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Provisional Peer-Reviewed Toxicity Values for

2,2-Difluoropropane
(CASRN 420-45-1)

Superfund Health Risk Technical Support Center
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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 2,2-DIFLUOROPROPANE (CASRN 420-45-1)

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 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

2,2-Difluoropropane, CASRN 420-45-1, belongs to the class of compounds known as aliphatic hydrofluorocarbons (HFCs) (Smart and Fernandez, 2000). Fluorinated hydrocarbons have a variety of uses (e.g., refrigerants), and other haloalkanes (e.g., halothane) are broadly used as anesthetics. This assessment could not identify a specific use for 2,2-difluoropropane. HFCs have been proposed as replacements for chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs) in industry due to their lower ozone depletion potential; however, HFCs have been found to have a greenhouse warming effect (Minor et al., 1995). 2,2-Difluoropropane has a global warming potential (GWP) of 144 (MPCA, 2015). It is not listed on U.S. EPA's Toxic Substances Control Act's public inventory (U.S. EPA, 2016), nor is it registered with Europe's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) program (ECHA, 2017). 2,2-Difluoropropane has been produced by the fluorination of 2,2-dichloropropane with antimony trifluoride (Minor et al., 1995).

The empirical formula for 2,2-difluoropropane is $C_3H_6F_2$ (see Figure 1). Table 1 summarizes the physicochemical properties of 2,2-difluoropropane. 2,2-Difluoropropane is a highly flammable, compressed liquefied gas at room temperature (Apollo Scientific, 2013). 2,2-Difluoropropane's estimated high vapor pressure indicates that it will exist solely as a gas in the atmosphere. Given its vapor pressure and high Henry's law constant, 2,2-difluoropropane is likely to volatilize from either dry or moist soil surfaces, and from water surfaces. The estimated moderate water solubility and low soil adsorption coefficient indicate that it may leach to groundwater or undergo runoff after a rain event, although not to an appreciable degree. Volatilization to the atmosphere will be the main transport pathway.

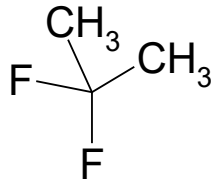


Figure 1. 2,2-Difluoropropane Structure

Table 1. Physicochemical Properties of 2,2-Difluoropropane (CASRN 420-45-1)

Property (unit)	Value
Physical state	Gas
Boiling point (°C)	−0.4[a, b]
Melting point (°C)	−105[a, b]
Density (g/mL)	0.92[b]
Vapor pressure (mm Hg at 25°C)	2,000 (estimated)[a]
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mg/L at 25°C)	262 (estimated)[a]
Octanol-water partition coefficient (log K_{ow})	2.29 (estimated)[a]
Henry's law constant (atm-m^3/mol at 25°C)	0.5 (estimated)[a]
Soil adsorption coefficient K_{oc} (L/kg)	44 (estimated)[a]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	5×10^{-15} (estimated)[a]
Atmospheric half-life (d)	2,000 (estimated)[a]
Relative vapor density (air = 1)	NV
Molecular weight (g/mol)	80.08[a, b]
Flash point (closed cup in °C)	NV

[a]U.S. EPA (2012b).
[b]Smart and Fernandez (2000).

NA = not applicable; NV = not available.

A summary of available toxicity values for 2,2-difluoropropane from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for 2,2-Difluoropropane (CASRN 420-45-1)

Source[a]	Value	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011)
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 (2017)
HEAST	NV	NA	U.S. EPA (2011)
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 August 2015, and updated in December 2016 and September 2017 for studies relevant to the derivation of provisional toxicity values for 2,2-difluoropropane (CASRN 420-45-1). 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)

There are no potentially relevant short-term-, subchronic-, or chronic-duration studies or developmental or reproductive toxicity studies in humans or animals, as shown in Tables 3A and 3B.

Table 3A. Summary of Potentially Relevant Noncancer Data for 2,2-Difluoropropane (CASRN 420-45-1)							
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**Reference (comments)**	**Notes**
Human							
1. Oral (mg/kg-d)							
ND: compound is a gas at standard temperature and pressure							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
ND: compound is a gas at standard temperature and pressure							
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 2,2-Difluoropropane (CASRN 420-45-1)							
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**Reference (comments)**	**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.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

No supporting studies containing acute toxicity, genotoxicity, toxicokinetic, or mechanistic data have been identified.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present summaries of noncancer and cancer reference values for 2,2-difluoropropane, respectively.

Table 4. Summary of Noncancer Reference Values for 2,2-Difluoropropane (CASRN 420-45-1)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	NDr						
Screening subchronic p-RfC (mg/m^3)	Rat/M	Leydig cell hyperplasia	3×10^1	$BMCL_{10}$ (HEC)	8,200 (based on a surrogate POD)	300	Collins et al. (1995) as cited in U.S. EPA (1995)
Screening chronic p-RfC (mg/m^3)	Rat/M	Leydig cell hyperplasia	3×10^1	$BMCL_{10}$ (HEC)	8,200 (based on a surrogate POD)	300	Collins et al. (1995) as cited in U.S. EPA (1995)

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; M = male(s); NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 5. Summary of Cancer Reference Values for 2,2-Difluoropropane (CASRN 420-45-1)

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

The absence of relevant oral data precludes the derivation of provisional reference doses (p-RfDs) for 2,2-difluoropropane directly. A tiered surrogate approach was attempted, but screening p-RfDs could not be derived due to a lack of oral toxicity values for potential surrogates (see Appendix A).

