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Provisional Peer-Reviewed Toxicity Values for

1,1,1-Trifluoroethane
(CASRN 420-46-2)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
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	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,1,1-TRIFLUOROETHANE (CASRN 420-46-2)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

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

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

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

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

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

INTRODUCTION

1,1,1-Trifluoroethane, CASRN 420-46-2, also referred to as HFC-143a, is a flammable hydrofluorocarbon used as a heat transfer agent and refrigerant in blends for air conditioning used for stationary and transport systems (Solvay, 2011). Although 1,1,1-trifluoroethane is flammable, blends containing this chemical are not considered flammable. Under EPA's Significant New Alternatives Policy (SNAP) program, blends containing 1,1,1-trifluoroethane have been approved as replacements for Class I and II ozone-depleting substances in various industrial, commercial, and household refrigeration systems, including refrigerated transport, retail food refrigeration, commercial ice machines, vending machines, and household refrigerators and freezers (U.S. EPA, 1995, 1994a, c). Blends containing 1,1,1-trifluoroethane are also approved as replacements for CFC-12 (dichlorodifluoromethane) in polystyrene boardstock and billet foams (U.S. EPA, 1994b).

1,1,1-Trifluoroethane exists primarily as a gas (its boiling point is −47.5°C), although it is generally supplied as a liquefied gas under pressure in compressed gas cylinders. It is flammable at concentrations ≥70,000 ppm (240,000 mg/m^3) (Brock et al., 1996). Although 1,1,1-trifluoroethane does not react with ozone and has no ozone-depleting properties, it has a very high global warming potential (GWP) of 3,800 (compared to 1 for carbon dioxide) (Solvay, 2011). 1,1,1-Trifluoroethane will react with hydroxy radicals in the atmosphere; its measured atmospheric OH rate constant indicates an atmospheric half-life of approximately 9 years (ChemIDplus, 2015). 1,1,1-Trifluoroethane has a moderate water solubility, but its high estimated Henry's Law constant indicates that, if released to water, it will rapidly volatilize from the water surface. Although 1,1,1-trifluoroethane may exhibit some leaching from moist soil to groundwater or undergo runoff after a rain event, the predominant environmental fate pathway is expected to be volatilization. The molecular formula for 1,1,1-trifluoroethane is $C_2H_3F_3$. A table of physicochemical properties for 1,1,1-trifluoroethane is provided in Table 1. The chemical structure is shown in Figure 1.

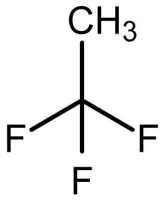

Figure 1. Chemical Structure of 1,1,1-Trifluoroethane

Table 1. Physicochemical Properties of 1,1,1-Trifluoroethane (CASRN 420-46-2)

Property (unit)	Value
Physical state	Colorless, odorless gas, typically supplied as a liquefied gas under pressure[a]
Boiling point (°C)	−47.5[b]
Melting point (°C)	−111[b]
Density (g/cm^3)	ND
Vapor pressure (mm Hg at 25°C)	9,540[b]
pH (unitless)	ND
pKa (unitless)	ND
Solubility in water (mg/L at 25°C)	760[a]
Octanol-water partition constant (log K_{ow})	1.74 (estimated)[c]
Henry's Law constant (atm-m^3/mol at 20°C)	7.70×10^{-1} (estimated)[c]
Soil adsorption coefficient K_{oc} (mL/g)	43.9 (estimated)[c]
Relative vapor density (air = 1)	2.9
Molecular weight (g/mol)	84.04[b]

[a]Solvay (2011).
[b]ChemIDplus (2015).
[c]U.S. EPA (2012a).

ND = no data.

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

Table 2. Summary of Available Toxicity Values for 1,1,1-Trifluoroethane (CASRN 420-46-2)

Source/ Parameter[a]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2015)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012b)
ATSDR	NV	NA	ATSDR (2015)
WHO	NV	NA	WHO (2015)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2015a); Cal/EPA (2015b)
OSHA	NV	NA	OSHA (2006b); OSHA (2006a); OSHA (2011)
NIOSH	NV	NA	NIOSH (2015)
ACGIH	NV	NA	ACGIH (2015)
AIHA/WEEL[b]	1,000 ppm (3,400 mg/m^3)	8-hr TWA; Based on low acute and subchronic toxicity in animals, analogy to other structurally related hydrofluorocarbons (i.e., HFC-152a, HFC-134a) and good industrial hygiene practices.	AIHA (1996); AIHA (2011)
Cancer			
IRIS	NV	NA	U.S. EPA (2015)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012b)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2015a); Cal/EPA (2015b)
ACGIH	NV	NA	ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; AIHA = American Industrial Hygiene Association; 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; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: TWA = time weighted average; WEEL = workplace environmental exposure levels.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in February 2015 and updated in September 2015 for studies relevant to the derivation of provisional toxicity values for 1,1,1-trifluoroethane (CASRN 420-46-2). 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 values: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, and OSHA.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases for 1,1,1-trifluoroethane, and include all potentially relevant short-term-, subchronic-, and chronic-duration toxicity studies as well as developmental and reproductive toxicity studies. Principal studies are identified. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05, unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,1,1-Trifluoroethane (CASRN 420-46-2)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Human								
1. Oral (mg/kg-d)[a]								
ND								
2. Inhalation (mg/m^3)[a]								
ND								
Animal								
1. Oral (mg/kg-d)[a]								
Subchronic	ND							
Chronic/ carcinogenicity	36 M/36 F (treated), 32 M/32 F (untreated control), 40 M/40 F (vehicle-only control), Alpk/Ap Wistar-derived, rat, gavage, 5 d/wk for 52 wk (sacrifice at Wk 125)	0, 300 ADD: 0, 214	Significantly decreased mean body weight in males from Wk 28–88	ND	NA	ND	Longstaff et al. (1984) (Uncertainty in dose received [see text] and magnitude of body-weight change precludes effect level identification)	PR
Reproductive	ND							
Developmental	ND							
2. Inhalation (mg/m^3)[a]								
Short-term	Initial experiment: 10 M/10 F, Crl:CDBR, rat, nose-only, inhalation, 6 hr/d, 5 d/wk, 4 wk Repeat experiment: 10 M/0 F, Crl:CDBR, rat, whole-body, inhalation, 6 hr/d, 5 d/wk, 4 wk	0, 2,000, 10,000, 40,000 ppm HEC: 0, 1,228, 6,138, 24,550	No treatment-related effects	24,550	NA	ND	Brock et al. (1996) (NOAEL determination based on the absence of exposure-related effects in the repeat experiment)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,1,1-Trifluoroethane (CASRN 420-46-2)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Subchronic	**20 M/20 F, Crl:CDBR rat, whole-body inhalation, 6 hr/d, 5 d/wk, 90 d**	**0, 2,000, 10,000, 40,000 ppm** **HEC: 0, 1,228, 6,138, 24,550**	**No treatment-related effects**	**24,550**	**NA**	**ND**	Brock et al. (1996)	**PR, PS**
Developmental	0 M/25 F, Crl:CDBR rat, whole-body inhalation, 6 hr/d, GDs 6–15	0, 2,000, 10,000, 40,000 ppm HEC: 1, 1719, 8,593, 34,380	No treatment-related effects	34,380	NA	ND	Brock et al. (1996)	PR
Developmental	0 M/24 F, New Zealand, rabbit, whole-body inhalation, 6 hr/d, GDs 6–18	0, 2,000, 10,000, 40,000 ppm HEC: 0, 1,719, 8,593, 34,380	No treatment-related effects	34,380	NA	ND	Brock et al. (1996)	PR

