19 December 2007

TEST PLAN FOR HFC-23

HFC-23 CAS No. 75-46-7	Data Available	Data Acceptable	Testing Required
	Y/N	Y/N	Y/N
PHYSICAL/CHEMICAL CHARACTERISTICS			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
ENVIRONMENTAL FATE			
Photodegradation	Y	Y	N
Stability in Water	Y	Y	N
Transport (Fugacity)	Y	Y	N
Biodegradation	Y	Y	N
ECOTOXICITY			
Acute Toxicity to Fish	Y[1]	Y	N
Acute Toxicity to Invertebrates	Y[1]	Y	N
Acute Toxicity to Aquatic Plants	Y[1]	Y	N
MAMMALIAN TOXICITY			
Acute Toxicity	Y	Y	N
Repeated Dose Toxicity	Y[2]	Y	N
Developmental Toxicity	Y	Y	N
Reproductive Toxicity	Y[2]	Y	N
Genetic Toxicity Gene Mutations	Y	Y	N
Genetic Toxicity Chromosomal Aberrations	Y	Y	N

[1]Data from an analogous chemical, HFC-134a, were used to fulfill the end point.
[2]Data from an analogous chemical, HFC-32, were used to fulfill the end point.

I U C L I D

Data Set

Existing Chemical	**:**	ID: 75-46-7
CAS No.	**:**	75-46-7
CAS Name	**:**	Methane, trifluoro-
Molecular Formula	**:**	CHF3

Producer related part

Company	**:**	E. I. du Pont de Nemours and Company
Creation date	**:**	19.01.2006

Substance related part

Company	**:**	E. I. du Pont de Nemours and Company
Creation date	**:**	19.01.2006
Status	**:**	
Memo	**:**	
Printing date	**:**	20.12.2007
Revision date	**:**	
Date of last update	**:**	13.12.2007
Number of pages	**:**	49
Chapter (profile)	**:**	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	**:**	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	**:**	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

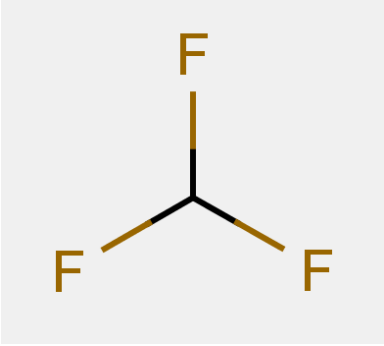
IUPAC Name :
Smiles Code : FC(F)F
Molecular formula : CHF3
Molecular weight : 70.01
Petrol class :

19.01.2006

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : gaseous
Purity :
Colour : clear, colorless
Odour : slight ethereal

Attached document : trifluoromethane structure.bmp



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1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Arcton® 1

19.01.2006

Carbon trifluoride

19.01.2006

FC-23

19.01.2006

FE-13

19.01.2006

Fluoroform

19.01.2006

Fluoryl

19.01.2006

Freon® 23

19.01.2006

Genetron® 23

19.01.2006

HC-23

19.01.2006

HFC-23

19.01.2006

Methyl trifluoride

19.01.2006

R 23

19.01.2006

Suva® 23

19.01.2006

Trifluoromethane

19.01.2006

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

Memo : DOT/IMO/IATA
Proper Shipping Name : Trifluoromethane
Hazard Class : 2.2
UN No. : 1984
DOT/IMO Label : Nonflammable Gas

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1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : other: DuPont Acceptable Exposure Limit (AEL) 8- and 12-hour TWA
Limit value : 1000 other: ppm

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1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: Germany
Labelled by : other: VwVwS (Germany), Annex 3
Class of danger : 1 (weakly water polluting)

Remark : WGK. German Water Hazard Class Substance List
Kenn-Number: 4380

19.01.2006 (6)

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

Remark : HFC-23 has no ozone depletion potential.
05.12.2007 (12)

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : EINECS
Additional information : EINCS No.: 200-872-4

19.01.2006 (6)

Type : TSCA
Additional information : July 2005 TSCA Inventory

19.01.2006 (6)

Type : DSL
Additional information : Supplement to Canada Gazette, Part I, January 26, 1991

19.01.2006 (6)

Type : ECL
Additional information : ECL Serial No.: KE-34244

19.01.2006 (6)

Type : ENCS
Additional information : ENCS No.: 2-47

19.01.2006 (6)

Type : PICCS
Additional information : 2000

19.01.2006 (6)

Type : other: SWISS
Additional information : SWISS No. G-4304
Toxic Category 5

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Type : other: ASIA-PAC
Additional information :

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Type : other: New Jersey Right-to-Know
Additional information : Special Health Hazard Code(s): None

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1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : -160 °C
Sublimation :
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.
13.02.2006 (30)

Value : -155.1 °C
Sublimation :
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.
Flag : Critical study for SIDS endpoint
13.02.2006 (31) (36)

2.2 BOILING POINT

Value : -84 °C at
Decomposition :
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.
13.02.2006 (30)

Value : -82.1 °C at
Decomposition :
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.
13.02.2006 (15) (16) (31)

Value : -82 °C at
Decomposition :
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions

2g. Data from handbook or collection of data.
Flag : Critical study for SIDS endpoint
13.02.2006 (12) (36)

2.3 DENSITY

Type :
Value : 1.44 g/cm³ at -82 °C
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.
Flag : Critical study for SIDS endpoint
13.02.2006 (15) (16) (36)

Type :
Value : 1.19 g/cm³ at 20 °C
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : Liquid density
Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.
13.02.2006 (12)

Type :
Value : .67 g/cm³ at 25 °C
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : Liquid density
Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.
13.02.2006 (12)

Type :
Value : .678 g/cm³ at 25 °C
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.
13.02.2006 (31)

Type :
Value : 2.4 at °C
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result	:	Vapor density: 2.4 (Air=1)
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.
14.02.2006		(15) (16)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	44820 hPa at 21.1 °C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Value: 4482 (kPa absolute @ 21.1°C); 650 (psia @ 70°F)
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.
14.02.2006		(12)
Value	:	45850 at 25 °C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Value: 4585 (kPa absolute @ 25 °C); 665 (psia @ 77 °F)
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.
Flag	:	Critical study for SIDS endpoint
14.02.2006		(12)
Value	:	47054 hPa at 25 °C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Experimental value
Result	:	Value: 3.52E+4 mm Hg at 25°C.
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.
04.10.2006		(7) (41)
Value	:	47298.33 hPa at 25 °C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Value: 686 psig @ 25°C
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.
14.02.2006		(15) (16)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	.64 at °C
pH value	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Experimental value
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.

14.02.2006 (24) (41)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	.1 other: WT% at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.
Flag	:	Critical study for SIDS endpoint

14.02.2006 (15) (16)

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	other: soluble
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable 4e. Document insufficient for assessment.

04.12.2007 (31)

Solubility in	:	other: ethanol

Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	other: very soluble
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
4e. Document insufficient for assessment.
04.10.2006 (31)

Solubility in	:	other: acetone
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	other: soluble
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
4e. Document insufficient for assessment.
04.10.2006 (31)

Solubility in	:	other: benzene
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	other: soluble
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
4e. Document insufficient for assessment.
04.10.2006 (31)

Solubility in	:	Water
Value	:	4090 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	

pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Experimental value
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.

14.02.2006 (41)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	No flash point
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.

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2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

Result	:	non flammable
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	HFC-23 is not flammable in air at temperatures up to 100°C at atmospheric pressure.
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.

14.02.2006 (15) (16) (30)

2.10 EXPLOSIVE PROPERTIES

Method	:	other: ASTM E681
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Flammable Limits in air, % by Volume: LEL : None per ASTM E681 UEL : None per ASTM E681

Autoignition: Not determined

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.

14.02.2006 (15) (16)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Conversion factors:
1 mg/L = 349 ppm
1 ppm = 2.9 mg/m³

23.01.2006

Memo : Critical temperature: 25.9°C

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.

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Memo : Extinguishing concentration (cup burner for heptane):
13% by volume, not life treatening

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.

14.02.2006 (12)

Memo : Heat of vaporization: 27.6 (BTU/lb) at 70°F; 15.3 (cal/g) at 21.1°C:

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.

14.02.2006 (12)

Memo : Ozone depletion potential: 0

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.

14.02.2006 (12)

Memo : Specific volume: 0.343 m³/kg @ 20°C

Reliability : (2) valid with restrictions
2g. Data from handbook or collection of data.

14.02.2006 (12)

3.1.1 PHOTODEGRADATION

Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Atmospheric OH Rate Constant: 3.10E-16 cm³/molecule-sec @ 25°C
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.