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The absence of relevant inhalation data precludes derivation of provisional reference concentrations (p-RfCs) for 2,2-difluoropropane directly. Instead, screening p-RfCs are derived in Appendix A using a tiered surrogate approach.

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 2,2-difluoropropane following both oral and inhalation exposure as shown in Table 6.

Table 6. Cancer WOE Descriptor for 2,2-Difluoropropane (CASRN 420-45-1)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No human data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	The available data do not support this descriptor.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**This descriptor is selected due to the absence of suitable data in humans or animals for an assessment of carcinogenicity.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this descriptor.

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

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The absence of suitable data precludes development of cancer potency values for 2,2-difluoropropane.

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 2,2-difluoropropane. 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 considerably more uncertainty is 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)

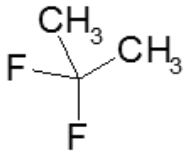
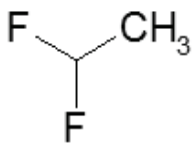
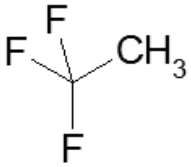
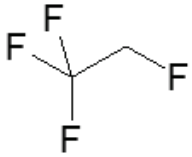
An initial surrogate search focused on identifying structurally similar chemicals with toxicity values from the Integrated Risk Information System (IRIS), PPRTV, Agency for Toxic Substances and Disease Registry (ATSDR), or California Environmental Protection Agency (Cal/EPA) databases to take advantage of the well-characterized chemical-class information. This was done by searching U.S. EPA's DSSTox database (DSSTox, 2016) and the National Library of Medicine's (NLM's) ChemIDplus database (ChemIDplus, 2017). Chemicals for consideration included hydrofluoroalkanes with chain lengths of 2−3 carbon atoms, as different halogen substitutions and differing carbon chain lengths would be expected to have an impact on toxicokinetics and toxicodynamics. To ensure similarity in overall reactivity, fully fluorinated chemicals (e.g., hexafluoroethane) and compounds containing other halogens (such as hydrochlorofluorocarbons [HCFCs]) or other potentially reactive features (such as alkenes) were not considered.

Three structural analogs to 2,2-difluoropropane having noncancer inhalation toxicity values were identified: 1,1-difluoroethane (U.S. EPA, 1994), 1,1,1-trifluoroethane (U.S. EPA, 2015), and 1,1,1,2-tetrafluoroethane (U.S. EPA, 1995). Table A-1 summarizes the analogs' physicochemical properties and similarity scores. The DSSTox similarity scores were 67 and 60% for 1,1-difluoroethane and 1,1,1,2-tetrafluoroethane, respectively, and <50% for 1,1,1-trifluoroethane. The ChemIDplus similarity scores were <50% for all potential surrogates. 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.

2,2-Difluoropropane and the potential surrogate compounds are highly volatile, as demonstrated by their high vapor pressures and Henry's law constants, suggesting that total absorption via the inhalation route of exposure is likely to be limited for all compounds, and steady-state blood concentrations may be achieved rapidly following inhalation. Whereas 1,1-difluoroethane has the least similar water solubility and octanol-water partition coefficient, there is no specific information at the structural or chemical properties tier to rule out any of the potential surrogates.

Table A-1. Physicochemical Properties of 2,2-Difluoropropane (CASRN 420-45-1) and Candidate Structural Surrogates[a]

Chemical	2,2-Difluoropropane	1,1-Difluoroethane	1,1,1-Trifluoroethane	1,1,1,2-Tetrafluoroethane
Structure				
CASRN	420-45-1	75-37-6	420-46-2	811-97-2
Molecular weight	80	66	84	102
DSSTox similarity score (%)[b]	100	67	<50%	60
ChemIDplus similarity score (%)[c]	100	<50%	<50%	<50%
Melting point (°C)	−105	−117	−111	−101
Boiling point (°C)	−0.4	−25	−48	−26
Vapor pressure (mm Hg at 25°C)	2×10^3 (estimated)	4.55×10^3	9.54×10^3	4.99×10^3
Henry's law constant (atm-m^3/mole at 25°C)	5×10^{-1} (estimated)	2.03×10^{-2}	8×10^{-1}(estimated)	5×10^{-2} (at 22°C)
Water solubility (mg/L)	262 (estimated)	3,200	550 (estimated)	670 (estimated)
Log K_{ow}	2.29 (estimated)	0.75	1.74 (estimated)	1.68 (estimated)
pKa	NV	NV	NV	NV

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

NV = not available.

Metabolic Surrogates

No toxicokinetic data are available for 2,2-difluoropropane. Available toxicokinetic data for the structurally similar compounds identified as potential surrogates are summarized in Table A-2 and discussed below.

