

Provisional Peer-Reviewed Toxicity Values for
1,1,2-Trichloro-1,2,2-trifluoroethane
(CASRN 76-13-1)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,1,2-TRICHLORO-1,2,2-TRIFLUOROETHANE (CASRN 76-13-1)

BACKGROUND

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

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

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

1,1,2-Trichloro-1,2,2-trifluoroethane, CASRN 76-13-1, also known as chlorofluorocarbon 113 (CFC-113) and Freon 113, is currently used as an intermediate for producing halogenated vinyl resins. Throughout this document, the chemical name is abbreviated as CFC-113. Former domestic uses include as a dry cleaning solvent, as a degreasing agent for cleaning semiconductor wafers and printed circuit boards, as a refrigerant in centrifugal compressor systems for water or brine chilling, as an organic tracer in hydrology, and as a foaming or blowing agent in the manufacture of flame-retardant polymers ([HSDB, 2013](#)). CFC-113 is regulated under the Clean Air Act (CAA), the Toxic Substances Control Act (TSCA) Sections 8a and 8d, the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313, the Federal Insecticide, Fungicide, and Rodenticide Act-Inerts (FIFRA-Inerts), and the Resource Conservation and Recovery Act (RCRA) ([U.S. EPA, 2015](#)).

The molecular formula for CFC-113 is $C_2Cl_3F_3$ (see Figure 1). Table 1 provides physicochemical properties for CFC-113. CFC-113 is a volatile, colorless liquid. Its high vapor pressure and high estimated Henry's law constant indicate that it will rapidly volatilize from both dry and moist surfaces. CFC-113 is virtually inert to reaction with photochemically generated radicals in the troposphere. However, if CFC-113 elevates to the stratosphere, it will react with ultraviolet radiation to release chlorine and cause ozone depletion ([U.S. EPA, 2012b](#)). It is expected to contribute to radiative forcing of the climate at magnitudes somewhat less than carbon dioxide and methane and somewhat more than nitrous oxide ([U.S. EPA, 2012b](#)). The moderate water solubility and moderate soil adsorption coefficient of CFC-113 indicate that it may leach to groundwater or undergo runoff after a rain event if deposited on soil. As a result, removal of CFC-113 from soil by leaching with water may compete with volatilization, depending on the local conditions (wet, dry, etc.).

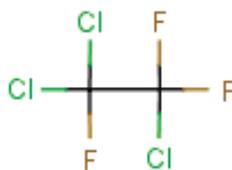


Figure 1. 1,1,2-Trichloro-1,2,2-trifluoroethane (CFC-113) Structure

Table 1. Physicochemical Properties of 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)	
Property (unit)	Value
Physical state	Clear, colorless liquid ^a
Boiling point (°C)	47.7 ^{a,b}
Melting point (°C)	-35.0 ^a
Density (g/cm ³ at 25°C)	1.564 ^b
Vapor pressure (mm Hg at 25°C)	362.5 ^a
pH (unitless)	NV
pKa (unitless)	NV
Solubility in water (mg/L at 25°C)	170 ^{a,b}
Octanol-water partition constant (log K _{ow})	3.16 ^{a,b}
Henry's law constant (atm-m ³ /mol at 20°C)	0.53 (estimated) ^{a,b}
Relative vapor density (air = 1)	6.5 ^b
Molecular weight (g/mol)	187.38 ^{a,b}

^a[U.S. EPA \(2012b\)](#).

^b[HSDB \(2013\)](#).

NV = not available.

A summary of available toxicity values for CFC-113 from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)			
Source (parameter)^{a,b}	Value (applicability)	Notes	Reference
Noncancer			
IRIS (RfD)	30 mg/kg-d	Based on route-to-route extrapolation from study showing no adverse effects observed in humans occupationally exposed at 5,358 mg/m ³ for 2.77 yr.	U.S. EPA (1987)
HEAST (sRfD)	3 mg/kg-d	Based on route-to-route extrapolation from study showing decreased body weight in rats exposed by inhalation for 24 mo.	U.S. EPA (2011)
HEAST (RfC)	30 mg/m ³	Based on decreased body weight in rats exposed by inhalation for 24 mo.	U.S. EPA (2011)
HEAST (sRfC)	30 mg/m ³	Based on decreased body weight in rats exposed by inhalation for 24 mo.	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2016)
IPCS	NV	NA	IPCS (2016); WHO (2016)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2016a); Cal/EPA (2016b)
OSHA (PEL)	1,000 ppm (7,600 mg/m ³)	8-hr TWA	OSHA (2014)
NIOSH (REL)	1,000 ppm (7,600 mg/m ³)	10-hr TWA during a 40-hr work week.	NIOSH (2015)
ACGIH (TLV-TWA)	1,000 ppm (7,670 mg/m ³)	Set to minimize the potential of narcosis, asphyxia, cardiac sensitization, and arrhythmia.	ACGIH (2015)
Cancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)

Table 2. Summary of Available Toxicity Values for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)			
Source (parameter)^{a,b}	Value (applicability)	Notes	Reference
Cal/EPA	NV	NA	Cal/EPA (2011) ; Cal/EPA (2016a) ; Cal/EPA (2016b)
ACGIH (WOE)	A4; not classifiable as a human carcinogen	Tumors in test animals were concluded to be not dose-related.	ACGIH (2015)

^aSources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Research; 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.

^bParameters: PEL = permissible exposure level; REL = recommended exposure limit; sRfC = subchronic reference concentration; sRfD = subchronic reference dose; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in February and September 2016 for studies relevant to the derivation of provisional toxicity values for 1,1,2-trichloro-1,2,2-trifluoroethane (CASRN 76-13-1). 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 values: ACGIH, ATSDR, Cal/EPA, 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 CFC-113, respectively, and include all potentially relevant acute, repeat-dose short-term-, subchronic-, and chronic-duration studies as well as reproductive and developmental toxicity studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)

Category ^a	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	BMDL/ BMCL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m³)^a								
Acute experimental	2 M/0 F, human, 1.5 hr	0, 1,500, 2,500, 3,500, 4,500 ppm (in series) 0, 11,500, 19,160, 26,820, 34,490	Deficits in complex psychomotor tasks (manual dexterity, Short Employment Test-Clerical, and card sorting with auxiliary task) and clinical signs of toxicity (loss of concentration, drowsiness, feeling of heaviness, effects on vision) at $\geq 19,160$ mg/m ³	11,500	NA	19,160	Haskell Laboratories (1964)	NPR
Short-term experimental	4 M/0 F, human, 6 hr/d (3-hr exposures twice daily), 5 d/wk stepwise increase in concentrations for 3 wk	0, 500, 1,000 ppm ADJ: 0, 958, 1,920 (in series; 1 concentration per wk)	No significant adverse effects on clinical signs (including temperature, pulse, and equilibrium assessments), hematological, clinical chemical, and urinalysis parameters; pulmonary function, or psychomotor parameters	1,920	NA	NDr	Reinhardt et al. (1971)	PR
Occupational	10 M/6 F, human, low concentration (precleaning rooms) or high concentration (cleaning rooms) during 7-hr work shifts 2 wk apart; average of 7.8 yr of employment	64.4, 442.1 ppm ADJ: 154, 1,059	No differences with respect to clinical signs or cardiac function (EKG parameters) during exposure in workers on high-exposure days compared to low-exposure days	1,059	NA	NDr	Egeland et al. (1992)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)

Category ^a	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	BMDL/ BMCL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Long-term occupational	6 M/0 F exposed, 11 M/0 F unexposed, human, mean duration of 2.5 yr	0, 523 ADJ: 0, 187 ^d	No significant adverse effects on liver function (based on clinical chemistry); observed changes in serum bile acid levels were of uncertain biological significance	187	NA	NDr	Neghab et al. (1997)	PR
Long-term occupational	50 M/0 F exposed and 50 M/0 F unexposed, human, average of 2.77 yr	0, 699 ppm ADJ: 0, 1,440 ^d	No significant effects with respect to physical examinations, EKG parameters, visual or auditory exams, chest x-ray or timed vital capacity, hematology, clinical chemistry, and urinalysis evaluations	1,440	DUB	NDr	Imbus and Adkins (1972)	PS, PR
Animal								
1. Oral (mg/kg-d)^a								
Developmental	0 M/8 F, rabbits (strain not specified), oral (not further specified), dosing for 4 d starting on GD 8	0, 1,000, 5,000	Does: high mortality; other effects in exposed animals included clinical signs of toxicity, reductions in food and water consumption, and decreased body weights Pups: high number of dead pups in high-dose group	ND	NA	NDr	Hazleton Laboratories (1967) (Treatment was stopped after the fourth dose owing to indications of severe toxicity)	NPR
2. Inhalation (mg/m³)^a								
Subchronic	20 M/20 F, S-D, rat, whole-body inhalation, 6 hr/d, 7 d/wk, 13 wk	0, 9,928.6 ppm HEC: 0, 19,023	No significant exposure-related effects with respect to mortality, clinical signs, food consumption, body weights, hematology, clinical chemistry or urinalysis parameters, organ weights, or macroscopic and microscopic examinations	19,023	NA	NDr	LPT (1976)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)

Category ^a	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	BMDL/ BMCL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Subchronic	3 M/3 F, beagle, dog, whole-body inhalation, 6 hr/d, 7 d/wk, 13 wk	0, 5,011.4 ppm HEC: 0, 9,601.6	No significant exposure-related effects with respect to mortality, clinical signs, food consumption, body weights, hematology, clinical chemistry or urinalysis parameters, heart function, organ weights, or macroscopic and microscopic examinations	9,601.6	NA	NDr	LPT (1976)	NPR
Subchronic	15 M/15 F, CD, rat, whole-body inhalation, 6 hr/d, 5 d/wk, 13 wk	0, 7,471, 12,414, 19,186 ppm HEC: 0, 10,220, 16,989, 26,257	No significant, exposure-related effects on clinical signs, body weights or body-weight gain, organ weight, or histopathology	26,257	NA	NDr	Haskell Laboratories (1981) (Tabular data in the study report were largely illegible)	NPR
Chronic toxicity	100 M/100 F, CrI:CDBR rat, whole-body inhalation, 6 hr/d, 5 d/wk for 2 yr with interim sacrifice of 10 rats/sex/group at 1 yr	0, 2,000, 10,000, 19,000 ppm HEC: 0, 2,740, 13,700, 26,000	Significantly decreased body weight in females in high concentration group throughout the study (frequently 10–14% lower than controls)	13,700	DUB	26,000	Trochimowicz et al. (1988) ; Haskell Laboratories (1985) (Bacterial infection starting in Week 59 caused mortality in all exposure groups (including controls); efforts to control the infection included quarantine and temporary cessation of exposure)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)

Category ^a	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	BMDL/ BMCL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Reproductive	12 M/24 F, Alderley Park Wistar-derived, rat, whole-body inhalation, 6 hr/d; 5 d/wk for 10 wk pre mating and 7 d/wk for 2 wk during mating (M); 5 d/wk for 3 wk pre mating, 7 d/wk for 2 wk during mating, and 7 d/wk for 3 wk during gestation (Subgroup A [F]); or 5 d/wk for 3 wk pre mating and 7 d/wk for 2 wk during mating (Subgroup B [F])	0, 5,019, 12,531 ppm HEC: 0, 7,327, 18,292 (M) HEC: 0, 8,586, 21,436 (Subgroup A [F]) HEC: 0, 7,968, 19,893 (Subgroup B [F])	Parental and reproductive: No significant exposure-related effects	21,436	NA	NDr	Central Toxicol Lab (1981b) (Significantly decreased numbers of corpora lutea were within the historical range for this rat strain. Significant reductions in implantations and fetuses were attributed to decreased numbers of corpora lutea)	NPR
Developmental	0 M/24 F, Alderley Park, rat, whole-body inhalation, 6 hr/d, GDs 6–15	0, 4,985, 12,532, 25,265 ppm HEC: 0, 9,551, 24,011, 48,407	Maternal: Decreased body-weight gain. No significant exposure-related effects on gravid uterine weight, numbers of corpora lutea, and implantations Developmental: Dose dependent increases in fourteenth rib. No significant exposure-related effects on, early or late deaths, or fetal body weights; no gross or soft tissue abnormalities	NDr 9,551	DUB NA	9,551 24,011	Central Toxicol Lab (1982)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)

Category ^a	Number of Male/Female, Strain Species, Study Type, Study Duration	Dosimetry ^b	Critical Effects	NOAEL ^b	BMDL/BMCL ^b	LOAEL ^b	Reference (comments)	Notes ^c
Developmental	0 M/12 F, NZW, rabbit, whole-body inhalation, 2 hr/d, GDs 8–16	0, 2,000, 20,000 ppm	Maternal: Slight eye irritation	1,280	NA	12,800	Hazleton Laboratories (1967)	NPR (Study limitations included small litter sizes and inadequate data reporting with no statistical analyses)
		HEC: 0, 1,280, 12,800	Developmental: No significant effects	12,800	NA	NDr		

^aDuration categories are defined as follows: Acute = exposure for ≤24 hours; short-term = repeated exposure for 24 hours to ≤30 days; long-term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) ([U.S. EPA, 2002](#)).

^bDosimetry: Values are presented as ADJs (mg/kg-day) for oral noncancer effects and as HECs (mg/m³) for inhalation noncancer effects. In contrast to other repeated exposure studies, values from animal gestational exposure studies are not adjusted for exposure duration in calculation of the ADD or HEC. The HEC from animal studies was calculated using the equation for extrarrespiratory effects from a Category 3 gas ([U.S. EPA, 1994](#)): HEC_{ER} = continuous concentration in mg/m³ (unadjusted concentration for gestational exposure studies) × ratio of animal:human blood-gas partition coefficients (default value of 1 applied).

^cNotes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

^dCONC (HEC) = CONC (mg/m³) × (VE_{ho} ÷ VE_h) × (5 days ÷ 7 days); where VE_{ho} = default minute volume for human occupational exposure based on an 8-hour shift (10 m³/day) and VE_h = default human minute volume for a 24-hour day (20 m³/day) ([U.S. EPA, 1994](#)).