[a]Dosimetry: Values are presented as adjusted daily dose (ADD, in mg/kg-day) for oral noncancer effects and as human equivalent concentration (HEC, in mg/m^3) for inhalation noncancer effects.
[b]Notes: PS = principal study; PR = peer reviewed.

Treatment/exposure duration (unless otherwise noted): Short-term = repeated exposure for >24 hours ≤30 days (U.S. EPA, 2002); long-term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (more than 30 days up to approximately 90 days in typically used laboratory animal species) (U.S. EPA, 2002); chronic = repeated exposure for >10% lifespan for humans (more than approximately 90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).

F = female; GD = Gestation Day; M = male; NA = not applicable; ND = no data.

Table 3B. Summary of Potentially Relevant Cancer Data for 1,1,1-Trifluoroethane (CASRN 420-46-2)						
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**BMDL/ BMCL[a]**	**Reference (comments)**	**Notes[b]**
Human						
1. Oral (mg/kg-d)						
ND						
2. Inhalation (mg/m^3)						
ND						
Animal						
1. Oral (mg/kg-d)[a]						
Carcinogenicity	36 M/36 F (treated), 32 M/32 F (untreated control), 40 M/40 F (vehicle-only control), Alpk/Ap Wistar-derived, rat, gavage, 5 d/wk, 52 wk (sacrifice at Wk 125)	0, 300 HED: 0, 51.4	No treatment-related neoplastic lesions were observed	NA	Longstaff et al. (1984) (This study is not considered an adequate basis for evaluating carcinogenicity because only one dose level was tested, the dose received by the animals is uncertain [see text], the study did not report quantitative information on results.)	PR
2. Inhalation (mg/m^3)						
ND						

[a]Dosimetry: the units for oral exposures are expressed as human equivalent dose (HED, mg/kg-day). HED = ADD (210 mg/kg-day) × default dosimetric adjustment factor (U.S. EPA, 2011b).
[b]Notes: PR = peer reviewed.

NA = not applicable; ND = no data.

HUMAN STUDIES

Oral Exposures

No studies investigating the toxicity or carcinogenicity of 1,1,1-trifluoroethane in humans exposed orally were located in the available literature. Because 1,1,1-trifluoroethane exists as a gas except at very low temperatures (its boiling point is −47.5°C), oral exposure to this compound is unlikely except in very unusual circumstances.

Inhalation Exposures

There are very limited data on effects of 1,1,1-trifluoroethane inhalation exposure in humans. In an acute experimental exposure study aimed at investigating the uptake, disposition, and selected effects of 1,1,1-trifluoroethane in humans (Gunnare et al., 2007), nine male volunteers were exposed whole-body to 1,1,1-trifluoroethane at 500 ppm (1,720 mg/m^3) for 2 hours during light physical exercise. Volunteers were permitted to participate in the study (conducted according to the Helsinki Declaration) after giving written consent and receiving approval by the Regional Ethics Committee at Karolinska Institutet (Stockholm, Sweden). All of the subjects in this study, although deemed healthy by an examining physician, had been occupationally exposed to hydrofluorocarbons, and previously participated in a study of 1,1,1,2-tetrafluoroethane. Acute effects from 1,1,1-trifluoroethane exposure were assessed by electrocardiogram (monitored throughout exposure), questionnaires regarding perceived discomfort with respect to irritation and CNS symptoms (including discomfort in the eyes, nose, throat, and airways, breathing problems, headache, fatigue, nausea, and dizziness; questionnaire administered prior to exposure, twice during exposure, and 220 minutes postexposure), and blood analyses for inflammatory markers (C-reactive protein, amyloid A protein, fibrinogen, D-dimer) and uric acid from samples collected prior to exposure and 21 hours postexposure. Symptoms were rated on an ordinal scale.

There were no exposure-related effects on electrocardiographic readings or on self-reported symptoms (Gunnare et al., 2007). The mean concentration of fibrinogen in plasma was significantly increased after exposure (by 11%; $p = 0.0006$) relative to the mean pre-exposure value; no other inflammatory marker was affected by exposure, nor was serum uric acid. The authors did not have any explanation as to why this marker was affected when more sensitive markers of inflammation were not. Gunnare et al. (2007) noted that they had observed the same effect in a related study on 1,1,1,2-tetrafluoroethane, which suggested that this finding warranted further examination. The biological significance of the finding is uncertain. Given its brief exposure duration and limited scope, this study is not suitable for the derivation of a reference toxicity value for 1,1,1-trifluoroethane.

In an abstract that appears to report additional results from the study published by Gunnare et al. (2007) and Gunnare et al. (2005) reported that blood samples, collected 22 hours after exposure, were tested for anti-CYP2E1 antibodies (these antibodies have been detected in humans accidentally exposed to hydrochlorofluorocarbons). No anti-CYP2E1 antibodies were detected in the blood of the nine male volunteers.

ANIMAL STUDIES

Oral Exposures

The database for the oral toxicity of 1,1,1-trifluoroethane is limited to a single chronic-duration/carcinogenicity study in rats using a single dose level. No other oral route toxicity studies were identified.

Chronic-Duration/Carcinogenicity Studies

Longstaff et al. (1984)

Alpk/Ap (Wistar-derived) 6-week-old rats (36/sex) were administered 1,1,1-trifluoroethane (99.5% pure) via gavage at 300 mg/kg-day 5 days/week for 52 weeks and sacrificed at Week 125; this dose corresponds to an adjusted daily dose (ADD) of 214 mg/kg-day and HED[1] of 51.4 mg/kg-day. Untreated (32/sex) and vehicle-only (40/sex) control groups were used. The test material was dissolved in corn oil and stored in pressurized, sealed containers at a temperature of 4°C to minimize volatilization; however, stability of the test solutions was not evaluated, and the dosing solutions were not verified analytically. All animals were examined daily for mortality and clinical signs of toxicity. Body weights were recorded weekly for the first 12 weeks and every 4 weeks thereafter. At study termination, all animals were subjected to necropsy; the lungs, liver, spleen, kidneys, brain, as well as gross lesions were examined microscopically. Statistical analysis was not described in the report.