Absorption data for 1,1-difluoroethane, 1,1,1-trifluoroethane, and 1,1,1,2-tetrafluoroethane are similar, with limited absorption (1−4%) into the blood following inhalation exposure (Avella et al., 2010; Ernstgård et al., 2010; ECETOC, 2006a, b). Human blood-air partition coefficients measured in vitro suggest higher pulmonary uptake for 1,1-difluoroethane (1.08), compared to 1,1,1-trifluoroethane (0.15) and 1,1,1,2-tetrafluoroethane (0.36) (Ernstgård et al., 2010). Distribution data for both 1,1,1-trifluoroethane and 1,1,1,2-tetrafluoroethane indicate that steady-state blood concentrations of these compounds are achieved rapidly (by ~30 minutes in humans), with no evidence of tissue or fat accumulation in rats following inhalation exposure (U.S. EPA, 2015; ECETOC, 2006a, b). Physiologically based pharmacokinetic (PBPK) modeling for 1,1,1-trifluoroethane also suggests that tissue accumulation is unlikely (ECETOC, 2006b). Observations in rats indicate that 1,1-difluoroethane is also rapidly distributed, with limited uptake into brain, heart, liver, and kidney (Avella et al., 2010). While, 1,1,1-trifluoroethane has the least similar blood-air partition coefficient, and 1,1-difluoroethane has the least similar octanol-water partition coefficient, there is no specific absorption or distribution information to discount any of the potential surrogates.

Fluoroalkane compounds are chemically stable due to the strength of the C-F bond (O'Hagan, 2008), and given the lack of other functional groups, 2,2-difluoropropane and the potential surrogate compounds are anticipated to be resistant to metabolism. Nevertheless, the available data on the potential surrogate compounds indicate that these compounds can undergo limited metabolic oxidation of the carbon skeletons (see Table A-2), particularly at positions having C-H bonds. 2,2-Difluoropropane contains two unfluorinated methyl groups and is therefore able to undergo similar reactions. The similarities in volatilities, aqueous/air partitioning, structures, and reactivity suggest that 2,2-difluoropropane and the potential surrogate compounds will have similar biological absorption and may be metabolized along similar pathways.

In rats, metabolism of 1,1,1,2-tetrafluoroethane is limited, with 67% of the absorbed dose excreted as unchanged parent compound in exhaled breath; the remaining 33% of the absorbed dose is recovered as oxidative metabolites in urine and feces, and as carbon dioxide (CO_2) in exhaled breath (ECETOC, 2006a). Toxicokinetic data for 1,1-difluoroethane and 1,1,1-trifluoroethane suggest that oxidative metabolism occurs at a slow rate (ECETOC, 2006b, 2004). Major urinary metabolites of 1,1,1-trifluoroethane and 1,1,1,2-tetrafluoroethane following inhalation exposure in rats include conjugates of trifluoroethanol, trifluoroacetaldehyde, and trifluoroacetic acid; oxidative defluorination can further break down these metabolites into fluoride ions (ECETOC, 2006a, b). Urinary metabolites identified for 1,1-difluoroethane include fluoride ions and trace amounts of acyl fluoride (ECETOC, 2004). In humans, elimination from the blood was biphasic, with half-lives of 4 and 300 minutes for 1,1,1-trifluoroethane, and 11 and 42 minutes for 1,1,1,2-tetrafluoroethane (ECETOC, 2006a, b). In rats, the half-life for elimination from the blood was also biphasic for potential surrogates, with half-lives of ~1 and 9 minutes for 1,1-difluoroethane (Avella et al., 2010), and an initial half-life of 4−7 minutes (followed by a second, slower elimination phase) for 1,1,1,2-tetrafluoroethane (ECETOC, 2006a, b). Rat liver metabolite in silico simulations for

2,2-difluoropropane performed with QSAR Toolbox 3.4 (OECD, 2016) predicted metabolites of 2,2-difluoropropanol, 2,2-difluoropropanaldehyde, and 2,2-difluoropropanoic acid, with no predicted relative abundance. Thus, 2,2-difluoropropane and its analogs have predicted or actual metabolites that show a common progressive oxidation of their terminal carbon atom to the alcohol, the aldehyde and the acid (presumably by CYP4502E1) prior to excretion.

Due to a lack of toxicokinetic data for 2,2-difluoropropane, it is not possible to select or reject any one of the candidate surrogates based on toxicokinetic similarities or differences. Available data on the toxicokinetic properties of the potential surrogate chemicals do not identify any major differences, as limited absorption and similar metabolism (oxidation of the carbon chain) is observed for all these chemicals. Therefore, each of the candidate compounds was considered an applicable metabolic surrogate for 2,2-difluoropropane.

