study of 1-bromo-3-fluorobenzene, but these metabolites cannot be definitively identified (see Figure A-1). Conjugation reactions for metabolites of 1,4-dibromobenzene and 1,2,4-tribromobenzene have not been well established; however, data showing limited excretion of mercapturic acids (formed via GSH conjugates) after exposure to these compounds (discussed further below) suggest a small role for GSH conjugation.

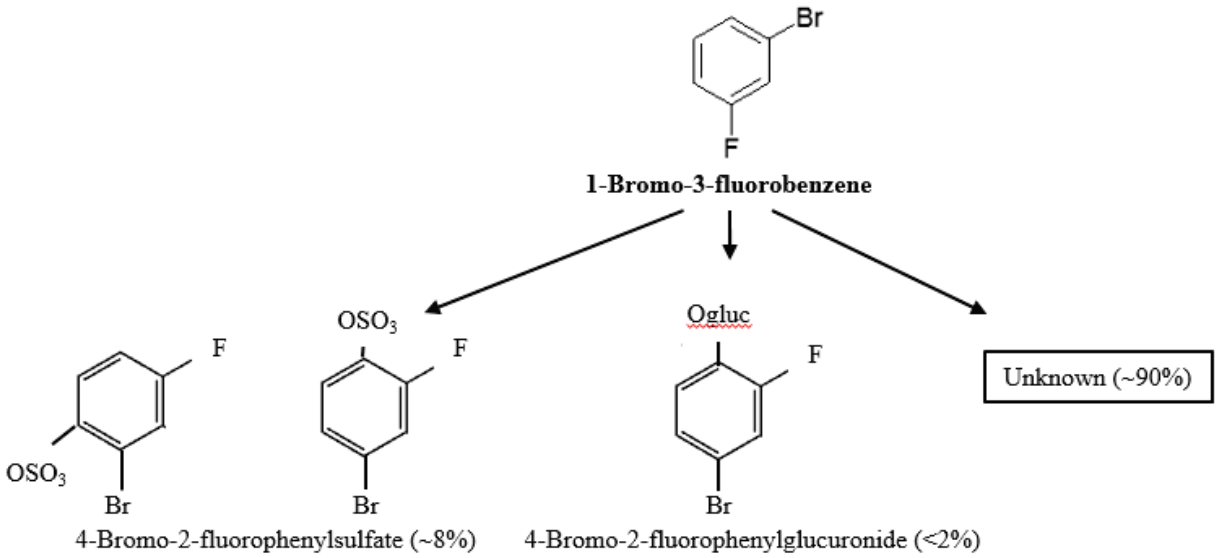


Figure A-1. Putative Metabolism of 1-Bromo-3-fluorobenzene [based on Soffers et al. (1994)]

Bromobenzene metabolites are largely excreted as mercapturic acids (Miller et al., 1990; Ogino, 1984; Zampaglione et al., 1973), primarily 4-bromophenyl mercapturic acid resulting from GSH conjugation of a 3,4-epoxide intermediate (U.S. EPA, 2009). In addition, as noted above, Soffers et al. (1994) suggested that the primary metabolites of 1-bromo-3-fluorobenzene, which were not definitively identified, might be products of GSH conjugation (i.e., mercapturic acids). In contrast, mercapturic or premercapturic acids, when they were reported, occurred in smaller quantities (<10% of administered dose when quantified) in the urine of animals exposed to fluorobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene. In a comparative metabolism study (Ogino, 1984), mercapturic acid derivatives were the major urinary metabolites of bromobenzene (35−38% of dose) in rats, mice, and rabbits exposed orally, while no mercapturic acid derivatives were recovered after exposure of rats or mice to 1,3- or 1,4-dibromobenzene. 1,2,4-Tribromobenzene was not tested in the study by Ogino (1984); however, a mercapturic acid derivative representing a small fraction of the administered dose was measured in the urine of rats exposed to its isomer, 1,3,5-tribromobenzene. No mercapturic acids were observed in the urine of rabbits exposed i.p. to bromobenzene, 1,4-dibromobenzene, or 1,2,4-tribromobenzene (Ruzo et al., 1976); however, it is not clear that the analytical methods used by the study authors would have identified these metabolites. Mercapturic acid derivatives of 1,4-dibromobenzene were tentatively identified in rat urine after i.p. exposure (Szymańska et al., 2002), but these compounds constituted a small fraction of the excreted metabolites. In an early study, Azouz et al. (1952) observed a small quantity of mercapturic acid metabolites (1.6% of dose) in the urine of rabbits exposed orally to fluorobenzene; by comparison, 21% of the administered dose of bromobenzene was excreted as mercapturic acids in this study. Koerts et al. (1997) hypothesized that unidentified metabolites detected in small quantities in the urine of rats exposed to fluorobenzene might be mercapturic acids or other sulfur-containing metabolites, but these metabolites cannot be definitively identified.