No significant effects on mortality or clinical signs of toxicity were reported (Longstaff et al., 1984). The study authors reported a significant decrease in the mean body weight of treated males (but not females) from study Weeks 28−88; however, the magnitude of the decrease was not provided, and body-weight data were not given in the study report. No histopathology data were shown; the study authors indicated only that there were no significant increases in the incidence of neoplasms relative to controls (with no mention of non-neoplastic effects). The lack of stability testing and/or analytical verification of the dosing solution is an important limitation of this study; because 1,1,1-trifluoroethane is extremely volatile, the actual dose received by the animals is highly uncertain in the absence of this information. Due to the uncertainty in dose and the lack of quantitative information on results, effect levels cannot be identified for this study, and it is not suitable for use in deriving a provisional oral reference dose for 1,1,1-trifluoroethane.

Inhalation Exposures

The inhalation toxicity of 1,1,1-trifluoroethane has been studied in two 4-week studies in rats, one 90-day study in rats, and in developmental toxicity studies in rats and rabbits, all published by Brock et al. (1996). No other repeated-exposure toxicity studies were identified.

Subchronic-Duration Studies

Brock et al. (1996) (4-week study)

In an initial study, Crl:CDBR rats (10/sex/group, 3−8-weeks-old) were exposed nose-only to 1,1,1-trifluoroethane (>99.9% pure) at 0, 2,000, 10,000, or 40,000 ppm 6 hours/day, 5 days/week, for 4 weeks. Chamber atmospheres were generated by metering the vapor from a cylinder through a flow meter into a mixing vessel where dilution air was added. The chemical/air mixture then flowed into the chamber. Chamber concentrations were controlled by varying the test material flow rates into the mixing vessel. These concentrations are equivalent to 0, 6,874, 34,370, and 137,500 mg/m^3. Animals were observed daily for mortality and clinical signs of toxicity. Body weights were recorded twice per week and food consumption was monitored weekly. Hematology (red blood cell [RBC] count, total and differential white blood cell [WBC] counts, hematocrit [Hct], hemoglobin [Hb], and mean corpuscular volume [MCV], hemoglobin [MCH], and hemoglobin concentration [MCHC]), clinical chemistry (activities of alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST],

[1]HED = ADD (214 mg/kg-day) × default dosimetric adjustment factor (0.24 for rats) (U.S. EPA, 2011b).

γ-glutamyl transferase [GGT], lactate dehydrogenase [LDH], creatine kinase [CK], serum glucose, blood urea nitrogen [BUN], albumin, globulin, creatinine, bilirubin, total protein, triglycerides, cholesterol, fluoride, sodium, potassium, chloride, and calcium), and urinalysis (color, volume, pH, specific gravity, sediment, occult blood, glucose, protein, urobilinogen, bilirubin, and ketones) parameters were evaluated at study termination. Ocular examinations were conducted 1 day prior to study initiation and at study termination. All animals were subjected to necropsy; select organ weights (of the brain, spleen, lungs, liver, kidneys, testes, ovaries, and adrenals) were recorded. Complete histopathological examinations (>45 tissues) were performed.

No data were shown for any of the endpoints evaluated (Brock et al., 1996). Measured exposure concentrations were not reported; however, procedural problems (including ill-fitting conical-restraining devices and exposure to excessively high temperatures), were noted by the study authors. Early deaths occurred in 1/10 males exposed at 6,874 and 34,370 mg/m^3 and 1/10 females exposed at 137,500 mg/m^3. These deaths were not considered by the study authors to be treatment-related. No significant clinical signs of toxicity were observed during or after cessation of exposure. Periodic reductions in the mean body weights of male (but not female) rats were reported in all exposure groups. No significant, exposure-related effects on food consumption, clinical pathology, ocular examinations, or organ weights were observed. Histopathological findings were confined to males. Male rats from all 1,1,1-trifluoroethane exposure groups showed degenerative changes of the testes, characterized by the accumulation of eosinophilic debris within the lumen of the seminiferous tubules; these lesions reportedly occurred in the absence of germ cell necrosis or tubular structural changes. Although incidence data from control animals were not provided, the study authors indicated that seven to eight animals in each exposure group were affected. Epididymal effects (decreased sperm density and increased exfoliated germ cell debris) were seen in conjunction with testicular damage. Histopathological changes to the epididymis occurred in 3/10 males exposed at 6,874 mg/m^3 (classified as very slight) and 7 to 8 males exposed at 34,370 and 137,500 mg/m^3 (minimal to mild). No NOAEL or LOAEL is established for testicular effects because: (1) the incidence rates in the control rats are unreported; (2) rats were exposed to extreme conditions associated with experimental procedure problems (e.g., high temperatures in habitat); and, (3) testicular injury could not be replicated in rats when extraneous factors were controlled (see below).

In a follow-up experiment to determine if testicular effects were related to test substance administration or temperature stress from the procedural problems encountered during the initial experiment, male Crl:CDBR rats (10/group) were exposed whole-body to 1,1,1-trifluoroethane under the same exposure conditions (Brock et al., 1996). In this study, no clinical signs of toxicity or testicular effects were observed at any exposure concentration. No further information was provided. Combined, these two studies identify a NOAEL of 137,500 mg/m^3. No LOAEL was determined. Exposure concentrations of 6,874, 34,370, and 137,500 mg/m^3 were adjusted for discontinuous exposure and converted to HECs of 1,228, 6,138, and 24,550 mg/m^3 (see derivation section for details).

Brock et al. (1996) (90-Day Study)

The 90-day rat study reported in Brock et al. (1996) is considered the principal study for derivation of the subchronic and chronic p-RfCs. Crl:CDBR rats (20 sex/group, 3−8-weeks-old; actual age not reported) were exposed whole-body to 1,1,1-trifluoroethane at 0,

2,000, 10,000, or 40,000 ppm (0, 6,874, 34,370, and 137,500 mg/m^3) 6 hours/day, 5 days/week, for 90 days. Mortality and clinical signs of toxicity were monitored daily; body weights and food consumption were recorded weekly. Hematology, clinical chemistry, and urinalysis parameters, organ weights, and gross and microscopic pathology were evaluated as described previously for the 4-week studies by the same authors (Brock et al., 1996). In addition to these endpoints, liver samples collected at study termination (from five rats/group; sex not specified) were analyzed for hepatic β-oxidation activity (a measure of peroxisome proliferation).