Table A-2. Comparison of Available Toxicokinetic Data for 2,2-Difluoropropane (CASRN 420-45-1) and Candidate Surrogates

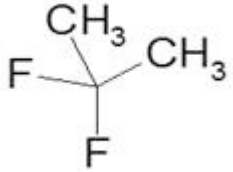
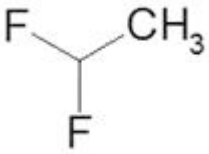
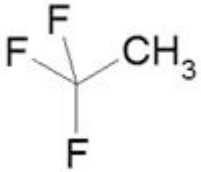
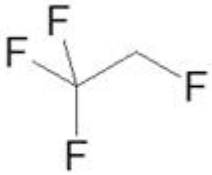
2,2-Difluoropropane (CASRN 420-45-1)	1,1-Difluoroethane (CASRN 75-37-6)	1,1,1-Trifluoroethane (CASRN 420-46-2)	1,1,1,2-Tetrafluoroethane (CASRN 811-97-2)
			
Absorption after inhalation exposure			
ND	Human: Blood-air partition coefficient of 1.08 (measured in vitro) Rat: ~4% of inhaled dose was absorbed	Human: Rapid, but low uptake; ~2% of inhaled dose was absorbed (measured in 9 volunteers exposed to 1,720 mg/m^3 for 2 hr); human blood-air partition coefficient of 0.15 (measured in vitro) Rat: Low absorption into blood; estimated rat blood-air partition coefficient of 0.91	Human: Rapid uptake (extent of uptake not reported) (measured in 4 M and 4 F volunteers exposed to concentrations between 4,170−33,400 mg/m^3 for 1 hr); human blood-air partition coefficient of 0.36 (measured in vitro) Rat: ~1% of inhaled dose was absorbed; blood-air partition coefficient of 0.48 was measured in vivo
Distribution after inhalation exposure			
ND	Rat: 68% blood, 8% brain, 4% heart, 10% liver, 8% kidney relative to the total absorbed dose	Human: Steady-state blood concentrations reached within the first few minutes of exposure; plateau blood concentration of 1.4 µg/g (measured in 9 volunteers exposed to 1,720 mg/m^3 for 2 hr) Rat: PBPK model calculations indicate poor solubility in tissues and rapid clearance from blood; accumulation in tissues unlikely	Human: Blood concentrations reached steady state within 30 min and were higher in males (measured in 4 M and 4 F volunteers exposed to concentrations between 4,170–33,400 mg/m^3 for 1 hr) Rat: No evidence of tissue or fat accumulation following inhalation exposure; crosses placental barrier (rats and rabbits)

Table A-2. Comparison of Available Toxicokinetic Data for 2,2-Difluoropropane (CASRN 420-45-1) and Candidate Surrogates

2,2-Difluoropropane (CASRN 420-45-1)	1,1-Difluoroethane (CASRN 75-37-6)	1,1,1-Trifluoroethane (CASRN 420-46-2)	1,1,1,2-Tetrafluoroethane (CASRN 811-97-2)
Metabolism after inhalation exposure			
Predicted metabolites from the QSAR Toolbox 3.4 (OECD, 2016) include difluoropropane, difluoropropanaldehyde, difluoropropanoic acid, and difluorpropanol	Rat: Oxidative metabolism at a slow rate; V_{MAX} and Km values of 7.8 mg/hr-kg BW and 27.9 mg/L, respectively; fluoride ion and trace acyl fluoride were identified in the urine; PBPK modeling estimates metabolic saturation at ~203,000 mg/m^3	Human: Low metabolic rate Rat: Slowly metabolized; primary urinary metabolite was trifluoroethanol; minor metabolites include glucuronide conjugates of trifluoroethanol, trifluoroacetaldehyde, and trifluoroacetic acid; also urea conjugate of trifluoroacetaldehyde	Human: ND Rat: Minimal metabolism following inhalation; primary metabolite was CO_2 in exhaled air; metabolites were detected in urine, plasma, and testicular tissue; urinary metabolites were trifluoro-ethanol (as glucuronide and aglycone conjugates), trifluoroacetaldehyde (as hydrate and urea adducts), and trifluoroacetic acid Oxidative defluorination via CYPIIE1was demonstrated in rat, rabbit, and human liver P-100 membrane fraction.
Excretion after inhalation exposure			
ND	Urinary metabolites (fluoride and acyl fluoride)	Human: Two elimination phases with half-lives of about 4 and 300 min; increased urinary fluoride concentration measured in 2/9 volunteers	Human: Biphasic elimination from blood, with half-lives of 11 and 42 min; mean residence time was 44 min Rat: 67% recovery as unchanged compound in exhaled breath; 33% recovered as metabolites in urine, feces, and as CO_2 in exhaled breath; biphasic elimination with initial half-life of 4−20 min; remaining radioactivity was excreted within 24 hr
ND	Avella et al. (2010); Ernstgård et al. (2010); ECETOC (2004)	U.S. EPA (2015); Ernstgård et al. (2010); ECETOC (2006b)	Ernstgård et al. (2010); ECETOC (2006a); U.S. EPA (1995)

BW = body weight; CO_2 = carbon dioxide; F = female(s); Km = Michaelis constant (turnover rate at half-saturating concentration); M = male(s); ND = no data; PBPK = physiologically based pharmacokinetic; QSAR = qualitative structure activity relationship; V_{MAX} = turnover rate of enzyme at saturating concentration.

Toxicity-Like Surrogates

There are no acute or repeated-dose oral toxicity data for 2,2-difluoropropane, and none of the potential surrogates have oral toxicity values.