ADJ = adjusted daily dose; DUB = data unsuitable for BMD modeling; EKG = electrocardiogram; F = female(s); GD = gestation day; HEC = human equivalent concentration; M = male(s); NA = not applicable; ND = no data; NDr = not determined; NZW = New Zealand white; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)

Category	Number of Male/Female, Strain, Species, Study Type, and Duration	Dosimetry ^a	Critical Effects	BMDL/BMCL ^a	Reference	Notes ^b
Human						
1. Oral (mg/kg-d)						
ND						
2. Inhalation (mg/m³)						
ND						
Animal						
1. Oral (mg/kg-d)						
ND						
2. Inhalation (mg/m³)^a						
Carcinogenicity	100 M/100 F, CrI:CDBR rat, whole-body inhalation, 6 hr/d, 5 d/wk for 2 yr with interim sacrifice of 10 rats/sex/group at 1 yr	0, 2,000, 10,000, 19,000 ppm HEC: 0, 2,740, 13,700, 26,000	Neoplastic: pancreatic islet cell adenomas (F) within historical control range for this rat strain; nasal passage tumors (not exposure-related)	NA	Trochimowicz et al. (1988) ; Haskell Laboratories (1985)	PR

^aDosimetry: The units for inhalation exposures are expressed as HECs (mg/m³).

^bNotes: PR = peer reviewed.

^cHEC_{ER} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × blood-gas partition coefficient (default value of 1 applied).

F = female(s); HEC = human equivalent concentration; M = male(s); MW = molecular weight; NA = not applicable; ND = no data.

HUMAN STUDIES

Oral Exposures

No human experimental or occupational oral exposure studies have been identified. A case report indicated that ingestion of an unknown quantity of CFC-113 resulted in no clinical complications ([Racon Inc, 1985](#)).

Inhalation Exposures

The database for inhalation exposure of humans to CFC-113 consists of short-term experimental and long-term occupational exposures to CFC-113, health hazard evaluations of workers exposed to CFC-113 alone or as the predominant component of a mixture, case reports of CFC-113 and/or solvent exposure, and occupational studies of chlorinated solvent exposure (including CFC-113).

Health hazard evaluations were conducted at sites in which workers were exposed to CFC-113 (alone or as the predominant component of a mixture). With one exception (workers evaluated at the Kennedy and Johnson Space Centers), measured levels of CFC-113 were below occupational standards set by OSHA (7,600 mg/m³). Therefore, signs reported by workers (including drowsiness, dizziness, headaches, chest pain, nausea, chills, fainting, and nasal, eye, and/or respiratory irritation) were not attributed to CFC-113 exposure ([NIOSH, 1983, 1981, 1979](#)). In the individual cases in which CFC-113 exposures were below 8-hour time-weighted average (TWA) occupational standards (mean exposures of 274 and 271 ppm [\sim 2,100 mg/m³], but short-term exposure exceeded OSHA short-term exposure limit of 1,250 ppm [\sim 9,600 mg/m³]), no significant cardiac dysrhythmias or changes in cardiac activity were observed ([NIOSH, 1991](#)).

Several case reports of acute inhalation exposure in workers exposed to CFC-113 were located; effects included death (attributed to cardiac arrhythmia/arrest and/or asphyxiation) to clinical signs (difficulty breathing, pain, paresthesia, and weakness in legs), neuropathy (based on decreased motor nerve conduction velocity), and psychological impairments (deficits in learning and memory) ([Voge, 1997](#); [Kaufman et al., 1994](#); [Mcgee et al., 1990](#); [NIOSH, 1989](#); [Rasmussen et al., 1988](#); [NIOSH, 1986](#); [Clark et al., 1985](#); [May and Blotzer, 1984](#); [Raffi and Violante, 1981](#)). “Parkinson-like” symptoms of motor dysfunction were described in a woman chronically exposed to vapors of CFC-113 and nitromethane ([Sandyk and Gillman, 1984](#)). A female worker exposed to CFC-113 and a wide range of other solvents over a 10-year period developed a scleroderma-like disease ([Altomonte et al., 1996](#)).

Several studies have reported associations between occupational exposure to chlorinated solvents (e.g., among metal degreasers, jet engine mechanics, etc, exposed predominantly to CFC-113, trichloroethylene [TCE], and other solvents) and effects on the liver ([Rasmussen et al., 1993a](#)), kidney (increased activity of *N*-acetyl glucosaminidase [NAG] in the serum or urine) ([Rasmussen et al., 1993a](#); [Brogren et al., 1986](#)), and nervous system (symptoms consistent with “psychoorganic syndrome” [characterized as mild dementia with impairments in cognitive function, personality changes, and decreased motivation/initiative] and neurobehavioral effects) ([Kilburn, 1999](#); [Rasmussen et al., 1993b, c](#); [Rasmussen and Sabroe, 1986](#)). Because exposures were based on total chlorinated solvents, no conclusions can be drawn with respect to these effects and CFC-113 exposure alone.

Two experimental studies ([Reinhardt et al., 1971](#); [Haskell Laboratories, 1964](#)) and four occupational studies ([Neghab et al., 1997](#); [Egeland et al., 1992](#); [Triebig and Burkhardt, 1978](#); [Imbus and Adkins, 1972](#)) evaluated the effects of CFC-113 exposure in humans. Only limited data are available from [Triebig and Burkhardt \(1978\)](#) because the study report is written in German; the English abstract indicates that the investigators observed no significant changes in clinical chemistry endpoints in 3 men and 10 women exposed to CFC-113 at workplace concentrations of 13–111 ppm (100–900 mg/m³). The remaining studies are discussed below.

Experimental Studies

Haskell Laboratories (1964)

In an unpublished study, volunteers (two males) were exposed to CFC-113 (with no detectable impurities) as a vapor at 0, 1,500, 2,500, 3,500, and 4,500 ppm (presumably in series, but not explicitly specified). These concentrations are equivalent¹ to 0, 11,500, 19,160, 26,820, and 34,490 mg/m³. Some additional tests were also reportedly conducted at 4,000 ppm (30,660 mg/m³). Prior to and following each exposure to CFC-113, control (air-only) exposures were performed. The total duration of exposure was 2.75 hours (45 minutes for chamber concentrations to reach desired levels, an additional 30 minutes for equilibrium [between the chamber atmosphere and the subjects' tissues] to be reached, and the effective exposure duration [with respect to constant CFC-113 exposure] of 1.5 hours). Clinical signs of toxicity were monitored regularly (time points were not specified). Twice during each exposure, subjects were evaluated in a series of performance tests, including the Crawford Small Parts Dexterity Test, the Short Employment Test-Clerical (SET clerical), and card sorting (with or without an auxiliary task). Average test scores (from two tests conducted during a single exposure) were compared to average scores for tests conducted during air-only exposures (prior to and following that exposure). At study initiation and study termination, hematological, liver function, and urinalysis tests were performed (not further specified).

Results were presented graphically in the study report, and represented as percent change from control values ([Haskell Laboratories, 1964](#)). Statistical analyses were not performed. No exposure-related effects on performance were reported at 11,500 mg/m³ (generally <10% deviation from control values). At 19,160 mg/m³, the subjects exhibited deficits in complex performance tests based on scores for manual dexterity, SET clerical, and card sorting with auxiliary task tests (~5–15% lower than control values). In general, test performance scores (all tests) decreased with increasing exposure concentration, so that at 34,000 mg/m³, scores ranged from about 60–90% of controls. Clinical signs of toxicity (including loss of concentration, drowsiness, feeling of heaviness in head, and slight loss of visual capabilities) were noted at the three highest exposure concentrations (presumably 19,160, 26,820, and 34,490 mg/m³, based on the initial concentrations tested). The authors reported no effects on clinical chemistry or urinalysis endpoints after exposure compared to pre-exposure values (data not shown). Although limited by the small number of subjects, lack of statistical analyses, and incomplete reporting of study results, the results of this study suggest a no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) of 11,500 and 19,160 mg/m³, respectively, for acute exposure to CFC-113 in humans based on neurological performance tests.

¹CONC (mg/m³) = CONC (ppm) × MW ÷ 24.45

Reinhardt et al. (1971)

Reinhardt et al. (1971) conducted a published, peer-reviewed inhalation study in which four male human subjects were exposed on consecutive weeks to CFC-113 (99.8% purity) at 0, 500, and 1,000 ppm, 6 hours/day (3-hour exposures twice daily) for 5 days/week. These exposure concentrations are equivalent to 0, 3,830, and 7,660 mg/m³. The exposure sessions were conducted such that subjects were exposed to air only during the first week, 3,830 mg/m³ during the second week, and 7,660 mg/m³ during the third week. Daily duration-adjusted concentrations were 0, 958, and 1,920 mg/m³ using the following equation: $CONC_{ADJ} = CONC (mg/m^3) \times (6 \text{ hours} \div 24 \text{ hours})$. Before and after CFC-113 exposure, subjects had a chest x-ray. Hematology (complete blood count), clinical chemistry (alkaline phosphatase [ALP], lactate dehydrogenase [LDH], aspartate aminotransferase [AST], total cholesterol, bilirubin, protein, lipids, albumin, globulin, albumin:globulin ratio, creatinine, glucose, blood urea nitrogen [BUN], and uric acid) and urinalysis endpoints (not further specified) were also evaluated. Clinical signs of toxicity and body temperature, pulse, and equilibrium were monitored daily during exposure. Pulmonary function (measured at the end of the day during the control week and biweekly during CFC-113 exposure periods) was assessed by measuring carbon monoxide diffusing capacity and the fractional uptake of carbon monoxide. Subjects completed psychomotor tests [the same tests described for Haskell Laboratories (1964), but including a time discrimination test] twice daily during exposure.

None of the subjects reported symptoms of toxicity (such as headache, dizziness, or drowsiness) at any CFC-113 concentration level (Reinhardt et al., 1971). There were no significant, exposure-related effects on body temperature, pulse, and equilibrium; hematological, clinical chemistry and urinalysis endpoints; pulmonary function; or psychomotor tests due to CFC-113 exposure. Performance on psychomotor tests improved over the course of the study; this improvement was attributed to learning. The results of this study suggest a NOAEL of 1,920 mg/m³ in humans with short-term repeated exposure to CFC-113. A LOAEL was not identified.

Occupational Studies

Egeland et al. (1992)

In a published, peer-reviewed study, Egeland et al. (1992) monitored cardiac activity of 16 healthy aerospace workers exposed to CFC-113 (purity not reported) while engaged in cleaning rocket and ground support equipment in precleaning (low-exposure) and clean (high-exposure) rooms. Workers normally rotated between the high- and low-exposure rooms every 2 weeks; therefore, data from a worker in the clean room could be compared with data from the same worker in the precleaning room. Air samples from the breathing zone were collected using a charcoal tube personal sampler worn by exposed workers ($n = 16$) during work hours (samples collected for periods ranging from 30–60 minutes). The mean 7-hour TWA exposure was 64.4 ± 59.5 ppm (range = 0–200 ppm) on the low-exposure day and 442.1 ± 300.2 ppm (range = 247–1,476 ppm) on the high-exposure day. The mean values for the low and high exposures are equivalent to 493 and 3,388 mg/m³, respectively. The subjects (10 males and 6 females; mean age = 41.7 years; average length of employment = 7.8 years) were simultaneously monitored using ambulatory electrocardiograms (EKGs) for about 7 hours/day. The EKG data collected included the rate of ventricular premature beats (VPBs), supraventricular premature beats (SPVBs), A-V block, t-wave inversion, ST segment depression, fluctuations in heart rate, and length of P-R interval. Data regarding smoking, caffeine intake, medication usage, and symptoms during monitoring days were collected.

There were no differences between EKG data during low and high exposures, and no symptoms (palpitations, dizziness, lightheadedness) of exposure were reported ([Egeland et al., 1992](#)). Although one individual exhibited sinus rhythm bradycardia for <15 minutes during a high-exposure day (short-term exposures up to 600 ppm or 4,600 mg/m³), similar EKG patterns were observed in a different worker with ST segment depression on both low- and high-exposure days. This study found no effect of exposure to CFC-113 on cardiac activity. The unusual study design suggests a NOAEL of 3,388 mg/m³ for acute (7-hour) exposure to CFC-113 relative to baseline exposure among chronically exposed workers. A LOAEL was not identified. The 7-hour mean exposure concentration of 3,388 mg/m³ was adjusted to 1,059 mg/m³ using the following equation: $CONC_{ADJ} = CONC (mg/m^3) \times (VE_{ho} \div VE_h) \times (7 \text{ hr} \div 8 \text{ hr}) \times (5 \text{ days} \div 7 \text{ days})$; where VE_{ho} = default minute volume for human occupational exposure based on an 8-hour shift (10 m³/day) and VE_h = default human minute volume for a 24-hour day (20 m³/day) ([U.S. EPA, 1994](#)).

[Neghab et al. \(1997\)](#)

[Neghab et al. \(1997\)](#) examined potential liver effects in workers of an Australian steel company exposed to CFC-113 (purity not reported) compared to unexposed office workers at the same company in a published, peer-reviewed study. The exposed workers included 4–6 males averaging 29 years of age (range = 21–41 years) with a mean duration of employment of 2.5 years (range = 0.1–4 years). Solvent concentrations in the breathing zone were measured using a charcoal tube personal sampler worn by exposed employees during work hours. The 8-hour TWA exposure was 68.2 ± 12.6 ppm (range 45–118 ppm), which is equivalent to 523 mg/m³. Blood samples were collected from fasting subjects before starting work on Monday and Friday to collect pre-exposure and postexposure samples (respectively). Blood samples were also taken prior to work on Monday from unexposed participants (11 males averaging 35 years of age [range = 22–44 years]). Blood was collected for clinical chemistry evaluations (ALP, AST, alanine aminotransferase [ALT], γ -glutamyl transferase [GGT], 5'-nucleotidase, albumin, protein, globulin, individual serum bile acids, and total serum bile acids).

