1, 1-DIFLUOROETHANE

Document History
Published: 1994
Revised: 2005
Rebranded: 2025

I. IDENTIFICATION

Chemical Name: 1, 1-Difluoroethane
Synonyms: Ethylidene difluoride; HFC-152a; Freon®152a; Fluorocarbon 152a; Dymel® 152a: Genetron® 152a
CAS Number: 75–37–6
Molecular Formula: $C_2H_4F_2$
Structural Formula: CHF_2CH_3

II. CHEMICAL AND PHYSICAL PROPERTIES[1]

Physical State: Colorless gas at 25°C (77°F)
Odor Description: Slight ethereal odor
Molecular Weight: 66.1
Conversion: 1 ppm(v/v) = 2.7 mg/m^3(w/v);
1 mg/m^3 = 0.37 ppm
Boiling Point: -25°C (-13°F) at 760 mm Hg
Vapor Pressure: 4492 mm Hg at 25°C (77°F)
Saturated Vapor Concentration: 591,053 ppm at 25°C (77°F)
Flammability Limits: 3.9%–16.9% by volume
Flash Point: < -50°C (-58°F) [Tag, open cup]
Specific Gravity: 0.90 g/mL at 25°C (77°F)
Relative Density of Saturated Air (Air = 1): 2.4 at 25°C (77°F)
Solubility in Water: 2.8 g/L at 25°C (77°F)
Stability: Material is stable. However, avoid open flames and high temperatures.
Reactivity and Incompatibilities: Incompatible with alkali or alkaline earth metals (Powdered Al, Zn, Be, etc.)

III. USES AND VOLUME

HFC-152a is a specialty liquefied fluorocarbon gas with principal end-use applications as an intermediate in the production of fluorinated polymers, aerosol propellants in certain specialty applications, and as a component in certain refrigerant blends. Because of its low environmental impact (no ozone-depleting potential; non-VOC status), HFC-152a is being considered in other applications such as blowing agents.[2]

IV. TOXICITY DATA

A. Acute Toxicity

1. Oral Toxicity

HFC-152a was administered to rats as a single oral dose (dissolved in corn oil) by intragastric intubation. One rat/dose was given either 200, 300, 450, 670, 1000, or 1500 (maximum feasible dose) mg/kg, and then observed for 14 days. Lethargy was seen at the two highest doses; diarrhea and yellow-stained perineum were observed in all rats 1 to 2 days after dosing. No mortality occurred at any dose level. The Approximate Lethal Dose (ALD) of HFC-152a in rats was reported as >1500 mg/kg.[3]

2. Dermal and Eye Toxicity

No specific studies were conducted to evaluate skin and eye irritation potential, since HFC-152a is a gas at room temperature. As a liquid under pressure, this fluorocarbon is not a skin or eye irritant due to its chemical reactivity. However, direct contact of skin or mucous membranes with liquid droplets (via aerosol, for example) would be expected to result in rapid evaporation and subsequent cracking and drying of the contacted area, especially after repeated exposure. In addition, no specific studies to evaluate allergic skin sensitization potential were conducted on HFC-152a. However, other HFCs, such as HFC-134a (1,1,1,2-tetrafluoroethane), for example, are not dermal sensitizers.

3. Inhalation Toxicity

a. Rats: four-hour ALC* = 383,000 ppm[4]

Three-minute ALC = >500,000 ppm[5]

b. Mice: two-hr LC50 = 369,000 ppm[6]

* ALC = Approximate Lethal Concentration; the lowest inhaled concentration tested that resulted in at least one fatality.

c. Dogs:

The cardiac sensitization potential of HFC-152a was evaluated in Beagle dogs exposed to various concentrations for approximately 5 minutes. The dogs were then given an intravenous injection of epinephrine and monitored for cardiac arrhythmias. The following results were obtained:

- 0 of 12 dogs sensitized at 50,000 ppm
- 3 of 12 dogs sensitized at 150,000 ppm

These experimental data suggest that HFC-152a has a weak potential to induce cardiac sensitization.[7]

d. All Species: The main physiologic action of HFC-152a was "weak anesthesia" at high inhaled concentrations

B. Genotoxicity

1. In vitro:

HFC-152a was not active in 3 separate Ames assays using several strains of *Salmonella typhimurium* bacteria,[8-10] nor in a similar assay[10] using *Escherichia coli* strain WP2uvrA, either in the presence or absence of an S9 metabolic activation system.