Phenolic metabolites that are not conjugated and/or excreted may be further hydroxylated to form benzenediol metabolites and/or reactive quinone intermediates. Benzenediol derivatives have been observed in the urine of rats and rabbits exposed to fluorobenzene and bromobenzene (Koerts et al., 1997; Miller et al., 1990; Zampaglione et al., 1973; Azouz et al., 1953). Hydroxylated phenolic derivatives of 1,4-dibromobenzene and 1,2,4-tribromobenzene are plausible, but have not been reported in available studies (Szymańska et al., 2002; Ogino, 1984; Ruzo et al., 1976). If formed, these metabolites are expected to occur in much lower quantities after exposure to 1,4-dibromobenzene or 1,2,4-tribromobenzene due to steric hindrance exerted by the bromines. Koerts et al. (1997) reported that steric hindrance of CYP450 attack on adjacent ring positions was significant for bromine. Steric hindrance of hydroxylation exerted by para-positioned bromines may explain the lower excretion of 1,4-dibromobenzene compared with 1-bromo-3-fluorobenzene and bromobenzene.

Debromination is an additional metabolic step for the higher brominated compounds. Debromination of 1,4-dibromobenzene or its metabolites was apparent from the detection of small quantities of monobromophenols in the urine of orally exposed mice and rats (Ogino, 1984). While debromination products were not seen in the single study of 1,2,4-tribromobenzene (Ruzo et al., 1976), these products were seen in rats and mice exposed orally to the related compound, 1,3,5-tribromobenzene (Ogino, 1984). Compounds excreted in urine after exposure to 1,3,5-tribromobenzene primarily consisted of the parent compound (14−15% of dose), 2,4,6-tribromophenol (13−14%), 3,5-dibromophenol (11−18%), 2-hydroxy-3,5-dibromothiophenyl-1-methyl (14−19%), 2-hydroxy-3,5-dibromothiophenyl-1-methyloxide (7−9%), and 3,5-dibromophenylmercapturic acid (6−7%) (Ogino, 1984). Thus, for 1,3,5-tribromobenzene, the majority of urinary metabolites had undergone debromination. No evidence for debromination was seen in studies of animals exposed to bromobenzene (Miller et al., 1990; Ogino, 1984; Ruzo et al., 1976; Zampaglione et al., 1973) or 1-bromo-3-fluorobenzene (Soffers et al., 1994).

In summary, the metabolism of 1-bromo-3-fluorobenzene and each of the candidate surrogates begins with ring hydroxylation via CYP450s followed by excretion, sulfate or glucuronide conjugation, or further ring hydroxylation. The higher brominated candidates may also undergo debromination. Data in several species indicate that bromobenzene metabolism to mercapturic acid derivatives likely occurs via an epoxide intermediate that is conjugated with GSH. In addition, sulfate and glucuronide conjugates represented a small quantity of excreted fluorine in the urine of rats exposed to the 1-bromo-3-fluorobenzene target chemical, leading Soffers et al. (1994) to postulate that the primary metabolites might reflect GSH conjugation. Importantly, however, the identity of these metabolites cannot be definitively determined. In contrast, data on fluorobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene do not indicate the formation of significant quantities of mercapturic acid derivatives, suggesting that GSH conjugation of these compounds may be more limited. In light of the common Phase I metabolic pathways, as well as the uncertainties surrounding potential similarities in excreted Phase II metabolites, bromobenzene, fluorobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene are all considered to be reasonable metabolic surrogates.

Toxicity-Like Surrogates

There are no oral toxicity data for 1-bromo-3-fluorobenzene or fluorobenzene. Table A-3 summarizes the available subchronic and chronic oral toxicity values for bromobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene. As the table shows, the liver is the target

organ for all of the brominated candidate surrogates, but kidney effects have also been seen at higher doses of bromobenzene and 1,4-dibromobenzene. While there are no repeated-dose oral data for fluorobenzene, the liver is also the target organ in the single available repeated-exposure study of fluorobenzene administered via inhalation (see Table A-4).

There are no inhalation toxicity data for 1-bromo-3-fluorobenzene. Among the candidate surrogates, only fluorobenzene and bromobenzene have inhalation toxicity values, as shown in Table A-4. As with the oral toxicity data, the available inhalation toxicity data confirm the liver as the primary target organ after exposure to the candidate surrogates.

The mode of action (MOA) for bromobenzene hepatotoxicity has been well studied, and is believed to be mediated by reactive metabolites. U.S. EPA (2009) suggested that some or all of the following intermediates may be involved in bromobenzene-induced hepatotoxicity: the 3,4-epoxide, the 2,3-epoxide, the oxide derivatives of 2- or 3-bromophenol, 4-bromophenol-5,6-oxide, 1,4-benzoquinone, 4-bromo-*o*-quinone, 2-bromo-*p*-quinone, or reactive oxygen species resulting from redox cycling of 2-bromo-*p*-catechol, 4-bromo-*o*-catechol, and/or the bromoquinones. Although there is support for the importance of the 3,4-epoxide, the relative importance of the other metabolites is not known (U.S. EPA, 2009). Molecular mechanisms proposed to be involved include decreased hepatocyte oxygen uptake and adenosine triphosphate (ATP) depletion, altered calcium homeostasis, and GSH depletion (U.S. EPA, 2009). Information on the hepatotoxic MOA(s) for fluorobenzene, 1,4-dibromobenzene, and 1,2,4-tribromobenzene was not available.