No data were shown for any of the endpoints evaluated (Brock et al., 1996). No mortality, clinical signs of toxicity, or changes in food intake were observed. Changes in body weights (direction and magnitude not reported; statistical significance of changes not specified) were observed "sporadically" throughout the study, but were not considered exposure-related as the changes were inconsistent and an exposure-response relationship was not evident. No changes in clinical pathology (hematology, clinical chemistry, or urinalysis parameters) or β-oxidation were reported. Organ weights were unaffected by exposure; no gross or adverse histopathological changes were noted. This study identifies a NOAEL of 137,500 mg/m^3. No LOAEL was determined. Exposure concentrations of 6,874, 34,370, and 137,500 mg/m^3 were converted to HECs of 1,228, 6,138, and 24,550 mg/m^3 as described previously for the 4-week study.

Developmental Studies

Brock et al. (1996) (rat study)

Mated female Crl:CDBR (about 25/group, 3−8-weeks-old; actual age not reported) were exposed whole-body to 1,1,1-trifluoroethane (>99.9% pure) at 0, 2,000, 10,000, or 40,000 ppm 6 hours/day on Gestation Days [GDs] 6−15. These concentrations are equivalent to 0, 6,874, 34,370, and 137,500 mg/m^3. Dams were monitored daily for mortality and clinical signs of toxicity; body weights were recorded on GDs 1, 7, 9, 11, 13, 15, 17, and at sacrifice. Food consumption was measured over each weighing interval. No maternal toxicity endpoint data was reported. Dams were sacrificed on GD 20. Endpoints evaluated included numbers of resorptions, implantations, corpora lutea, and live and dead fetuses. The uteri of nonpregnant rats were stained with ammonium sulfide to detect early resorptions. Fetuses were weighed, sexed, and then examined for external malformations. Live fetuses were sacrificed (time point not specified) and evaluated for visceral (including delays in renal development) and skeletal variations. Fetuses with external malformations were likewise examined for delays in development (no further information was provided). Preimplantation loss was calculated as a percentage by subtracting the number of total implantations from the number of corpora lutea divided by the number of corpora lutea. Similarly, the percentage of postimplantation loss was determined by subtracting the number of live young from the number of total implantations divided by the number of implantations. Litter weights and mean fetal weights were calculated from individual fetal weights. Data from rats with whole litter loss and those that did not become pregnant were excluded from statistical analyses. Statistical analyses were performed using the litter as the unit of measure.

No mortality among dams or fetuses was reported (Brock et al., 1996). Dams showed no clinical signs of toxicity, and there were no significant effects on body weight/body-weight gain or food consumption. No exposure-related effects on the numbers of resorptions, corpora lutea, implantations (pre and postimplantation loss), or live and dead fetuses were observed. Fetal body weights were unaffected by exposure. Litter data for one of the high-dose dams were

missing from the tabulated data on malformations and variations. The publication does not indicate any reason for this other than the statement that data from rats with whole litter loss and those that were not pregnant were excluded; however, the dam was apparently pregnant as it was included in the data on corpora lutea, implants, resorptions, live young, and fetal weights. The incidence of total malformations (combined across skeletal, soft tissue, and external) in the exposed groups was not significantly different from controls (data for individual types of malformations were not provided by the study authors).

No external variations were observed in any group. When all variations (visceral and skeletal) were combined, the mean percentage per litter of fetuses with variations was statistically significantly increased at the highest concentration, with mean values of 7.9, 12.8, 12.6, and 16.7% for the control, low-, mid-, and high-concentration groups, respectively (see Table B-1). The mean percentage per litter of fetuses with visceral variations due to delayed development was statistically significantly increased at all concentrations relative to the control group, with mean percentages of 1.6, 10.5, 8.7, and 10.0% for the control, low-, mid-, and high-concentration groups, respectively (see Table B-1) (Brock et al., 1996). The percentages per litter of fetuses with skeletal variations owing to delayed development were not provided in the study report. The increased incidence in visceral variations was attributable to patent ductus arteriosus and small papilla; the increase in skeletal variations was attributed to wavy ribs, partially ossified/unossified skull, partially ossified sternebra, and partially ossified vertebra (see Table B-1). The incidences of skeletal variations in exposed animals did not differ significantly from the incidences in controls, and there were no indications of dose-response relationships in the incidences of skeletal variations (see Table B-1).

The study authors considered the significant increase in visceral variations at all concentrations to be a reflection of an unusually low incidence (1.6%) in the control group. The historical control range for visceral variations in developmental inhalation toxicity studies in rats for the laboratory ranges from 6.8−16.2%, with a mean of ~10.5%. Thus, the incidence of visceral variations in the control group for this study is not within the historical control range. Furthermore, the historical control average is similar to the mean observed for the 1,1,1-trifluoroethane-exposed groups for visceral variations in this study. This unusually low incidence in the control also affects the total variations (which includes visceral variations). It is also important to note that the numbers of litters with all variations actually decreases with dose. Based on the rational above and because no other developmental effects were observed, the increased incidence of visceral variations in this study is not considered by U.S. EPA to be clearly related to exposure to 1,1,1-trifluoroethane. As no effects that were considered to be treatment-related occurred, the NOAEL for maternal and developmental toxicity is 137,500 mg/m^3, and no LOAEL is identified. Exposure concentrations in this study were equivalent to HECs of 0, 1,719, 8,593, and 34,380 mg/m^3 based on an adjustment for discontinuous exposure of 6 hours/day, and the default value of 1 for the ratio of blood:air partition coefficients between rats and humans.

Brock et al. (1996) (rabbit study)

In a developmental toxicity study, artificially inseminated New Zealand 4−5-month-old female rabbits (24/group) were exposed to 1,1,1-trifluoroethane (>99.9% pure) at concentrations of 0, 2,000, 10,000, or 40,000 ppm via whole-body inhalation for 6 hours daily on GDs 6−18. These concentrations are equivalent to 0, 6,874, 34,370, and 137,500 mg/m^3, respectively. Although chamber concentrations were monitored periodically during the exposures, measured

1,1,1-trifluoroethane concentrations were not reported. The animals were observed daily for clinical signs and were weighed on GDs 0, 6−19, 24, and 29. Food consumption was determined daily. No maternal toxicity endpoint data were reported. On GD 29, the maternal animals were sacrificed and the internal organs evaluated for gross abnormalities. The ovaries and uteri were examined for the number of corpora lutea, live young, early and late embryo/fetal deaths, and fetal abnormalities. Total litter weights were calculated from individual fetal weights. The same criteria as described above for the developmental toxicity study in rats (Brock et al., 1996) were used to evaluate fetal deaths. Uteri without macroscopic evidence of nidation were examined for early implantation loss. Live young were examined externally for malformations. Visceral and skeletal malformations and variations were characterized.