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Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman, 1988), HFC-23, which has a vapor pressure of 3.53X10E+4 mm Hg at 25°C (Daubert and Danner, 1995), is expected to exist solely as a vapor in the ambient atmosphere. The rate constant for the vapor-phase reaction of HFC-23 with photochemically-produced hydroxyl radicals has been measured as 2.4X10E-16 cm³/molecule-sec at 25°C (SRC, n.d.) using a structure estimation method (Atkinson, 1989; SRC, n.d.). This corresponds to an atmospheric half-life of about 180 years at an atmospheric concentration of 5X10E+5 hydroxyl radicals per cm³ (Atkinson, 1989; SRC, n.d.). This relatively slow half-life in the lower atmosphere suggests that some HFC-23 may gradually diffuse into the stratosphere (SRC, n.d.). The diffusion half-life for transport from the troposphere to the stratosphere is on the order of 20 years (Dilling, 1982).
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

05.12.2007 (1) (2) (7) (8) (38)

3.1.2 STABILITY IN WATER

Deg. product	:	
Method	:	
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	A base-catalyzed second-order hydrolysis rate constant of 4.3X10E-2 L/mol-sec (SRC, n.d.) was estimated using a structure estimation method (Mill et al., 1987); this corresponds to half-lives of 5.1 years and 190 days at pH values of 7 and 8, respectively (Mill, 1987; SRC, n.d.) suggesting that hydrolysis is not expected to be an important process (SRC, n.d.).
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

17.02.2006 (34) (38)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	
Media	:	other: soil
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: estimated
Year	:	
Result	:	Based on a classification scheme (Swann et al., 1983), an estimated Koc value of 53 (SRC, n.d.), determined from a log Kow of 0.64 (Hansch et al., 1995) and a regression-derived equation (Lyman et al., 1990), indicates that HFC-23 is expected to have high mobility in soil (SRC, n.d.). Volatilization of HFC-23 from moist soil surfaces is expected to be an important fate process (SRC, n.d.) given a Henry's Law constant of 9.52x10E-2 atm-m³/mole (Hine and Mookerjee, 1975). The potential for volatilization of HFC-23 from dry soil surfaces may exist (SRC, n.d.) based on a vapor pressure of 3.53x10E+4 mm Hg (Daubert and Danner, 1995).
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint
05.12.2007		(7) (24) (26) (33) (38) (40)

Type	:	
Media	:	other: water
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: estimated
Year	:	
Result	:	Based on a classification scheme (Swann et al., 1983), an estimated Koc value of 53 (SRC, n.d.), determined from a log Kow of 0.64 (Hansch et al., 1995) and a regression-derived equation (Lyman et al., 1990), indicates that HFC-23 is not expected to adsorb to suspended solids and sediment in water (SRC, n.d.). HFC-23 is expected to volatilize rapidly from water surfaces (Lyman et al., 1990; SRC, n.d.) based on a Henry's Law constant of 9.52X10E-2 atm-m³/mole (Hine and Mookerjee, 1975). Based on this Henry's Law constant, the estimated volatilization half-life from a model river (1 m deep, flowing 1 m/sec, wind velocity of 3 m/sec) is estimated as approximately 2.5 hours (Lyman et al., 1990; SRC, n.d.). The estimated volatilization half-life from a model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec) is estimated as approximately 3.3 days (Lyman

et al., 1990; SRC, n.d.).

Reliability : (2) valid with restrictions
2f. Accepted calculation method.

Flag : Critical study for SIDS endpoint

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3.3.2 DISTRIBUTION

Remark : Estimated Henry's Law constant = 0.0952 atm-m3/mole

Reliability : (2) valid with restrictions
2f. Accepted calculation method.

05.12.2007 (26) (41)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Contact time :

Degradation : (±) % after

Result : under test conditions no biodegradation observed

Deg. product :

Method :

Year : 1999

GLP : no data

Test substance : as prescribed by 1.1 - 1.4

Method : Mycobacterium vaccae JOB5 was grown in 2-L shaker flasks. The flasks were plugged with Teflon-coated rubber stoppers and sealed with Parafilm. A sterile needle was passed through the stopper, which was then attached to a sterile syringe filter and a three-way valve. A total of 180 mL of propane gas was added to the cultures daily through the filter after first removing the existing headspace using a vacuum pump. The remaining headspace was filled with filtered room air. M. vaccae JOB5 was grown on ATTC medium 990 for starter cultures and was then subcultured in BSM supplemented with propane in the headspace. The cultures were incubated on a rotary shaker at 30°C.

The bottle degradation assay was performed in 50-mL serum vials with Teflon-lined crimp-sealed tops. Cells were suspended in buffer containing formate. Negative controls consisted of buffer plus formate, the test compound without cells, and heat-killed cells in buffer to monitor abiotic losses. Cultures were tested for the presence and proper enzyme activity and function. HFC-23 was added by injection through the septa, and the vials shaken prior to sampling. Gas chromatography was performed using direct on-column injections of the headspace. The injector temperature was 108°C and the detector temperature 300°C. The retention time was 2.0 minutes. Concentration of HFC-23 ranged from 2 to 200 µM and the concentration of the biocatalyst ranged from 1x10E+8 to 1x10E+9 cells/mL.

Result : No degradation was detected when HFC-23 was tested with the bacterial strain Mycobacterium vaccae JOB5 in a 24-hour bottle assay.

Test substance : HFC-23, purity not reported

Reliability : (2) valid with restrictions
2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

Flag : Critical study for SIDS endpoint

13.12.2007 (39)

Deg. product	:	
Method	:	
Year	:	1997
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The degradation and possible inhibitory effect of HFC-23 in pure cultures of methanotrophs (Methylosinus trichosporium OB3b and Methylobacter albus BG8) and by soils that consume atmospheric methane was studied. Soils were collected from a mixed hardwood-coniferous forest. Test concentrations were 10 and 10,000 ppm HFC-23. Analysis of atmospheric methane and HFC-23 consumption were conducted by gas chromatography. The possible effects of copper and ammonium on HFC-23 degradation were also examined.
Result	:	HFC-23 (up to 5%) did not inhibit methane or ammonium oxidation by Methylosinus trichosporium OB3b or Methylobacter albus BG8. Methane mononoxygenases sMMO and pMMO appeared equally insensitive to HFC-23. HFC-23 did not inhibit aptmosperic methane consumption by soils at either low (10 ppm) or high (1%) concentrations, nor was HFC-23 degraded at low or high concentrations in soils from a mineral horizon.
Test substance	:	HFC-23, purity not reported
Reliability	:	(2) valid with restrictions 2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag	:	Critical study for SIDS endpoint

13.12.2007 (28)

Remark	:	Highly fluorinated compounds such as HFC-23 are not expected to biodegrade rapidly.
Reliability	:	(2) valid with restrictions 2g. Data from handbook or collection of data.

15.02.2006 (3)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Elimination	:	
Method	:	other: estimated
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	An estimated BCF of 3.2 was calculated for trifluoromethane (SRC, n.d.), using a log Kow of 0.64 (Hansch et al., 1995) and a regression-derived equation (Lyman et al., 1990). According to a classification scheme (Franke et al., 1994), this BCF suggests that bioconcentration in aquatic organisms is low (SRC, n.d.).
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

15.02.2006 (22) (24) (33) (38)

3.8 ADDITIONAL REMARKS

Memo	:	Residence time of HFC-23 in fruits, vegatables, and meats.
Method	:	Samples (30-250 mg) of the peel from apples, oranges and carrots; lettuce; 80% lean ground hamburger; and butcher's plastic wrap were exposed to neat HFC-23 vapor. HFC-23 concentration in the samples was measured at 10, 15, and 30 minutes (friut, vegetables, and plastic wrap) and 15, 30, and 60 minutes (hamburger).
Result	:	The HFC-23 concentration was below the limit of quantitation (1.25 ppm) for all samples at all timepoints. All exposed foodstuffs appeared visually the same as unexposed foodstuffs.
Test substance	:	HFC-23, purity not reported
Reliability	:	(2) valid with restrictions 2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