As shown in Table A-3, liver pathology findings in studies of the candidate surrogates were remarkably consistent: the critical effect was generally hepatocyte swelling/cytomegaly, associated with increased liver weight and induction of hepatic enzymes; at higher doses of bromobenzene (400 mg/kg-day) and 1,2,4-tribromobenzene (25 mg/kg-day), hepatocyte vacuolation and necrosis were reported in rats. At higher doses of bromobenzene and 1,4-dibromobenzene (100−500 mg/kg-day), renal effects were seen; available studies of 1,2,4-tribromobenzene (Dodd et al., 2012; Carlson and Tardiff, 1977) did not evaluate potential kidney effects.

In summary, all of the structurally related candidate surrogates exhibit remarkably similar acute toxicity potencies, target organ toxicity, effect levels (human equivalent doses [HEDs]) for repeated-dose oral toxicity, and resultant histopathological lesions, supporting the inference that 1-bromo-3-fluorobenzene is hepatotoxic too. However, in the absence of repeated-exposure toxicity data for 1-bromo-3-fluorobenzene, there is no information with which to identify or rule out candidate surrogates based on toxicity comparisons.

Table A-3. Comparison of Available Subchronic and Chronic Oral Toxicity Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

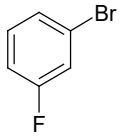
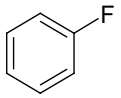
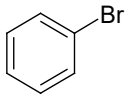
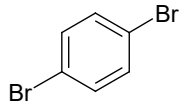
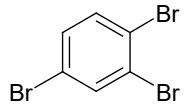
	1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
CASRN	460-00-4	462-06-6	108-86-1	106-37-6	615-54-3
Structure					
POD (mg/kg-d)	NA	NA	24.1	10	5
POD (HED) mg/kg-d[a]	NA	NA	3.51[b]	2[c]	1[c]
POD type	NA	NA	$BMDL_{10}$	NOAEL	NOAEL
Subchronic UF_C	NA	NA	1,000 ($UF_A \times UF_D \times UF_H$)	NA	NA
Subchronic RfD (mg/kg-d)	NA	NA	2×10^2	NA	NA
Chronic UF_C	NA	NA	3,000 ($UF_A \times UF_D \times UF_H \times UF_S$)	1,000 ($UF_A \times UF_H \times UF_S$)	1,000 ($UF_A \times UF_H \times UF_S$)
Chronic RfD (mg/kg-d)	NA	NA	8×10^{-3}	1×10^{-2}	5×10^{-3}
Critical effects	NA	NA	Hepatocellular cytomegaly	Increased relative liver weight (liver:body-weight ratio) and hepatic microsomal enzyme induction	Increased relative liver weight (liver:body-weight ratio) and hepatic microsomal enzyme induction

Table A-3. Comparison of Available Subchronic and Chronic Oral Toxicity Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

	1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
Other effects	NA	NA	Mortality (600 mg/kg-d) and reduced body weight (≥400 mg/kg-d) in males; increased absolute and relative liver weight (≥50 mg/kg-d); increased serum SDH (≥200 mg/kg-d); additional liver histopathology (necrosis [≥400 mg/kg-d], mineralization [≥400 mg/kg-d], inflammation [600 mg/kg-d]).	NA	NA
Species (strain)	NA	NA	Mouse ($B6C3F_1$)	Rat (S-D)	Rat (S-D)
Duration	NA	NA	90 d	90 d	90 d
Route (method)	NA	NA	Oral (gavage)	Oral (gavage)	Oral (gavage)

Table A-3. Comparison of Available Subchronic and Chronic Oral Toxicity Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