There are no acute or repeated-dose inhalation toxicity data for 2,2-difluoropropane. In a qualitative structure activity relationship (QSAR) paper by Eriksson et al. (1993), the authors' models predicted median lethal dose (LD_{50}) values for the super-category of halogenated aliphatic hydrocarbons. The LD_{50} values for the majority of the compounds (33/38) differed by less than an order of magnitude. The most similar categorical subset, that of fluoroalkanes, differed by less than a factor of two, and are thus toxicologically similar.

Table A-3 summarizes available inhalation toxicity data for the structurally similar compounds identified as potential surrogates for 2,2-difluoropropane. For 1,1-difluoroethane, the chronic inhalation reference concentration (RfC) is based on a lack of adverse effects in a comprehensive 2-year toxicity study at concentrations up to 12,051 mg/m^3 (U.S. EPA, 1994). Similarly, the subchronic and chronic provisional reference concentrations (p-RfCs) for 1,1,1-trifluoroethane are based on a lack of adverse effects in a comprehensive 13-week toxicity study at concentrations up to 24,550 mg/m^3 (U.S. EPA, 2015; Brock et al., 1996). Additional studies indicate a lack of maternal, reproductive, or developmental effects following gestational exposure to 1,1,1-trifluoroethane or 1,1-difluoroethane at concentrations up to 137,500 or 135,000 mg/m^3, respectively (U.S. EPA, 2015, 1994). For 1,1,1,2-tetrafluoroethane, the critical effect in a comprehensive 2-year study was increased incidence of Leydig cell hyperplasia at 37,250 mg/m^3 (U.S. EPA, 1995). Adverse effects observed at higher concentrations of 1,1,1,2-tetrafluoroethane in rat developmental studies include reduced fetal weight with increased variations (≥208,600 mg/m^3) and increased fetal malformations in the presence of maternal toxicity (1,252,000 mg/m^3). No fetal effects were observed in a rabbit developmental study that produced maternal toxicity (166,900 mg/m^3) (U.S. EPA, 1995). Reversible central nervous system (CNS) depression was observed in acute and short-term-duration studies for 1,1-difluoroethane and 1,1,1,2-tetrafluoroethane, and cardiac sensitization was observed for 1,1,1,2-tetrafluoroethane, but not 1,1,1-trifluoroethane (U.S. EPA, 2015, 1995).

Taken together, available data indicate low systemic toxicity for all potential surrogate chemicals following subchronic or chronic inhalation exposure, as demonstrated by the lack of adverse effects observed at exposure concentrations up to ~25,000 mg/m^3 (U.S. EPA, 2015, 1995, 1994). This may be related to the limited absorption of these compounds into blood (1−4%, see "Metabolic Surrogates" section above). Effects that were noted in chronic-duration or developmental studies at higher concentrations for 1,1,1,2-tetrafluoroethane included testicular damage and developmental effects in rats; these effects occurred at concentrations higher than those tested for comparable effects for the other potential surrogates. Available data regarding 2,2-difluoropropane are inadequate to identify toxicity targets; thus, it is not possible to select, or to rule out, any of the candidates based on a comparison between 2,2-difluoropropane and candidate surrogates.

Table A-3. Comparison of Available Inhalation Toxicity Data for 2,2-Difluoropropane (CASRN 420-45-1) and Candidate Surrogates

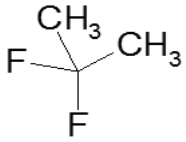
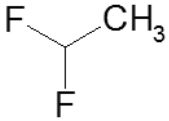
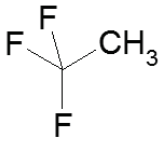
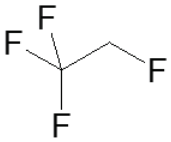
Chemical	2,2-Difluoropropane (CASRN 420-45-1)	1,1-Difluoroethane (CASRN 75-37-6)	1,1,1-Trifluoroethane (CASRN 420-46-2)	1,1,1,2-Tetrafluoroethane (CASRN 811-97-2)
Structure				
Repeated-exposure toxicity—subchronic RfCs				
POD (mg/m^3)	NA	NA	24,550	NA
POD type	NA	NA	NOAEL (HEC)	NA
UF_C (subchronic)	NA	NA	100 (3 UF_A, 10 UF_H, 3 UF_D)	NA
Subchronic p-RfC (mg/m^3)	NA	NA	2×10^2	NA
Critical effects	NA	NA	No exposure-related effects on clinical signs, body weight, food consumption, hematology, serum chemistry, urinalysis, selected organ weights, or comprehensive gross and microscopic pathology	NA
Other effects	NA	NA	NA	NA
Species	NA	NA	Rat (M and F)	NA
Duration	NA	NA	13 wk	NA
Route	NA	NA	Inhalation (whole body)	NA

Table A-3. Comparison of Available Inhalation Toxicity Data for 2,2-Difluoropropane (CASRN 420-45-1) and Candidate Surrogates