15.02.2006 (17)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	450
Limit test	:	
Analytical monitoring	:	yes
Method	:	Directive 84/449/EEC, C.1 "Acute toxicity for fish"
Year	:	1991
GLP	:	yes
Test substance	:	other TS
Method	:	To prevent loss of the substance from the solutions, closed vessels were used. The test was conducted under semistatic conditions with daily renewal of the test solutions. Chemical analyses of the test solutions were performed to check the exposure of the organisms to the test chemical. If the difference between nominal and mean measured concentrations was more than 20%, the endpoint of the test was based on mean measured concentrations. Saturated solutions were prepared. HFC-134a was bubbled for 60 minutes through medium via a sintered glass diffuser. This solution was diluted with oxygen saturated solutions to restore the amount of oxygen in the test solutions. The EC50 value was determined using the method of Stephan, 1977 (Stephan, C. E. (1977). Methods for calculating an LC50. Proceedings first annual symposium on aquatic toxicology. In: Mayer, F. L. and J. L. Hamelink (eds). Aquatic toxicology and hazard evaluation, ASTM STP 634:65-84).
Remark	:	Data provided on analog chemical (similar non-chlorinated fluorocarbon) to strengthen the use of ECOSAR to characterize the toxicity of HFC-23.
Result	:	No mortality was found after 96 hours of exposure at mean measured concentrations of 180 and 300 mg/L, but symptoms of toxicity were observed at these concentrations (dark discoloration, quiescence, and sounding behavior). No symptoms of toxicity occurred at a mean measured concentration of 87 mg/L.
Test substance	:	HFC-134a (1,1,1,2-tetrafluoroethane), purity not specified
Reliability	:	(2) valid with restrictions 2a. Guideline study without detailed documentation.
Flag	:	Critical study for SIDS endpoint
05.12.2007		

Type	:	
Species	:	other: Fish
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	985.3
Method	:	other: Modeled (ECOSAR v0.99h)
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	og10 Kow = 0.64
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

05.12.2007 (18)

Type	:	
Species	:	other: Fish
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	985.3
Method	:	other: Modeled (ECOSAR v0.99h)
Year	:	
GLP	:	no
Test substance	:	other TS
Remark	:	Data provided on analog chemical (similar non-chlorinated fluorocarbon) to strengthen the use of ECOSAR to characterize the toxicity of HFC-23. log10 Kow = 1.5
Test substance	:	HFC-134a (1,1,1,2-tetrafluoroethane), purity not specified
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

05.12.2007 (18)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	980
Analytical monitoring	:	yes
Method	:	Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year	:	1991
GLP	:	yes
Test substance	:	other TS
Method	:	To prevent loss of the substance from the solutions, closed vessels were used. The test was conducted under static conditions. Chemical analyses of the test solutions were performed to check the exposure of the organisms to the test chemical. If the difference between nominal and mean measured concentrations was more than 20%, the endpoint of the test was based on mean measured concentrations. Saturated solutions were prepared. HFC-134a was bubbled for 60 minutes through medium via a sintered glass diffuser. This solution was diluted with oxygen saturated solutions to restore the amount of oxygen in the test solutions. The EC50 value was determined using the method of Stephan, 1977 (Stephan, C. E. (1977). Methods for calculating an LC50. Proceedings first annual symposium on aquatic toxicology. In: Mayer, F. L. and J. L. Hamelink (eds). Aquatic toxicology and hazard evaluation, ASTM STP 634:65-84).
Remark	:	Data provided on analog chemical (similar non-chlorinated fluorocarbon) to strengthen the use of ECOSAR to characterize the toxicity of HFC-23.
Result	:	The acute test with Daphnia magna showed a steep concentration-immobility curve. At mean measured concentrations of 870 and 1100 mg/L the immobility after 48 hours was 0 and 100%, respectively.
Test substance	:	HFC-134a (1,1,1,2-tetrafluoroethane), purity not specified
Reliability	:	(2) valid with restrictions 2a. Guideline study without detailed documentation.
Flag	:	Critical study for SIDS endpoint

05.12.2007

Type	:	
Species	:	other: Daphnid
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	213
Method	:	other: Modeled (ECOSAR v0.99h)
Year	:	
GLP	:	no
Test substance	:	other TS
Remark	:	log10 Kow = 1.5
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

05.12.2007 (18)

Type	:	
Species	:	other: Daphnid
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	961.1
Method	:	other: Modeled (ECOSAR v0.99h)
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	og10 Kow = 0.64
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

05.12.2007 (18)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	other algae: Green algae
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	165
Method	:	other: Modeled (ECOSAR v0.99h)
Year	:	
GLP	:	no
Test substance	:	other TS
Remark	:	log10 Kow = 1.5
Test substance	:	HFC-134a (1,1,1,2-tetrafluoroethane), purity not specified
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.

05.12.2007

Species	:	other algae: Green algae
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	555.6
Method	:	other: Modeled (ECOSAR v0.99h)
Year	:	
GLP	:	no

Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	og10 Kow = 0.64
Reliability	:	(2) valid with restrictions 2f. Accepted calculation method.
Flag	:	Critical study for SIDS endpoint

05.12.2007 (18)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: Approximate Lethal Concentration (ALC)
Value	:	> 663000 ppm
Species	:	rat
Strain	:	other: ChR-CD®
Sex	:	male
Number of animals	:	
Vehicle	:	other: air
Doses	:	18900, 186000, 663000 ppm
Exposure time	:	4 hour(s)
Method	:	
Year	:	1980
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of 6 male rats, 8 weeks old and weighing 238-285 g were exposed to HFC-23 for single 4 hour periods. Atmospheres were generated by metering the test gas through a single stage regulator and a flowmeter. The test gas was diluted with air and oxygen before entering the exposure chamber. Standards were prepared daily and the chamber atmospheres were determined by comparison with a standard curve. Chamber temperature and oxygen were also monitored. During exposure, all rats were observed and clinical signs noted. Following exposure, rats were weighed and observed daily for a 14-day recovery period.

Result : Mean HFC-23 concentration, standard deviation and oxygen concentration were 18,900 ppm, 1700 ppm, 21%; 186,000 ppm, 28,000 ppm, 21%; and 663,000 ppm, 42,700 ppm, 19.7%, respectively. No deaths occurred. No clinical signs of toxicity were noted in the 18,900 ppm group. At 186,000 ppm, the animals showed a reduced response to sound, characteristic of an anesthetic effect. At 663,000 ppm, the rats showed no response to sound, gasping, labored breathing, sluggishness, and compulsive gnawing on the basket by one rat. Mild weight loss was observed for one to two days post-exposure, but normal weight gain was achieved thereafter. Chamber temperature never exceeded 27°C.

Test substance : HFC-23, purity 99.936%

Reliability : (2) valid with restrictions
2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

Flag : Critical study for SIDS endpoint

05.12.2007 (11)

Type	:	other: Approximate Lethal Concentration (ALC)
Value	:	> 200000 ppm
Species	:	guinea pig
Strain	:	other: albino
Sex	:	male
Number of animals	:	12
Vehicle	:	
Doses	:	20% (v/v) (200,000 ppm)
Exposure time	:	2 hour(s)
Method	:	

Year	:	1960
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Observations for clinical signs were made during exposure, upon removal from the exposure chamber, and during the 10-day observation period following exposure. Body weights were recorded. Gross and microscopic pathological examinations were conducted on all animals.
Result	:	Except for occasional weight losses, there no clinical signs of toxicity were observed. Pathological examination revealed no significant pathological changes attributable to the test compound.
Test substance	:	HFC-23, purity not reported
Reliability	:	(2) valid with restrictions 2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

05.12.2007 (10)

Type	:	other: Cardiac sensitization
Value	:	
Species	:	dog
Strain	:	other: mongrel
Sex	:	female
Number of animals	:	5
Vehicle	:	
Doses	:	80%
Exposure time	:	
Method	:	
Year	:	1968
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	HFC-23 (80%) was administered with oxygen to 5 unanesthetized dogs for periods of 5 to 10 minutes. After sufficient exposure and without inteupting administration, 10 µg/kg of epinephrine hydrochloride, diluted 1:100,000 with saline solution, was injected into the saphenous vein. Electrocardiographic records were obtained before, during, and after HFC-23 exposure. The electrocardiogram for each epinephrine challenge was recorded at the beginning of, and for at least 60 seconds after injection. Control electrocardiograms, to observe the effects of the epinephrine challenge alone, were similary obtained.
Result	:	Tracings following the epinephrine challenge to the 80% HFC-23-oxygen mixture did not show any sensitizing capacity to increase myocardial irritability.
Test substance	:	HFC-23, purity not reported
Reliability	:	(3) invalid 3b. Significant methodological deficiencies

05.12.2007 (27)