	1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
Notes	NA	NA	In a subchronic-duration rat study, clinical signs included mortality, emaciation, tremors, ataxia, hypoactivity, and ocular discharge (600 mg/kg-d); reduced body weight (≥400 mg/kg-d); increased absolute and relative liver and kidney weights (≥50 mg/kg-d); increased serum enzymes (ALT [400 mg/kg-d], AST [400 mg/kg-d], SDH [100 mg/kg-d]; no dose-response relationship); liver histopathology (cytomegaly [≥200 mg/kg-d], necrosis [≥400 mg/kg-d], mineralization [600 mg/kg-d], inflammation [≥200 mg/kg-d]); and kidney histopathology (brown staining of cytoplasm [400 mg/kg-d]) [NTP (1985b) as cited in U.S. EPA (2009)].	In 28-d rat gavage study published in Japanese with English tables (JECDB, 2015a, b), increased total cholesterol (≥100 mg/kg-d), triglycerides (500 mg/kg-d), bilirubin (≥100 mg/kg-d), BUN (500 mg/kg-d), and GGT (500 mg/kg-d) seen in males; increased total protein, albumin, ALT, total cholesterol, triglycerides seen in females (500 mg/kg-d); decreased prothrombin time (≥20 mg/kg-d) and increased activated partial thromboplastin time (500 mg/kg-d); increased absolute and relative liver and kidney weights (≥100 mg/kg-d); hepatocellular swelling (≥100 mg/kg-d); renal histopathology (eosinophilic bodies in proximal tubule [≥20 mg/kg-d; no dose-response relationship], hyaline droplets in proximal tubular epithelium [≥100 mg/kg-d], dilatation of glomerular capillary [≥100 mg/kg-d]); and vacuolization of mucosal epithelium in small intestine and in cortical cells of adrenal glands (500 mg/kg-d). The study authors identified a NOEL of 4 mg/kg-d. In a combined reproduction/developmental toxicity study (JECDB, 2015a, b), male pup body weight was decreased at 100 mg/kg; there were no other significant findings apart from liver toxicity at 100 mg/kg.	Dodd et al. (2012) published a 13-wk study of 1,2,4-tribromobenzene in rats exposed by gavage; effects included increased liver weight (≥10 mg/kg-d), increased incidence and severity of centrilobular cytoplasmic alteration (≥5 mg/kg-d; not considered to be toxicologically relevant by study authors), hepatocyte hypertrophy (≥10 mg/kg-d), and hepatocyte vacuolation (≥25 mg/kg-d).
Source	NA	NA	NTP (1985b) as cited in U.S. EPA (2009)	Carlson and Tardiff (1977)	Carlson and Tardiff (1977)

Table A-3. Comparison of Available Subchronic and Chronic Oral Toxicity Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

	1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
Acute toxicity					
Rat oral LD_{50} (mg/kg)	2,700	4,399	2,383	ND	ND
Toxicity target	Tremor, changes in motor activity, ataxia, weight loss (Haskell Laboratories, 1985b)	NR (ChemIDplus, 2016b)	Gastrointestinal hypermotility/diarrhea; chromodacryorrhea (ChemIDplus, 2016a)	ND	ND

[a]Following U.S. EPA (2011c) guidance, candidate surrogate PODs were converted to HEDs through the application of a DAF. DAFs are calculated as follows: DAF = ($BW_a^{1/4} \div BW_h^{1/4}$), where BW_a = animal body weight and BW_h = human body weight. For all DAF calculations, a reference human body weight (BW_h) of 70 kg (U.S. EPA, 1988) was used.
[b]DAF was calculated using reference body weight (BW_a) for male $B6C3F_1$ mice following subchronic-duration exposure (U.S. EPA, 1988).
[c]DAF was calculated using reference body weight (BW_a) for male S-D rats following subchronic-duration exposure (U.S. EPA, 1988).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; BUN = blood urea nitrogen; BW = body weight; DAF = dosimetric adjustment factor; GGT = γ-glutamyl transferase; HED = human equivalent dose; LD_{50} = median lethal dose; NA = not applicable; ND = no data; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; NR = not reported; POD = point of departure; RfD = reference dose; S-D = Sprague-Dawley; SDH = sorbitol dehydrogenase; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Table A-4. Comparison of Available Subchronic and Chronic Inhalation Toxicity Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

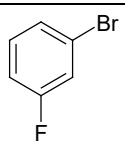
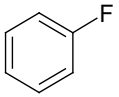
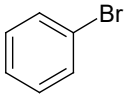
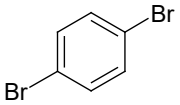
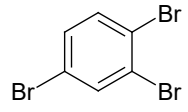
	1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
CASRN	460-00-4	462-06-6	108-86-1	106-37-6	615-54-3
Structure					
POD (mg/m^3)	NA	8.9	63	NA	NA
POD type	NA	$BMCL_{10}$ (HEC)	$BMCL_{10}$ (HEC)	NA	NA
Subchronic UF_C	NA	300 ($UF_A \times UF_D \times UF_H$)	300 ($UF_A \times UF_D \times UF_H$)	NA	NA
Subchronic RfC (mg/m^3)	NA	3×10^{-2} (screening value because principal study is unpublished)	2×10^{-1}	NA	NA
Chronic UF_C	NA	NA	1,000 ($UF_A \times UF_D \times UF_H \times UF_S$)	NA	NA
Chronic RfC (mg/m^3)	NA	NA	6×10^{-2}	NA	NA
Critical effects	NA	Centrilobular hepatocyte enlargement	Hepatocellular cytomegaly	NA	NA
Other effects	NA	Clinical signs (hunched posture and piloerection) (≥375 mg/m^3); increased absolute and relative liver weights (≥375 mg/m^3); increased relative kidney weight (1,560 mg/m^3); eosinophilic droplets in renal proximal tubular epithelium (≥375 mg/m^3); basophilic or dilated tubules (1,560 mg/m^3)	Increased relative liver weight (≥642 mg/m^3)	NA	NA
Species (strain)	NA	Rat (S-D)	Mouse ($B6C3F_1$)	NA	NA
Duration	NA	28 d	90 d	NA	NA
Route (method)	NA	Inhalation (vapor)	Inhalation (vapor)	NA	NA

Table A-4. Comparison of Available Subchronic and Chronic Inhalation Toxicity Data for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9) and Candidate Surrogates