Chemical	2,2-Difluoropropane (CASRN 420-45-1)	1,1-Difluoroethane (CASRN 75-37-6)	1,1,1-Trifluoroethane (CASRN 420-46-2)	1,1,1,2-Tetrafluoroethane (CASRN 811-97-2)
Additional toxicity data (from other studies)	NA	NA	• No exposure-related effects on electrocardiograph readings or self-reported symptoms in volunteers exposed to 1,720 mg/m^3 for 2 hr during light exercise; serum inflammatory markers were not increased • No exposure-related effects in a 28-d inhalation study in rats (concentrations up to 24,550 mg/m^3) • No maternal, reproductive, or developmental effects were observed in rat or rabbit gestational exposure studies (GDs 6−15 for rats; GDs 6−18 for rabbits) using inhalation concentrations up to 137,500 mg/m^3 • No evidence of cardiac sensitization in dogs	No fetal effects were observed in a rabbit developmental study that produced maternal toxicity (166,900 mg/m^3)
Source	NA	NA	U.S. EPA (2015)	(U.S. EPA, 1995)
Repeated-exposure toxicity—chronic RfCs				
POD (mg/m^3)	NA	12,051	24,550	8,200
POD type	NA	NOAEL (HEC)	NOAEL (HEC)	$BMCL_{10}$ (HEC)[a]
UF_C	NA	300 (3 UF_A, 10 UF_H, 10 UF_D)	1,000 (3 UF_A, 10 UF_H, 3 UF_D, 10 UF_S)	100 (3 UF_A, 10 UF_H, 3 UF_D)
Chronic RfC (mg/m^3)	NA	4×10^1	2×10^1	8×10^1

Table A-3. Comparison of Available Inhalation Toxicity Data for 2,2-Difluoropropane (CASRN 420-45-1) and Candidate Surrogates

Chemical	2,2-Difluoropropane (CASRN 420-45-1)	1,1-Difluoroethane (CASRN 75-37-6)	1,1,1-Trifluoroethane (CASRN 420-46-2)	1,1,1,2-Tetrafluoroethane (CASRN 811-97-2)
Critical effects	NA	No exposure-related effects on clinical signs, body weight, food consumption, hematology, serum chemistry, urinalysis, or comprehensive gross and microscopic pathology	No exposure-related effects on clinical signs, body weight, food consumption, hematology, serum chemistry, urinalysis, selected organ weights, or comprehensive gross and microscopic pathology	Increased incidence of Leydig cell hyperplasia at 37,250 mg/m^3
Other effects (in principal study)	NA	NA	NA	Increased absolute and relative testes weight; no exposure-related effects on clinical signs, body weight, food consumption, hematology, serum chemistry, or weight or histology of other major organs
Species	NA	Rat (M and F)	Rat (M and F)	Rat (M)
Duration	NA	2 yr	13 wk	2 yr
Route	NA	Inhalation (method NR)	Inhalation (whole body)	Inhalation (whole body)

Table A-3. Comparison of Available Inhalation Toxicity Data for 2,2-Difluoropropane (CASRN 420-45-1) and Candidate Surrogates

Chemical	2,2-Difluoropropane (CASRN 420-45-1)	1,1-Difluoroethane (CASRN 75-37-6)	1,1,1-Trifluoroethane (CASRN 420-46-2)	1,1,1,2-Tetrafluoroethane (CASRN 811-97-2)
Additional toxicity data (from other studies)	ND	• No maternal, reproductive, or developmental effects were observed in a rat gestational exposure study (GDs 6−15) using 13,500 or 135,000 mg/m^3 • Reversible CNS depression was seen in rats exposed to ≥27,000 mg/m^3 for 2 hr or 2 wk	See "Subchronic" sections	• No adverse effects were observed in rats exposed for 14 d (417,000 mg/m^3) or 13 wk (up to 208,600 mg/m^3) • Clinical signs of neurotoxicity and decreased food consumption, and body-weight gain were seen in pregnant rats exposed to 1,252,000 mg/m^3 on GDs 6−15; reduced mean fetal weight, increased percent of malformed fetuses/litter, and increased mean percent of fetuses with variations/litter were also seen at this concentration • Rat fetal effects observed in the absence of maternal toxicity included decreased mean fetal weight and increased incidence of unossified or partially ossified bones (exposure to 208,600 mg/m^3 on GDs 6−15)

Table A-3. Comparison of Available Inhalation Toxicity Data for 2,2-Difluoropropane (CASRN 420-45-1) and Candidate Surrogates

Chemical	2,2-Difluoropropane (CASRN 420-45-1)	1,1-Difluoroethane (CASRN 75-37-6)	1,1,1-Trifluoroethane (CASRN 420-46-2)	1,1,1,2-Tetrafluoroethane (CASRN 811-97-2)
Continued:	Continued:	Continued:	Continued:	Continued: • Decreased body-weight gain was observed in pregnant rabbits exposed to 166,900 mg/m^3 on GDs 7−19; no reproductive or developmental effects were observed in this study • Reversible CNS depression was seen in acute rat studies; rat LC_{50} was 3,100,000 mg/m^3 for 30 min • Cardiac sensitization was seen in dogs exposed to >33,000 mg/m^3 for 10 min
Source	NA	U.S. EPA (1994)	U.S. EPA (2015)	U.S. EPA (1995)
Acute inhalation toxicity				
Rat inhalation LC_{50} (mg/m^3)	NA	173,000	>1,900,000	1,500,000
Toxic effects	NA	NA	NA	NA
Mouse inhalation LC_{50} (mg/m^3)	NA	977	NA	1,750,000
Toxic effects	NA	NA	NA	NA
Source	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)	ChemIDplus (2017)

[a]U.S. EPA (1995) reported the POD as a BMC_{10} (HEC); independent modeling performed for this review confirmed that the POD value was a $BMCL_{10}$ (HEC) from the Multistage and Weibull models for the incidence of Leydig cell hyperplasia in male rats in the principal study.

