1,1-Difluoroethane; CASRN 75-37-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 1,1-Difluoroethane

File First On-Line 09/01/1994

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	09/01/1994*
Carcinogenicity Assessment (II.)	not evaluated	

*A comprehensive review of toxicological studies was completed 01/01/05 - please see section I.B.6 for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 1,1-Difluoroethane
CASRN — 75-37-6
Primary Synonym — HCFC-152a

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 1,1-Difluoroethane
CASRN — 75-37-6
Primary Synonym — HCFC-152a
Last Revised — 09/01/1994

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
No adverse effects observed **2-Year Inhalation Study** **McAlack and Schneider, 1982**	NOAEL: 67,500 mg/cu.m (25,000 ppm) NOAEL(ADJ): 12,051 mg/cu.m NOAEL(HEC): 12,051 mg/cu.m LOAEL: None LOAEL(ADJ): None LOAEL(HEC): None	300	1	4E+1 mg/cu.m

* Conversion Factors and Assumptions -- MW = 66. Assuming 25 C and 760 mmHg, NOAEL(mg/cu.m) = 25,000 ppm x MW/24.45 = 67,485. NOAEL(ADJ) = 67,485 x 6 hours/24

hours x 5 days/7 days = 12,051 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental animal species (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = 12,051 x [b:a lambda(a)/b:a lambda(h)] = 12,051 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

McAlack, J.W. and P.W. Schneider, Jr. 1982. Two-year inhalation study with ethane, 1,1-difluoro (FC-152a) in rats. E.I. Du Pont de Nemours and Co., Inc. Haskell Laboratory for Toxicology and Industrial Medicine. Haskell Laboratory Report No. 8-82.

CD rats (30/sex/group) were exposed to 0, 2000, 10,000, or 25,000 ppm 1,1- difluoroethane (HCFC-152a) (99.88% pure) (0, 5399, 26,994, or 67,485 mg/cu.m, respectively) for 6 hours/day, 5 days/week, for 2 years (McAlack and Schneider, 1982). Duration-adjusted concentrations are 0, 964, 4821, or 12,051 mg/cu.m, respectively. Interim sacrifices were performed on 10 rats/sex/group after 3 or 12 months of exposure. The animals were exposed in 4.6-cu.m stainless steel and glass chambers using a one-pass, flow-through mode of air flow (air flow rate = 1200 L/minute). The test atmosphere was generated by diluting HCFC-152a vapor with air. The concentration of the test atmosphere was analyzed approximately every 30 minutes during each exposure period by gas chromatography, and mean chamber concentrations were found to be within 15% of nominal concentrations. Animals were observed twice daily and several times during exposure for clinical signs of toxicity and moribundity. Body weights and food consumption were measured biweekly for the first 14 weeks and monthly thereafter. Hematology, clinical chemistry, and urinalysis were conducted at 1, 3, 6, 12, 18, and 24 months on 10 rats/sex/group. Gross and microscopic evaluation of approximately 40 tissues was conducted in all animals at terminal sacrifice and in the high-concentration and control animals at the 3- and 12-month sacrifices (10 rats/sex). Kidney and nasal tissues from the low- and intermediate-concentration groups were also examined microscopically. The number of cross-sections examined in the nasal tissue ranged from three to six (Trochimowicz, 1992).

There were no statistically significant exposure-related effects on survival or body weight gain. Clinical signs noted at a higher incidence, when summed across exposure periods, in both sexes exposed to 25,000 ppm HCFC- 152a included ocular/nasal discharges and wet/stained perinea. The 25,000-ppm females also exhibited significantly elevated incidences of stained body/face. These observations suggested chronic low-level irritation or stress in the animals exposed to HCFC-152a at the highest exposure level but were not observed consistently across exposure periods or exposure levels nor supported by histopathology. Although several statistically significant hematological changes were noted, none were considered to be toxicologically significant. For example, females exposed to 10,000 and 20,000 ppm HCFC-152a exhibited increased mean corpuscular volumes, and all exposed females exhibited increased serum

bilirubin; increased hematocrits and mean corpuscular volumes were seen in males exposed to 10,000 and 25,000 ppm HCFC-152a. However, hematopoietic tissues and red blood cell counts were normal in these animals, which does not support the hemolytic effect that is suggested by the changes listed above. Statistically significant reductions in eosinophils and monocytes also were observed in some of the treated groups.

Urinary fluoride was increased statistically in both sexes at all concentrations, indicating metabolism of HCFC-152a. Biochemical changes (significant increases in serum creatinine in the females exposed to 10,000 and 25,000 ppm HCFC-152a), increased urine volume, and decreased urine osmolality seen throughout the study suggested renal toxicity. The only organ weight or histopathology data to support this functional deficit was decreased kidney weight and renal tubular damage noted in the high-concentration animals at the 3-month sacrifice. The tubular lesions were reported in the original report as "slight cytoplasmic vacuolation, luminal dilation, and the presence of occasional vesiculated nuclei" and were seen in 4/10 males and 7/10 females. These changes were not seen at the other scheduled evaluations, however, and a subsequent peer review of these data (Bruner, 1992) determined that the renal tubular changes reported at the 3-month sacrifice were artifactual changes due to tissue processing rather than a treatment-related nephrotoxicity.