Exposed workers showed significantly increased serum concentrations of individual and total serum bile acids relative to controls (see Table B-1). The study authors reported that bile acid levels returned to normal 2 weeks after cessation of exposure (data not available). The researchers suggested that increased bile acid levels may be indicative of exposure, but that no pathological sequelae or other manifestations of liver injury were likely to be observed in combination with this effect. Chronic occupational exposure to low concentrations of chlorinated aliphatic hydrocarbon solvents such as trichloroethylene also appears to alter cholesterol metabolism in the absence of noticeable hepatocellular damage, as evidenced by lack of increase in serum liver transaminases ([Nagaya et al., 1993](#)). Similarly, serum concentrations of total and individual bile acids were significantly elevated in a group of workers exposed to trichloroethylene ([Neghab et al., 1997](#)). Similar alterations in bile acid status have been observed in experimental animals exposed to trichloroethylene and its metabolites. Because no association was observed between elevated plasma bile acids and conventional markers of liver injury, it was concluded that this perturbation in bile acid homeostasis could be indicative of early changes in liver function independent of hepatocellular damage ([NRC, 2006](#)). Therefore, significant increases in bile acid levels alone after exposure to CFC-113 were not defined as adverse.

There were no significant changes in other clinical chemistry endpoints. Therefore, this study identifies a NOAEL of 523 mg/m³ for long-term occupation exposure to CFC-113. A LOAEL was not identified. The mean exposure concentration of 523 mg/m³ was adjusted to 187 mg/m³ using the following equation:

$$\text{CONC}_{\text{ADJ}} = \text{CONC} (\text{mg}/\text{m}^3) \times (\text{VE}_{\text{ho}} \div \text{VE}_{\text{h}}) \times (5 \text{ days} \div 7 \text{ days});$$
 where VE_{ho} = default minute volume for human occupational exposure based on an 8-hour shift (10 m³/day) and VE_{h} = default human minute volume for a 24-hour day (20 m³/day) ([U.S. EPA, 1994](#)).

Imbus and Adkins (1972)

In a published cross-sectional study, clinical and laboratory examinations were performed on a group of 50 male workers occupationally exposed to CFC-113 in three clean rooms at Kennedy Space Center, Florida, and the results compared to those of 50 unexposed male workers ([Imbus and Adkins, 1972](#)). Air samples ($n = 161$) were collected over a 3-week period and analyzed by gas chromatography. Personal sampling methods were not used. The measured concentrations of CFC-113 in the three clean room areas ranged from 46–4,780 ppm (median = 435 ppm or 3,330 mg/m³), with a mean concentration of 699 ppm (equivalent to 5,360 mg/m³). The mean concentration was reported as 699 ppm in the text of the study report and 669 ppm (5,130 mg/m³) in an accompanying figure. Because there were no significant exposure-related effects observed in this study, a higher value of 699 ppm is selected as the exposure concentration. Fifty male employees, who had worked in the clean rooms for an average of 2.77 years (maximum duration 4.5 years), were randomly selected as the exposed subjects. The average time of exposure to CFC-113 was 6 hours per day. The average age of the exposed and unexposed employees was 34 years (range = 23–51) and 37 years (range = 25–63), respectively. Additional details were not provided about the unexposed subjects. The examination of each subject included a complete history, complete physical examination, EKG taken while the subjects were at rest, visual profile, audiometry, chest x-ray, and timed vital capacity. Blood was collected for hematology (complete blood count) and clinical chemistry (ALP, AST, LDH, BUN, cholesterol, calcium, inorganic phosphorous, total bilirubin, albumin, total protein, uric acid, and glucose) evaluations. Urine was collected for urinalysis, but the specific tests were not reported.

There were no significant exposure-related differences in any evaluated physical, clinical, or laboratory measurements between the exposed and unexposed groups ([Imbus and Adkins, 1972](#)). These data identify the mean concentration tested (5,360 mg/m³) as the NOAEL in male workers. The mean exposure concentration of 5,360 mg/m³ was adjusted to 1,440 mg/m³ using the following equation:

$$\text{CONC}_{\text{ADJ}} = \text{CONC} (\text{mg}/\text{m}^3) \times (\text{VE}_{\text{ho}} \div \text{VE}_{\text{h}}) \times (6 \text{ hours} \div 8 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days});$$
 where VE_{ho} = default minute volume for human occupational exposure based on an 8-hour shift (10 m³/day) and VE_{h} = default human minute volume for a 24-hour day (20 m³/day) ([U.S. EPA, 1994](#)).

ANIMAL STUDIES

Oral Exposures

The effect of oral exposure of animals to CFC-113 has been evaluated in a developmental toxicity study in rabbits ([Hazleton Laboratories, 1967](#)). No oral subchronic- or chronic-duration toxicity studies, reproductive toxicity studies, or carcinogenicity studies have been identified.

Developmental Studies

Hazleton Laboratories (1967)

In a poorly reported study summary, pregnant rabbits (eight/group; strain not reported) were orally (route not further specified) administered Freon TF (CFC-113) at 0, 1,000, or 5,000 mg/kg-day beginning on Gestation Day (GD) 8. Owing to indications of severe toxicity, dosing was stopped after 4 days. Substantial mortality occurred during dosing; two and three animals treated at 1,000 and 5,000 mg/kg-day died, respectively. The death of a single control animal (prior to the dosing period) was attributed to mucoid enteritis. Clinical signs of toxicity including increased docility at 1,000 mg/kg-day and marked reductions in food and water consumption and body weights at 5,000 mg/kg-day were reported (data not shown). Necropsies performed on CFC-113-treated animals that died during the dosing period showed discoloration of the lungs (not further described). For does that survived the dosing period (including one animal/CFC-113 treatment group that died in the postdosing period), data with respect to pregnancy status and litter size (including numbers of live and dead pups) were reported on an individual basis only. In general, pregnancy rates were low (3–6 pregnant/group) in all treatment groups (including controls; pregnancy status was not determined for animal that died on or before GD 8). Three to five litters were produced at each dosage level, and does from each treatment group delivered live young. The total numbers of live and dead pups, respectively, were 21 and 3 at 0 mg/kg-day, 32 and 0 at 1,000 mg/kg-day, and 12 and 20 at 5,000 mg/kg-day (statistical analyses for these data were not performed). Although the study authors concluded that it was not possible to determine whether maternal deaths were due to the test substance or to the dosing technique, no control animals died during the dosing period. No effect levels were derived for this study due to poor reporting and inadequate study design and execution.

Inhalation Exposures

The effects of inhalation exposure of animals to CFC-113 were evaluated in three 13-week subchronic-duration toxicity studies, including two “tolerance” studies in rats and dogs exposed to a single concentration of CFC-113 ([LPT, 1976, 1975](#)) and one study in rats using multiple exposure concentrations ([Haskell Laboratories, 1981](#)), one chronic toxicity/carcinogenicity study in rats ([Trochimowicz et al., 1988](#)), a one-generation reproductive toxicity study in rats ([Central Toxicol Lab, 1981a](#)), and two developmental studies in rats and rabbits ([Central Toxicol Lab, 1982](#); [Hazleton Laboratories, 1967](#)).

Subchronic-Duration Studies

LPT (1976)

In an unpublished study, Sprague-Dawley (S-D) rats (20/sex/group) were exposed whole-body to CFC-113 (unknown purity) at 0 and 9,928.6 ppm, 6 hours/day, 7 days/week for 90 days. These concentrations are equivalent to 0 and 76,091 mg/m³. The animals were monitored daily for mortality and clinical signs of toxicity. Food consumption was also measured daily; water intake was monitored regularly (but not quantified). Body weights were recorded weekly. At study termination, hematology (total and differential white blood cell [WBC], red blood cell [RBC], reticulocyte [Ret], platelet counts [PLAT], hemoglobin [Hb], hematocrit [Hct], methemoglobin [MetHb], Heinz bodies, and clotting time); clinical biochemistry (glucose, BUN, total protein, total bilirubin, sodium, potassium, calcium, chloride, uric acid, albumin, globulin, creatinine, total cholesterol and lipids, ALT, AST, ALP, and bromsulphathalein liver function test); and urinalysis (color, specific gravity, protein, glucose, bilirubin, hemoglobin, ketone bodies, pH, and sedimentation) were evaluated. A limited number

of clinical biochemistry endpoints (serum glucose, BUN, and ALT and ALP activities) were also evaluated at earlier time points (prior to exposure, and after 7 days and 6 weeks of exposure). Prior to necropsy, the animals were subjected to ophthalmology exams and tests of auditory acuity; dentition was also inspected. All animals underwent necropsy; organ weights (heart, lungs, liver, spleen, kidney, adrenal, thymus, pituitary, thyroid, brain, and gonads) were recorded. Histopathology (27 tissues) was performed (10 rats/sex/group). Statistical analyses were conducted at a significance level of $p \leq 0.01$.

No mortality or clinical signs of toxicity were reported ([LPT, 1976](#)). There were no significant exposure-related effects on food consumption, body weights, hematology, clinical chemistry, or urinalysis. Clinical examinations performed just prior to sacrifice did not show any irregularities. Organ weights of exposed rats were not significantly different from controls. Macroscopic and microscopic examinations of the tissues did not identify any lesions related to CFC-113 exposure. Although there are study limitations (only one concentration was tested); the study data identify a NOAEL of 76,091 mg/m³, the only dose tested. No LOAEL was identified. The exposure concentration of 76,091 mg/m³ was adjusted for discontinuous exposure and converted to a human equivalent concentration (HEC) of 19,023 mg/m³ for extrapulmonary effects².

[LPT \(1975\)](#)

In a similarly designed study (unpublished), beagle dogs (three/sex/group) were exposed to CFC-113 (unknown purity) at 0 and 5,011.4 ppm, 6 hours/day, 7 days/week for 90 days. These concentrations are equivalent to 0 and 38,406 mg/m³. The same endpoints were evaluated as in the rat study with the following modifications: (1) with the exception of a few endpoints measured only at 13 weeks (blood methemoglobin and Heinz bodies, and serum total and free cholesterol and fatty acids, triglycerides, total lipids, and phosphatide), all hematology, clinical chemistry, and urinalysis evaluations, as well as clinical examinations (ophthalmology, hearing, and dentition), were conducted prior to exposure and after 6 and 13 weeks exposure; (2) additional evaluations with respect to hematology (blood sedimentation), clinical chemistry (serum free cholesterol, total and free fatty acids, triglycerides, and phosphatide, glycogen in the heart muscle and liver, and phenolsulphonphthalein plasma test of renal function); and heart function (electrocardiography and tests of circulatory function, including diastolic and systolic pressure, and hypertension under norepinephrine stress at 13 weeks) were performed; and (3) one additional organ (prostate or uterus) was weighed.

No clinical signs of toxicity were reported, and no deaths occurred ([LPT, 1975](#)). There were no significant exposure-related effects on food consumption, body weights, hematology, clinical chemistry, urinalysis, or heart function. Clinical examinations did not show any irregularities. Organ weights of exposed dogs were not significantly different from controls. Macroscopic and microscopic examinations of the tissues did not identify any lesions related to CFC-113 exposure. Although there are study limitations (one concentration tested with few numbers of animals), these data identify the highest dose tested (38,406 mg/m³) as a NOAEL. No LOAEL was identified. The exposure concentration of 38,406 mg/m³ was adjusted for

²HEC (mg/m³) = CONC (mg/m³) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × ratio of blood-air partition coefficients ([U.S. EPA, 1994](#)). In the absence of data for blood-air partition coefficients in rodents (a predicted value is available in humans, as discussed in the “Metabolism/Toxicokinetic Studies” section), the default ratio of 1 was applied.

discontinuous exposure and converted to a HEC of 9,601.6 mg/m³ for extrarespiratory effects based on the methodology described for the rat study above.

Haskell Laboratories (1981)

In another unpublished, non-peer-reviewed study, male and female CD rats (15/sex/group) were exposed whole-body to CFC-113 (100% purity) at nominal concentrations of 0, 7,500, 12,500, and 17,500–20,000 ppm, 6 hours/day, 5 days/week for 13 weeks. The high concentration was changed from 17,500 to 20,000 ppm on Study Day 29 (nineteenth day of exposure). The reported TWA concentrations in the exposure chamber were 0, 7,471, 12,414 and 19,186 ppm, respectively. These exposure concentrations are equivalent to 0, 57,260, 95,138, and 147,040 mg/m³. The rats were observed once daily for clinical signs of toxicity. Body weights were recorded weekly. No hematology, clinical chemistry, or urinalysis endpoints were evaluated. An interim sacrifice of five rats/sex/group was conducted on Study Day 45 (after 30 exposures); the remaining rats were sacrificed on Study Day 94 or 95 (after 63 exposures). At interim and terminal sacrifice, organ weights (brain, heart, lungs, liver, spleen, kidneys, testes, thymus, adrenals, and pituitary glands) were recorded. Histopathological examinations (~36 tissues) were performed for all animals in the control and high-exposure groups.

Significant exposure-related effects are reported in Table B-2 (Haskell Laboratories, 1981). Owing to illegibility of the data tables, not all of the data for significant effects can be reported with certainty. One female rat in the control group was sacrificed in extremis on Day 72 (cause of death not reported). Sporadic signs of narcosis were noted at 147,040 mg/m³ (but not at lower exposure concentrations). There were no significant effects on body weight/body-weight gain in either sex. Statistically significant changes in absolute and relative organ weights (absolute testis weight and relative brain and lung weights in males and absolute adrenal gland weight and relative lung and liver weights in females) were noted at interim sacrifice (Day 45); however, these alterations were not considered to be related to CFC-113 exposure because they were sporadic in nature (not supported by an exposure-response relationship) and did not correlate with macroscopic or microscopic findings.