	1-Bromo-3-fluorobenzene	Fluorobenzene	Bromobenzene	1,4-Dibromobenzene	1,2,4-Tribromobenzene
Notes	NA	NA	In a subchronic-duration rat study, renal cortical tubular regeneration without degeneration or necrosis (1,926 mg/m^3) [NTP (1985b) as cited in U.S. EPA (2009)]	NA	NA
Source	NA	Safepharm Labs, Ltd. (1993) as cited in U.S. EPA (2011b)	NTP (1985b) as cited in U.S. EPA (2009)	NA	NA
Acute toxicity					
Rat inhalation LC_{50} (mg/m^3)	18,000 (4 hr)	26,908 (duration not specified)	20,411 (duration not specified)	ND	ND
Toxicity target	Tremor, changes in motor activity, red nasal discharge, darkened eyes, and dyspnea	NR	NR	ND	ND
Source	Haskell Laboratories (1985a)	ChemIDplus (2016b)	ChemIDplus (2016a)	NA	NA

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; LC_{50} = median lethal concentration; NA = not applicable; ND = no data; NR = not reported; POD = point of departure; RfC = reference concentration; S-D = Sprague-Dawley; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Weight-of-Evidence Approach

A WOE approach is used to evaluate information from potential candidate surrogates as described by Wang et al. (2012). Commonalities in structural/physicochemical properties, toxicokinetics, metabolism, toxicity, or MOA between potential surrogates and chemical(s) of concern are identified. Emphasis is given to toxicological and/or toxicokinetic similarity over structural similarity. Surrogate candidates are excluded if they do not have commonality or demonstrate significantly different physicochemical properties and toxicokinetic profiles that set them apart from the pool of potential surrogates and/or chemical(s) of concern. From the remaining potential surrogates, the most appropriate surrogate (most biologically or toxicologically relevant analog chemical) with the highest structural similarity and/or most conservative toxicity value is selected.

Similarity scores for the particular set of aryl halide compounds examined in this PPRTV assessment may be of limited use due to the small number of structural descriptors, so this information was not used to select among the potential candidate surrogates. The available data suggest commonalities in the toxicokinetics of the 1-bromo-3-fluorobenzene target chemical and the four candidate surrogates. Among those compounds with toxicokinetic data, all are absorbed after oral exposure and primarily excreted in the urine. Available in vivo data on the metabolism of 1-bromo-3-fluorobenzene and the candidate surrogates confirmed that the major Phase I pathway for all of the compounds is ring hydroxylation via CYP450s. However, several uncertainties remain regarding the importance of Phase I and Phase II metabolism in toxicity, as well as the specific metabolite(s) that are responsible for the observed liver effects of the brominated benzene compounds (discussed below). Toxicity data on the structurally related candidate surrogates confirm the liver as the target organ for all candidates; however, the lack of repeated-dose toxicity data on 1-bromo-3-fluorobenzene precludes identifying one or more of the candidates as a better "toxicity-like" surrogate (i.e., a surrogate that exhibits similar target organ toxicity as 1-bromo-3-fluorobenzene).

Given the absence of data on the toxicity of 1-bromo-3-fluorobenzene, as well as remaining questions regarding the specific metabolite(s) responsible for the remarkably similar liver effects and effect levels (HEDs) observed across the brominated benzene compounds, it is prudent to select the most health-protective option among the candidate surrogates. Thus, 1,2,4-tribromobenzene was selected as the surrogate for deriving a screening chronic provisional reference dose (p-RfD) for 1-bromo-3-fluorobenzene because its point of departure (POD) (a no-observed-adverse-effect level [NOAEL] [HED] of 1 mg/kg-day) is lower than the PODs (HEDs) for bromobenzene and 1,4-dibromobenzene. A subchronic p-RfD derived by the EPA is not available for 1,2,4-tribromobenzene; however, the study upon which the chronic IRIS RfD was based (Carlson and Tardiff, 1977) was of subchronic duration and could be used to derive a screening subchronic p-RfD for 1-bromo-3-fluorobenzene.

Subchronic and chronic provisional reference concentrations (p-RfCs) are available for bromobenzene, and a subchronic p-RfC is available for fluorobenzene; neither of the other candidate surrogates has an inhalation toxicity value. Thus, based on the WOE approach described above, fluorobenzene is selected as the surrogate for deriving a subchronic p-RfC for 1-bromo-3-fluorobenzene because the subchronic POD (10% benchmark concentration lower confidence limit human equivalent concentration [$BMCL_{10}$ (HEC)] of 8.9 mg/m^3) is lower than the POD for bromobenzene (see Table A-4). The choice of fluorobenzene as the surrogate for deriving a screening subchronic p-RfC precludes the derivation of a screening chronic p-RfC for

1-bromo-3-fluorobenzene, as the only available study of exposure to fluorobenzene is a 28-day study, and it is imprudent to extrapolate a chronic value from a 28-day study in the absence of chronic-duration toxicity information for either the target chemical or the chosen surrogate.