Type	:	other: Cardiac sensitization
Value	:	
Species	:	dog
Strain	:	Beagle
Sex	:	male
Number of animals	:	6
Vehicle	:	
Doses	:	10, 15, 20, 25, 30, 50%
Exposure time	:	
Method	:	
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Individual responses to adrenaline were determined for each dog. HFC-23 was administered to 6 dogs on six days (with at least one calendar day between each exposure session) to sequential concentrations of 10, 15, 20, 25, 30, and 50%. Auxiliary oxygen was added to the 50% concentration. Adrenaline was administered by intravenous injection before and during exposure. The effect of the adrenaline on electrocardiogram patterns was examined.
Result	:	HFC-23 was found to have no potential to cause cardiac sensitization in beagle dogs at concentrations of up to 30% in air or 50% in air with auxiliary oxygen. There were no positive responses, no questionable positive responses, and no ventricular tachycardia or ectopic bursts.
Test substance	:	HFC-23, purity not reported
Reliability	:	(2) valid with restrictions 2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag	:	Critical study for SIDS endpoint

05.12.2007 (13)

Type	:	
Value	:	
Species	:	dog
Strain	:	
Sex	:	no data
Number of animals	:	2
Vehicle	:	
Doses	:	80%
Exposure time	:	
Method	:	
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	HFC-23 mixed with oxygen was administered using a dog face mask.
Result	:	Although the dogs appeared dazed, there was no loss of consciousness, and analgesia was questionable.
Reliability	:	(2) valid with restrictions 2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

05.12.2007 (46)

Type	:	
Value	:	
Species	:	guinea pig
Strain	:	
Sex	:	male
Number of animals	:	2
Vehicle	:	other: air
Doses	:	3% (v/v)
Exposure time	:	6 hour(s)
Method	:	
Year	:	1945
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Two male guinea pigs weighing about 500 grams were exposed for 6 hours to a concentration of 10 lb HFC-23 in 1000 ft3 of air (approximately 3% by volume). They were observed for one week after exposure and then sacrificed for pathological evaluation.
Result	:	Respiration was not affected. Weight gain during the week following exposure was good. There were no gross or microscopic pathology findings.
Test substance	:	HFC-23, purity not reported

Reliability	:	(3) invalid 3a. Ducumentation insufficient for assessment.
05.12.2007		(9)
Type	:	other: Cardiac sensitization
Value	:	
Species	:	other: baboon (Papio anubis)
Strain	:	
Sex	:	male/female
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	1994
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The acute cardiac and CNS effects of HFC-23 were studies in 4 male and 4 female baboons. Four exposure sessions were used, each separated by 4 days. Before each session, animals were anesthetized with ketamine and diazepam, and anesthesia was maintained by repeated intravenous administration of anesthetics. In the first session, animals were exposed to control gases only. In the second session, escalated doses of HFC-23 (70% followed by 10, 30, 50, and then 70%) were administered at 30-minute intervals. In the third session, only control and 60% HFC-23 levels were tested. In the final session, animals were exposed to 70% HFC-23 after treatment with atropine. Epinephrine was also administered during the sessions to asses HFC-23-induced alterations in cardiac sensitivity. Blood pressure and respiratory rate were measured for each animal, and referential EEGs were recorded from 4 locations. EKGs were taken before and after epinephrine exposure.
Result	:	A dose-response effect was established for respiratory rate, electroencephalogram, and cardiac sinus rate, which exhibited a stepwise decrease starting with 10% HFC-23. No spontaneous arrhythmias were noted, and arterial blood pressure was unchanged at any exposure level. Intravenous epinephrine infusions (1 µg/kg) induced transient cardiac arrhythmia in one animal only at 70% HFC-23. HFC-23 appeared to induce mild dose-related physiological changes indicative of an anesthetic effect at levels of 30% or greater.
Test substance	:	HFC-23, purity 99.999%
Reliability	:	(3) invalid 3b. Significant methodological deficiencies
05.12.2007		(5)
Remark	:	HFC-23 has moderate narcotic properties. Exposure at 900,000 ppm caused distinct, but not complete, narcosis.
Reliability	:	(4) not assignable 4a. Abstract.
05.12.2007		(37)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	90 days
Frequency of treatm.	:	6 hours/day
Post exposure period	:	
Doses	:	0, 10,000 ppm
Control group	:	yes
LOAEL	:	> 10000 ppm
Method	:	
Year	:	1983
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 20 male and 20 female Sprague-Dawley rats was exposed 6 hours a day for 90 days to 10,000 ppm HFC-23. A control group of 20 male and 20 female animals was exposed to an air flow without test gas. The following parameters were studied: feces, food and water consumption, body weight gain, haematology, clinical biochemistry, urinalysis, sight, hearing, and dentition. Macroscopic and histologic pathologic examinations were performed.
Result	:	No adverse effects were noted. Histologic examination revealed no compound-related pathologic changes.
Test substance	:	HFC-23, purity >99.9%
Reliability	:	(4) not assignable 4e. Document insufficient for assessment.

05.12.2007 (29)

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	inhalation
Exposure period	:	6 hours per day, 5 days per week for 13 weeks
Frequency of treatm.	:	daily
Post exposure period	:	
Doses	:	0, 5000, 15,000 and 50,000 ppm
Control group	:	yes
Method	:	OECD Guide-line 413 "Subchronic Inhalation Toxicity: 90-day Study"
Year	:	1996
GLP	:	yes
Test substance	:	other TS
Method	:	Groups of 10 male and 10 female adult Wistar rats were exposed whole body to gaseous difluoromethane, 6 hours per day, 5 days per week for 13 weeks. Ten additional animals from the control and highest dose groups

were used as a satellite group and were kept for observation for 28 days after the completion of the 90-day exposure period.

The target concentrations of difluoromethane were 0, 5000, 15,000, or 50,000 ppm. Animals were observed every 30 minutes during exposure and following exposure. More detailed clinical examinations were made once weekly. Necropsy was performed in week 14 for the main study group and in week 18 for the satellite group.

Remark : Data provided on analog chemical HFC-32.

Result : The target concentrations of difluoromethane were 0, 5000, 15,000, or 50,000 ppm. The measured concentrations were 0, 4940 ± 160, 14,600 ± 470, or 49,100 ± 1600 ppm (0, 10,650, 31,950 and 106,500 mg/m3, respectively).

There were no deaths, no clinical abnormalities and no ophthalmic changes that could be attributed to treatment. No biologically significant and/or treatment-related variations in body weights, food consumption, urinalysis, haematological and blood clinical chemistry parameters occurred, with the exception of a non-biologically significant increase in triglyceride (1.4-fold) in males exposed to 50,000 ppm at weeks 5 and 15, and an increase in serum alanine transferase activity (1.3-fold) in females from all exposure groups at week 5.

No changes in organ weights of treated animals compared to controls occurred and no macroscopic findings were noted that suggested a treatment-related effect. Microscopic findings suggested an absence of treatment-related effects.

In conclusion, the treatment of rats with 4940, 14,600 and 49,100 ppm difluoromethane for 90 days resulted in a few minor and biologically insignificant changes.

Test substance : HFC-32 (difluoromethane), purity: 99.94%.

Reliability : (1) valid without restriction
1a. GLP guideline study.

Flag : Critical study for SIDS endpoint

05.12.2007 (19)

Type : Sub-acute
Species : dog
Sex : male/female
Strain : Beagle
Route of admin. : inhalation
Exposure period : 90 days
Frequency of treatm. : 6 hours/day
Post exposure period :
Doses : 0, 5000 ppm
Control group : yes
LOAEL : > 5000 ppm
Method :
Year : 1983
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : A group of 3 male and 3 female beagle dogs was exposed 6 hours a day for 90 days to 5000 ppm HFC-23. A control group of 3 male and 3 female animals was exposed to an air flow without test gas. The following parameters were studied: feces, food and water consumption, body weight gain, haematology, clinical biochemistry, urinalysis, electrocardiography, circulatory functions, sight, hearing, and dentition. Macroscopic and histologic pathologic examinations were performed.

Result : No adverse effects were noted. Histologic examination revealed no compound-related pathologic changes.

Test substance	:	HFC-23, purity >99.9%
Reliability	:	(4) not assignable 4e. Document insufficient for assessment.

05.12.2007 (29)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537, and TA1538
Test concentration	:	10, 50, 100%
Cycotoxic concentr.	:	100%
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471
Year	:	1996
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method :

The Salmonella/Ames assays were conducted using the pour-plate incorporation technique, modified for a gas phase test substance with freshly grown bacterial cultures. Molten top agar was mixed with an aliquot of the bacterial culture. Histidine and biotin were added to the top agar. To incorporate metabolic activation, S9 mix (S9 fraction with an NADP generating co-factor mixture) was added where appropriate or PBS for the nonactivated portion. The contents of the test tube were swirled on a vortex mixer and poured over previously prepared plates. Plates were exposed to the test agent in triplicate in sealed Tedlar bags and incubated at 37 ± 1 °C for 24 hours. At the end of the exposure period, plates were removed from the bags and incubated for an additional 24-48 hours before counting revertant colonies.