At terminal sacrifice, absolute and relative lung weights were significantly increased in male rats at 147,040 mg/m³ only. Owing to the illegibility of the data tables, the magnitude of change in absolute lung weights cannot be quantified with certainty, but relative lung weights appeared to be increased by about 23% in 147,040-mg/m³ males relative to controls (see Table B-2). However, the changes in lung weights were also likely associated with pneumonia (the incidence of which was high in exposed male rats and controls). In female rats only, significant increases in absolute and relative adrenal weights (of 20 and 13%, respectively) were observed at 147,040 mg/m³. Additional statistically significant changes in absolute and relative organ weights (relative kidney weight in males; absolute and relative liver weight and absolute spleen weight in females) at terminal sacrifice were not clearly associated with CFC-113 exposure (i.e., an exposure-response relationship was not observed). Other than focal/multifocal granulomatous interstitial pneumonia, noted in male rats exposed at 147,040 mg/m³, no remarkable histopathological findings were reported. The incidence of pneumonia was 9/10 in 147,040-mg/m³ males compared to 5/10 in controls. Based on a Fisher's exact test performed for this review, the incidence of this effect was not significantly increased in 147,040-mg/m³ males ($p > 0.05$) relative to controls. However, the severity of this effect tended to be greater in the males exposed to CFC-113 (severity was not evaluated quantitatively, and no

further information was provided in the study report). The study authors suggested that CFC-113 exposure exacerbated an existing pneumonic condition in male rats. Although study limitations are apparent (most notably the illegibility of the data tables and the limited number of endpoints evaluated), a NOAEL of 147,040 mg/m³ is identified. Exposure concentrations of 57,260, 95,138, and 147,040 mg/m³ were adjusted for discontinuous exposure and converted to respective HECs of 10,220, 16,989, and 26,257 mg/m³ for extrarrespiratory effects using the methodology described previously.

Chronic-Duration/Carcinogenicity Study

Haskell Laboratories (1985); Trochimowicz et al. (1988)

Trochimowicz et al. (1988) exposed CrI:CD(SD)BR rats (100/sex/group) whole-body to CFC-113 (99.9% pure) at 0, 2,000, 10,000, and 19,000 ppm, 6 hours/day, 5 days/week for 24 months in a published, peer-reviewed study. Additional unpublished data from this study are reported by *Haskell Laboratories (1985)*. The tested exposure concentrations are equivalent to 0, 15,300, 76,600, and 145,600 mg/m³. The animals were examined for mortality and clinical signs of toxicity twice daily Monday through Friday and once daily on weekends and holidays. Rats were weighed and examined clinically once a week for the first 11 weeks of the study, every 2 weeks thereafter, and just prior to sacrifice. After 3, 6, 12, 18, and 24 months of exposure, hematology (total and differential WBC, RBC, reticulocyte, platelet counts, Hb, Hct, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH]), clinical chemistry (ALP, ALT, AST, GGT, BUN, bilirubin, cholesterol, creatinine, glucose, and total protein), and urinalysis (volume, color, osmolality, pH, sediment, fluoride, blood, sugar, protein, urobilinogen, bilirubin, and ketones) evaluations were performed (10 rats/sex/group). An interim sacrifice (10 rats/sex/group) was conducted 12 months after study initiation. All remaining rats were sacrificed after 24 months of exposure. All rats were subjected to necropsy. Selected organ weights (adrenals, brain, heart, kidneys, liver, lungs, pituitary, spleen, testes, and thymus) were recorded. Complete histopathological examinations (~33 tissues) were performed for animals terminated in extremis, animals found dead, and animals in the control and high-exposure groups. In addition, tissues with gross lesions and/or tissue masses and the nasal turbinates (based on findings of nasal tumors in 76,600-mg/m³ males terminated in extremis) were examined microscopically in rats exposed at 15,300 and 76,600 mg/m³.

During Week 59 of the study, a male in the 145,600-mg/m³ group died from a respiratory infection caused by *Corynebacterium kutscheri* (*Trochimowicz et al., 1988*). Although efforts were made to control the onset and spread of infection (quarantine and cessation of exposure for 76,600- and 145,600-mg/m³ males from Weeks 61–63 [14 exposures], and tetracycline therapy in all animals in Weeks 61–62 and 71–79), mortality as a consequence of infection was 18–35% in males and 5–8% in females (all exposure groups, including controls), apart from mortality due to unrelated causes (see Table B-3). Data for these animals were excluded from subsequent analyses. Causes of mortality unrelated to bacterial infection were not reported. No clinical signs of toxicity attributed to exposure were observed. The mean body weights of male and female rats exposed at 145,600 mg/m³ and females exposed at 76,600 mg/m³ were statistically significantly decreased relative to controls; however, the body weights of males were within about 3–9% of the values for control males throughout the exposure period (based on weekly body weights provided in the unpublished report). In females, body weights at interim sacrifice were decreased by 11 and 14% at 76,600 and 145,600 mg/m³, respectively, compared to controls. Body weights of females exposed at 145,600 mg/m³ were 10–14% lower than controls throughout the second year of the study (body weights were typically decreased by ≤5% during

the same time period in females exposed at 76,600 mg/m³). Body-weight decreases in females were no longer evident at termination after 2 years of exposure. Other than a transient decrease in serum glucose in 145,600-mg/m³ males (but not females) at 6 months and increased urinary fluoride excretion (in 145,600-mg/m³ males at all time points and in 76,600- and 145,600-mg/m³ females at 3 and/or 6 months) (see Table B-4), clinical pathology tests (hematology, clinical chemistry, and urinalysis evaluations) did not indicate any consistent, exposure-related effects. The study authors indicated that increased urinary fluoride concentrations might reflect a metabolism of CFC-113.

Organ weights at interim and terminal sacrifice were provided in the unpublished report ([Haskell Laboratories, 1985](#)). After exposure for 1 year, males showed significantly increased absolute and relative liver weight (at $\geq 15,300$ mg/m³) and absolute and relative kidney weight (at 145,600 mg/m³ and $\geq 15,300$ mg/m³, respectively) (see Table B-5). However, these dose-dependent effects on organ weights were not observed in males exposed for 2 years (see Table B-6). Females exposed for 1 year showed significantly increased absolute and relative liver weight and relative (but not absolute) lung and spleen weights (statistically) compared to controls at 76,600 and 145,600 mg/m³ (see Table B-5). No consistent and significant exposure-related effects on organ weights were seen in females after 2 years of exposure (see Table B-6). There were no findings at gross necropsy and no significant microscopic non-neoplastic changes that appeared to be related to CFC-113 exposure. Although significant effects on organ weights were observed at the interim sacrifice, these changes are not considered biologically significant because they occurred in the absence of accompanying clinical or histopathological effects indicative of organ damage, and the similar organ-weight effects were not observed at the end of 2-year exposure. This study identifies a LOAEL of 145,600 mg/m³ in female rats based on significantly decreased body weight throughout much of the study. The NOAEL is 76,600 mg/m³. Exposure concentrations of 15,300, 76,600, and 145,600 mg/m³ were adjusted for discontinuous exposure and converted to respective HECs of 2,740, 13,700, and 26,000 mg/m³ for extrarrespiratory effects using the methodology described previously.

There was a statistically significant increase in pancreatic islet cell adenomas in 145,600-mg/m³ females (5/86 compared to 0/85 in controls; see Table B-7). The incidence of adenomas in females (all exposure groups) was within the normal historical background levels for the laboratory, and no such tumors were seen in females exposed at 15,300 and 76,600 mg/m³. Although this tumor type was also seen in the males, tumors were observed at 0, 15,300, and 145,600 mg/m³ with no apparent exposure-response relationship. The study authors also indicated that in a concurrent chronic inhalation study conducted by the authors, female controls showed an incidence of 6 out of 95 pancreatic islet cell adenomas. Tumors of the nasal passages were also noted in one 15,300-mg/m³ male rat and four 76,600-mg/m³ rats (three males and one female). These tumors were not attributed to CFC-113 exposure because they were not of the same cell type, an exposure-related response was not apparent, and there were no other histopathological changes in nasal turbinates. Therefore, there was no adequate evidence of carcinogenicity following inhalation exposure in this chronic rat study.

Reproductive Study

Central Toxicol Lab (1981a)

In a single-generation reproductive toxicity study that was not published or peer-reviewed, Alderley Park Wistar rats (12 males and 24 females/group) were exposed

whole-body to CFC-113 (measured impurities <0.4%) at 0, 5,019, or 12,531 ppm. These exposure concentrations are equivalent to 0, 38,465, and 96,035 mg/m³. Males were exposed for 6 hours/day, 5 days/week during pre mating (10 weeks) and 6 hours/day, 7 days/week during mating (up to 2 weeks). Females (Subgroups A and B) were exposed 6 hours/day, 5 days/week for 3 weeks during pre mating, 6 hours/day, 7 days/week until successful mating (maximum of 2 weeks), and 6 hours/day, 7 days/week on GDs 1–20 (Subgroup A females only). All dams were examined for mortality and clinical signs of toxicity prior to exposure, twice daily during exposure, and every 3–4 days thereafter. Body weights and food intake were recorded prior to study initiation, weekly during pre mating, and every 3–4 days after pairing (of one male with two females); these parameters were not evaluated during mating. Males were sacrificed and subjected to necropsy within 1 week of successful mating or the end of the 2-week mating period. The precoital interval (time in days until positive signs of mating) was evaluated for each male rat, and coital and pregnancy success rates were determined for each female rat. Half of the females (Subgroup A) that showed positive signs of mating were exposed until GD 20 and permitted to deliver; offspring were monitored until 4 weeks-of-age. For the remaining half of females (Subgroup B), exposure was stopped after successful mating occurred, and gross necropsies (including evaluations of the numbers of resorptions and live and dead fetuses) were performed on GDs 17–20. Endpoints evaluated for offspring of Subgroup A females included the duration of gestation, numbers and sex of live and dead pups per litter (monitored daily until 4 weeks-of-age), pup weights (recorded at birth and every 3–4 days thereafter), and pup development (ages at which pinna unfolding, hair growth, eye opening, and weaning occurred). Among Subgroup A females, only dams that: (1) did not produce litters by Day 24; (2) produced litters that did not survive until 4 weeks-of-age; or (3) did not survive 4 weeks postpartum were subjected to necropsy.

One 38,465-mg/m³ female from Subgroup B and one 96,035-mg/m³ female from Subgroup A died on study ([Central Toxicol Lab, 1981a](#)). These deaths occurred on GD 12 and on Postpartum Day 24, respectively. These animals exhibited clinical manifestations of toxicity (blood stains on whiskers and/or nose, hunched posture), decreased body weight, and/or findings at gross necropsy (resorbed fetuses or regressed corpora lutea, macroscopic kidney and bladder effects). However, no clinical signs of toxicity were reported in the surviving animals. No consistent, exposure-related effects on body weights or body-weight gains were observed. Statistically significant reductions in food consumption (9–13% lower than controls) were occasionally observed in 96,035-mg/m³ females (during the first week of pre mating and on GDs 12/13 and 19/20 for Subgroup A females). No postmortem findings were reported in males. There were no significant effects on precoital interval (males) or coital and pregnancy success rates (females) among CFC-113-exposed rats and controls.

Females in Subgroup A (permitted to deliver) showed no statistically significant effects on the duration of gestation, mean litter size, sex of pups, percent pup mortality, or lactation index (defined as the number of pups alive at Day 28 ÷ number alive at Day 4) ([Central Toxicol Lab, 1981a](#)). No significant effects on fetal body weights or fetal development were observed. One control female (Subgroup A) was subjected to necropsy on Postnatal Day (PND) 7, owing to the death of all of its pups by PND 6; the study authors attributed these deaths to impaired lactation. No remarkable findings attributed to CFC-113 exposure were identified in five additional Subgroup A females (two controls, two dams exposed at 38,465 mg/m³, and one dam exposed at 96,035 mg/m³) subjected to necropsy because they failed to produce litters by Day 24.

In females exposed to CFC-113 and subjected to necropsy after successful mating (Subgroup B), there were no significant exposure-related effects on pre- or postimplantation loss ([Central Toxicol Lab, 1981a](#)). Subgroup B females exposed at 96,035 mg/m³ and examined on GDs 17–20 showed statistically significant reductions in the mean numbers of implantations, corpora lutea, and fetuses (12–14% lower than controls; [see Table B-8]). While the numbers of corpora lutea and implantations were not evaluated in Subgroup A females, there was no significant effect on litter size (i.e., the number of fetuses) in Subgroup A females, which, by virtue of being exposed during gestation, were more exposed to CFC-113 than Subgroup B females. Moreover, the study authors indicated that the numbers of corpora lutea, while statistically significantly decreased, were within the overall range for this strain of rat (citing a range of 11.67–14.26 based on studies conducted by the study authors since 1979). Reductions in the numbers of implantations and fetuses were considered by the authors to be downstream effects of decreased numbers of corpora lutea.

Several study deficiencies are noted: (1) only two exposure levels were evaluated; (2) only half of the females on study (Subgroup A) were exposed during gestation; (3) no females were exposed to CFC-113 during the postpartum period; (4) necropsies were not performed on Subgroup A females or their offspring (precluding an assessment of the consistency of effects observed in Subgroup B females and in Subgroup A females); (5) organ weights were not recorded and sperm parameters were not evaluated; and (6) different lots of the test material were used throughout the study. Nonetheless, this study identifies a NOAEL of 96,035 mg/m³ for systemic and reproductive/developmental effects. The slight decrease in number of corpora lutea observed in the 96,035-mg/m³ group was considered to be incidental to treatment because the numbers were within the historical control range for this strain and because there was no supporting effect on litter size in Subgroup A. TWA HECs for extraréspiratory effects of 0, 7,327, and 18,292 mg/m³ for males; 0, 8,586, and 21,436 mg/m³ for Subgroup A females; and 0, 7,968, and 19,893 mg/m³ for Subgroup B females were calculated for this review³.