No clinical signs were noted in maternal animals at any exposure level during or after the exposures (Brock et al., 1996). No statistically significant effects on maternal body weights, body-weight gains, or food consumption were noted. There were no treatment-related effects on corpora lutea or implants. A slight increase in the incidence of combined (external, skeletal, and soft tissue) malformations, expressed as mean percentage per litter, was observed in the low- and high-concentration groups, with values of 3.1, 8.2, 3.4, and 7.1% for the control, low-, mid-, and high-concentration groups, respectively; however, these changes were not statistically significant (see Table B-2). The authors noted that the increase was primarily related to an increase in skeletal malformations at the low and high concentrations; the percentage incidences per litter were as follows: 1.5, 7.5, 3.4, and 6.3% for the control, low-, mid-, and high-concentration groups, respectively. The incidences of external and soft tissue malformations were similar to controls. The increase in skeletal malformations was primarily associated with rib anomalies (e.g., extra site of ossification) and vertebral anomalies. No clear concentration-response relationship was apparent for either the types or numbers of malformations, and the incidence in all dose groups was well within the historical laboratory control range for total malformations (0−12.9%). The study authors considered the modest increases in skeletal malformations at the low and high concentrations to be unrelated to 1,1,1-trifluoroethane exposure. The skeletal or visceral variations are considered not treatment-related effects based on Carney and Kimmel (2007). As no effects that were considered to be treatment-related occurred, the NOAEL for maternal and developmental toxicity is 137,500 mg/m^3, and no LOAEL is identified. Exposure concentrations in this study were equivalent to HECs of 0, 1,719, 8,593, and 34,380 mg/m^3 based on an adjustment for discontinuous exposure of 6 hours/day, and the default value of 1 for the ratio of blood:air partition coefficients between rabbits and humans.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Acute Toxicity

Brock et al. (1996) also evaluated the acute lethality of 1,1,1-trifluoroethane in rats. Crl:CDBR rats (6 males/group, 3−8-weeks-old; actual age not reported) were administered 1,1,1-trifluoroethane (>99.9% pure) at concentrations of 97,000 (333,400 mg/m^3) or 540,000 ppm (1,856,000 mg/m^3) via nose-only exposure for 4 hours. The animals were weighed and observed for clinical signs during a 14-day postexposure observation period. No mortalities or treatment-related clinical signs occurred during the study. Body-weight losses were observed at both concentrations on the day following exposure. The body-weight losses were considered to be slight at the low concentration (<10 g/rat) and moderate to severe at the high concentration (10 − >20 g/rat); however, bodyweight data were not provided in the study report. Normal body-weight gains were observed by postexposure Day 2 and throughout the remainder of the 14-day observation period. The results of this study are consistent with other acute lethality

studies on other hydrofluorocarbons (ECETOC, 2006), which show median lethal concentration (LC_{50}) values >500,000 ppm.

A study of the cardiac sensitization potential of 1,1,1-trifluoroethane was also reported by Brock et al. (1996). Male Beagle dogs (5−6/group, 16−20-months-old) were administered 1,1,1-trifluoroethane (>99.9% pure) at concentrations of 0, 50,000, 100,000, 150,000, 200,000, 250,000, or 300,000 ppm (171,860, 343,720, 515,580, 687,440, 859,310, and 1,031,200 mg/m^3) via single-pass-through face mask while the dog was restrained in a canvas sling (the dogs had been previously trained to accept this sling). Electrocardiogram (ECG) leads were placed on each dog and the ECG was recorded throughout the 17-minute exposure pretest. After 2 minutes of breathing only room air, a subthreshold intravenous dose of epinephrine (i.e., control dose at 2−12 µg/kg determined based on a preliminary study to confirm the tolerable dose for each dog) was administered to each dog in order to establish a background ECG response. Five minutes after the control dose of epinephrine was administered, vapor administration of 1,1,1-trifluoroethane was initiated for 10 minutes. After 5 minutes of 1,1,1-trifluoroethane exposure, epinephrine was administered again, and changes in the ECG recording were noted. Evidence of cardiac sensitization was determined if multiple ectopic beats (>5) or ventricular fibrillation was observed.

No evidence of cardiac sensitization was observed at 171,860, 343,720, or 515,580 mg/m^3 (Brock et al., 1996). At 687,440 mg/m^3, 1/6 dogs exhibited an equivocal response consisting of two ectopic beats with normal sinus rhythm occurring between the ectopic beats. At 859,300 mg/m^3, however, none of the dogs exhibited an arrhythmia, including the dog that previously showed an equivocal response at 687,440 mg/m^3. Therefore, the response observed in the one dog exposed to 687,440 mg/m^3 was classified as a negative response. At 1,031,200 mg/m^3, 2/5 dogs showed evidence of a cardiac sensitization response, including multiple ectopic beats or a burst of ventricular fibrillation. Another dog exhibited whole-body tremors, verging on convulsions, a response that interferes with the ECG readings; thus, no higher concentrations of 1,1,1-trifluoroethane were tested. The study authors concluded that 1,031,200 mg/m^3 represented the threshold for cardiac sensitization in dogs under the conditions of the study.

Genotoxicity

1,1,1-Trifluoroethane did not induce gene mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, or TA1538, or in *Escherichia coli* strain WP2uvrA, either in the presence or absence of metabolic activation (Brock et al., 1996). Although an additional study (Longstaff et al., 1984; Central Toxicol Lab, 1976) also showed that mutations were not induced in strains TA98 and TA1538, this study showed that 1,1,1-trifluoroethane was positive for gene mutations in strains TA100 and TA1535, both with and without metabolic activation. The reason(s) for the discrepancy in results between the studies conducted by Brock et al. (1996) and Longstaff et al. (1984) is unknown. However, the 50% concentration (above the explosive concentration) in the Longstaff et al. (1984) studies may have had nonspecific mutagenic effects (changes in pH, etc) that could account for the discrepancy. 1,1,1-Trifluoroethane was negative for cell transformation (Styles assay) in BHK21 cells in the presence of metabolic activation (Longstaff et al., 1984). 1,1,1-Trifluoroethane did not induce chromosomal aberration in vitro in cultured human lymphocytes, either with or without metabolic activation (Brock et al., 1996). The frequency of micronuclei was not increased in polychromatic erythrocytes of 7-week-old mice exposed to 1,1,1-trifluoroethane via inhalation

6 hours/day for 2 days (Brock et al., 1996). Table 4 provides an overview of genotoxicity studies of 1,1,1-trifluoroethane.