The only other microscopic change observed in the animals exposed to HCFC- 152a was atrophy of the nasal olfactory epithelium at the final sacrifice. The incidence of this lesion in the total number of nasal tissues examined was 0/97, 5/87, 2/92, and 8/89 in the males exposed to 0, 2000, 10,000, and 25,000 ppm HCFC-152a, respectively, and 0/95, 9/88, 0/91, and 17/95 in the females exposed to 0, 2000, 10,000, and 25,000 ppm HCFC-152a, respectively. The authors characterized this lesion as consisting of a reduction in thickness and disorganization of the olfactory mucosa likely resulting from a decrease in the number with a shortening or flattening of the epithelial lining cells, which was sometimes accompanied by cellular debris and inflammatory infiltrates. Although the incidence of atrophy was statistically significant for a trend among male treatment groups but not among female treatment groups, there was no trend relative to severity or time to development. Other nasal changes, including focal rhinitis/exudate and focal mucosal metaplasia were not related to concentration and occurred in similar incidences in control and treated groups of both sexes. A peer review (Bruner, 1992) was performed of all available nasal tissues from female rats sacrificed at both the 3-month and 1-year evaluations and additional nasal sections from all females that died incidental to the 2-year exposure. Smaller numbers of male rat tissues were examined at all sacrifice periods to ensure that sex was not a factor in determining pathophysiologic responses. Atrophy of the nasal olfactory epithelium was observed in the peer review only in the materials from the 2- year sacrifice and was present in female rats in the low- and high- concentration groups, but was not observed in controls or the intermediate- concentration group.

The nasal olfactory epithelial atrophy was not designated as the critical effect for a number of reasons. The effect was observed only at the 2-year sacrifice, and the concentration response showed a trend only for incidence and only in the male rats, whereas no trends were significant for either severity or duration. This suggests that the effect was more statistically significant than toxicologically significant, and it also has been indicated that atrophy of the nasal olfactory epithelium may occur as a spontaneous aging change in rats. All other changes in the nasal region were focal in nature and were not concentration-related changes. Further, the peer review indicated that this change was distributed unilaterally (i.e., in one side of the nasal cavity only) in all low-exposed and in over one-half of the high- exposed females. This asymmetrical distribution is not considered to be typical of inhaled irritants and, together with the lack of convincing concentration-response data in the original study, did not provide sufficient evidence for an upper respiratory tract effect.

The 25,000 ppm concentration is therefore designated as a free-standing NOAEL in this study. The NOAEL(HEC), calculated based on an extrarespiratory effect, is 12,051 mg/cu.m. It is used as the basis for the operational derivation of the RfC because the only other data, including a NOAEL for maternal toxicity and developmental effects at 50,000 ppm in rats (Culik and Kelly, 1980), are short in duration. Reversible CNS depression has been demonstrated at 100,000 ppm. It is unlikely that future chronic investigations will be performed at higher concentrations than that in the critical study because the lower flammability limit for this compound is 37,000 ppm (ZBA, 1992).

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — The UF of 300 reflects a factor of 10 to protect unusually sensitive individuals, 3 for interspecies extrapolation, and 10 for database deficiencies that include the lack of chronic inhalation and developmental studies in a second species and two-generation reproductive toxicity studies. The total UF is 300.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

HCFC-152a is practically nontoxic following acute inhalation exposure. No deaths were observed in male albino rats (2/group) acutely exposed to 74,000, 100,000, or 200,000 ppm HCFC-152a for 2 hours (Limperos and Zapp, 1951). These rats were examined 4-7 days after exposure, and no gross or histopathologic changes were observed. Moore (1976) exposed male CD rats (10/group) to 0 or 100,000 ppm HCFC-152a for 6 hours/day, 5 days/week for 2 weeks. Five rats from each group were sacrificed for histopathologic examination at 0 and 14 days postexposure. During exposure, the animals appeared to be anesthetized, as indicated by sleeping

and unresponsiveness to sound. No hematological, blood chemistry, or histopathological effects were observed, except for a slight increase in urinary fluoride at the end of exposure. Thus, the most pronounced effect of acute or sub-acute exposures to HCFC-152a is reversible CNS depression at high concentrations (100,000 ppm or greater). This CNS effect was not observed at any of the concentrations tested in the critical study of chronic duration.

In an unpublished Haskell Laboratory study (HLR 699-75), adult male rats (10/group) were exposed to 0 or 100,000 ppm for 6 hours/day, 5 days/week for 2 weeks. Five rats from each group were sacrificed for gross and histopathologic examinations at the end of the last exposure, and the remaining animals were sacrificed similarly and examined after a 14-day recovery period. Hematological, urine, and biochemical indices were measured in all animals. No effects on these indices nor on histopathology were observed. The rats appeared lethargic and were poorly responsive to sound during exposures, consistent with the reversible CNS depression noted above.