Developmental Toxicity Studies

Central Toxicol Lab (1982)

In an unpublished, non-peer-reviewed study, groups of 24 female Alderley Park rats were exposed to CFC-113 (>99.95% purity) at 0, 4,985, 12,532, or 25,265 ppm (equivalent to 0, 38,200, 96,043, and 193,630 mg/m³), 6 hours/day on GDs 6–15. Dams were observed daily for mortality and clinical signs of toxicity. Body weights were recorded on GDs 0 and 5 (prior to exposure), daily after exposure (GDs 6–15), and on GDs 16, 18, and 21 (postexposure period). Food consumption was measured on GD 1, daily on GDs 6–16, and GDs 19 and 21 (observations were based on pairs of females sharing the same food source). At necropsy on GD 21, the following endpoints were assessed: gravid uterine weight, numbers of corpora lutea, implantations, early and late intrauterine deaths, and fetal body weights. Live fetuses were weighed and examined for gross external abnormalities (including cleft palate). Approximately two-thirds of the fetuses were examined for skeletal anomalies (morphological development and

³TWA exposures were based on exposures at 0, 38,465, and 95,798 mg/m³ for 6 hours/day: 5 days/week for 10 weeks pre-mating and 7 days/week for 2 weeks during mating (males); 5 days/week for 3 weeks pre-mating, 7 days/week for 2 weeks during mating, and 7 days/week for 3 weeks during gestation (Subgroup A females); and 5 days/week for 3 weeks pre-mating and 7 days/week for 2 weeks during mating (Subgroup B females).

degree of ossification); the remaining third were stained, sexed, and examined for soft tissue abnormalities. The litter was considered the basis for statistical tests.

Effects in maternal animals and fetuses exposed to CFC-113 are shown in Table B-9 ([Central Toxicol Lab, 1982](#)). No exposure-related mortalities were reported. Slight and transient hyperactivity was observed in dams exposed at 193,630 mg/m³ during 9 of 13 exposure periods; this effect subsided within 1 hour after cessation of exposure. Statistically significant reductions in maternal body-weight gain (19–40% lower than controls) were observed during exposure (GDs 5–15) at all exposure concentrations. Even though body-weight gains among all groups of exposed rats were similar to controls during the postexposure period (GDs 15–21), overall body-weight gains for 193,630-mg/m³ females (GDs 0–21) remained significantly lower than controls (by about 10% based on data presented graphically in the study report). Only data for body-weight gain (and not mean maternal body weights) were provided. During the exposure period, females in the 193,630-mg/m³ group also exhibited a significant reduction in food consumption (14% lower than controls). Thus, without the data on absolute body weight changes, the changes in the body weight were considered biologically significant. There were no significant and exposure-related effects on pre- or postimplantation loss, numbers of early or late intrauterine deaths, sex of fetuses, or fetal body weights. No gross external abnormalities were reported, and no soft tissue abnormalities attributed to CFC-113 exposure were observed. Compared with controls, there was a significantly increased incidence of extra (fourteenth) ribs in all groups of CFC-113–exposed rats (based on analyses for both fetuses and litters; [see Table B-9]). The fetal incidence of vestigial ribs was significantly increased relative to controls at $\geq 96,043$ mg/m³ (based on data for left vestigial rib, and any or both vestigial ribs); the litter incidence of an extra rib was significantly increased starting at 38,200 mg/m³ (based on vestigial rib-any). The study authors indicated that although these changes were statistically significant, the (fetal) incidence of this effect in all groups was approximately within the background range (8–36%) for this variant. However, consistent dose-dependent increases occurred at $\geq 96,043$ mg/m³ based on both fetal and litter incidence.

There were skeletal variations (increased vestigial ribs) observed from exposure to CFC-113 at $\geq 96,043$ mg/m³; however, maternal toxicity occurred at all exposure levels. A maternal NOAEL could not be established. A maternal LOAEL of 38,204 mg/m³ is identified based on decreased body-weight gain during exposure (GDs 5–15). The developmental NOAEL is 38,200 mg/m³ and LOAEL is 96,043 mg/m³ based on skeletal variations. Exposure concentrations in this study were equivalent to HECs of 0, 9,551, 24,011, and 48,407 mg/m³ based the default value of 1 for the ratio of blood-air partition coefficients.

Hazelton Lab (1967)

In an unpublished, non-peer-reviewed teratogenicity study, New Zealand white (NZW) rabbits (12/group) were exposed whole-body to CFC-113 (purity not reported) at 0, 2,000, or 20,000 ppm (equivalent to 0, 15,300, and 153,000 mg/m³), 2 hours/day on GDs 8–16. The animals were observed daily for mortality and clinical signs of toxicity. The rabbits were weighed weekly during gestation and at study termination. The does (five–six/group) were sacrificed on GDs 29 or 30, and cesarean sections were performed. The developmental endpoints evaluated in these animals included the number and placement of uterine implantation sites; numbers of live, dead, and resorbed fetuses; and fetal weight and length, external anatomy, and gross visceral features. The remaining does were permitted to deliver. Endpoints evaluated included the numbers of live and dead pups, pup weight and length, and external anatomy. Does

that failed to deliver were sacrificed starting on GD 35. All animals (does and fetuses/pups) were subjected to necropsy, and all fetuses and pups were examined (together) for skeletal abnormalities (including relative differences in size, location, normal or abnormal structure or formation, degree of ossification, and presence or absence of bone structure). Statistical analyses were not performed.

One doe exposed at 153,000 mg/m³ was found dead on GD 20 ([Hazelton Lab, 1967](#)). Examination of the uterine contents of this animal revealed seven resorption sites (right uterine horn) and no implantation sites (left uterine horn). Additionally, a 153,000-mg/m³ female aborted two dead pups (one of which was reportedly partially mutilated) on GD 29. Although the cause of death was not reported, the study authors did not attribute the death (or abortion) to CFC-113 exposure. Slight eye irritation (during exposure only) was noted in all rabbits at 153,000 mg/m³ (and no animals exposed at 0 or 15,000 mg/m³). The mean body weights of CFC-113 exposed rabbits remained within 10% of controls throughout the study (including the time points encompassing exposure [on GDs 8 and 15]). Fertility was low in all groups, including controls (four, four, and seven does exposed at 0, 15,300, and 153,000 mg/m³, respectively, became pregnant). Although the numbers of litters evaluated were small (one to three litters/group, counting the cesarean and natural born litters separately), there were no significant exposure-related effects on parameters examined at cesarean section or after natural delivery. Various findings were noted at gross necropsy of does and fetuses/pups; the most notable of these effects (owing to incidences that possibly correlate with exposure levels) was pale kidneys in two offspring exposed at 15,300 mg/m³ and six offspring exposed at 153,000 mg/m³. However, the number of total fetuses/pups examined for these effects at each exposure level is unclear. Based on data for skeletal abnormalities, it appears that as many as 38, 27, and 43 fetuses were examined at 0, 15,300, and 153,000 mg/m³, respectively, (the mutilated fetus mentioned previously, and one dead control fetus and one dead 15,300-mg/m³ fetus [both too small for analyses] were excluded). No significantly increased incidences of visceral or skeletal abnormalities were observed in exposed fetuses/pups compared to controls. The study appears to identify a NOAEL of 15,300 mg/m³ and LOAEL of 153,000 mg/m³ for maternal effects, based on slight eye irritation. The high concentration of 153,000 mg/m³ appears to be a NOAEL for fetal effects. Limitations of the study include short daily exposure durations, small group sizes, poor reporting, and no statistical analyses. Exposure concentrations in this study were equivalent to HECs of 0, 1,280, and 12,800 mg/m³ based on the default value of 1 for the ratio of blood-air partition coefficients. No adjustment for discontinuous exposure was made because this was a developmental toxicity study.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tests Evaluating Genotoxicity and/or Mutagenicity

Only a few genotoxicity tests of CFC-113 have been conducted (see Table 4). Tests of mutagenicity in bacteria have produced negative results with or without metabolic activation at concentrations up to 20% as a vapor ([Benigni et al., 1991](#); [Hoechst-Celanese, 1989](#); [Longstaff, 1988](#); [Longstaff et al., 1984](#); [Haskell Laboratories, 1977](#); [Simmon et al., 1977](#); [Haskell Laboratories, 1976](#)). Dominant lethal mutations were not induced in mice administered a single intraperitoneal (i.p.) dose of CFC-113 at up to 1,000 mg/kg during pregnancy ([Epstein et al., 1972](#)).

Table 4. Summary of 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation ^a	Results with Activation ^a	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutation	<i>Salmonella typhimurium</i> strains TA1535, TA1537, TA100, and TA98	0, 2, 6, 10, 19% vapor	–	–	Vapor exposure chamber assay, 48-hr exposure. Positive and negative controls responded appropriately. Toxicity evidenced by thinning of background lawn was seen in TA98 at concentrations $\geq 2\%$ in a second trial; no toxicity observed in first trial.	Benigni et al. (1991) ; Longstaff et al. (1984) ; Haskell Laboratories (1977) ; Simmon et al. (1977)
Mutation	<i>S. typhimurium</i> strains TA1535, TA1537, TA1538, TA100, and TA98	0, 4.6–4.8, 12.0–13.4% vapor	–	–	Vapor exposure chamber assay, 6-hr exposure.	Haskell Laboratories (1976)
Mutation	<i>S. typhimurium</i> strains TA1537, TA1535, TA100, and TA98	0, 10% vapor	–	–	Vapor exposure chamber assay, 48-hr exposure.	Hoechst-Celanese (1989)
Mutation	<i>S. typhimurium</i> strains TA1535 and TA100	Not specified; up to 10% (TA1535) and 20% vapor (TA100)	– (The study authors did not indicate whether metabolic activation system was used.)	– (The study authors did not indicate whether metabolic activation system was used.)	Vapor exposure chamber assay, 72-hr exposure. The ratios of test/control reversion frequencies were 2.0 and 1.3 for TA1535 and TA100, respectively.	Longstaff (1988)

Table 4. Summary of 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) Genotoxicity

Endpoint	Test System	Doses/ Concentrations Tested	Results without Activation ^a	Results with Activation ^a	Comments	References
Genotoxicity studies—in vivo						
Dominant lethal mutagenicity	7–9 males, ICR/Ha Swiss mice were administered a single dose of CFC-113 (in either water or tricapylin) via i.p. injection. Treated males were mated with untreated virgin females for 8 consecutive wk after treatment. Females were sacrificed 13 d after the midweek of their presumptive mating, and scored for percent pregnancy, total implants, and early fetal deaths per pregnancy.	200, 1,000 mg/kg	–	–	No treated male mice died. Pregnancy parameters were within control limits, showing no evidence of dominant lethal mutation.	Epstein et al. (1972)

^a– = negative.

i.p. = intraperitoneal

Acute Toxicity Studies

The acute inhalation and oral toxicity of CFC-113 is generally low.

- The 4-hour inhalation median lethal concentration (LC₅₀) values in rats range from 295,000–464,000 mg/m³ ([Haskell Laboratories, 1973](#); [PRL, 1973](#); [Haskell Laboratories, 1971b](#)).
- The 2-hour inhalation LC₅₀ in rabbits is 456,000 mg/m³ ([Hazleton Laboratories, 1967](#)). An LC₅₀ was not reported in guinea pigs, but deaths (of “several” animals) were reported at 383,000 and 728,000 mg/m³ 2–3 days after exposure ([Eastman Kodak, 1971](#)).
- The oral median lethal dose (LD₅₀) in rats is 43,000 mg/kg ([Haskell Laboratories, 1978](#); [Eastman Kodak, 1971](#)).
- The oral LD₅₀ in guinea pigs is >10,000 mg/kg ([Dow Chemical Company, 1949](#)).

Clinical signs of toxicity from CFC-113 exposure (via inhalation) included labored or irregular respiration, excitability, anesthesia, dyspnea, tremors, convulsions, loss of coordination, hyperemia, and prostration ([Haskell Laboratories, 1992, 1975a, b, 1973](#); [PRL, 1973](#); [Huntingdon Research Center, 1972](#); [Eastman Kodak, 1971](#); [Haskell Laboratories, 1971b](#); [Hazleton Laboratories, 1967](#); [Haskell Laboratories, 1961](#)). Pathology findings were rarely identified and, when reported, were mostly limited to the animals that died. Effects consisted of bronchial obstruction, thymus congestion, and pulmonary congestion, edema, and/or hemorrhage ([PRL, 1973](#); [Hazleton Laboratories, 1967](#); [Haskell Laboratories, 1954](#)).

Short-Term Studies

[Carter et al. \(1970\)](#)

In 14-day studies, rhesus monkeys (4 females/group), dogs (8 females/group), rats (50 males/exposed group and 25 control males), and mice (40 males/exposed group and 20 control males) were exposed to CFC-113 whole-body at 0 or 2,000 ppm (15,300 mg/m³). Other than minimal effects on the thyroid glands (enlarged in monkeys) and kidney weight (increased in rats), which were not clearly associated with exposure, no effects on mortality, clinical signs of toxicity, body weights, hematology and clinical chemistry (endpoints not specified), relative organ weights (not specified), or electroencephalographic (EEG) recordings were reported. Data were not shown, and no further information was provided.

[Vainio et al. \(1980\)](#)

Groups of male Wistar rats (five/group) were exposed to CFC-113 whole-body as a vapor at 0, 200, 1,000, or 2,000 ppm (0, 1,530, 7,660, and 15,300 mg/m³), 6 hours/day, 5 days/week for 1 or 2 weeks. At study termination, the livers and kidneys were retained for histopathological and/or biochemical analyses. The medial lobe of the liver was stained (hematoxylin and eosin, van Gieson, and periodic acid Schiff [PAS]), embedded in paraffin, and examined microscopically. Electron microscopy was performed on samples from two control animals and one animal/treatment group/time point. Two biopsies of the medial lobe (fixed and embedded in Epon) were taken from each animal; ultrathin sections of midzonal areas were examined using electron microscopy. Biochemical analyses included reduced glutathione (GSH) and microsomal cytochrome P450 (CYP450) content, and the activities of 7-ethoxycoumarin *O*-deethylase, NADPH cytochrome c reductase, and UDP glucuronosyltransferase.