Metabolism/Toxicokinetic Studies

1,1,1-Trifluoroethane is absorbed rapidly after inhalation exposure. As part of the acute human exposure study by Gunnare et al. (2007), the toxicokinetics of 1,1,1-trifluoroethane were evaluated in nine male volunteers exposed for 2 hours to 500 ppm (1,720 mg/m^3) during light physical exercise. Samples of the volunteers' blood, urine, and exhaled air were collected before, during, and for up to 19 hours after the end of exposure, for analysis of 1,1,1-trifluoroethane by gas chromatography. Concentrations in blood rapidly (within a few minutes) reached steady-state and remained unchanged during the exposure period. At the end of exposure, blood levels declined rapidly; 1,1,1-trifluoroethane could not be detected in blood 1 day after exposure. Analysis of exhaled air showed no measureable differences between the concentration in inhaled and exhaled air, suggesting low respiratory uptake. As with blood levels, 1,1,1-trifluoroethane levels in exhaled air declined rapidly upon cessation of exposure, with a decay time profile parallel to that of blood. Small amounts of unchanged 1,1,1-trifluoroethane were measured in the urine. Based on analysis of urine samples, the half-life of 1,1,1-trifluoroethane in urine was calculated to be 53 minutes. Total urinary excretion was estimated to represent 0.0007% of the amount inhaled, suggesting very poor absorption; however, the study authors indicated that absorption could not be estimated from the experimental data.

The measured blood and exhaled air levels were in good agreement with values simulated using a perfusion-limited physiologically based toxicokinetic model developed by (Ernstgård et al., 2014; Gunnare et al., 2007). The model predicted that relative respiratory uptake of 1,1,1-trifluoroethane was ~2% of the inhaled dose.

Ernstgård et al. (2010) measured the blood:air partitioning coefficient for 1,1,1-trifluoroethane in human blood using a modified head-space vial equilibrium method. The blood:air partitioning coefficient for 1,1,1-trifluoroethane was 0.15. No experimental data on the blood:air partitioning of 1,1,1-trifluoroethane in rat blood were available. Loizou et al. (1996) estimated the rat blood:air partitioning coefficient for 1,1,1-trifluoroethane based on the relationship between measured rat blood:air partitioning for other trihaloethanes and the amount retained in the body in rats exposed via inhalation. The estimated value for 1,1,1-trifluoroethane was 0.91.

Mechanistic Studies

Loizou et al. (1996) exposed rats to concentrations of 0, 10,000, 15,000, 20,000, or 30,000 ppm 1,1,1-trifluoroethane (34,370, 51,555, 68,740 and 103,110 mg/m^3, respectively) for 3 hours. Blood was collected 2 hours later for analysis of serum sorbitol dehydrogenase (SDH), glutamate dehydrogenase (GDH), and LDH. In addition, glutathione and glutathione disulfide levels in liver and lung were measured. No changes to serum dehydrogenase levels were observed at any concentration. Total glutathione in the liver was significantly decreased at all exposure levels; glutathione disulfide levels were not affected in either organ, nor were glutathione levels in the lung. The authors attributed the decline in liver glutathione to P450 uncoupling (in which the fluorinated compound forms a P450-substrate complex, triggering electron flow to the cytochrome and oxygen activation), which leads to formation of reactive oxygen species.

Table 4. Summary of 1,1,1-Trifluoroethane Genotoxicity Studies

Endpoint	Test System	Doses/Concentrations Tested	Results Without Activation[a]	Results With Activation[a]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	*S. typhimurium* strains TA97, TA98, TA100, TA1535 (Test 1); *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 (Test 2)	Test 1: 0, 0.5, 1.5, 2.5, 3.5% (v/v) (±S9) (gas dissolved in liquid) Test 2: 0, 20, 40, 60, 80,100% (Trial 1; −S9); 0, 10, 30, 50, 70, 90% (Trial 2; ±S9) (gas in air space)	–	–	Preincubation assay (closed vessels at 37°C for 48 hr). Exposure concentrations were changed after the first trial of Test 2 because of difficulty in generating a vapor with 100% concentration.	Brock et al. (1996)
Mutation	*S. typhimurium* strain TA98, TA100, TA1535, TA1538	Test 1: 0, 1, 33, 50% Test 2: 50% (TA100 and TA1535 only)	+ TA100, TA1535 – TA98, TA1538	+ TA100, TA1535 – TA98, TA1538	Modified Ames assay for testing gases; incubation for 24 hr (Test 1) or 48 hr (Test 2). Gas In air space.	Longstaff et al. (1984); Central Toxicol Lab (1976)
Mutation	*E. coli* strain WP2uvrA (pkm 101) (Test 1); *E. coli* strain WP2uvrA (Test 2)	Test 1: 0, 0.5, 1.5, 2.5, 3.5% (v/v) (±S9) (gas dissolved in liquid) Test 2: 0, 20, 40, 60, 80,100% (Trial 1; −S9); 0, 10, 30, 50, 70, 90% (Trial 2; ±S9) (gas in air space)	–	–	Preincubation assay (closed vessels at 37°C for 48 hr). Exposure concentrations were changed after the first trial of Test 2 because of difficulty in generating a vapor with 100% concentration.	Brock et al. (1996)

Table 4. Summary of 1,1,1-Trifluoroethane Genotoxicity Studies

Endpoint	Test System	Doses/Concentrations Tested	Results Without Activation[a]	Results With Activation[a]	Comments	References
Genotoxicity studies in mammalian cells in vitro						
Chromosomal aberrations	Human lymphocytes	0, 17,190, 51,560, 95,930, 120, 300 mg/m^3	–	–	No significant increase in the frequency of aberrations at 95,930 or 120,300 mg/m^3. Scoring was not conducted at 17,190 and 51,560 mg/m^3 because of the lack of findings at higher concentrations.	Brock et al. (1996)
Cell transformation	BHK21 cells	NR	NA	–	No significant increase in cell transformation.	Longstaff et al. (1984)
Genotoxicity studies in vivo						
Mouse bone marrow MN test (inhalation)	Mice (5/sex/group; unspecified strain) exposed 6 hr/d for 2 consecutive days, and sacrificed 24−48 hr after second exposure for analysis of bone marrow smears	0, 2,000, 10,000, 40,000 ppm (0, 6,874, 34,370, 137,500 mg/m^3)	–		No significant increase in micronucleated polychromatic erythrocytes.	Brock et al. (1996)

NA = not available; NR = not reported.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer reference values, respectively.