2. In vivo:

In an older, sex-linked recessive study[11,12] in *Drosophila melanogaster* (fruit fly), HFC-152a was reported to be mutagenic. However, all gases tested in this limited study showed increased mutagenic rates in *Drosophila*. It is apparent from the exposure system design that the chamber containing the fruit flies during test gas exposures rapidly purged oxygen from the atmosphere. The authors themselves concluded that anoxia might be the reason for the increased mutation rates observed in their test system. The preceding *in vitro* mutagenicity assays[8-10] utilizing bacteria show that HFC-152a is not mutagenic, and a 2-year rodent assay (described in detail later) demonstrated no evidence of carcinogenicity.

C. Metabolism and Pharmacokinetics

A study[13] was conducted to investigate the potential metabolism of inhaled HFC-152a in 3 male rats/group exposed at 0, 370, 470, 1500, or 2650 ppm for 4 to 5 hours in a closed, recirculating chamber. Partition coefficients (air and blood; liver, fat, muscle) were determined and, using data for the rate of chemical loss from chambers, kinetic constants for metabolism were estimated using a physiologically based pharmacokinetic (PBPK) model. Group urine samples were also collected from each chamber at the end of exposure and analyzed for metabolites by ^{19}F-NMR.

Partition coefficients for HFC-152a were: 1.69 for blood:air, 1.69 for liver: air, 5.63 for fat: air and 1.47 for muscle: air. Analysis of gas uptake data in combination with a PBPK model showed a measurable metabolism of HFC-152a. The estimated V_{max} and K_m were 7.8 ± 0.9 mg/hr/kg and 27.9 ± 3.7 mg/L, respectively, with the best fit to the model achieved by using Michaelis-Menton kinetics. The concentration at which metabolism was saturated was approximately 75,000 ppm. Analysis by ^{19}F-NMR showed fluoride ion and traces of an acyl fluoride in the urine. This indicates that HFC-152a is predominantly metabolized at the $–CF_2$ carbon with the likely end product of metabolism being acetic acid.

In addition, in a lifetime inhalation toxicity study[14] described in detail later, an increase in urinary fluoride was seen in rats exposed to 5000 ppm and above, suggesting that HFC-152a is metabolized, at least to a small extent, to fluoride ion and acetic acid.

D. Developmental and Reproductive Toxicity

1. Groups of 27 ChR-CD pregnant rats were exposed to 0, 5000 or 50,000 ppm HFC-152a for 6 hours/day on Days 6 through 15 of gestation. There were no significant differences between control and treated groups relative to the outcome of pregnancy, fetal development, or teratogenicity. In addition, there was no evidence of maternal toxicity at either exposure concentration.

   Under these experimental conditions, HFC-152a was not embryotoxic, teratogenic or maternally toxic to pregnant rats exposed to ≤50,000 ppm during a critical part of gestation.[15]

2. Although no specific experimental studies to evaluate reproductive performance were conducted, the absence of histopathological effects on the reproductive organs of male and female ChR-CD rats exposed to ≤50,000 ppm HFC-152a in a lifetime inhalation toxicity study,[14] coupled with the absence of adverse effects in the preceding developmental toxicity,[15] would suggest that HFC-152a is unlikely to be a reproductive toxin.

E. Subacute/Subchronic Toxicity

1. A group of 10 ChR-CD rats was exposed to either 0 or 100,000 ppm of HFC-152a 6 hours/day, 5 days/week, for 2 weeks. No adverse effects were seen relative to body weight, hematology, blood chemistry, or histopathology. There was a slight increase in urinary fluoride, suggesting that this fluorocarbon may be metabolized to a small extent. During exposure, rats did seem to be anesthetized as indicated by sleeping and unresponsiveness to sound, specifically a sharp knock on the exposure chamber wall.[16]

2. Eight rats were exposed to 100,000 ppm of HFC-152a for 16 hours/day for 2 months. No adverse clinical signs were seen. Gross examination at autopsy showed no adverse effects. Microscopic examination of rats exposed to HCFC-152a did show a mild, diffuse infiltration of small and large round cells in the lung, indicating mild irritation.[5] No concurrent control data were reported.