Microscopic examinations (of Epon, but not paraffin sections) of the livers of treated rats showed evidence of lipid accumulation in hepatocytes, Kupffer cells, and lipocytes. Although these data were not quantified, the study authors suggested that changes in lipid accumulation were dose related. Electron microscopy of the liver revealed slight to moderate increases in smooth endoplasmic reticulum (SER) with vacuolization at 7,660 and 15,300 mg/m³ after 1 or 2 weeks of exposure, accompanied by increased numbers of autophagous vacuoles, decreased glycogen content, and mitochondrial condensation in rats exposed for 2 weeks. GSH was decreased slightly at 15,300 mg/m³ (6% after 1 or 2 weeks), and microsomal CYP450 content was decreased by 10% at 7,660 mg/m³ and 25% at 15,300 mg/m³ after 1 week of exposure (no significant changes after 2 weeks exposure). The activity of the liver enzymes, NADPH cytochrome c reductase tended to be decreased (as much as 19 and 36% at 15,300 mg/m³, $p < 0.05$), and UDP glucuronosyltransferase was increased (34–120% at 7,660 and 15,300 mg/m³, $p < 0.05$). The activities of these enzymes were unchanged in the kidneys of treated rats.

Savolainen and Pfaffli (1980)

Male Wistar rats (15/group) exposed whole-body to CFC-113 at 0, 200, 1,000, or 2,000 ppm (0, 1,530, 7,660, and 15,300 mg/m³), 6 hours/day, 5 days/week for up to 2 weeks were evaluated after 1 week of exposure, 2 weeks of exposure, and 1 week postexposure (5 rats/time point) with respect to CFC-113 levels in the area surrounding the kidneys and the brain (right cerebral hemisphere). Samples from the left cerebral hemisphere were analyzed biochemically (activities of azoreductase, glutathione peroxidase, and NADPH-diaphorase and total ribonucleic acid [RNA] and GSH levels). During exposure, CFC-113 accumulated in the brain and in perirenal fat in an exposure-related manner. Effects noted after 1 week of exposure only included increased NADPH-diaphorase activity (all exposure levels, but with no strict exposure-response) and significantly decreased GSH (at 15,300 mg/m³). After 2 weeks of exposure, glutathione peroxidase activity was significantly decreased, and total RNA tended to be decreased (not statistically significant) at 15,300 mg/m³. With the exception of RNA levels, which were significantly decreased at 15,300 mg/m³, all effects returned to control levels within 1 week after cessation of exposure. The study authors suggested that while some of the observed effects may have been adaptive, the observation of decreased glutathione peroxidase activity may be biologically significant, as it protects cells from oxidative damage. The authors also noted that at least one effect (decreased RNA in the postexposure period) is similar to that observed for other neurotoxicants (ethanol or styrene), and may partially explain clinical nervous system effects observed in workers exposed to CFC-113 and other fluorohydrocarbons.

Cardiac Sensitization Studies

In a series of unpublished studies, CFC-113 has been consistently shown to induce arrhythmias and cardiac sensitization in animals. Male Swiss mice were administered epinephrine intravenously at 0.006 mg/kg prior to acute (6 minutes) vapor exposures to CFC-113 at concentrations of 5 and 10% (383,000 and 766,000 mg/m³) ([Aviado and Belej, 1974](#)). During exposure, a second (challenge) dose of epinephrine was administered. Additional groups of animals (three/group) were exposed to CFC-113 alone. Based on constant monitoring of EKG data, one animal exposed to CFC-113 alone (at 766,000 mg/m³) showed evidence of a heart irregularity (inverted T-wave). In mice challenged with epinephrine, one of three and three of three mice exposed to CFC-113 at 383,000 and 766,000 mg/m³, respectively, showed evidence of cardiac arrhythmias (ventricular ectopics and ventricular bigeminy). Therefore, CFC-113 induced arrhythmias and also sensitized the mouse heart to epinephrine.

Similarly designed experiments conducted in dogs have also provided evidence for the sensitizing potential of CFC-113. Beagles (usually males) exposed to vapors of CFC-113 (commercial grade) and a challenge dose of epinephrine (0.004 or 0.008 mg/kg) showed evidence for arrhythmias following exposures as low as 0.5% (38,300 mg/m³) CFC-113 for 5–10 minutes ([Haskell Laboratories, 2000, 1989b](#)). Multiple ventricular beats or ventricular fibrillation with cardiac arrest was observed in ≥35% of dogs exposed to 38,300 mg/m³ for 10 minutes in the presence of epinephrine; 100% of animals were affected at 2% (153,000 mg/m³) CFC-113 (exposure groups ranged from 2–29 animals) ([Haskell Laboratories, 2000](#)). Exposures as short as 30 seconds could induce cardiac sensitization at higher concentrations of CFC-113. In an experiment using purified CFC-113, it was shown that the cardiac sensitization potential of purified CFC-113 is similar to that of its commercial counterpart (four of six dogs affected after exposure at 0.5% [38,300 mg/m³] for 5 minutes) ([Haskell Laboratories, 1989b](#)). Other experiments comparing the effect of epinephrine with “fright” responses (noise or shock) showed that CFC-113 sensitized the dog heart to epinephrine (one of six dogs affected after exposures ≥2,000 ppm [15,300 mg/m³] for ≥30 minutes), but not to other stimuli ([Haskell Laboratories, 1989a](#)). Higher exposures to CFC-113 (about 10% [766,000 mg/m³]) in conjunction with epinephrine have been shown to induce ventricular marked fibrillation ([Haskell Laboratories, 1989c](#)).

Metabolism/Toxicokinetic Studies

Studies in humans have shown that CFC-113 can penetrate the human skin, as evidenced by its presence in the end-tidal breath of volunteers administered CFC-113 via the dermal route of exposure ([Haskell Laboratories, 1971a](#)). CFC-113 applied to the scalp was absorbed more readily than sites such as the hand or forearm, possibly owing to the scalp’s increased vascularity ([Haskell Laboratories, 1968](#)). Data from inhalation exposures in volunteers indicate that only small amounts of CFC-113 (≤~20%) are retained after exposure; a majority of CFC-113 (>50%) is rapidly eliminated in expired air unchanged ([Woollen et al., 1990; Morgan et al., 1972](#)). In rats exposed to CFC-113 by both the oral and inhalation routes of exposure, expired air was also the primary route of elimination, accounting for ≥94% of the total administered radioactive dose ([Haskell Laboratories, 1982](#)).

With respect to the fraction that is absorbed, an initial increase in CFC-113 levels in the blood is observed after exposure. Data from a study in dogs showing higher arterial (than venous) concentrations of CFC-113 during exposure and higher venous (than arterial) concentrations of CFC-113 in the postexposure period suggest that CFC-113 is distributed to and slowly released from the tissues (presumably unchanged) ([Trochimowicz et al., 1974](#)). Studies in rodents exposed continuously to CFC-113 (or chlorofluorocarbons in general) have shown preferential partitioning of CFC-113 to lipid-rich tissues including the adipose tissue and (in lesser amounts) the brain, liver, and kidney (including perirenal fat) ([Furuya, 1980; Savolainen and Pfaffli, 1980; Carter et al., 1970](#)). A blood-air partition coefficient of 0.240 was predicted for CFC-113 based on algorithms using partition coefficient values for water:air and octanol:water ([Haick et al., 2014](#)).

In general, toxicokinetic studies provide little evidence for significant metabolism of CFC-113. Based on studies in humans and rats (oral and inhalation), the amount of CFC-113 excreted in the urine (and feces) is negligible (below the limits of detection in humans and ≤3% of the administered dose in animals) ([Woollen et al., 1990; Haskell Laboratories, 1982](#)).

However, radioactivity detected in the urine of rats was not unchanged CFC-113, suggesting that metabolism may occur for a small proportion of CFC-113 ([Haskell Laboratories, 1982](#)).

A physiologically based pharmacokinetic (PBPK) model developed to predict concentrations of CFC-113 in the end-tidal breath and the blood of humans generally showed good correlations with experimental data (with predicted blood concentrations falling below experimental values over time). Blood and breath concentrations of CFC-113 (during and after exposure) were not sensitive to metabolic clearance; therefore, the role of metabolism in human exposures is uncertain ([Auton and Woollen, 1991](#)).

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer reference values, respectively. IRIS data are indicated in the tables, if available.

Table 5. Summary of Noncancer Reference Values for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)							
Toxicity Type (units)	Species	Critical Effect	p-Reference Value	POD Method	POD (HEC)	UF _C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	Oral RfD value of 3×10^1 is available on IRIS (U.S. EPA, 1987)						
Subchronic p-RfC (mg/m ³)	Human	No effects observed	5×10^1	NOAEL _{ADJ}	1,440	30	Imbus and Adkins (1972)
Chronic p-RfC (mg/m ³)	Human	No effects observed	5	NOAEL _{ADJ}	1,440	300	Imbus and Adkins (1972)

HEC = human equivalent concentration; NOAEL_{ADJ} = no-observed-adverse-effect level adjusted daily dose; NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)				
Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF (mg/kg-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

Derivation of a Subchronic Provisional Oral Reference Dose

No subchronic oral exposure studies are identified in the literature for derivation of a subchronic provisional reference dose (p-RfD). Although a developmental toxicity study in rabbits is available, it is of limited utility owing to poor reporting and inadequate study design and execution. IRIS has developed a chronic oral RfD of 3×10^1 mg/kg-day based on a route-to-route converted human equivalent NOAEL from a human occupational inhalation exposure study that examined physical, clinical, or laboratory measurements in a cohort of Kennedy Space Center workers ([Imbus and Adkins, 1972](#)). In the absence of suitable subchronic oral studies, and uncertainties associated with the route-to-route extrapolation from occupational inhalation study to oral exposure, no subchronic p-RfD is derived.

Derivation of a Chronic Provisional Reference Dose

An RfD of 3×10^1 mg/kg-day is available in the IRIS database ([U.S. EPA, 1987](#)) based on a human occupational inhalation study by [Imbus and Adkins \(1972\)](#). Users should check the current IRIS database to determine whether any changes have been made.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The cross-sectional study of occupational exposure in humans exposed by inhalation to CFC-113 for an average of 2.77 years ([Imbus and Adkins, 1972](#)) is selected as the principal study for the derivation of the subchronic provisional reference concentration (p-RfC). In this study, no significant effects related to CFC-113 exposure were observed.

Justification for the Critical Effect

The NOAEL_{ADJ} of 1,440 mg/m³ from the cross-sectional occupational study by [Imbus and Adkins \(1972\)](#) is selected for the derivation of a subchronic p-RfC. A wide range of endpoints were assessed in this study ([Imbus and Adkins, 1972](#)), and this NOAEL value represents the highest NOAEL from the available studies of long-term human occupational exposure; the only human LOAEL identified was based on slight impairment of psychomotor performance reported in two male volunteers exposed to CFC-113 concentrations of 19,160 mg/m³ for 1.5 hours ([Haskell Laboratories, 1964](#)). Additional support from human and animal studies for the selection of this point of departure (POD) includes:

- 1) Other human occupational exposure studies did not identify significant adverse effects from CFC-113 exposure. No significant adverse effects on liver function were observed in humans occupationally exposed to CFC-113 at a TWA exposure level of 523 mg/m³ (duration adjusted to 187 mg/m³) for 2.5 years ([Neghab et al., 1997](#)), and no effects on cardiac activity were noted in workers exposed to CFC-113 for 7-hour shifts at TWA exposure levels of 3,388 mg/m³ (duration-adjusted exposure of 1,059 mg/m³) ([Egeland et al., 1992](#)).
- 2) A short-term experimental study revealed no effects on clinical pathology or psychomotor activities in human subjects exposed to CFC-113 at up to 7,660 mg/m³, 6 hours/day for 5 days (duration-adjusted exposure of 1,920 mg/m³) ([Reinhardt et al., 1971](#)).
- 3) Thirteen-week subchronic toxicity studies in animals identified no significant treatment-related effects at up to 26,257 mg/m³ (HEC) in rats and 9,602 mg/m³ (HEC) in dogs ([Haskell Laboratories, 1981](#); [LPT, 1976, 1975](#)).

- 4) A chronic study in rats observed effects (decreased body weight in females) only at 26,000 mg/m³ (HEC) ([Trochimowicz et al., 1988](#)). There were no effects at 13,700 mg/m³ (HEC) or lower.
- 5) A single-generation reproduction study in rats found no reproductive effects associated with exposure to CFC-113 at concentrations up to 21,436 mg/m³(HEC) ([Central Toxicol Lab, 1981b](#)).
- 6) Developmental toxicity studies in rats and rabbits do not identify the fetus as a sensitive target for CFC-113 exposure. There were some skeletal variations (increased fourteenth rib) in rats at doses ($\geq 24,011$ mg/m³ [HEC]) associated with maternal toxicity. There were no developmental effects in rats exposed at 9,551 mg/m³ (HEC) on GDs 6–15 ([Central Toxicol Lab, 1982](#)) or in rabbits exposed at 12,800 mg/m³ (HEC) on GDs 8–16 ([Hazleton Laboratories, 1967](#)).

Justification for the Principal Study

The cross-sectional human study by [Imbus and Adkins \(1972\)](#) included environmental sampling of workroom air (161 samples collected over a 3-week period) and examined 50 exposed and 50 unexposed workers at a single time with respect to physical exams (including visual and hearing tests), EKGs, lung capacity and chest x-rays, and hematology, clinical chemistry, and urinalysis parameters. Thorough analyses were conducted, and the NOAEL_{ADJ} of 1,440 mg/m³ from this study represents the highest NOAEL from studies of long-term human occupational exposure. Animal studies only identified significant exposure-related effects on body weights, but at a much higher exposure concentration (26,000 mg/m³ HEC).

Approach for Deriving the Subchronic p-RfC

The NOAEL from the study of occupational exposure in humans exposed via inhalation to CFC-113 for an average of 2.77 years was selected as the POD for the p-RfC. The subchronic p-RfC for CFC-113 based on this POD is derived as follows:

$$\begin{aligned}\text{Subchronic p-RfC} &= \text{NOAEL}_{\text{ADJ}} \div \text{UF}_C \\ &= 1,440 \text{ mg/m}^3 \div 30 \\ &= \mathbf{5 \times 10^1 \text{ mg/m}^3}\end{aligned}$$

Table 7 summarizes the uncertainty factors for the subchronic p-RfC for CFC-113.