Table 5. Summary of Reference Values for 1,1,1-Trifluoroethane (CASRN 420-46-2)

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						
Subchronic p-RfC (mg/m^3)	Rat, M/F	NR	2×10^2	$NOAEL_{HEC}$	24,550	100	Brock et al. (1996)
Chronic p-RfC (mg/m^3)	Rat, M/F	NR	2×10^1	$NOAEL_{HEC}$	24,550	1,000	Brock et al. (1996)

NDr = not determined; NR = none reported.

Table 6. Summary of Cancer Values for 1,1,1-Trifluoroethane (CASRN 420-46-2)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
Provisional oral slope factor (p-OSF)	NDr			
Provisional inhalation unit risk (p-IUR)	NDr			

NDr = not determined.

DERIVATION OF ORAL REFERENCE DOSES

The database for oral exposure to 1,1,1-trifluoroethane is limited to a single chronic-duration study of rats exposed by gavage (Longstaff et al., 1984). In this study, a significant decrease in the mean body weight of treated males (but not females) from study Weeks 28−88 was reported, but the magnitude of change was not provided and body-weight data were not given. No other effects were observed. Longstaff et al. (1984) did not perform analytical verification of the dosing solutions. Because 1,1,1-trifluoroethane is extremely volatile, the actual doses received by the animals are highly uncertain in the absence of analytical verification. Due to the uncertainty in doses and the lack of quantitative information on results, these data are not considered to be suitable for use in deriving a provisional oral RfD for 1,1,1-trifluoroethane.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The peer-reviewed experiments published by Brock et al. (1996) include short-term, subchronic, and developmental toxicity assays in rats, and a developmental toxicity study in rabbits. None of these studies identified any statistically or biologically significant health effects attributable to 1,1,1-trifluoroethane exposure at HEC concentrations as high as 24,550 mg/m^3 for 90 days or 34,380 mg/m^3 during gestation. The Brock et al. (1996) experiments, along with an acute lethality and a cardiac sensitization experiment described in the same publication, comprise the entire database of information on inhalation toxicity of 1,1,1-trifluoroethane in experimental animals. In the acute lethality and cardiac sensitization studies, no mortality was seen among

groups of six rats exposed for 4 hours to concentrations up to 1,856,000 mg/m^3, but evidence for cardiac sensitization was observed in dogs exposed to 1,031,200 mg/m^3 1,1,1-trifluoroethane for 10 minutes.

The low systemic toxicity of 1,1,1-trifluoroethane is supported by toxicokinetic studies indicating low absorption of this compound after inhalation exposure, and by similar findings in studies of the related compound, 1,1-difluoroethane. The IRIS chronic RfC for 1,1-difluoroethane is based on a NOAEL of 67,500 mg/m^3 (25,000 ppm) from a 2-year inhalation study (U.S. EPA, 2005).

1,1,1-Trifluoroethane is flammable at concentrations ≥240,000 mg/m^3 (70,000 ppm) (Brock et al., 1996). Thus, it is unlikely that repeated exposure toxicity testing will be performed at concentrations much higher than those already tested (137,500 mg/m^3 or 40,000 ppm).

Derivation of Subchronic p-RfC

The $NOAEL_{HEC}$ of 24,550 mg/m^3 from the 90-day principal study (Brock et al., 1996) is chosen as the POD for the derivation of a subchronic p-RfC, because this experiment used the longest exposure duration and examined comprehensive toxicity endpoints. Because there were no significant responses at the highest concentration tested, BMD modeling is not conducted; thus, the $NOAEL_{HEC}$ is used as the POD. The $NOAEL_{HEC}$ was calculated based on extrarespiratory effects, as the only health effect observed in any of the experiments by Brock et al. (1996) was cardiac sensitization in dogs.

Exposure concentration adjustment for continuous exposure:

$NOAEL_{ADJ}$ = NOAEL × (MW ÷ 24.45) × (hours exposed ÷ 24) × (days exposed ÷ 7 days)

= 40,000 ppm × (84.04 ÷ 24.45) × (6 hours ÷ 24 hours) × (5 days ÷ 7 days)

= 24,550 mg/m^3

HEC conversion for extrarespiratory effects:

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ × DAF;

DAF (dosimetric adjustment factor for the specific site of effects such as extrarespiratory regions).

The DAF for gases/vapors with toxicity effects at sites remote of the respiratory tract (extrarespiratory effects) is based on the ratio of the animal blood:gas partition coefficient ($H_{b/g\text{-}animal}$) and the human blood:gas partition coefficient ($H_{b/g\text{-}human}$).

DAF = $([H_{b/g}]_A \div [H_{b/g}]_H)$

[The value of 1.0 is used when the rat partition coefficient exceeds the human partition coefficient, as recommended by U.S. EPA (1994b).]

$NOAEL_{HEC} = NOAEL_{ADJ} \times DAF$

$= 24{,}550 \times 1.0$

$= 24{,}550\ mg/m^3$

The provisional subchronic p-RfC of 2 x 10^2 mg/m^3 was calculated as follows:

Provisional Subchronic p-RfC = $NOAEL_{HEC} \div UFc$
= $24{,}550\ mg/m^3 \div 100$
= **$2 \times 10^2\ mg/m^3$**

The uncertainty factors are described in Table 7.

Table 7. Uncertainty Factors for the Subchronic p-RfC for 1,1,1-Trifluoroethane

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_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of 1,1,1-trifluoroethane in humans.
UF_D	3	A UF_D of 3 is applied because there are two 4-wk studies and a subchronic study conducted in rats and developmental toxicity studies in rats and rabbits via the inhalation route; however, there are no two-generation reproduction studies.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic study is utilized as the principal study.
UF_C	100	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

The confidence descriptors for the subchronic p-RfC are explained in Table 8.

Table 8. Confidence Descriptors for Subchronic p-RfC for 1,1,1-Trifluoroethane

Confidence Categories	Designation	Discussion
Confidence in study	M	The principal study included appropriate numbers of animals in exposure and control groups for meaningful statistical analyses and assessment of a wide range of toxicological endpoints (clinical signs, body weight, food consumption, hematology, serum chemistry, urinalysis, selected organ weights, and comprehensive gross and microscopic pathology). The major factor restricting confidence in the principal study is the failure to include an exposure concentration high enough to permit identification of a LOAEL.
Confidence in database	M	Confidence in the database is medium. The inhalation database for noncancer effects of 1,1,1-trifluoroethane consists of two 4-wk studies in rats, a subchronic study in rats, and developmental toxicity studies in rats and rabbits. There are no pertinent human data, and no reproductive toxicity studies in animals.
Confidence in subchronic p-RfC	M	The overall confidence in the subchronic p-RfC for 1,1,1-trifluoroethane is medium.

M = medium.