ORAL TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Dose

Based on the overall WOE approach presented in this PPRTV assessment, 1,2,4-tribromobenzene is selected as the surrogate for 1-bromo-3-fluorobenzene for deriving a screening subchronic p-RfD. The study used for the U.S. EPA (2004) chronic RfD for 1,2,4-tribromobenzene is a 90-day rat study and thus suitable for use in deriving a screening subchronic p-RfD. U.S. EPA (2004) described the study as follows:

> *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 critical effects in this study were increased relative liver weight and hepatic microsomal enzyme induction; the NOAEL (HED) of 1 mg/kg-day is used as the POD for 1,2,4-tribromobenzene (U.S. EPA, 2004). U.S. EPA (2014) performed an updated literature search (2004−2013) for 1,2,4-tribromobenzene and identified an additional subchronic-duration study by Dodd et al. (2012). In that study, 10 male Sprague-Dawley (S-D) rats/dose were exposed by gavage (7 days/week) to 1,2,4-tribromobenzene (>97% purity) in corn oil at doses of 0, 2.5, 5, 10, 25, or 75 mg/kg-day for one of the following durations: 5 days, 2 weeks, 4 weeks, or 13 weeks. Apart from mortality and clinical signs of toxicity, the only endpoints evaluated were related to the liver (serum chemistry and liver weight and histopathology). For the 13-week experiment, Dodd et al. (2012) identified a NOAEL of 5 mg/kg-day based on increased liver weight and increased incidence of hepatocyte hypertrophy at 10 mg/kg-day. The NOAEL and lowest-observed-adverse-effect level (LOAEL) from this study are identical to those in the Carlson and Tardiff (1977) study used as the POD in the IRIS assessment of 1,2,4-tribromobenzene, providing support for the continued use of the POD from the Carlson and Tardiff (1977) study. The POD was not adjusted for molecular-weight differences in the derivation of the 1-bromo-3-fluorobenzene provisional toxicity value because the molecular-weight difference between the two compounds is less than twofold (Wang et al., 2012). Furthermore, because the current practice is to only adopt existing PODs, benchmark

dose (BMD) modeling is not performed when applying the alternative surrogate approach (Wang et al., 2012) in PPRTV assessments.

The NOAEL of 5 mg/kg-day is converted to an 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 a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, EPA 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 deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not for portal-of-entry effects.

A validated human physiologically based pharmacokinetic (PBPK) model for 1,2,4-tribromobenzene is not available for use in extrapolating doses from animals to humans. The selected POD is based on increased relative liver weight and hepatic microsomal enzyme induction, which is not a portal-of-entry effect. Therefore, scaling by $BW^{3/4}$ is relevant for deriving HEDs for this effect.

Following U.S. EPA (2011c) guidance, the POD for increased relative liver weight and hepatic microsomal enzyme induction in male rats 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 0.267 kg for S-D rats following subchronic-duration exposure and a reference BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.25. Applying this DAF to the NOAEL of 5 mg/kg-day yields a POD (HED) as follows:

$$\begin{aligned} \text{POD (HED)} &= \text{NOAEL (mg/kg-day)} \times \text{DAF} \\ &= 5 \text{ mg/kg-day} \times 0.25 \\ &= 1 \text{ mg/kg-day} \end{aligned}$$

For the derivation of the screening subchronic p-RfD for 1-bromo-3-fluorobenzene, a composite uncertainty factor (UF_C) of 300 is applied, based on a 3-fold uncertainty factor value for interspecies extrapolation (UF_A, reflecting use of a dosimetric adjustment) and 10-fold uncertainty factor values for both intraspecies variability (UF_H) and database deficiencies (UF_D, reflecting lack of any repeated-exposure toxicity information for 1-bromo-3-fluorobenzene). The screening subchronic p-RfD for 1-bromo-3-fluorobenzene is derived as follows:

Screening Subchronic p-RfD = Surrogate POD (HED) ÷ UF_C
= 1 mg/kg-day ÷ 300
= **3×10^{-3} mg/kg-day**

Table A-5 summarizes the uncertainty factors for the screening subchronic p-RfD for 1-bromo-3-fluorobenzene.

Table A-5. Uncertainty Factors for the Screening Subchronic p-RfD for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)

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 rats and humans following 1-bromo-3-fluorobenzene exposure. The toxicokinetic uncertainty has been accounted for by calculating an 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, 2011c).
UF_D	10	A UF_D of 10 is applied to account for the absence of toxicity data for 1-bromo-3-fluorobenzene.
UF_H	10	A UF_H of 10 is applied for intraspecies 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-3-fluorobenzene 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-duration study was selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

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

1,2,4-Tribromobenzene is also selected as the surrogate for 1-bromo-3-fluorobenzene for derivation of a screening chronic p-RfD. The IRIS chronic RfD for 1,2,4-tribromobenzene was based on the 90-day rat study described in the "Derivation of a Screening Subchronic Provisional Dose" section [Carlson and Tardiff (1977) as cited in U.S. EPA (2014)]. In deriving the screening chronic p-RfD for 1-bromo-3-fluorobenzene, 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 subchronic-to-chronic uncertainty factor (UF_S) of 10 is applied to account for extrapolation from a subchronic to a chronic duration. Thus, the screening chronic p-RfD for 1-bromo-3-fluorobenzene is derived using a UF_C of 3,000.