Lester and Greenberg (1950) exposed eight adult male rats to a concentration of 100,000 ppm for 16 hours/day for 2 months. (No exposure generation or experimental design data are available at this time). No signs of ill health were apparent at any time. The only remarkable histopathology was a mild diffuse infiltration of small and large round cells in 5/8 rats, which may be suggestive of mild chronic irritation.

The potential for aerosol propellants, including HCFCs, to produce cardiopulmonary toxicity was evaluated in a series of studies using various species. HCFC-152a was evaluated in Rhesus monkeys, mongrel dogs, Wistar rats, and Swiss mice (Belej et al., 1974; Aviado and Belej, 1974; Belej and Aviado, 1975; Doherty and Aviado, 1975; Aviado and Smith, 1975). "Cardiotoxicity" was defined as the potential to induce arrhythmias and myocardial contractions, and aortic blood pressure, cardiac output, pulmonary vascular resistance, and heart rate were monitored. Pulmonary resistance, compliance, and response minute volume were measured as indices of bronchopulmonary function. HCFC-152a was delivered at various concentrations through a respirator for a period of 5 minutes. HCFC-152a did not affect pulmonary mechanics nor any cardiopulmonary endpoint in dogs, mice, and monkeys at concentrations up to 200,000 ppm, although epinephrine-induced arrhythmia was reported at 150,000-ppm dogs in a different investigation (Mullin, 1969). No epinephrine-induced arrhythmias were reported in dogs exposed to 50,000 ppm. In rats, HCFC-152a resulted in a decreased heart rate at 100,000 ppm or greater. Because the causative mechanisms for cardiotoxicity are not well understood, the basis of this species difference is not clear. Further, because the relevance of exogenous epinephrine concentration (used for challenge in some studies) to physiologic epinephrine levels is not clear, the significance of these findings is difficult to evaluate conclusively.

One developmental toxicity study is available on HCFC-152a. In this study, pregnant CD rats (27/group) were exposed to 0, 5000, or 50,000 ppm HCFC-152a (0, 13,500, 135,000 mg/cu.m) for 6 hours/day on gestation days 6-15 (Culik and Kelly, 1980). No evidence of maternal toxicity (behavior, body weight, gross abnormalities in vital organs, ovaries, or uterine horns) was found in the exposed animals. All parameters of reproductive function and fetotoxicity (number of corpora lutea, implantation sites, live fetuses per litter, early and late resorptions, fetal weight, and fetal crown-rump length) were unaffected by exposure. No statistically significant increases in the incidence of any of external gross, soft-tissue, or skeletal anomalies were observed in the fetuses from exposed dams. Thus, this study establishes a NOAEL for maternal and developmental toxicity in rats at exposure concentrations up to 50,000 ppm.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

The principal study was well conducted and used a sufficient number of animals. It is given medium confidence because, although slight renal and nasal effects were suggested, they were not definitive nor concentration- related and only a NOAEL was established. The database is given a medium level of confidence due to the lack of both a chronic inhalation study and a developmental toxicity study in a second species and because there are no two- generation reproductive toxicity studies. A medium confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 09/24/1992

Verification Date — 09/24/1992

A comprehensive review of toxicological studies published through 2004 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfC for 1,1-Difluoroethane and a change in the RfC is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,1-Difluoroethane
CASRN — 75-37-6
Primary Synonym — HCFC-152a

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — 1,1-Difluoroethane
CASRN — 75-37-6
Primary Synonym — HCFC-152a

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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Mullin, L.S. 1969. Cardiac sensitization. E.I. Du Pont de Nemours and Co., Inc. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE. Haskell Lab. Rep. No. 354-69.

Trochimowicz, H.J. 1992. Haskell Laboratory for Toxicology and Industrial Medicine, E.I. Du Pont de Nemours and Company, Newark, DE. Letter to Dr. Reva Rubenstein, U.S. EPA. September 1. Chronic study of HFC-152a: Pathology procedure for nasal turbinae examination.

ZBA, Inc. 1992. Assessment of CFC substitutes in refrigeration and air conditioning for SNAP program. Cincinnati, OH. Prepared for U.S. EPA, Washington, DC. ZBA 1437. June.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — 1,1-Difluoroethane
CASRN — 75-37-6
Primary Synonym — HCFC-152a

Date	Section	Description
09/01/1994	I.B.	Inhalation RfC on-line
10/28/2003	I.B.6.	Screening-Level Literature Review Findings message has been added.
03/03/2005	I.B.6	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — 1,1-Difluoroethane
CASRN — 75-37-6
Primary Synonym — HCFC-152a
Last Revised — 10/01/1992

- 75-37-6
- Ethane, 1,1-difluoro-
- FREON 152A
- Hydrofluorocarbon 152a
- 1,1-difluoroethane
- ALGOFRENE TYPE 67
- Ethylene fluoride
- Ethylidene difluoride
- Ethylidene fluoride
- FC 152a
- Fluorocarbon 152a
- Genetron 100
- Genetron 152A
- HSDB 5205
- Propellant 152a
- R 152a
- HCFC-152a