Table 7. Uncertainty Factors for the Subchronic p-RfC for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)		
UF	Value	Justification
UF _A	1	A UF _A of 1 is applied because the POD is based on a study of human exposure; therefore, there is no need to account for uncertainty associated with extrapolating animal data to humans.
UF _H	10	A UF _H of 10 is applied to account for human variability and susceptibility, in the absence of information to assess the toxicokinetic and toxicodynamic variability of CFC-113 in humans.
UF _D	3	A UF _D of 3 is applied. The database includes three 13-wk subchronic-duration toxicity studies, including two “tolerance” studies in rats and dogs exposed to a single concentration (LPT, 1976, 1975) and one study in rats using multiple exposure concentrations (Haskell Laboratories, 1981); one chronic toxicity/carcinogenicity study in rats (Trochimowicz et al., 1988); two developmental studies in rats and rabbits (Central Toxicol Lab, 1982 ; Hazleton Laboratories, 1967); and a one-generation reproductive/developmental study in rats (Central Toxicol Lab, 1981b) via the inhalation route of exposure. No two-generation reproduction studies are available. Slight impairment of psychomotor performance was reported in humans exposed to high concentration of CFC-113, but there are no neurobehavioral studies in animals.
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 the POD comes from a subchronic-duration study. The duration of exposure in male workers averaged 2.77 yr.
UF _C	30	Composite UF = UF _A × UF _H × UF _D × UF _L × UF _S .

NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor.

Confidence in the subchronic p-RfC for CFC-113 is medium as explained in Table 8.

Table 8. Confidence Descriptors for the Subchronic p-RfC for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)		
Confidence Categories	Designation	Discussion
Confidence in study	M	Relatively thorough analyses were conducted in the cross-sectional human study by Imbus and Adkins (1972) . The study included environmental sampling of workroom air (161 samples collected over a 3-wk period) and examined 50 exposed and 50 unexposed male workers with respect to physical exams (including visual and hearing tests), EKGs, lung capacity and chest x-rays, and hematology, clinical chemistry, and urinalysis parameters. However, this study only identified a NOAEL while the only human LOAEL identified was based on slight impairment of psychomotor performance reported in only two male volunteers exposed to CFC-113 for a short period of time (1.5 hr).
Confidence in database	M	Confidence in the database is medium. The database includes three 13-wk subchronic-duration toxicity studies, including two “tolerance” studies in rats and dogs exposed to a single concentration (LPT, 1976, 1975) and one study in rats using multiple exposure concentrations (Haskell Laboratories, 1981); one chronic toxicity/carcinogenicity study in rats (Trochimowicz et al., 1988); two developmental toxicity studies in rats and rabbits (Central Toxicol Lab, 1982 ; Hazleton Laboratories, 1967); and a one-generation reproductive/developmental study in rats (Central Toxicol Lab, 1981b). No two-generation reproduction studies are available. Slight impairment of psychomotor performance was reported in humans exposed to high concentration of CFC-113, but there are no neurobehavioral studies in animals.
Confidence in subchronic p-RfC ^a	M	The overall confidence in the subchronic p-RfC is medium.

^aThe overall confidence cannot be greater than the lowest entry in the table (medium).

EKG = electrocardiogram; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; p-RfC = provisional reference concentration.

Derivation of a Chronic Provisional Reference Concentration (p-RfC)

A chronic p-RfC for CFC-113 is derived from the same POD as used in the derivation of the subchronic p-RfC. Justifications for selecting the principal study and the POD are described in the previous section of this document.

The chronic p-RfC for CFC-113, based on a NOAEL_{ADJ} of 1,440 mg/m³ in male workers exposed to CFC-113 for an average of 2.77 years, is derived as follows:

$$\begin{aligned}
 \text{Chronic p-RfC} &= \text{NOAEL}_{\text{ADJ}} \div \text{UF}_C \\
 &= 1,440 \text{ mg/m}^3 \div 300 \\
 &= \mathbf{5 \text{ mg/m}^3}
 \end{aligned}$$

Table 9 summarizes the uncertainty factors for the chronic p-RfC for CFC-113.

Table 9. Uncertainty Factors for the Chronic p-RfC for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)		
UF	Value	Justification
UF _A	1	A UF _A of 1 is applied because the POD is based on a study of human exposure; therefore, there is no need to account for uncertainty associated with extrapolating animal data to humans.
UF _H	10	A UF _H of 10 is applied to account for human variability and susceptibility, in the absence of information to assess the toxicokinetic and toxicodynamic variability of CFC-113 in humans.
UF _D	3	A UF _D of 3 is applied. The database includes three 13-wk subchronic-duration toxicity studies, including two “tolerance” studies in rats and dogs exposed to a single concentration (LPT, 1976, 1975) and one study in rats using multiple exposure concentrations (Haskell Laboratories, 1981); one chronic toxicity/carcinogenicity study in rats (Trochimowicz et al., 1988); two developmental studies in rats and rabbits (Central Toxicol Lab, 1982 ; Hazleton Laboratories, 1967); and a one-generation reproductive/developmental study in rats (Central Toxicol Lab, 1981b) via the inhalation route of exposure. No two-generation reproduction studies are available. Slight impairment of psychomotor performance was reported in humans exposed to high concentration of CFC-113, but there are no neurobehavioral studies in animals.
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 the POD comes from a subchronic-duration human study. The duration of exposure in male workers averaged 2.77 yr.
UF _C	300	Composite UF = UF _A × UF _H × UF _D × UF _L × UF _S .

NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor.

Confidence in the chronic p-RfC for CFC-113 is medium as explained in Table 10.

Table 10. Confidence Descriptors for the Chronic p-RfC for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)		
Confidence Categories	Designation	Discussion
Confidence in study	M	Relatively thorough analyses were conducted in the cross-sectional study by Imbus and Adkins (1972) . The study included environmental sampling of workroom air (161 samples collected over a 3-wk period) and examined 50 exposed and 50 unexposed workers with respect to physical exams (including visual and hearing tests), EKGs, lung capacity and chest x-rays, and hematology, clinical chemistry, and urinalysis parameters. However, this study only identified a NOAEL while the only human LOAEL identified was based on slight impairment of psychomotor performance reported in only two male volunteers exposed to CFC-113 for a short period of time (1.5 hr).
Confidence in database	M	Confidence in the database is medium. The database includes three 13-wk subchronic-duration toxicity studies, including two “tolerance” studies in rats and dogs exposed to a single concentration (LPT, 1976, 1975) and one study in rats using multiple exposure concentrations (Haskell Laboratories, 1981); one chronic toxicity/carcinogenicity study in rats (Trochimowicz et al., 1988); two developmental toxicity studies in rats and rabbits (Central Toxicol Lab, 1982 ; Hazleton Laboratories, 1967); and a one-generation reproductive/developmental study in rats (Central Toxicol Lab, 1981b). No two-generation reproduction studies are available. Slight impairment of psychomotor performance was reported in humans exposed to high concentration of CFC-113, but there are no neurobehavioral studies in animals.
Confidence in chronic p-RfC ^a	M	The overall confidence in the chronic p-RfC is medium.

^aThe overall confidence cannot be greater than the lowest entry in the table (medium).

EKG = electrocardiogram; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; p-RfC = provisional reference concentration.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 11 identifies the cancer weight-of-evidence (WOE) descriptor for CFC-113.

Table 11. Cancer WOE Descriptor for 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)			
Possible WOE Descriptor	Designation	Route of Entry	Comments
<i>“Carcinogenic to Humans”</i>	NS	NA	There are no human data to support this.
<i>“Likely to Be Carcinogenic to Humans”</i>	NS	NA	Results from available animal studies are not sufficient to support this, and no human data are available.
<i>“Suggestive Evidence of Carcinogenic Potential”</i>	NS	NA	Results from available animal studies are not sufficient to support this, and no human data are available.
<i>“Inadequate Information to Assess Carcinogenic Potential”</i>	Selected	Inhalation and oral	No adequate evidence of carcinogenicity was seen following inhalation exposure in a chronic rat study (Trochimowicz et al., 1988). No carcinogenicity studies are available that evaluated oral exposure.
<i>“Not Likely to Be Carcinogenic to Humans”</i>	NS	NA	The available data do not support this.

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

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of a Provisional Oral Slope Factor

No studies on the oral carcinogenicity of CFC-113 have been identified; therefore, derivation of a provisional oral slope factor (p-OSF) is precluded.

Derivation of a Provisional Inhalation Unit Risk

The chronic inhalation study by [Trochimowicz et al. \(1988\)](#) does not provide sufficient evidence for carcinogenicity and, thus, precludes the derivation of a provisional inhalation unit risk (p-IUR). Although the incidence of pancreatic islet cell adenomas in females at the high-dose group (5/86) was significantly increased compared with the control and low- and mid-dose groups (0/85, 0/36, and 0/30, respectively), the study authors did not consider the occurrence to be treatment related because it was within historical control levels for the laboratory. Additionally, a concurrent chronic inhalation study conducted by the same study authors showed an incidence of 6/95 pancreatic islet cell adenomas in the control group.

APPENDIX A. SCREENING PROVISIONAL VALUES

No provisional screening values are derived.

APPENDIX B. DATA TABLES

Table B-1. Concentrations of Serum Bile Acids in Workers Exposed to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1)^a				
Bile Acid (µmol/L)	Control (n = 11)	Pre-exposure (n = 4)	Postexposure (n = 6)	p-Value
GC	0.46 ± 0.23 ^b	0.46 ± 0.16 (0)	2.44 ± 0.43*** (430)	0.0003
GCDC	1.98 ± 0.34	2.76 ± 0.31 (39)	3.91 ± 0.47* (97)	0.007
Subtotal (GTOT)	3.22 ± 0.68	3.91 ± 0.55 (21)	7.37 ± 0.89*** (129)	0.003
TC	0.33 ± 0.06	0.18 ± 0.05 (-45)	0.78 ± 0.20*** (136)	0.009
TUDC	0.15 ± 0.04	0.12 ± 0.04 (-20)	0.27 ± 0.03** (80)	0.05
TCDC	0.59 ± 0.13	0.85 ± 0.19 (44)	1.53 ± 0.18*** (159)	0.001
Subtotal (TTOT)	1.44 ± 0.27	1.52 ± 0.31 (6)	3.21 ± 0.51*** (123)	0.005
Total (TSBA)	7.10 ± 1.00	7.06 ± 0.74 (-1)	13.35 ± 1.48*** (88)	0.002

^a[Neghab et al. \(1997\)](#).

^bValues represent means ± standard error of the mean (percent change from control).

*Significantly different from control at $p < 0.05$ (Duncan's multiple comparison test).

**Significantly different from pre-exposure group only at $p < 0.05$ (Duncan's multiple comparison test).

***Significantly different from both control and pre-exposure group at $p < 0.05$ (Duncan's multiple comparison test).

GC = glycocholic acid; GCDC = glycochenodeoxycholic acid; GTOT = subtotal of glycine conjugated bile acids; TC = taurocholic acid; TUDC = taurosodeoxycholic acid; TCDC = taurochenodeoxycholic acid; TTOT = subtotal of taurine conjugated bile acids; TSBA = total serum bile acids.

Table B-2. Organ-Weight Effects in CD Rats Exposed to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) 6 Hours/Day, 5 Days/Week for 13 Weeks^a

Parameter ^c	Exposure Group, mg/m ³ (HEC) ^b			
	0	57,260 (10,230)	95,138 (16,988)	147,040 (26,257)
Males				
Number of animals	10	10	10	10
Lung weight:				
Absolute (g)	1.919 ± 0.161 ^c	2.133 ± 0.249 ^d (11)	2.137 ± 0.240 ^d (11)	2.304 ± 0.368 ^{d*} (20)
Relative (% BW) ^c	0.403	0.435 (8)	0.440 (9)	0.495* (23)
Females				
Number of animals	9	10	10	10
Adrenal weight:				
Absolute (g)	0.076 ± 0.011	0.088 ± 0.009 ^{*d} (16)	0.077 ± 0.009 (1)	0.091 ± 0.007* (20)
Relative (% BW) ^c	0.024	0.025 (4)	0.023 ^d (-4)	0.027* (13)

^aHaskell Laboratories (1981).

^bAnalytical concentrations have been converted to HECs based on the following equation:

CONC (HEC) = CONC (mg/m³) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood-air partition coefficient ratio (U.S. EPA, 1994). The value for the rat blood-air partition coefficient is unknown (a predicted value for humans is available), so the default ratio of 1 was applied.

^cValues are expressed as mean ± standard deviation when possible (percent change compared with control).

^dValues are not clearly legible in the study report.

^eStandard deviation for relative organ weights were not provided in the study report.

*Significantly different ($p < 0.05$) from control based on statistics performed by the study authors.

BW = body weight; HEC = human equivalent concentration.

Table B-3. Mortality in Rats Exposed to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) Vapor for 2 Years^{a,b}					
Parameter		Exposure Group, mg/m³ (HEC)^c			
		0	15,300 (2,740)	76,600 (13,700)	145,600 (26,000)
Males					
First 18 mo	<i>Corynebacterium kutscheri</i> -related mortality	0	1	16	15
	Mortality from other causes	16	23	18	11
18–24 mo	<i>C. kutscheri</i> -related mortality	35	26	2	11
	Mortality from other causes	23	22	29	22
Survival to 2 yr		16	18	25	31
Females					
First 18 mo	<i>C. kutscheri</i> -related mortality	1	0	2	1
	Mortality from other causes	20	11	11	11
18–24 mo	<i>C. kutscheri</i> -related mortality	7	7	3	2
	Mortality from other causes	25	24	24	19
Survival to 2 yr		37	48	50	57

^a[Trochimowicz et al. \(1988\)](#).

^b*n* = 90; does not include 10 rats/sex/group terminated at 12 months.

^cAnalytical concentrations have been converted to HECs based on the following equation:

CONC (HEC) = CONC (mg/m³) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood-air partition coefficient ratio ([U.S. EPA, 1994](#)). The value for the rat blood-air partition coefficient is unknown (a predicted value for humans is available), so the default ratio of 1 was applied.