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

Table A-6 summarizes the uncertainty factors for the screening chronic p-RfD for 1-bromo-3-fluorobenzene.

Table A-6. Uncertainty Factors for the Screening Chronic p-RfD for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)

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 rats and humans following 1-bromo-3-fluorobenzene exposure. The toxicokinetic uncertainty has been accounted for by calculating an 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, 2011c).
UF_D	10	A UF_D of 10 is applied to account for the absence of toxicity data for 1-bromo-3-fluorobenzene.
UF_H	10	A UF_H of 10 is applied for intraspecies 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-3-fluorobenzene 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-duration study was selected as the principal study.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

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.

INHALATION TOXICITY VALUES

Derivation of Screening Subchronic Provisional Reference Concentration

Based on the overall WOE approach presented in this PPRTV assessment, fluorobenzene is selected as the surrogate for 1-bromo-3-fluorobenzene for deriving a screening subchronic p-RfC. The study used for the U.S. EPA (2011b) screening subchronic p-RfC for fluorobenzene was a 28-day rat study. As stated above, the choice of fluorobenzene as the surrogate for deriving a screening subchronic p-RfC precludes deriving a screening chronic p-RfC for 1-bromo-3-fluorobenzene, as the only available study of exposure to fluorobenzene is the aforementioned 28-day study, and it is imprudent to extrapolate a chronic value from a 28-day study in the absence of chronic-duration toxicity information for either the target chemical or the chosen surrogate. U.S. EPA (2011b) described the study as follows:

> *In an unpublished, Good Laboratory Practice (GLP)-certified, subacute inhalation toxicity study, Safepharm Labs, Ltd. (1993) exposed groups of 10 Sprague-Dawley rats (5 per gender) per dose to concentrations of 0.4, 1.5, and 6.0 mg/L fluorobenzene (purity not reported) for 6 hours/day, 7 days a week, for 28 days. The study authors exposed a control group of five animals per sex to air only. The test substance was kept in glass flasks that were held in water baths at 20°C. Compressed air was passed through a water trap and respiratory quality filters before entering the system. The main air supply went through a tangential channel at the top of each exposure chamber. Some of this air was bubbled through the test substance before reaching the exposure chamber, which had a volume of approximately 30 L. Temperature and relative humidity were measured daily, and oxygen levels were measured weekly. Concentration of the test substance was measured daily. Mean atmospheric concentrations of*

fluorobenzene were calculated as 0, 0.37, 1.50, and 6.24 mg/L for the 0-, 0.4-, 1.5-, and 6.0-mg/L-dose groups, respectively. The corresponding exposure concentrations adjusted for continuous exposure in Sprague-Dawley rats are 0, 92.5, 375, and 1560 mg/m^3. During exposure, rats were individually restrained by a polycarbonate tube, and only the nose was exposed to the test atmosphere. Animals were gradually acclimatized to the restraint procedure, and during the study period, they were rotated to account for any variation within the chambers. Rats were monitored throughout each exposure period for changes in appearance, respiration, and behavior.

Clinical observations were noted before each exposure period and after removal from the test chambers. Body weight was measured at Days 0, 7, 14, 21, and 28; food consumption was measured weekly; and water consumption was initially inspected and then measured daily from Day 15 onward. Home cage, open field, and neurotoxicity functional observations were completed the day before initial dosing and then on Days 13 and 14 for females and Days 27 and 28 for males. Hematology and blood chemistry were analyzed prior to necropsy on Day 29; no fasting occurred before samples were taken. Urine samples following 2 weeks postdosing were also collected over a period of approximately 16 hours while rats were kept in metabolism cages. Animals were fasted, with water provided. Hematology measurements and calculations were performed, including hematocrit, hemoglobin, erythrocyte count, total leukocyte count, differential leukocyte count, platelet count, mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration. Blood chemistry calculations or measurements were done for blood urea, total protein, albumin, albumin/globulin ratio, sodium, potassium, chloride, calcium, inorganic phosphorus, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose, and total bilirubin. In urine, researchers measured volume, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, reducing substances, and blood, as well as microscopic examination of sediment. At the study's end, all animals were necropsied; organ weights and relative organ weights were calculated for adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, and testes (including epididymides). Samples of approximately 35 tissues were collected, including adrenals, aorta, bone and bone marrow, brain, cecum, kidneys, larynx, liver, lungs, lymph nodes, mammary gland, muscle, nasal cavity, esophagus, ovaries, pancreas, pituitary, prostate, rectum, salivary glands, sciatic nerve, seminal vesicles, skin, spinal cord, spleen, stomach, testes with epididymides, thymus, thyroid/parathyroid, trachea, urinary bladder, and uterus. All preserved tissues from control and high-dose groups were stained and prepared for microscopic examinations. Lungs, gross lesions, liver, and kidneys from the other dose groups were examined as well. Samples of the sternum bone and the teeth were taken from each rat and pooled to analyze for fluoride.