The metabolic activation system was a post mitochondrial supernatant (S9 fraction) prepared from rat liver homogenates of male Sprague Dawley rats induced with Aroclor 1254.

A toxicity test was conducted on HFC-23 with and without S9 activation at 10, 50, and 100% per plate using strain TA100. Air was the solvent.

The positive controls (and test strains) were sodium azide (TA1535 and TA100), 2-nitrofluorene (TA1538 and TA98), 9-aminoacridine (TA1537), and 2-aminoanthracene (all strains to evaluate S9 activation). DMSO was the solvent for all positive control dilutions.

Revertant colonies were counted using an automated electronic colony counter or hand counted.

The criteria for a positive response was met if the mean induced revertant number equaled 3.0 or more than the mean solvent control number of colonies for strains TA1535, TA1537, and TA1538, and 2.0 or more for strains TA98 and TA100. This increase must be accompanied by a dose-dependent response to increasing test substance concentrations. A sample was considered weakly positive if there was no dose response but one or more doses exhibited a doubling/tripling over solvent controls or if there was a dose response but no doses exhibited an appropriately high number of revertants.

Result : Based on the 50% reduction in the number of revertants per plate in both the presence and absence of metabolic activation at 100% HFC-23 in the toxicity assay, the top dose for the assay was set at 100% HFC-23 per plate in both the presence and absence of S9 activation.

In the mutation assay, there was no significant mutagenic response in any of the 5 strains, either in the presence or absence of metabolic activation. Strain TA98 at 25% HFC-23 exhibited a mean that was 2.1 times the mean of the 100% air control. However, this was due to a single high plate count and was not considered biologically relevant. The positive controls exhibited a significant increase in mutant colonies in all strains both with and without S9. A reduction in the number of revertants per plate was observed with both 100% HFC-23 and 100% nitrogen is strains TA1538, TA98, and TA100 both with and without S9 indicating this effect was most likely due to oxygen deprivation and not test substance associated toxicity.

Test substance : HFC-23, purity not reported
Reliability : (1) valid without restriction
1a. GLP guideline study.
Flag : Critical study for SIDS endpoint
12.12.2007 (42)

Type : Salmonella typhimurium reverse mutation assay
System of testing : S. typhimurium strains TA1535, TA1538, TA98, TA100
Test concentration : 10, 30, 50%
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method :
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The basic method was that described by Ames et al. (Ames BN, McCann J, and Yamasaki E (1975). Methods for detecting carcinogens and mutagens with the Salmonella/mammalian microsome mutagenicity test. Mutat. Res.,31:347-364), but a protocol for testing gases was adopted (Longstaff E and McGregor DB (1978). Mutagenicity of a halocarbon refrigerant monochlorodifluoromethane (R22) in Salmonella typhimurium. Toxicol. Lett., 2:1-4). The incubation period was 72 hours. The activation system was a liver postmitochondrial supernant fraction (S-9 mix) prepared from male Sprague-Dawley rats induced with Aroclor 1254. A positive response was recorded when there was a reproducible increase in reversion frequency such that more than doubling of the spontaneous mutation frequency occurred with a dose relationship in a least one tester strain with or witout S-9 mix.
Result : For TA1535 and TA100, the concentration for maximum effect was 50% and 30%, respectively, and the ratio test/control reversion frequency was 1.5 and 0.9, respectively. No biologically significant results were observed with strains TA1538 or TA98. HCFC-23 was nonmutagenic.
Test substance : HFC-23, purity 99.5%
Reliability : (2) valid with restrictions
2d. Test procedure in accordance with national standard methods with acceptable restrictions.
05.12.2007 (32)

Type : Chromosomal aberration test
System of testing : Chinese hamster ovary (CHO) -K1 cells
Test concentration : 50, 60, 70, 80, 90, 100%
Cycotoxic concentr. : 100%
Metabolic activation : with and without
Result : positive
Method : OECD Guide-line 473
Year : 1996
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Exponentially growing CHO-K1 cells were seeded in complete medium for

each treatment condition at approximately 2.4x10E4 cells/cm². The flasks were incubated at 37±1 °C in a humidified atmosphere of 5±1% CO2 in air. Air, the dilution vehicle, was included as the negative control. Mitomicin C (MMC) was used as the positive control in the nonactivated experiment. Cyclophosphamide (CP) at was used as the positive control in the S9-activated experiment. Doses of HFC-23 were freshly mixed in air on the day of treatment.

On the day of treatment, culture flasks were refed with a reduced volume of media to facilitate diffusion of the gaseous test substance to the cells. Flasks were sealed in plastic Tedlar bags, the ambient air removed by vacuum, and test substance doses introduced via a stainless steel valve stem.

A preliminary toxicity test was performed at 5, 10, 25, 50, 75, and 100% HFC-23. A 100% nitrogen gas control was included to test the effects of oxygen deprivation on toxicity. Duplicate cultures were evaluated. In the chromosomal aberration test, cells were exposed for 4 hours at 37 ±1 °C in the absence or presence of S9 to 50, 60, 70, 80, 90, and 100% HFC-23. A 100% nitrogen gas control was included to test the effects of oxygen deprivation. At the end of the exposure period, the treatment medium was removed, the cells were washed, refed with complete medium, and returned to the incubator. Two hours before the end of the incubation period, cell division was arrested by the addition of Colcemid®, cells were harvested, and slides prepared. Whenever possible, a minimum of 200 metaphase spreads from each dose group (100 metaphase cells per duplicate culture) were scored for chromatid and chromosome gaps and breaks and chromatid and chromosome aberrations. In addition, the proportion of cells at metaphase (mitotic index) based on 1000 cells per culture, and the polyploidy index, based on 100 metaphase cells per culture, was determined for each culture. The data were analyzed statistically with a one-tail Cochran-Armitage trend test and a one-tailed Fisher's Exact Test for pairwise comparison of each dose group against the concurrent control. The test substance was classified as positive if there was a significant, dose-dependent increase in the percentage of metaphase cells containing at least one chromosomal aberration and a statistically significant increase for at least one treatment dose in the percentage of metaphase cells containing at least one chromosomal aberration.

Result **:** Based on the results of the preliminary toxicity tests, the maximum dose of HFC-23 tested in the main study was selected to be 100%. In the initial toxicity test the osmolality and pH in the nonactivated cultures were not altered. The osmolality and pH in the activated cultures were depressed 50% at 75% HFC-23 and 28% at 100% HFC-23. The osmolality and pH in the 100% nitrogen control cultures were not altered.

In the absence of metabolic activation, HFC-23 was found to induce a significant increase in chromosomal damage, based on a significant trend test and by obtaining a significant increase in chromosomal damage at all three doses (80, 90, and 100%) evaluated for clastogenicity. The types of induced chromosomal aberrations consisted predominantly of chromatid-type aberrations. The positive control MMC and 100% nitrogen were clastogenic, inducing predominantly chromatid-type damage. The chromosomal damage in the 100% nitrogen control was of the same magnitude as that in the HFC-23 treated cultures, suggesting the possibility that the response may reflect changes in oxygen levels rather than effects of HFC-23 specifically.

A significant depression in the mitotic index (MI) was observed in cultures treated with HFC-23 at 70 and 100%, with a depression of >50% observed at 100%. The frequency of polyploidy cells was statistically significantly altered; however, no single dose was significantly different from the

concurrent control culture. Cell density among treated cultures was significantly altered, with a significant decrease at 70% HFC-23 only. For cultures treated with 100% nitrogen, the MI was depressed by almost 20%, a marginal nonsignificant response, while cell density was not depressed and the polyploidy index was not increased.

In the presence of metabolic activation, HFC-23 did not induce a significant increase in the percentage of damaged cells at any dose level (80, 90, and 100%) evaluated for clastogenicity. The positive control CP was significantly clastogenic, while 100.0% nitrogen induced a nonsignificant increase in clastogenic damage.

A significant decline in MI was observed among all HFC-23 treated cultures, with the greatest depression being 40% at 100% HFC-23. In contrast, cell density was not significantly depressed and the percentage polyploidy cells was not increased at any concentration. For the 100% nitrogen exposed cultures, the MI was depressed but not significantly, while the percentage of polyploidy cells and cell density were not altered.

The level of induced damage was about the same in both the nonactivated and S9 activated HFC-23 treated cultures while the percentage of aberrant cells was 0% and 2% in the nonactivated and S9 activation control cultures, respectively, suggesting that this may account for the statistically positive increase without S9 and a statistically nonsignificant increase with S9.