HEC = human equivalent concentration.

Table B-4. Effects in S-D-Derived Rats Exposed to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) 6 Hours/Day, 5 Days/Week for up to 2 Years^a				
Parameter	Exposure Group, mg/m³ (HEC)^b			
	0	15,300 (2,740)	76,600 (13,700)	145,600 (26,000)
Males				
Number of animals	10	10	10	10
Serum glucose (mg %): 6 mo	105 ± 6 ^c	104 ± 9 (-1)	104 ± 8 (-1)	92 ± 4* (-12)
Urinary fluoride (µg) ^d :				
3 mo	17 ± 4	18 ± 4 (6) ^c	21 ± 5 (24)	28 ± 6* (65)
6 mo	16 ± 7	21 ± 5 (31)	23 ± 7 (44)	26 ± 8* (63)
12 mo	18 ± 6	18 ± 4 (0)	22 ± 4 (22)	26 ± 6* (44)
24 mo	17 ± 3	22 ± 8 (29)	22 ± 4 (29)	24 ± 5* (41)
Females				
Number of animals	10	10	10	10
Serum glucose (mg %): 6 mo	122 ± 11	116 ± 6 (-5)	120 ± 10 (-2)	116 ± 8 (-5)
Urinary fluoride (µg) ^d :				
3 mo	9 ± 3	9 ± 4 (0)	15 ± 5* (67)	16 ± 3* (78)
6 mo	11 ± 3	14 ± 3 (27)	13 ± 5 (18)	17 ± 6* (55)
12 mo	11 ± 3	12 ± 3 (9)	13 ± 5 (18)	16 ± 6 (45)
24 mo	15 ± 5	17 ± 6 (13)	17 ± 2 (13)	20 ± 3 (33)

^aHaskell Laboratories (1985); Trochimowicz et al. (1988).

^bAnalytical concentrations have been converted to HECs based on the following equation:
 $\text{CONC (HEC)} = \text{CONC (mg/m}^3) \times (\text{hours exposed} \div 24 \text{ hours}) \times (\text{days exposed} \div 7 \text{ days}) \times \text{blood-air partition coefficient ratio (U.S. EPA, 1994)}$. The value for the rat blood-air partition coefficient is unknown (a predicted value for humans is available), so the default ratio of 1 was applied.

^cValues are expressed as mean ± standard deviation (percent change compared with control).

^dTotal F⁻ = µg/mL F⁻ × mL (urine volume).

*Significantly higher than controls, $p \leq 0.05$, statistical test performed by the study authors.

HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-5. Organ-Weight Effects in S-D-Derived Rats Exposed to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) 6 Hours/Day, 5 Days/Week for 1 Year^a

Parameter ^c	Exposure Group, mg/m ³ (HEC) ^b			
	0	15,300 (2,740)	76,600 (13,700)	145,600 (26,000)
Males				
Number of animals	10	10	10	10
BW at necropsy (g)	773.3 ± 90.1	743.7 ± 50.7 (-4)	745.6 ± 86.1 (-4)	748.3 ± 83.7 (-3)
Liver weight:				
Absolute (g)	18.450 ± 4.433	21.517 ± 2.917 (17)	22.512 ± 3.137* (22)	23.618 ± 3.518* (28)
Relative (% BW)	2.361 ± 0.397	2.900 ± 0.391* (23)	3.039 ± 0.420* (29)	3.153 ± 0.266* (34)
Kidney weight:				
Absolute (g)	3.975 ± 0.842	4.316 ± 0.225 (9)	4.299 ± 0.506 (8)	4.615 ± 0.811 (16)
Relative (% BW)	0.511 ± 0.068	0.583 ± 0.048* (14)	0.584 ± 0.098* (14)	0.617 ± 0.086* (21)
Females				
Number of animals	10	10	10	10
BW at necropsy (g)	388.2 ± 71.6	347.3 ± 43.6 (-11)	346.2 ± 35.8 (-11)	334.9 ± 63.8 (-14)
Liver weight:				
Absolute (g)	9.506 ± 1.448	9.008 ± 1.567 (-5)	12.175 ± 1.310* (28)	11.730 ± 1.387* (23)
Relative (% BW)	2.472 ± 0.216	2.584 ± 0.235 (5)	3.537 ± 0.406* (43)	3.593 ± 0.675* (45)
Kidney weight:				
Absolute (g)	2.312 ± 0.253	2.272 ± 0.359 (-2)	2.382 ± 0.313 (3)	2.318 ± 0.262 (0)
Relative (% BW)	0.607 ± 0.084	0.652 ± 0.045 (8)	0.696 ± 0.115 (15)	0.713 ± 0.144 (17)
Lung weight:				
Absolute (g)	1.650 ± 0.151	1.679 ± 0.224 (2)	1.750 ± 0.133 (6)	1.765 ± 0.160 (7)
Relative (% BW)	0.434 ± 0.060	0.485 ± 0.044 (12)	0.510 ± 0.060* (18)	0.539 ± 0.081* (24)
Spleen weight:				
Absolute (g)	0.493 ± 0.112	0.514 ± 0.083 (4)	0.529 ± 0.087 (7)	0.534 ± 0.060 (8)
Relative (% BW)	0.127 ± 0.018	0.148 ± 0.016 (16)	0.155 ± 0.034* (22)	0.164 ± 0.035* (29)

^aHaskell Laboratories (1985); Trochimowicz et al. (1988).

^bAnalytical concentrations have been converted to HECs based on the following equation:

CONC (HEC) = CONC (mg/m³) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood-air partition coefficient ratio (U.S. EPA, 1994). The value for the rat blood-air partition coefficient is unknown (a predicted value for humans is available), so the default ratio of 1 was applied.

^cValues are expressed as mean ± standard deviation (percent change compared with control).

*Significantly different ($p < 0.05$) from control, statistical tests performed by study authors.

BW = body weight; HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-6. Organ-Weight Effects in S-D–Derived Rats Exposed to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) 6 Hours/Day, 5 Days/Week for 2 Years^a

Parameter ^c	Exposure Group, mg/m ³ (HEC) ^b			
	0	15,300 (2,740)	76,600 (13,700)	145,600 (26,000)
Males				
Number of animals	16	18	25	31
BW at necropsy (g)	789.0 ± 137.9	810.5 ± 183.1 (2.7)	832.5 ± 138.9 (5.5)	810.5 ± 94.1 (2.7)
Liver weight:				
Absolute (g)	23.363 ± 4.478	27.962 ± 7.848* (20)	26.256 ± 5.087 (12)	24.063 ± 4.472 (3.0)
Relative (% BW)	2.9737 ± 0.4178	3.5376 ± 1.1416* (19)	3.1906 ± 0.5960 (7)	2.9779 ± 0.4798 (0.1)
Kidney weight:				
Absolute (g)	5.497 ± 0.899	5.924 ± 1.580 (7.8)	6.200 ± 2.061 (13)	5.467 ± 1.516 (-0.5)
Relative (% BW)	0.7072 ± 0.1231	0.7508 ± 0.2283 (6.2)	0.7539 ± 0.2392 (6.6)	0.6789 ± 0.1873 (-4.0)
Females				
Number of animals	37	48	50	57
BW at necropsy (g)	476.5 ± 95.6	474.6 ± 90.7 (-0.4)	464.9 ± 83.6 (-2.4)	450.6 ± 89.0 (-5.4)
Liver weight:				
Absolute (g)	16.238 ± 4.533	16.342 ± 4.147 (6.4)	15.576 ± 4.324 (-4.1)	15.356 ± 3.878 (-4.4)
Relative (% BW)	3.4076 ± 0.6648	3.4425 ± 0.5856 (1.0)	3.3325 ± 0.5097 (-2.2)	3.4207 ± 0.6491 (0.4)
Kidney weight:				
Absolute (g)	3.121 ± 0.744	3.186 ± 0.531 (2.1)	3.153 ± 1.534 (1.0)	2.893 ± 0.521 (-7.3)
Relative (% BW)	0.6701 ± 0.1887	0.6902 ± 0.1503 (3.0)	0.6969 ± 0.3859 (4.0)	0.6518 ± 0.1023 (-2.7)

^aHaskell Laboratories (1985); Trochimowicz et al. (1988).

^bAnalytical concentrations have been converted to HECs based on the following equation:
 $CONC (HEC) = CONC (mg/m^3) \times (hours\ exposed \div 24\ hours) \times (days\ exposed \div 7\ days) \times \text{blood-air partition coefficient ratio}$ (U.S. EPA, 1994). The value for the rat blood-air partition coefficient is unknown (a predicted value for humans is available), so the default ratio of 1 was applied.

^cValues are expressed as mean ± standard deviation (percent change compared with control).

*Significantly different ($p < 0.05$) from control, statistical tests performed by study authors.

BW = body weight; HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-7. Neoplastic Effects in S-D–Derived Rats after Exposure to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) 6 Hours/Day, 5 Days/Week for 2 Years^a				
Parameter	Exposure Group, mg/m ³ (HEC) ^b			
	0	15,300 (2,740)	76,600 (13,700)	145,600 (26,000)
Pancreatic islet adenomas:				
Males	2/88 ^c	1/64	0/58	2/87
Females	0/85	0/36	0/30	5/86*

^a[Trochimowicz et al. \(1988\)](#); [Haskell Laboratories \(1985\)](#).

^bAnalytical concentrations have been converted to HECs based on the following equation:
 $CONC (HEC) = CONC (mg/m^3) \times (hours\ exposed \div 24\ hours) \times (days\ exposed \div 7\ days) \times \text{blood-air partition coefficient ratio}$ ([U.S. EPA, 1994](#)). The value for the rat blood-air partition coefficient is unknown (a predicted value for humans is available), so the default ratio of 1 was applied.

^cNumber observed/number examined.

*Significantly higher than controls, $p < 0.05$, statistical test performed by study authors.

HEC = human equivalent concentration; S-D = Sprague-Dawley.

Table B-8. Effects in Female Alderley Park Wistar Rats (Subgroup B) Exposed to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1) 6 Hours/Day, 5 Days/Week during Premating and 6 Hours/Day, 7 Days/Week during Mating^a			
Parameter	Exposure Concentration, mg/m ³ (HEC) ^b		
	0	38,465 (7,968)	96,035 (19,893)
Number of pregnant females	11	7 ^c	10
Number of implantations	13.55 ± 2.34	12.86 ± 1.07 (-5)	11.90 ± 1.45* (-12)
Number of corpora lutea	14.18 ± 1.54	13.71 ± 1.60 (-3)	12.40 ± 0.70** (-13)
Number of fetuses	13.55 ± 2.34	12.57 ± 1.13 (-7)	11.60 ± 1.58* (-14)

^a[Central Toxicol Lab \(1981b\)](#).

^bAnalytical concentrations have been converted to HECs based on the following equation:
 $CONC (HEC) = CONC (ppm) \times (molecular\ weight \div 24.45) \times (hours\ exposed \div 24\ hours) \times (days\ exposed \div 7\ days) \times \text{blood-air partition coefficient ratio}$ ([U.S. EPA, 1994](#)). The value for the rat blood-air partition coefficient is unknown (a predicted value for humans is available), so the default ratio of 1 was applied.

^cOne female from this group was excluded from analyses because it died on GD 12.

^dValues are expressed as mean ± standard deviation (percent change compared with control).

*Significantly different from the control group mean, $p < 0.05$, statistical test performed by study authors.

**Significantly different from the control group mean, $p < 0.01$, statistical test performed by study authors.

GD = gestation day; HEC = human equivalent concentration.

Table B-9. Effects in Alderley Park Rats Exposed to 1,1,2-Trichloro-1,2,2-trifluoroethane (CASRN 76-13-1), 6 Hours/Day on GDs 6–15^a				
Parameter	Exposure Concentration, mg/m³ (HEC)^b			
	0	38,200 (9,511)	96,043 (24,011)	193,630 (48,407)
Maternal effects				
Number of pregnant females	24	22	23	23
Body-weight gain (g): GDs 5–15	43.5 ^c	34.3* (-21)	35.2** (-19)	26.3** (-40)
Food consumption (g/day) ^d : GDs 6/7–15/16	28.1	28.3 (1)	27.5 (-2)	24.3** (-14)
Fetal effects				
Extra rib; fetal incidence:				
Fourteenth left, vestigial	2/184 (1%) ^e	7/169 (4%)	14/161** (9%)	17/169** (10%)
Fourteenth right, vestigial	5/184 (3%)	11/169 (7%)	7/161 (4%)	8/169 (5%)
Fourteenth both, vestigial	11/184 (6%)	13/169 (8%)	19/161* (12%)	38/169** (23%)
Fourteenth any, vestigial	18/184 (10%)	31/169 (18%)	40/161** (25%)	63/169** (37%)
Extra rib; litter incidence:				
Fourteenth left, vestigial	2/24 (8%) ^e	5/22 (23%)	10/23** (43%)	8/23* (35%)
Fourteenth right, vestigial	3/24 (13%)	8/22 (36%)	6/23 (26%)	8/23 (35%)
Fourteenth both, vestigial	5/24 (21%)	8/22 (36%)	8/23 (35%)	15/23** (65%)
Fourteenth any, vestigial	6/24 (25%)	15/22** (70%)	15/23** (65%)	19/23** (83%)

^aCentral Toxicol Lab (1982).

^bAnalytical concentrations have been converted to HECs based on the following equation:

CONC (HEC) = CONC (ppm) × (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood-air partition coefficient ratio (U.S. EPA, 1994). The value for the rat blood-air partition coefficient is unknown (a predicted value for humans is available), so the default ratio of 1 was applied.

^cData represent means (percent change compared with control). No measures of variance (standard error or standard deviation) were provided in the study report.

^dThe number of observations were 12, 10, 11, and 11 at 0, 5,000, 12,500, and 25,000 ppm, respectively.

^eNumber affected/number examined (percent incidence).

*Significantly different from the control group mean ($p < 0.05$) based on statistics performed by study authors.

** $p < 0.01$.

GD = gestation day; HEC = human equivalent concentration.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

There are no benchmark dose (BMD) modeling outputs.

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