Data were analyzed to yield group means and standard deviations, where necessary. Absolute and relative organ weights and hematological and blood chemistry parameters were analyzed using one-way analysis of variance incorporating the F-max test for homogeneity variance. Data with heterogeneous

variance were tested using the Kruskal-Wallis analysis of variance and Mann-Whitney U-test.

There was no mortality during the study. Red/brown staining of the exterior body and wetness of the fur were seen in all groups. The study authors concluded that these observations were a result of restraint. Hunched posture and piloerection were seen at the 375- and 1560-mg/m^3 doses. Incidence increased with progression of the study, and by Day 24, all animals exposed to a concentration of 1560 mg/m^3 showed these behaviors. Animals exposed to 375 mg/m^3 showed these signs from Day 21 and continuing through the study. Rats did not show any significant signs of neurotoxicity. There were no significant adverse effects indicated by body weight, food or water consumption, hematology, blood chemistry, or urine composition. Necropsies revealed no treatment-related macroscopic abnormalities. The males exposed to 375 and 1560 mg/m^3 (medium and high exposures) experienced significant ($p < 0.01$) increases in absolute (126−129%) and relative (115−125%) liver weights; relative liver weight was also elevated (113%) in the high-dose female group (see Tables B.1 and B.2). Relative kidney weight was also significantly increased in the high-dose male group. There were no effects detected in the low-dose group. The results of the histopathology examination of tissues from the control and high-dose animals showed irregularities in the high-dose males consisting of hepatocyte enlargement in the centrilobular liver and abnormal quantities of eosinophilic material in the renal proximal tubular epithelium as well as groups of basophilic/dilated tubules (see Table B.3). Other adaptive kidney changes were reported, including hydrocarbon nephropathy in males in all dose groups. Eosinophilic droplets were seen in the tubular epithelium of the kidneys of male rats at the medium and high doses. This was noted as a treatment-related effect, typical of hydrocarbon administration. There were no treatment-related respiratory effects found. Additionally, a substantial increase in fluoride was measured in teeth and sternum samples from all groups (see Table B.4).

Authors established a NOAEL of 0.37-mg/L (NOAEL$_{ADJ}$ of 92.5-mg/m^3) fluorobenzene, based on the lack of treatment-related adverse effects at this dose level. A LOAEL$_{ADJ}$ of 375 mg/m^3 is identified based on increased liver weight (absolute and relative) in male rats, which is supported by an increase in incidence of centrilobular hepatocyte enlargement at the higher dose. Although an increase in relative kidney weight, supported by histopathology changes, was observed in treated animals, the effects were only significant in the high-dose group (1560 mg/m^3), making the liver a more sensitive indicator of exposure. This study is GLP certified, and the procedures were based on guideline recommendations Method B8, Annex V of the European Economic Community (EEC) Commission Directive 84/449/EEC, and Organisation for European Economic Co-operation (OECD) Guideline 412 (OECD, 1997). Despite the lack of peer review and the shortness in exposure duration, the quality of the study supports its use in the derivation of a screening subchronic p-RfC.

The critical effect in this study was centrilobular hepatocyte enlargement (U.S. EPA, 2011b). U.S. EPA (2011b) used a $BMCL_{10}$ (HEC) of 8.9 mg/m^3, obtained by modeling the incidences of centrilobular hepatocyte enlargement in male rats, for the POD. The POD was not adjusted for molecular-weight differences in the derivation of the 1-bromo-3-fluorobenzene provisional toxicity value because the molecular-weight difference between the two compounds is less than twofold (Wang et al., 2012).

In deriving a screening p-RfC for 1-bromo-3-fluorobenzene, a UF_C of 300 is applied, based on a 3-fold uncertainty factor value for UF_A (reflecting use of a dosimetric adjustment) and 10-fold uncertainty factor values for both UF_H and UF_D (reflecting lack of any repeated-exposure toxicity information for 1-bromo-3-fluorobenzene). The screening subchronic p-RfC for 1-bromo-3-fluorobenzene is derived as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfC} &= \text{Surrogate POD (HEC)} \div UF_C \\ &= 8.9\ mg/m^3 \div 300 \\ &= \mathbf{3 \times 10^{-2}\ mg/m^3} \end{aligned}$$

Table A-7 summarizes the uncertainty factors for the screening subchronic p-RfC for 1-bromo-3-fluorobenzene.

Table A-7. Uncertainty Factors for the Screening Subchronic p-RfC for 1-Bromo-3-fluorobenzene (CASRN 1073-06-9)

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 rats and humans following 1-bromo-3-fluorobenzene exposure. The toxicokinetic uncertainty has been accounted for by calculating a HEC.
UF_D	10	A UF_D of 10 is applied to account for the absence of toxicity data for 1-bromo-3-fluorobenzene.
UF_H	10	A UF_H of 10 is applied for intraspecies 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-3-fluorobenzene in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a $BMCL_{10}$.
UF_S	1	A UF_S of 1 is applied because a 28-d study was selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; 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.

APPENDIX B. REFERENCES

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