F. Chronic Toxicity

In a lifetime inhalation toxicity study,[14] 120 ChR-CD rats were exposed to HFC-152a for 6 hours/day, 5 days/week, for 24 months at exposure levels of 0, 2000, 5000, or 25,000 ppm (v/v). General adverse effects at the highest exposure level included an increased incidence of swollen ears and ocular/nasal discharge, possibly indicating mild irritation. High exposure rats also exhibited an increased incidence of staining of the body and face and wet/stained perinea. An increase in urinary fluoride was also observed in both the 5000 and 25,000 ppm groups. None of these findings at the high exposure level had an adverse effect on survival.

After 90 days' exposure, rats exposed at 25,000 ppm showed lower kidney weights, clinical laboratory findings, and histopathologic changes in renal tubules, suggestive of compound-related kidney damage. None of these changes, however, were seen again at any interim (12 months, for example) or final (24 months) sacrifice. Furthermore, a study[17] involving the re-examination of tissues and slides resulted in a diagnosis of these microscopic findings at 90 days as "artifactual changes due to tissue processing."

One other finding reported in the chronic study was an atrophy of the nasal olfactory epithelium at final sacrifice (24 months) in some rats (mainly female) from all treatment groups except the 5000 ppm level. However, there was no dose-response in terms of severity or the time course to development of the lesion and a similar lesion was seen in controls. Also, in most treated rats, the lesion was unilateral in distribution (on one side of the nasal cavity only), a finding not typical of inhaled irritants. In addition, one group of investigators[18] reported that atrophy of the olfactory epithelium may occur as a spontaneous aging change in rats. These findings strongly suggest that these olfactory changes were spontaneous aging changes and not attributable to HFC-152a exposure. Also, there was no evidence that HFC-152a was carcinogenic in rats at chronic exposure levels of ≤25,000 ppm.

Under the conditions of this study, HFC-I52a was not carcinogenic, did not adversely affect survival, and produced no significant adverse effects in rats at chronic inhalation exposure levels as high as 25,000 ppm.

V. HUMAN USE AND EXPERIENCE

Several volunteers were exposed to 500,000 ppm of HFC-152a for several minutes. Analgesia and an impending loss of consciousness were reported.[19]

VI. RATIONALE

HFC-152a has a very low order of acute inhalation toxicity. Its 4-hour ALC in rats is 383,000 ppm and its threshold for cardiac sensitization in dogs is 150,000 ppm (5-minute exposure followed by epinephrine injection). Pharmacokinetic studies in rats exposed by inhalation suggest a very low level of metabolism with urinary fluoride ion and acetic acid as the major metabolites. This fluorocarbon was not embryotoxic, teratogenic, or maternally toxic in rats at exposure levels as high as 50,000 ppm, and has shown no evidence of mutagenicity in *Salmonella typhimurium* (Ames test). In repeated exposure studies, rats exposed at 100,000 ppm for 6 hours/day, 5 days/week for 2 weeks showed only slight, reversible anesthetic effects during exposure. Even when rats were exposed at the same concentration level for 16 hours/day for 2 months, the only effect was slight microscopic evidence of respiratory irritation. When rats were exposed to HFC-152a for 6 hours/day, 5 days/week for 24 months, no effects on survival, carcinogenicity, or significant adverse effects attributable to exposure were observed at levels as high as 25,000 ppm.

Based on the preceding results from the lifetime inhalation study in rats, the general low level of toxicity seen in a variety of acute and repeated exposure toxicity studies, and on the basis of good industrial hygiene practice, an OEL of 1000 ppm (v/v; 8-hr TWA) should provide an adequate margin of safety.

VII. RECOMMENDED OEL

1000 ppm (2700 mg/m^3): 8-hour time-weighted average (TWA)