Test substance : HFC-23, purity not reported
Reliability : (1) valid without restriction
1a. GLP guideline study.
Flag : Critical study for SIDS endpoint
12.12.2007 (45)

Type : Mammalian cell gene mutation assay
System of testing : Chinese hamster ovary (CHO) AS52/XPRT cells (gpt locus)
Test concentration : 50, 60, 70, 80, 90, 100%
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 476
Year : 1996
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The purpose of the study was to evaluate the ability of HFC-23 and/or its metabolites to induce gene mutations in the guanine phosphoribosyl-transferase (gpt) locus of cultured AS52 Chinese hamster ovary cells. AS52 cells were cultured in Ham's F-12 medium with 5% fetal bovine serum plus additives at 37±1 °C in a humidified atmosphere of 5±1% CO2 in air. Doses of HFC-23 were freshly prepared in air on the day of treatment. On the day of treatment, culture flasks were refed with a reduced volume of media to facilitate diffusion of the gaseous test substance to the cells. Flasks were sealed in plastic Tedlar bags, the ambient air removed by vacuum, and test substance doses introduced via a stainless steel valve stem. The negative control consisted of cultures treated with 100% air only. The positive controls were ethylmethanesulfonate and dimethylnitrosamine. Both positive control substances were dissolved in dimethylsulfoxide.

Preliminary toxicity tests were performed. Cells were exposed to solvent alone and 5 concentrations of HFC-23 in duplicate for 5 hours in the presence and absence of S9. Concentrations evaluated were 10, 25, 50, 75, and 100% HFC-23, and 100% nitrogen (to determine the effects of oxygen deprivation).

Six concentrations of HFC-23 (50, 60, 70, 80, 90,and 100%) with and without S9 mix (plus concurrent solvent and positive controls) were used in the mutagenicity assay. Cells were exposed in duplicate for 5 hours at 37±1 °C in the presence and absence of S9 (day 0). After treatment, medium was removed, the cells were washed, and complete medium without additives was added for an additional 18-24 hours incubation.

Cytotoxicity determination was demonstrated by a lack of colony development. On day 1, 18-24 hours after treatment, flasks were subcultured, counted, and an aliquot of AS52 cells seeded. After 7-10 days incubation, colonies were fixed and stained, air dried, and counted. Cytotoxicity was expressed as relative cloning efficiency (RCE). To determine phenotypic expression, on day 1, duplicate treatment flasks were trypsinized, counted, and an aliquot of AS52 cells seeded. Cells were subcultured on days 4 and 6 and selected for 6-TG resistance on day 6. For mutant selection, on day 6, plates from each treatment group were trypsinized, counted, and plated in F-12 medium with 6-TG. For cloning efficiency at the time of selection cells were also plated in F-12 medium without 6-TG. After 7-8 days of incubation, colonies were fixed, stained, and later counted for cloning efficiency and mutant selection. Results were analyzed statistically with a one-tail trend test and student's t test for pairwise comparison. An alpha level of 0.05 was used to indicate statistical significance. Due to the possibility of fluctuation, samples with less than 1 x 10E5 viable cells after treatment were not considered as valid data points. The test substance was classified as positive if there was a dose-dependent increase in mutant frequency with one or more of the six doses tested, and a mutant frequency at least twice that of the negative control and increased above the negative control by at least 10 mutants per million clonable cells.

Result : In the preliminary toxicity tests no toxicity was observed in the nonactivated cultures (HFC-23 treated and nitrogen control). In the activated cultures, a dose dependent decrease in the RCE of 45% was observed at 100% HFC-23. In the initial toxicity tests the mean osmolality in the nonactivated and activated cultures was 285-296 and 272-282 mOSMs, respectively. The osmolality in the nonactivated and activated 100% nitrogen control cultures was 283 and 269 mOSMs, respectively. The pH was normal in all initial toxicity cultures. Based on the results of the preliminary toxicity tests, the maximum dose of HFC-23 tested in the main study was selected to be 100%.

In the mutagenicity assay in the absence of metabolic activation, HFC-23 did not induce a significant increase in mutant frequency (based on one million clonable cells). The 100% nitrogen control was also not mutagenic compared to the mutant frequency of the negative controls. The positive control, EMS was mutagenic compared to mutant frequency of the negative controls.

A depression in the RCE immediately following dosing was not observed among treated cultures, with a mean RCE of 95.6% observed at the top dose of 100% HFC-23. The mean absolute cloning efficiency of the negative controls was well within the acceptable range.

HFC-23 did not induce a significant increase in mutant frequency (based on one million clonable cells), as demonstrated by both a nonsignificant one-tailed trend test and the lack of a significant increase in mutant frequency at each dose group compared to the concurrent control. The 100% nitrogen gas control was also not mutagenic compared to the mutant frequency of the negative controls. The positive control, DMN, was significantly mutagenic at 50 µg/mL but not 100 µg/mL.

A significant depression in the RCE immediately following dosing was not

observed among treated cultures, with the lowest mean depression of 69.3% observed at 80% HCF-23. The mean absolute cloning efficiency of the negative control cultures at the time of selection was 65.4%, just above the acceptable range.

HFC-23, either in the presence or absence of metabolic activation, did not induce a significant increase in the mutant frequency at the gpt locus in cultured AS52 cells.

Test substance : HFC-23, purity not reported
Reliability : (1) valid without restriction
1a. GLP guideline study.
Flag : Critical study for SIDS endpoint
12.12.2007 (44)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Drosophila SLRL test
Species : Drosophila melanogaster
Sex :
Strain : other: Canton-Special
Route of admin. : inhalation
Exposure period : 10 minutes
Doses :
Result : positive
Method :
Year : 1974
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Newly hatched flies were treated with HFC-23 for 5 minutes at a flow rate of 12 mL/min and remained in the gaseous atmosphere another 5 minutes. The flies were removed and upon recovery untreated females were placed with treated males. The percentage of recessive lethal mutations induced in the flies was determined. The data were analyzed statistically with a t-test and/or Steven's test.

Result : Among the progeny of the gas treated P1 males, several lethal mutations and one semilethal, counted as 0.5 mutation, were found. This gave a total of 7.5 recessive lethal mutations in 271 cultures tested; or a frequency of 2.7%. When the 0.23% spontaneous control rate was subtracted for the 2.7% induced rate, a frequency of 2.47% remained. The t-test showed that HFC-23 treatment significantly increased the number of recessive lethal mutants (P=0.01). Some deviant phenotypes were observed among the 24,390 progeny of the HFC-23 treated males. Eye color, tumor, and wing mutations were frequent types.

This study was included in the U.S. E.P.A. Report of the Gene-Tox Program (Lee WR, Abrahamson S, Valencia R, von Halle ES, Wurgler FE, and Zimmering S (1983) The sex-linked recessive lethal test for mutagenesis in Drosophila melanogaster. A report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat. Res. 123(2):183-279). HFC-23 could not be classified as positive or negative because of inadequate sample size, the category ranking given was 3 (less than 1000 chromosomes tested).

Test substance : HFC-23, purity minimum 98.0%
Reliability : (2) valid with restrictions
2d. Test procedure in accordance with national standard methods with acceptable restrictions.
Flag : Critical study for SIDS endpoint
05.12.2007 (21)

Type	:	Drosophila SLRL test
Species	:	Drosophila melanogaster
Sex	:	
Strain	:	other: Canton-Special
Route of admin.	:	inhalation
Exposure period	:	
Doses	:	
Result	:	positive
Method	:	
Year	:	1974
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Result	:	Mutation rate was 1.66 ± 0.04
Test substance	:	HFC-23, purity 99.5-99.9%
Reliability	:	(3) invalid 3a. Ducumentation insufficient for assessment.

15.03.2006 (23)

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	inhalation
Exposure period	:	6 hours/day for 3 consecutive days
Doses	:	50, 26, 13% HFC-23; 50% air/50% nitrogen; 100% air
Result	:	negative
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	1996
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Mice were treated by inhalation exposure 6 hours/day (5 mice/sex/dose group) on 3 consecutive days. Animals were sacrificed 24 hours after administration of the final dose. Dose levels were 50, 26, and 13% HFC-23; 50% air/50% nitrogen; and 100% air. The purpose of the 50% air/50% nitrogen was to evaluate the effect of a decrease in oxygen. The positive control group was administered, by intraperitoneal injection, cyclophosphamide (25 mg/kg) dissolved in phosphate buffered saline.