BMC_{10} = 10% benchmark concentration; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; CNS = central nervous system; F = female(s); GD = gestation day; HEC = human equivalent concentration; LC_{50} = median lethal concentration; M = male(s); NA = not applicable; ND = no data; NOAEL = no-observed-adverse-effect level; NR = not reported; POD = point of departure; p-RfC = provisional reference concentration; RfC = inhalation reference concentration; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Weight-of-Evidence Approach—Oral

Due to lack of oral toxicity values for potential surrogates, a screening subchronic or chronic provisional reference dose (p-RfD) cannot be derived using the surrogate approach.

Weight-of-Evidence Approach—Inhalation

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 target chemical. 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.

No toxicity or toxicokinetic data were available for 2,2-difluoropropane. Three potential surrogates having similar chemical structures and physicochemical properties were identified. A single best surrogate could not be selected on the basis of chemical structure, absorption potential, or metabolic transformations; the available data for all of the potential surrogates indicated that they all exhibited similar low absorption, limited metabolism, and low systemic toxicity. One of the candidates (1,1,1-trifluoroethane) has the least similar blood-air partition coefficient in the category. Another of the candidates (1,1-difluoroethane) has the least similar octanol-water partition coefficient of the category, but neither of these properties was judged to be sufficient to completely rule out either of these compounds as potential surrogates. Suggestions of testicular toxicity are found in all of the potential surrogates. For example, decreased testicular-weight changes were observed (although only at the 90-day sacrifice) for 1,1-difluoroethane. Similarly, suggestions of a potential testicular effect were seen, but ultimately discounted, in the 1,1,1-trifluoroethane PPRTV assessment (U.S. EPA, 2015). Additionally, both relative and absolute testis-weight changes, as well as Leydig cell hyperplasia, were seen in 1,1,1,2-tetrafluoroethane exposed rats. This combination of similar health effects, similar metabolism, and similar physicochemical properties provides the basis for the identification of a chemical category (short-chain fluoroalkanes). The representative surrogate from this category was, therefore, chosen based on available toxicity values and health protectiveness. For both subchronic and chronic durations of inhalation exposure, 1,1,1,2-tetrafluoroethane was selected as the surrogate because: (1) the RfC value is based on a chronic-duration study (unlike 1,1,1-trifluoroethane), (2) it was the only compound for which statistically significant effects were observed following repeated inhalation exposure (unlike both 1,1-difluoroethane and 1,1,1-trifluoroethane, in which only NOAELs were identified), and (3) in the absence of other discriminating evidence that further informs selection among the potential surrogates, the chronic point of departure (POD) value for 1,1,1,2-tetrafluoroethane was the most health protective.

ORAL TOXICITY VALUES

Derivation of Screening Subchronic and Chronic Provisional Reference Doses

No subchronic or chronic oral reference values have been identified for candidate analogs for 2,2-difluoropropane (U.S. EPA, 2015, 1995, 1994), precluding the derivation of p-RfD values for 2,2-difluoropropane based on a tiered surrogate approach.

INHALATION TOXICITY VALUES

Derivation of Screening Subchronic and Chronic Provisional Reference Concentrations

Based on the overall tiered surrogate approach presented in this PPRTV assessment, 1,1,1,2-tetrafluoroethane was selected as the surrogate for 2,2-difluoropropane for deriving both a screening subchronic and screening chronic p-RfC for reasons discussed in the "Weight-of-Evidence Approach—Inhalation" section above. The principal study for 1,1,1,2-tetrafluoroethane is a 2-year inhalation study in male and female Wistar rats by Collins et al. (1995) as cited in U.S. EPA (1995), in which the critical effect is Leydig cell hyperplasia in the male rat testis. The IRIS summary for 1,1,1,2-tetrafluoroethane (U.S. EPA, 1995) described this study as follows:

> *A 2-year inhalation exposure study with 1,1,1,2-tetrafluoroethane (HFC-134a) was conducted (Collins et al., 1995; Hext and Parr-Dobrzanski, 1993), and the interim report described results through 52 weeks (Collins et al., 1995; Hext and Mould, 1991). In this study, groups of 85 Wistar-derived rats/sex were whole-body exposed to 0, 2500, 10,000, or 50,000 ppm (0, 10,400, 41,700, and 208,600 mg/m^3) HFC-134a (99.8% pure) for 6 hours/day, 5 days/week (duration-adjusted concentrations = 1860, 7450, or 37,250 mg/m^3, respectively). The animals were observed for clinical signs of toxicity at least once daily and several times during exposure. Body weight and food consumption were monitored weekly during the first 14 weeks and biweekly thereafter. Hematological, clinical chemistry, and urinalysis evaluations conducted on 10 rats/sex/group at 14, 27, 52, and 104 weeks. Ten rats/sex/group were sacrificed after 1 year of exposure for gross and microscopic tissue examination of over 40 tissues, including the nose, trachea, and lung. The remaining animals were examined after 104 weeks of exposure. The HFC-134a vapor was generated by evaporating the liquid test material in a stream of metered air. The test atmosphere concentration was assayed at 1-hour intervals by gas chromatography. Mean daily chamber concentrations were found to be within 90-100% of the nominal concentrations.*
>
> *There were no exposure-related effects on mortality, clinical signs, food consumption, body weight, behavior, or ocular characteristics. In males, slight concentration-related decreases were noted in hemoglobin, hematocrit, RBCs, and WBCs after 14 weeks of exposure (but not after 27, 53, 104 weeks). Slightly elevated plasma glucose was noted in males at week 14, but not in succeeding weeks, and in females at week 27 (but not weeks 52 or 104). There were no treatment-related effects on plasma cholesterol or triglycerides. In animals necropsied after intercurrent deaths (too few per group for meaningful statistical comparisons) and in the 10 animals killed after 52 weeks, there were no treatment-related effects on organ weight or histopathology. The only treatment-related effects after 104 weeks of exposure were found in the testes. A statistically significant increase in absolute and relative testes weight was found at the terminal sacrifice (n=75, relative weights were 0.6, 0.39, 0.61, and 0.66 in the 0-, 2500-, 10,000-, and 50,000-ppm groups, respectively). In addition, there was a significant increase in the incidence of Leydig cell hyperplasia (incidence of 27, 25, 31, and 40 in the 0-, 2500-, 10,000-, and 50,000-ppm groups, respectively). The testicular effects were considered adverse. This study*

establishes a LOAEL of 50,000 [$LOAEL_{HEC}$ = 37,250 mg/m^3] and a NOAEL of 10,000 ppm [$NOAEL_{HEC}$ = 7,450 mg/m^3].

The critical effect for the chronic-duration rat inhalation study was increased incidence of Leydig cell hyperplasia. The U.S. EPA (1995) indicated that the POD was a human equivalent benchmark concentration (BMC_{10} [HEC]) of 8,200 mg/m^3 based on a benchmark response of 10% for the incidence of Leydig cell hyperplasia in male rats. However, independent modeling performed for this assessment revealed that the POD value was actually a benchmark concentration lower confidence limit 10% ($BMCL_{10}$ [HEC]) from the Multistage and Weibull models, not a BMC_{10} (HEC). As this $BMCL_{10}$ is identified as the surrogate POD for both the subchronic and chronic p-RfC derivation for 2,2-difluoropropane, a composite uncertainty factor (UF_C) of 300 is applied. This UF_C is applied for both the subchronic and chronic p-RfC and is based on a 3-fold uncertainty factor for interspecies extrapolation (interspecies uncertainty factor [UF_A], reflecting use of a dosimetric adjustment) and 10-fold uncertainty factor values for both intraspecies variability (UF_H) and database deficiencies (database uncertainty factor [UF_D], reflecting lack of any repeated-exposure toxicity information for 2,2-difluoropropane). The screening subchronic and chronic p-RfC for 2,2-difluoropropane is derived as follows:

Screening Subchronic/Chronic p-RfC = Surrogate POD (HEC) ÷ UF_C
= 8,200 mg/m^3 ÷ 300
= **3×10^1 mg/m^3**

Table A-4 summarizes the uncertainty factors for the screening subchronic and chronic p-RfCs for 2,2-difluoropropane.

Table A-4. Uncertainty Factors for the Screening Subchronic and Chronic p-RfC for 2,2-Difluoropropane (CASRN 420-45-1)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed.
UF_D	10	A UF_D of 10 is applied to account for the absence of repeated-dose toxicity data including reproductive and developmental studies for 2,2-difluoropropane.
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 2,2-difluoropropane in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a $BMCL_{10}$ (HEC).
UF_S	1	A UF_S of 1 is applied because a chronic-duration study was selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

$BMCL_{10}$ = 10% benchmark concentration lower confidence limit; HEC = human equivalent concentration; POD = point of departure; p-RfC = provisional reference concentration; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies variability uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Consideration of Potential Carcinogenicity

As discussed above, 1,1,1,2-tetrafluoroethane was selected as the surrogate for 2,2-difluoropropane for derivation of a screening subchronic and chronic p-RfC using an alternative surrogate approach (Wang et al., 2012). 1,1,1,2-Tetrafluoroethane was previously identified by the International Programme on Chemical Safety (IPCS) as having limited evidence of carcinogenicity (WHO/IPCS, 1998). This information suggests that 2,2-difluoropropane might have carcinogenic potential as well but does not preclude the development of noncancer surrogate-derived screening provisional peer-reviewed toxicity values within this document. There is currently a lack of formal methodology through which to evaluate the comparative cancer-specific effects of potential surrogate chemicals. Therefore, only noncancer surrogate-derived screening provisional peer-reviewed toxicity values are provided in in this PPRTV assessment and derivation of screening provisional cancer potency values using an alternative surrogate approach is precluded.

APPENDIX B. REFERENCES

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