VIII. REFERENCES

1. **DuPont Company:** *Material Safety Data Sheet-Dymel 152a Aerosol Propellant* (MSDS# DU001260). E.I. du Pont de Nemours & Co, Chemicals Business Center, Chestnut Run, P.O. Box 80709, Wilmington, DE 19880-0709. 1998.
2. **Trochimowicz, H.J.:** 1, 1-Difluoroethane. [Personal communication to the AIHA WEEL Committee]. [Unpublished data.] Haskell Laboratory, E.I. du Pont de Nemours & Co., Eikton Road, P.O. Box 50, Newark, DE 19714. 1991.
3. **Malek, D.E.:** Approximate Lethal Dose (ALD) Study of HFC-152a in Rats. [Unpublished Haskell Laboratory Report No. 524-90], Haskell Laboratory, E.I. du Pont de Nemours Co., Elkton Road, P.O. Box 50, Newark, DE 19714. 1990.
4. **Moore, B.L.:** Acute Inhalation Toxicity Study. [Unpublished Haskell Laboratory Report No. 699-75], Haskell Laboratory, E.I. du Pont de Nemours & Co., Elkton Road, P.O. Box 50, Newark, DE 19714 (November 17, 1975).
5. **Lester, D., and L.A. Greenberg:** Acute and Chronic Toxicity of Some Halogenated Derivatives of Methane and Ethane. *Arch. Ind. Hyg. Occup. Med. 2*:335–344 (1950).
6. **Izmerov, N.F., I.V. Sanotsky, and K.K. Sidorov:** *Toxicometric Parameters of Industrial Toxic Chemicals under Single Exposure.* Moscow: USSR State Committee for Science and Technology,1982. [Russian]
7. **Reinhardt, C.F., A. Azar, M.E. Maxfield, P.E, Smith, and L.S. MuIIin:** Cardiac Arrthymias and Aerosol "Sniffing." *Arch. Environ. Health 22*:265–279 (1971).
8. **Koops, A.:** Mutagenic Activity of Ethane, 1,1-Difluoro in the Salmonella/Microsome Assay. [Unpublished Haskell Laboratory Report No. 731-77], Haskell Laboratory, E.I. du Pont de Nemours & Co., Elkton Road, P.O. Box 50, Newark, DE 19714. 1977.
9. **Longstaff, E., M. Robinson, C. Bradbrook, J.A. Styles, and I.F.H. Purchase:** Genotoxicity and Carcinogenicity of Fluorocarbons: Assessment by Short-Term *In Vitro* and Chronic Exposure in Rats. *Toxicol. Appl. Pharmacol. 72*:15–31. (1984).
10. **Araki, A, T. Noguchi, F. Kato, and T. Matsushima:** Improved Method for Mutagenicity Testing of Gaseous Compounds by Using a Gas Sampling Bag. *Mutat. Res. 307(1)*:335–344. (1994).
11. **Foltz, V.C., and R. Fuerst:** Mutation Studies with *Drosophila melanogaster* Exposed to Four Fluorinated Hydrocarbon Gases. *Environ. Res. 7*:275–283. (1974).
12. **Garrett, S., and R. Fuerst:** Sex-Linked Mutations in Drosophila after Exposure to Various Mixtures of Gas Atmospheres. *Environ. Res. 7*:286–293. (1974).
13. **Keller, D.A., D.C. Roe, and P.H. Lieder:** Fluoroacetate-Mediated Toxicity of Fluorinated Ethanes. *Fundam. Appl. Toxicol. 30(2)*:213–219. (1996).
14. **McAlack, J.W., and P.W. Schneider:** Two-Year Inhalation Study with Ethane, 1,1-Difluoroethane (HFC-152a) in Rats. [Unpublished Haskell Laboratory Report No. 8-82], Haskell Laboratory, E.I. du Pont de Nemours & Co., Elkton Road, P.O. Box 50, Newark, DE 19714. 1982.
15. **Culik, R., and D.P. Kelly:** Embryotoxicity and Teratogenicity Studies in Rats with 1,1-Difluoroethane (FC-152a). [Unpublished Haskell Laboratory Report No. 437-79], Haskell Laboratory, E.I. du Pont de Nemours & Co., Elkton Road, P.O. Box 50, Newark, DE 19714. 1980.
16. **Moore, B.L.:** Subacute Two-Week Inhalation Toxicity. [Unpublished Haskell Laboratory Report No. 158-76], Haskell Laboratory, E.I. du Pont de Nemours &. Co., Elkton Road, P.O. Box 50, Newark, DE 19714. 1976.
17. **Bruner, R.H.:** *Pathology Peer Review of a Two-Year Inhalation Study of HFC-152a in CD Rats.* Prepared by Pathology Associates, Inc., West Chester, Ohio, for E.I du Pont de Nemours & Co., Haskell Laboratory, Newark, DE. 1992.
18. **Boorman, G.A., K.T. Morgan, and L.C. Uriah:** "Nose, Larynx, and Trachea" (Chapter 20) in *Pathology of the Fischer Rat.* San Diego, Academic Press, Inc., 1990.
19. **Van Poznak, A., and J.F. Artusio Jr.:** Anesthetic Properties of a Series of Fluorinated Hydrocarbons. (I. Fluorinated Compounds.) *Toxicol. Appl. Pharmacol. 2*:363–373. (1960).