Slides were prepared and stained with acridine orange. The number of polychromatic erythrocytes (PCEs) among a total of 200 erythrocytes was determined per animal. For micronuclei evaluation, 2000 PCEs/animal were evaluated in continuous field at 1000x magnification for the presence of micronuclei. The scored elements were the number of micronucleated cells, not the number of micronuclei. Results were analyzed statistically. A two-way ANOVA was used to determine if a sex-dependent difference in response occurred and depending on the reponse obtained, male and female data were analyzed separately or pooled together. A one-tailed trend test based on the proportion of micronucleated cells among mice was used to determine if a treatment-related increase in DNA damage occurred. An ANOVA using individual animal responses was used to evaluate the effect of treatment on erythropoiesis. In addition, pairwise comparisons between each exposure group; and the corresponding control group was conducted using a Pearson Chi-square test for micronuclei data or student's t test for percentage of PCE data.

Result : Due to a limited number of inhalation exposure chambers, the study was conducted in two experiments. In the first experiment, mice were treated with 50% HCF-23, 50% air/50% nitrogen, or 100% air. In the second experiment, mice were treaed with 26% HCF-23, 13% HFC-23, or 100% air. Cyclophosphamide was included as a positive control in both experiments. One of five female mice died in the positive control group in

the second experiment. Due to a difference between experiments in the mean MN-PCE frequencies of the 100% air control groups, control data were not polled across experiments.

Treatment with HFC-23 did not result in a significant increase in the frequency of micronucleated PCE in either males or females for experiment 1 or 2. Based on an ANOVA analysis, the percentage of PCE was not significantly depressed in males or females in experiment 1 or 2.

In experiment 1, exposure to 50% air/50% nitrogen did not increase the frequency of micronucleated PCE in males or females and did not alter the percentage of PCE in females. However, the percentage of PCE was altered in males (P=0.024). The positive control, cyclophosphamide at 25 mg/kg, induced a significant increase in MN frequency in both experiments (P < 0.001) inr both males and females with a significant depression in the percentage of PCE in males (P=0.007 in experiment 1 and P=0.020 in experiment 2) but not in females.

Repeated inhalation with HFC-23 did not significantly increase the frequency of micronucleated PCEs in the bone marrow of male or female B6C3F1 mice and/or significantly affect the percentage of PCEs in either sex.

Reliability : (1) valid without restriction
1a. GLP guideline study.

Flag : Critical study for SIDS endpoint

12.12.2007 (43)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	other: Crl:CD®(SD)BR
Route of admin.	:	inhalation
Exposure period	:	days 7-21 of gestation
Frequency of treatm.	:	daily
Duration of test	:	6 hours/day
Doses	:	0, 5000, 20,000, 50,000 ppm
Control group	:	yes
other: NOEL Maternal Tox.	:	50000 ppm
other: NOEL Developmental Tox.	:	50000 ppm
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1997
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : The study complied with U.S. EPA Pesticide Assessment Guidelines, Subdivision F, 83-3; OECD Guidelines for Testing of Chemicals, Section 4, No. 414; and MAFF Testing Guidelines for Toxicology Studies, NohSan 59, No. 4200.

Female rats were 62 days old at receipt and weighed between 179.9 and

227.7 g. Male rats used for mating were 77 days old at receipt and weighed between 304.1 and 370.2 g. Food and water were available ad libitum except during exposures. Rats were housed individually except during mating. A 12 hour light/dark cycle was controlled via an automatic timer. Temperature and relative humidity were monitored throughout the study.

Females were cohabited with males (1:1) until copulation was confirmed by the presence of a copulation plug in the vagina or on the cageboard. Checks for copulation plugs were made each morning; the day copulation was confirmed was designated day 1 of gestation (day 1G). Rats were exposed via whole-body inhalation for 6 hours/day during days 7 through 21 of gestation. Exposure levels evaluated were 5000, 20,000, and 50,000 ppm. A chamber-exposed sham-air treated control group of comparable size was also tested. The exposure chambers were constructed of stainless steel and glass. The internal nominal volume of the chambers was approximately 150 L.

HFC-23 vapor was generated by metering the test material from the sample cylinder through stainless steel tubing into a liquid trap, and into mass flow meters; a separate flow meter was used for each test chamber. The vapor was diluted by house-line air to the desired concentrations for each of the three test chambers. The atmospheric concentration of HFC-23 was determined by gas chromatography at approximately 60-minute intervals during each six-hour exposure. Chamber airflow, temperature, and relative humidity were monitored continually.

Body weights, clinical signs, and food consumption were recorded. Animals were sacrificed on day 22 of gestation and given a gross postmortem evaluation. Corpora lutea, implantation sites, types of implants (live and dead fetuses, and resorptions) and their relative positions, fetal sex, fetal weight, and a gross fetal external examination were recorded. Approximately 50% of the fetuses from each litter were examined for soft tissue (visceral and head) alterations. After alcohol fixation and alizarin staining, all fetuses were examined for skeletal alterations.

For litter parameters, the litter mean was used as the experimental unit for statistical evaluation. Maternal weight, weight changes, and food consumption were evaluated by the linear contrast of means. Live fetuses, dead fetuses, resorptions, implantations, corpora lutea, and incidence of fetal alterations were evaluated by the Jonckheere's test. Incidence of pregnancy, clinical observations, maternal mortality, females with total resorptions, and abortions/early deliveries were evaluated by the Cochran-Armitage test. Fetal weight (covariates: litter size and sex ratio) and sex ratio (covariate: litter size) were evaluated by linear contrast of least square means.

Result : The daily exposure chamber mean concentrations were generally consistent throughout the study, with minimal day-to-day variability. The analytically determined mean concentrations +/- SD were 5600 +/- 45, 21,000 +/- 48, and 51,000 +/- 72 ppm, respectively, for the 24 exposures.

The daily mean chamber temperatures for the four chambers during this study ranged from 23 to 24°C, the daily mean chamber relative humidities ranged from 44 to 50%.

There were no mortalities observed at any dose level. There were no compound-related effects on maternal body weight, weight changes, adjusted body weight, or weight change calculated using the adjusted body weight.

At 50,000 ppm, there was a statistically significant increase in body weight gain over days 11-13G followed by a significant decrease over days 13-

15G. The significant decrease was not believed to be toxicologically relevant because it appeared to have been caused by the preceding significant increase which was approximately equal in magnitude. There were no other corroborating indications of maternal toxicity; maternal body weights and food consumption were unaffected. In addition, there was no biologically or statistically detectable effect on weight gain when evaluated for the entire exposure period. In addition, there was a slight, statistically significant reduction in maternal weight gain over days 19-21G. Average weight gain for the high level during this interval was 29.2 grams compared to an average of 32.2 grams for the control group. This was not believed to a toxicologically relevant finding; the reduction in gain was very small and in fact appeared to be due to a very slight, but significant, reduction in food consumption for that interval. In addition, there was no effect on maternal weight gain at any exposure level when considered for the entire exposure period (days 7-22G).

There were no compound-related effects on maternal food consumption. At 50,000 ppm, there was a slight, statistically significant reduction in maternal food consumption over days 19-21G. Average food consumption for the high level during this interval was 25.9 grams compared to an average of 27.1 grams for the control group. This was not believed to be a toxicologically relevant finding; this reduction was very small and was not corroborated by effects on food consumption over any other interval or when the exposure period is considered in its entirety (days 7-22G).

There were no compound-related effects on maternal clinical observations. There were no significant postmortem findings at any exposure level. There were no compound-related effects on reproductive outcome parameters (dams with either total resorptions or that delivered early, mean corpora lutea, mean number of implantations, litter size, or sex ratio).

There were no compound-related effects on fetal mortality (resorptions, or dead fetuses). There was no compound-related effect on mean fetal weight. There were no compound-related effects on the incidence of fetal malformations.

A summary of reproductive outcomes is provided in the table below:

Concentration (ppm)	0	5000	20000	50000
No. Mated	25	25	25	25
No. Pregnant	24	23	25	22
No. Delivered Early	0	0	0	0
No Deaths	0	0	0	0
No. With Resorptions	0	0	0	0
No. Litters	24	23	25	22
Means/litter				
Corpora lutea	17.3	17.0	17.0	16.6
Implantations	15.8	16.0	15.8	15.8
No. of Resorptions	0.5	0.3	0.5	0.9
Dead Fetuses	0.0	0.0	0.0	0.0
Total No. of Live Fetuses	15.3	15.6	15.4	15.0
Mean Fetal Weight (g)	5.12	5.09	5.14	5.20
Sex Ratio (total number male fetuses/total number fetuses per litter)	0.49	0.48	0.45	0.53

There were no compound-related effects on the incidence of fetal variations. At 50,000 ppm, there was a statistically significant increase in the incidence of small renal papilla (sizes 1, 2, and 3). For the 0, 5000, 20,000, and 50,000 ppm groups, the incidences were [given as "no. fetuses (no. litters)"] 45 (17), 25 (13), 35 (19), and 47 (19). The increase at

the high level was not believed to be biologically significant; although the increase was statistically significant, there did not appear to be a dose-response relationship evident in the data. Additionally, at 50,000 ppm, the incidence of this frequently observed and thus, highly variable finding was only slightly higher than that observed for the concurrent control group. Finally, the incidences for all groups on this study fell within the range of historical control data for eight recently conducted rat developmental toxicity studies (data shown below).