Derivation of Chronic p-RfC

In the absence of chronic data from which to derive the provisional chronic p-RfC, the $NOAEL_{HEC}$ from the subchronic experiment (Brock et al., 1996) is selected as the POD for the provisional chronic p-RfC.

The provisional chronic p-RfC of 2×10 mg/m^3 is derived as follows:

$$\textbf{Provisional chronic p-RfC} = NOAEL_{HEC} \div UFc$$
$$= 24{,}550 \text{ mg/m}^3 \div 1{,}000$$
$$= \mathbf{2 \times 10^1 \text{ mg/m}^3}$$

The uncertainty factors are described in Table 9.

Table 9. Uncertainty Factors for the Chronic p-RfC for 1,1,1-Trifluoroethane

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_H	10	UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of 1,1,1-trifluoroethane in humans.
UF_D	3	A UF_D of 3 is applied because there are two 4-wk studies and a subchronic study conducted in rats and developmental toxicity studies in rats and rabbits via the inhalation route; however, there are no two-generation reproduction studies.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	10	A UF_S of 10 is applied because a subchronic study is used as the principal study, and there is no chronic study in the database.
UF_C	1,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

The confidence descriptors for the chronic p-RfC are explained in Table 10.

Table 10. Confidence Descriptors for Chronic p-RfC for 1,1,1-Trifluoroethane

Confidence Categories	Designation	Discussion
Confidence in study	M	The study included appropriate numbers of animals in exposure and control groups for meaningful statistical analyses and assessment of a wide range of toxicological endpoints (clinical signs, body weight, food consumption, hematology, serum chemistry, urinalysis, selected organ weights, and comprehensive gross and microscopic pathology). The major factor restricting confidence in the principal study is the failure to include an exposure concentration high enough to permit identification of a LOAEL.
Confidence in database	L	Confidence in the database is low. The inhalation database for noncancer effects of 1,1,1-trifluoroethane consists of two 4-wk studies in rats, a subchronic study in rats, and developmental toxicity studies in rats and rabbits. There are no pertinent human data, and no chronic and reproductive toxicity studies in animals. All of the available experiments were conducted by Brock et al. (1996), and apart from cardiac sensitization after acute exposure to a very high concentration, no health effects were observed.
Confidence in chronic p-RfC	L	The overall confidence in the subchronic p-RfC for 1,1,1-trifluoroethane is low.

M = medium; L = low.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 11 provides the cancer WOE descriptor for 1,1,1-trifluoroethane.

Table 11. Cancer Weight-of-Evidence Descriptor for 1,1,1-Trifluoroethane

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	NA
"Likely to Be Carcinogenic to Humans"	NS	NA	NA
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	NA
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No studies assessing the carcinogenicity of 1,1,1-trifluoroethane in humans exposed by any route or in animals exposed by inhalation are available in the literature. Longstaff et al. (1984) evaluated the carcinogenicity of 1,1,1-trifluoroethane administered by gavage to rats for 52 wk; however, this study is not considered an adequate basis for evaluating carcinogenicity because only 1 dose level was tested, the dose received by the animals is uncertain, the study did not report quantitative information on results, and the exposure duration and observation period were less than the animals' lifespan.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	NA

NA = not applicable; NS = not selected.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

There are insufficient data to assess the carcinogenic potential of 1,1,1-trifluoroethane via any route; therefore, derivation of provisional cancer potency values is precluded.

APPENDIX A. SCREENING PROVISIONAL VALUES

No provisional screening values were derived.

APPENDIX B. DATA TABLES

Table B-1. Developmental Toxicity of 1,1,1-Trifluoroethane in Rats[a]

Endpoint	Exposure Concentration in mg/m^3 (ppm)			
	0	**6,874 (2,000)**	**34,370 (10,000)**	**137,500 (40,000)**
Malformations and variations				
Number of fetuses examined for malformations[b] (litters)	341 (22)	357 (24)	352 (23)	273 (19)
Number of fetuses with malformations[b] (litters)	2 (2)	0 (0)	1 (1)	0 (0)
Mean percent of fetuses with malformations[b] per litter	0.6	0	0.4	0
Number of fetuses examined for visceral variations[c] (litters)	178 (22)	185 (24)	181 (23)	142 (19)
Number of fetuses with visceral variations[c] (litters)	3 (3)	19 (11)	15 (8)	14 (9)
Mean percent of fetuses with visceral variations[c] per litter	1.6	10.5*	8.7*	10.0*
Number of fetuses with all variations[d] (litters)	27 (17)	42 (16)	42 (18)	48 (14)
Mean percent of fetuses with all variations[d] per litter	7.9	12.8	12.6	16.7*
Visceral variations				
Number of fetuses with patent ductus arteriosus (litters)	0	0	5 (1)	1 (1)
Number of fetuses with small papilla (litters)	3 (3)	19 (11)	10 (8)	13 (8)
Skeletal variations				
Number of fetuses with wavy ribs (litters)	3 (2)	2 (2)	0	2 (1)
Number of fetuses with skull partially ossified (litters)	8 (7)	13 (9)	11 (5)	13 (7)
Number of fetuses with sternebra partially ossified (litters)	2 (2)	4 (2)	2 (5)	5 (4)
Number of fetuses with vertebra partially ossified (litters)	14 (7)	6 (4)	14 (9)	19 (7)

[a]Brock et al. (1996).
[b]Combined incidence of skeletal, soft tissue, and external malformations.
[c]Visceral variations due to delayed development (does not include skeletal or external variations).
[d]Total variations due to delayed development; includes visceral, external, and skeletal variations.
*Significantly different ($p < 0.05$) by Jonckheere's test variation (performed by the study authors).

Table B-2. Developmental Toxicity Potential of 1,1,1-Trifluoroethane in Rabbits[a]

Endpoint	Exposure Concentration in mg/m^3 (ppm)			
	0	6,874 (2,000)	34,370 (10,000)	137,500 (40,000)
Malformations[b] and variations				
Number of fetuses examined for malformations (litters)	98 (21)	147 (22)	125 (19)	149 (24)
Number of fetuses with malformations (litters)	4 (3)	14 (7)	5 (2)	5 (5)
Mean percent of fetuses with malformations/litter	3.1	8.2	3.4	7.1
Mean percent of fetuses with visceral variations/litter	20.1	23.4	14.5	16.1
Mean percent of fetuses with skeletal variations/litter	67.5	62.4	66.6	60.0
Mean percent of fetuses with total variations/litter	71.4	69.1	69.1	69.1

[a]Brock et al. (1996).
[b]Combined incidence of skeletal, soft tissue, and external malformations.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

There are no benchmark dose (BMD) modeling outputs.

APPENDIX D. REFERENCES

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