At 20,000 and 50,000 ppm, there were statistically significant increases in the incidence of retarded sternebral ossification. For the 0, 5000, 20,000, and 50,000 ppm groups, the incidences were [given as "no. fetuses (no. litters)"] 2(2), 2(2), 13(6), and 9(5). These increases were not believed to be biologically significant for reasons similar to those outlined above for the kidney observations. Although the incidences for the two high level groups were statistically significantly increased, they were not increased in a dose-dependent fashion. In addition, the control group value for the current study was very low and outside the range of concurrent historical control data (data shown below) for this endpoint. Finally, the incidences for the 20,000 and 50,000 ppm groups are well within the range of recent control data.

	Kidney Small Renal Papilla no. fetuses (no. litters)	Sternebra Retarded Ossification no. fetuses (no. litters)
Study 1	50 (21)	14 (6)
Study 2	38 (15)	50 (15)
Study 3	23 (11)	8 (5)
Study 4	39 (17)	13 (5)
Study 5	25 (13)	4 (3)
Study 6	23 (11)	30 (13)
Study 7	14 (9)	13 (8)
Study 8	23 (13)	6 (5)

The maternal and developmental no-observed-effect level (NOEL) was 50000 ppm.

Test substance : HFC-23, purity >99%
Reliability : (1) valid without restriction
1a. GLP guideline study.
Flag : Critical study for SIDS endpoint
05.12.2007 (14)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type :
In vitro/in vivo : In vivo
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : inhalation
Exposure period : 13 weeks
Frequency of treatm. : daily
Duration of test : 6 hours per day, 5 days per week
Doses : 0, 5000, 15,000, or 50,000 ppm.
Control group : yes
Method :
Year : 1996
GLP : yes
Test substance : other TS

Method : Rats were exposed whole-body for 6 hours per day, 5 days per week for 90

days to HFC-32 at concentrations up to 50,000 ppm v/v. For additional infomation regarding methods, refer to Section 5.4, Repeated Dose Toxicity.

Remark : Data provided on analog chemical HFC-32.
Result : There were no significant changes macroscopic or histopathological changes observed in reproductive organs or on testes weight.
Test substance : HFC-32 (difluoromethane), purity: 99.94%.
Reliability : (2) valid with restrictions
2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag : Critical study for SIDS endpoint
05.12.2007 (19)

5.9 SPECIFIC INVESTIGATIONS

Endpoint :
Study descr. in chapter :
Reference :
Type :
Species : cat
Sex :
Strain :
Route of admin. :
No. of animals :
Vehicle :
Exposure period :
Frequency of treatm. :
Doses : 60, 70%
Control group :
Observation period :
Result :
Method :
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : To study HFC-23 as a potential gaseous indicator in nuclear magnetic resonance measurements of cerebral blood flow, the effects of HFC-23 on cerebral blood flow in 17 cats and on the electroencephalogram and electrocardiogram in 9 cats were examined.
Result : Inhaled at 60%, HFC-23 had no effect on cerebral blood flow, the cerebral metabolic rate for oxygen, or oxyhemoglobin content. At 70%, the compound sensitized the cats' hearts to epinephrine and produced only moderate changes in cerebral electrical activity as measured by the electroencephalogram.
Test substance : HFC-23, purity not reported
Reliability : (2) valid with restrictions
2e Study well documented, meets generally accepted scientific principles, acceptable for assessment
20.09.2006 (4)

5.10 EXPOSURE EXPERIENCE

Type of experience : Human

Method : HFC-23 was evaluated as an indicator for cerebral blood flow (CBF) during nuclear magnetic resonance (NMR) imaging. As part of the evaluation, the neurobehavioral and physiological effects of HFC-23 were examined in 6

male volunteers. Individuals were exposed to 10, 20, 40, or 60% of HFC-23 at escalating concentrations. Control gases, 40% nitrous oxide (positive control) and room air (negative control), were randomly administered on one of the study days. There was a maximum of 6 study days, each separated by at least three days. The study gas was administered as 8 pulses of 3 minutes each, with 2-minute clearance periods between each pulse. Subjects were fasted at least 8 hours prior to administration.

A baseline screening was performed for each subject, and included history and physical examination, serum chemistry, complete blood count, urinalysis, electrocardiogram, and two practice trials of the neuropsychological test batteries (baseline). In addition, questionnaires to assess mood and other subjective psychological traits were administered. The baseline screen (excluding neuropsychological tests) was administered prior to each study day. Serum chemistries and mood questionnaires were administered 24-38 hours after administration.

Physiological measurements (serum chemistries, blood pressure, pulse, heart rate and rhythm, temperature, oximetry, respiratory rate, and end-tidal CO2) were measured during exposure. Performance on a computerized neurophysiological test were determined during 6 of the 8 pulses, and the neuropsychological test battery was repeated. If a subject did not perform as well on the neuropsychological test battery compared to his baseline, the test was repeated until baseline values were achieved. Thirty days after study completion, the subjects were asked to return for assessment of possible chronic toxicity. All baseline studies were repeated at this time, as well as an assessment of subjective responses.

Repeated-measures analysis of variance was used to compare treatment and time effects of treatments on heart rate, respiratory rate, and end tidal CO2. The interaction of treatment and time was tested to determine significant of the interaction. If no interaction was present, then the treatment effect and the time effect were tested separately.

The maximum tolerated concentration, defined as the concentration at which no subject experienced any clinically significant changes in heart rate, blood pressure, heart rhythm, or unacceptable neurophysiological performance, were determined.

Result : The first subject exposed to HFC-23 completed the 8 pulses but experienced an anesthetic effect and nausea at 60%. Although other physiologic parameters remained stable, the subject's response was considered intolerable. The second subject to inhale 40% HFC-23 experienced discomfort after 1 minute, and requested discontinuation of exposure. Both the 40 and 60% levels were then dropped from further evaluation. The remaining 4 subjects tolerated the 30% level of HFC-23. Therefore, 30% was considered to be the MTC (maximum tolerated dose). Subjects reported anesthetic effects (light-headedness, drowsiness, clumsiness, difficulty concentrating, mild euphoria, tingling and numbness of lips and extremities, burning in the back of the throat, unsettled stomach, and/or hyperacusis). No effects were noted in blood pressure, heart rate or rhythm, oxygenation, respiratory rate, temperature, end tidal CO2, or serum chemistries. However, when one subject received the 30% concentration during an NMR imaging study, an anesthetic effect with intolerable hyperacusis was demonstrated and the subject was unable to tolerate conditions long enough to obtain an image of CBF.

Reliability : (2) valid with restrictions
2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

Flag : Critical study for SIDS endpoint
06.12.2007 (20) (25)

Type of experience : Human

Method	:	The contribution of neuropsychological methods in the determination of the maximum tolerated concentration of 30% HFC-23 in the above study was assessed. Two batteries of neurophychological tests were used to monitor potential toxicity during exposure and cognitive status immediately prior to and following exposure. Motor steadiness, verbal-auditory memory, executive control, motor speed, visual memory, attention, reasoning, visuomotor performance, anxiety, and motivation were evaluated. Subjective assessments were taken daily.
Result	:	Doses of 40% and 60% HFC-23 produced greater impairment of neuropsychological function than 40% N2O. However, neither clinically significant nor unacceptable neuropsychological impairment was observed at doses of 30% HFC-23 or less. Performance during 30% HFC-23 administration fell between room air and N2O inhalation, demonstrating anesthetic properties of HFC-23. No subjects were unacceptably impaired at posttesting, within one hour post exposure. Although no clear dose-response relationship between HFC-23 and neuropsychological functioning was detected, reported adverse subjective states increased linearly with increasing HFC-23 concentration. Subjective ratings of symptoms and mood state indicated differences between doses, with significant differences of negative mood ratings. The results indicated that physiological measures were least sensitive to HFC-23 exposure, neuropsychological tests more sensitive, and subjective ratings most sensitive. This relationship may have been influenced by the reported novelty of the inhalation experience.
Reliability	:	(2) valid with restrictions 2e. Study well documented, meets generally accepted scientific principles, acceptable for assessment.

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5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT