1,1-Dichloro-1-Fluoroethane

Document History
Published: 2008
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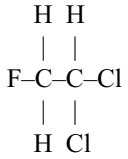
I. IDENTIFICATION

Chemical Name: 1,1-Dichloro-1-fluroroethane
Synonyms: 1, 1-dichloro-1-fluoro-ethane, HCFC-141b, Fluorocarbon 141b, HFA 141b, Refrigerant 141b, R-141b
CAS Number: 1717-00-6
Molecular Formula: $C_2Cl_2FH_3$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1,2]

Physical State: Colorless liquid at 25°C (77°F)
Odor Description: Faint ethereal odor
Odor Threshold: N/A
Molecular Weight: 116.95
Conversion: 1 ppm(v/v) = 4.85 mg/m^3(w/v); 1 mg/m^3 = 0.206 ppm
Melting Point: N/A
Boiling Point: 31°C (88°F) at 760 mm Hg
Vapor Pressure: 412 mm Hg at 25ºC (70ºF)
Saturated Vapor Concentration: ~542,000 ppm @ 25°C (70°F)
Flammability Limits: Nonflammable
Flash Point: None between room temperature and boiling point
Specific Gravity: 1.24 g/mL at 21ºC (70ºF)
Vapor Density (Air = 1): 4.0
Solubility in Water: 3.6 g/L at 25ºC (77ºF)
Stability: Material is stable except in open flames and high temperatures.
Reactivity and Incompatibilities: Nonreactive under most conditions

III. USES

HCFC-141b is a replacement for the current chlorofluorocarbons (CFCs) and is used in the production of rigid polyurethane and polyisocyanurate or phenolic insulating foams. These foams are used in insulation for commercial buildings, in insulation foam boards for residences, in residential wall insulation, or in foam fill for refrigerators. HCFC-141b may also be employed as a solvent for the removal of soldering flux from printed circuit boards, in precision cleaning of intricate parts, and, in combination with a surfactant, for the removal of trace water from intricate parts.

IV. TOXICOLOGY DATA

A. Acute Toxicity

1. Oral Toxicity

HFC-141b was administered to rats as a single oral dose (dissolved in corn oil) by gastric intubation. The oral LD_{50} was >5000 mg/kg.[3,4]

2. Dermal Toxicity

HCFC-141b produced no dermal irritation in 1 male or 5 female rabbits when 0.5 mL of undiluted material was administered under an occlusive patch for up to 24 hours.[5]

In two different dermal absorption toxicity studies[6,7], a single dose of 2000 mg/kg HCFC-141b was applied to the clipped intact skin of 5 male and 5 female rabbits and of 5 male and 5 female rats. All animals were observed for 14 days. No deaths occurred in either study and the dermal LD_{50} was reported as >2000 mg/kg for both rabbits and rats.

Twenty male albino guinea pigs were tested for delayed contact hypersensitivity. HCFC-141b, in a 5% v/v Alembicol D Solution, was administered in three pairs of intradermal injections in a 4 x 6 cm area of skin on the scapular region of the guinea pig that was clipped free of hair. One week after the injections, a topical application using a patch saturated with 0.4 mL of HCFC-141b was taped on the skin in the same area. A challenge test

was conducted two weeks after the initial injection. There was no evidence of delayed contact hypersensitivity after 72 hours. HCFC-141b was not a skin sensitizer.[8]

3. *Eye Irritation*

In two separate primary eye irritation studies[8] in rabbits, mild reversible irritation with no corneal or iridal involvement was reported. Under the conditions of this study, HCFC-141b was considered a mild eye irritant.

4. *Inhalation Toxicity*

a. Rats: 4-hour LC_{50} = 61,647 ppm[8]

Five rats/sex were exposed whole-body by the inhalation route to measured concentrations of 29,958, 45,781, 68,143 or 77,215 ppm for 4 hours. No mortality occurred at the two lowest levels. Mortalities did occur at 68,143 ppm (4 of 5 males;1 of 5 females) and at 77,215 ppm (5 of 5 males; 5 of 5 females). The calculated 4-Hour LC_{50} for male and female rats combined was 61,647 ppm. The main toxicological action of HCFC-141b at these high exposure levels was on the central nervous system. During exposure, signs included increased respiration rate, staggering gait, restless behavior, and reduced motor activity. If death did not occur during exposure, rats recovered without sequelae within several hours.

b. Dogs and Monkeys

In a study[8,9] on cardiac sensitization potential, HCFC-141b was evaluated in Beagle dogs (2/exposure level) and monkeys (1 or 2/exposure level) exposed at various concentrations for approximately 5 minutes. The animals were then given an intravenous injection of epinephrine and monitored for cardiac arrhythmias. Dogs were exposed at concentrations between 9000 and 20,000 ppm. At the lowest concentration tested (9000 ppm), 1 of 2 dogs showed a serious cardiac response;10,000 ppm induced no cardiac responses in 2 of 2 dogs. Concentrations between 14,000 and 20,000 ppm also induced serious cardiac responses. For the monkey, concentrations of 3000, 5000, and 10,000 ppm were tested. No serious ECG response was seen in the only monkey tested at 3000 ppm; 5000 ppm produced a serious cardiac response in one of 2 monkeys; 10,000 ppm induced a serious response in 2 of 2 monkeys. In an earlier study[8,10] (similar protocol) utilizing as many as 10 dogs/level, a clear NOEL for cardiac sensitization was seen in 10 of 10 dogs at 2600 ppm; 5200 ppm produced a serious cardiac response in one of 10 dogs; 10,000 ppm induced a serious cardiac arrhythmia resulting in death in one of 10 dogs; and 21,600 ppm induced fatal arrhythmias in 2 of 2 dogs tested.

From the preceding data, the threshold for cardiac sensitization in the monkey (only one or 2/ test concentration) appears to be in the 5000 to 10,000 ppm range. For the dog, the threshold for cardiac sensitization is 5200 ppm. Exposure to CFC-11 produced similar results; the threshold for cardiac sensitization ranged from 5000 to 10,000 ppm in both the dog and the monkey.[8]

These data suggest that HCFC-141b, like CFC-11, has a moderate-to-strong potential to induce cardiac sensitization.

B. Genotoxicity

1. *In Vitro:*

HFC-141b was not mutagenic in an Ames assay using five strains of *Salmonella typhimurium* bacteria (TA98, TA1538, TA100, TA1535 and TA1537) nor in a similar assay using *Escherichia coli* strain *WP2 uvrA*, either in the presence or absence of an S9 metabolic activation system. This Ames assay utilized 5 test concentrations of fluorocarbon (0.3, 1, 3, 10 and 30%) and agar plates seeded with tester strains, which were then exposed to HCFC-141b vapor.[11] In other *in vitro* assays, HCFC-141b was positive in chromosomal aberration tests on CHO cells but negative in similar tests on human lymphocytes.[12]

2. *In Vivo:*

Male and female mice (15/sex/level) were exposed to HCFC-141b vapor concentrations of 0, 3600, 10,000 or 34,000 ppm for 6 hours. Under the conditions of this test, there was no evidence at any test concentration of induced chromosomal or other damage leading to micronucleus formation in bone marrow erythrocytes of exposed mice sacrificed 24, 48 or 72 hours post-exposure.[12]

C. Metabolism and Pharmacokinetics

In one study[13], individual male rats were exposed whole-body by the inhalation route to HCFC-141b

at concentrations ranging from 70 to 2540 ppm for periods up to 16 hours. No measurable metabolism of HCFC-141b was detected. The analytical method employed could have detected a metabolism of 1% of the inhaled HCFC-141b present in the chamber.

Gas uptake pharmacokinetics and metabolism of HCFC-141b were studied in rats after exposure to 1000, 3000, 5000, 8000 or 10,000 ppm vapor for 6 hours in a closed inhalation chamber system. *In vivo* uptake of fluorocarbon was characterized by a rapid initial phase followed by a slow linear phase. Uptake was best described by a pharmacokinetic model incorporating saturable andfirst-order processes. The Michaelis constant (K_m) and maximum velocity (V_{max}) were 7.0 mg/L and 0.2 mg/kg/hr, respectively. The half-life for uptake during the linear phase was 0.5 hour. Over a 24-hour post-exposure period, no HCFC-141b was detected in the urine. Urinary excretion of 2,2-dichloro-2-fluoroethanol (the major metabolite) increased linearly with HCFC-141b exposure concentration.[14]

In another study[15], human subjects (6 males, 2 females) were exposed by inhalation to 250, 500, or1000 ppm HCFC-141b for 4 hours and urine was collected over the next 24 hours for metabolite analysis. Blood measurements were made prior to, during and after exposure. The major metabolite detected was 2,2-dichloro-2-fluoroethanol (excreted as its glucuronide conjugate), similar to results seen in the rat. In addition, the relationship between exposure concentration and blood level of HCFC-141b appeared to be linear based on three collection intervals during the same 24-hour post-exposure period. Pharmacokinetic data suggested that <6% of the inhaled dose was metabolized.

D. Developmental and Reproductive Toxicity

1. Developmental Toxicity Studies in Rats and Rabbits

Groups of 25 pregnant rats were exposed to HCFC-141b at exposure levels of 0, 3200, 8000 or 20,000 ppm for 6 hours/day on days 6 through 15 of gestation. At 20,000 ppm, the dams showed signs of central nervous system (CNS) depression decreased food and water intake, and a decreased rate of weight gain. In the pups at this exposure level, there was an increase in embryonic deaths, reduced fetal weight, retarded maturity and delayed calcification, effects often associated with maternal toxicity. Even under these maternally-toxic conditions, no teratogenic effects were observed. At 8000 ppm, maternal toxicity was limited to slight CNS effects and a transient decrease in rate of weight gain while pups showed no evidence of toxicity. At the lowest level (3200 ppm), no remarkable adverse effects were seen in the dams or the pups.[16]

In a second inhalation study, groups of 16 pregnant albino rabbits were exposed to HCFC-141b at exposure levels of 0, 1400, 4200 or 12,600 ppm for 6 hours a day on Days 7 through 19 of gestation. At the two highest exposure levels, dams showed a slight decrease in rate of weight gain and mild CNS effects; there was no evidence of maternal toxicity at 1400 ppm. Pups showed no teratogenic nor other developmental effects at any exposure level.[16]

Based on the preceding studies in rats and rabbits, fetal toxicity is not a more sensitive toxicological endpoint than maternal effects

2. Two-Generation Reproduction Study in Rats

In this study[16] conducted by the inhalation route, 32 male and 32 female rats [Crl: CD (SD) BR VAF/Plus Strain] per exposure level were exposed to HCFC-141b for six hours/day, seven days/week at concentrations of 0, 2000, 8000, and 20,000 ppm. The F0 animals (32/sex/group) were treated continuously from seven weeks of age for 10 weeks prior to pairing; treatment continued throughout two pairing phases. A second mating was done because of an inferior mating performance at 20,000 ppm. Females and litters were sacrificed on Day 4 postpartum. The F1 generation (28/sex/group) was derived from litters of the first mating. Selected weanlings were reared to maturity and mated at 16 weeks of age.

Adult rats exposed to 20,000 ppm HCFC-141b, and to a lesser extent 8,000 ppm, showed a well-defined response relative to water and food intake and body weight gain. At 20,000 ppm, there was an apparent impairment of fertility of F0 animals seen as a reduction in pregnancy rate and fertility index at both matings. There was some sign of delayed sexual maturation of male offspring (F1 generation) at this exposure, possibly associated with reduced mean pup weight. At post mortem, seminal vesicle/prostate weights of the F1 offspring were lower than controls. Although the fertility of F1 animals was not affected by treatment, there was an increase in implantation loss as reflected in the lower litter size at birth.

At 8000 ppm, fertility of the F0 and F1 animals was not impaired, but there was a slight indication of delayed sexual maturation of male offspring. There were no other effects on reproductive performance or on pup survival and growth during the pre-weaning periods. At 2000 ppm, there were no effects on fertility of F0 and F1 animals, sexual maturation of F1 males or females, or on pup survival and growth. The 2000 ppm exposure level represented a clear NOEL for all indices examined.

E. Subacute/Subchronic Toxicity

1. A group of 10 rats/sex was exposed to 0, 5000, 8500, 14,000 or 20,000 ppm of HFC-141b for 6 hr/day 5 days/week for 2 weeks. The only adverse effects seen were a slight decrease in rate of weight gain and mild central nervous system effects, mainly at the two highest exposure levels. No mortality occurred and histopathology at study termination was unremarkable.[17]

2. In a 90-day inhalation toxicity study[8], 15 rats/sex were exposed to HCFC-141b at levels of 0, 2000, 8000, or 20,000 ppm for 6 hours/day, 5 days/week for 13 consecutive weeks. No mortality occurred in this study. At 20,000 ppm, there was a slight decrease in food consumption and rate of weight gain as well as central nervous system depression during the exposure periods. At 8000 ppm, milder CNS effects (a slight decrease in startle response, for example) were reported. No adverse clinical observations were seen in rats exposed at 2000 ppm. Histopathological examinations were unremarkable at all exposure levels. The 8000 ppm exposure level was considered a NOAEL and 2000 ppm was a NOEL for this study.

F. Chronic Toxicity and Carcinogenicity

In a lifetime inhalation toxicity study[12], 80 rats/sex/group [Crl: CD (SD) BR] were exposed to HFC-141b for 6 hr/day, 5 days/week for 24 months at exposure levels of 0, 1500, 5000, or 15,000 ppm. Due to a lack of significant toxicity in the group inhaling 15,000 ppm after 17 weeks on test, the highest exposure level was increased to 20,000 ppm for the remaining duration of the study (Week 18 through Week 104). No treatment-related mortality or adverse clinical signs were observed throughout the study at any exposure level, except for slight, intermittent decreases in food intake and rate of weight gain at the highest exposure level. In addition, no exposure-related adverse effects were seen at any exposure level relative to clinical chemistry, hematology, urinalysis, or organ weights. At necropsy, no treatment-related histopathological effects were seen in female rats exposed chronically to HCFC-141b at any test level. In males, treatment-related histopathology was confined to one organ — the testis. The incidence of testicular masses, reduced size, flaccid condition, and the presence of white, subtunical striae was greater in high-concentration rats. An increased incidence of benign interstitial cell tumors was detected in rats from the 20,000 and 5000 ppm groups at the end of the 24-month study. However, the incidence was higher in the 5000 ppm group (~20%) than in the 15,000–20,000 ppm group (~17%), indicating a lack of a dose-concentration relationship. An increased incidence of moderate interstitial cell hyperplasia was also detected in the testes from rats exposed to 20,000 ppm and, even more markedly, from rats exposed at 5000 ppm. No testicular histopathology was seen in male rats exposed chronically to 1500 ppm of HCFC-141b.

In summary, lifetime inhalation exposure of male and female rats at concentrations of HCFC-141b as high as 20,000 ppm had no effect on survival, minimal effects on body weight, no histopathology in female rats, and only adverse effects on the testes of male rats — a nonlinear increase in hyperplasia and benign interstitial cell tumors. This type of testicular tumor occurs commonly in the aging rat, although the incidences at the two highest exposure levels were higher than historical controls. In addition, interstitial cell adenomas in the rat rarely progress to malignancy.[18] The authors of the preceding chronic study[12] attributed these testicular tumors (and hyperplasia) in aging rats to a change of the senile hormonal balance in geriatric rats, a mechanism associated with a non-linear concentration-response and an epigenetic tumorigen. Such a species-specific occurrence is not considered to be a risk factor for humans.[12]

The relative sensitivity of humans to the occurrence of testicular interstitial cell tumors (Leydig cell tumors; LCT) is an important issue for discussion in view of the chronic study findings. LCT incidence in man has been reported to be approximately 0.4 per million compared with an incidence in rodents ranging from 5% for Sprague-Dawley rats to nearly 88% for Fischer 344 rats.[19] Although the incidence in humans might actually be somewhat greater due to a lack of detection, the incidence is still very low. Several physiological and endocrine differences between rats and humans also support the conclusion that the occur-

rence of LCT has little relevance to humans.[20] A number of chemicals and drugs (nicotine and lactose, for example) have been shown to produce interstitial cell hyperplasia and LCT in chronic rat studies. Surveillance databases for those chemicals and drugs have detected no increased incidence in man[19] suggesting that human Leydig cells are not predisposed to chemically-induced neoplasia. It is also interesting to note that a National Research Council[21] subcommittee on alternative fluorocarbons did not consider an increase in rat Leydig cell tumors relevant to humans. Finally, primarily negative results seen in mutagenicity studies also support a conclusion of no carcinogenic risk for man.

V. HUMAN USE AND EXPERIENCE

Information on one fatality attributable to the use of HCFC-141b was found.[22] A 40-year old man was found dead inside a degreasing tank in which pure HCFC-141b was used as the degreasing solvent. The tank was free of liquid at the time and the man wore no protective clothing. High concentrations of fluorocarbon were found in the tissues (e.g.,14 mg/L in blood).

A clinical study[15] was conducted in which 8 volunteers (6 males, 2 females) were exposed to < 1000 ppm HCFC-141b for 4 hours. No adverse effects were seen relative to clinical signs, nasal irritation, cardiopulmonary evaluations and neurobehavioral indices. Hematology, clinical chemistry, and urinalysis evaluations were also unremarkable.

Occupational experience with HCFC-141b is limited. According to the European Center for Ecotoxicology and the Toxicology of Chemicals (ECETOC)[1], typical 8-hour TWA values for different occupations in a HCFC-141b production plant ranged from 1 to 70 ppm. In a research laboratory where machines using dichlorofluoroethane (isomer not described) were operating, grab sample results ranged from 10 to100 ppm. Eight-hour TWA values for technicians working in the machine room and a contiguous room were approximately 2 to 9 ppm.

VI. RATIONALE

HCFC-141b has a very low order of acute inhalation toxicity. Its 4-hour LC_{50} in rats is approximately 62,000 ppm and its threshold for cardiac sensitization in dogs or monkeys is 5000-to-10,000 ppm (5-minute exposures followed by epinephrine injection). This fluorocarbon was not teratogenic in rats at exposure levels as high as 8,000 ppm, nor in rabbits at exposure levels as high as 12,600 ppm. A weight of evidence analysis suggests that HCFC-141b is not a mutagen. On a repeated exposure basis, rats were exposed for 6 hours/day, 5 days/week for 13 weeks at exposure levels as high as 20,000 ppm with only minimal signs of toxicity; an exposure level of 8000 ppm was considered a NOAEL. Based on the preceding information, an AIHA OEL value of 500 ppm (8-hour TWA) was established for HCFC-141b in 1991. The present OEL Documentation for HCFC-141b has now been revised to incorporate pertinent toxicity data (pub- lished and unpublished) generated since 1991. Addi- tional pharmacokinetic studies have confirmed that HCFC-141b is metabolized to a minimal extent in the rodent and man and that the main metabolite in both rodent and man is dichlorofluoroethanol (excreted as its glucuronide conjugate). HCFC-141b was also shown not to be a skin sensitizer in guinea pigs and was found not to be mutagenic in an *in vitro* human lymphocyte assay, in contrast to earlier positive findings in an *in vitro* CHO assay. In a two-generation reproduction study in rats by the inhalation route, reproductive indices were adversely affected at 20,000 ppm but not at 8000 ppm (slight adult weight loss only; no effects on pups) or at 2000 ppm (overall NOEL). In a human clinical study, inhalation exposure for 4 hours at < 1000 ppm evoked no adverse effects relative to clinical signs, cardiopulmonary evaluations, or neurobehaviorial indices; hematology, clinical chemistry and urinalysis evaluations were also unremarkable.

Finally, a lifetime inhalation toxicity/carcinogenicity study in rats was conducted on HCFC-141b. When rats were exposed to HCFC-141b for 6 hours/day, 5 days a week for 24 months at exposure levels of 0, 1500, 5000, and 15,000 (20,000) ppm, there were no effects on survival and no adverse effects relative to clinical observations, hematology, clinical chemistry, urinalysis, or organ weights. At the highest exposure level, a slight reduction in food intake and rate of weight gain were observed in both sexes. Upon necropsy at the end of the study, female rats showed no histopathological effects at any exposure level. Male rats showed no abnormal histopathology at 1500 ppm. At 5000 ppm and 15,000 (20,000) ppm, males exhibited testicular pathology (interstitial cell hyperplasia and adenomas) only in a non-concentration-related pattern. However, these species-specific changes are common in aging male rats and not considered relevant to humans.

Based on the available review of the toxicological literature from 1991 to the present, the general low level of toxicity seen in a variety of earlier acute and repeated exposure toxicity studies, an OEL of 500 ppm (v/v; 8-hr TWA) is appropriate and should provide an adequate margin of safety for workers.

In addition, in cardiac sensitization studies utilizing a 5-minute inhalation exposure to HCFC-141b followed by an intravenous epinephrine challenge, the threshold for induction of a life-threatening arrhythmia was ≥5000 ppm in both the dog and the monkey. No seri-

ous arrhythmia was seen in dogs or monkeys at 3200 or 3000 ppm, respectively. Based on the preceding data, a 5-minute STEL of 3000 ppm is also proposed for HCFC-141b. This value will provide an adequate margin of safety to protect against the potential acute toxic effects of HCFC-141b.

VII. RECOMMENDED OEL

500 ppm (2370 mg/m^3): 8-hour time-weighted average (TWA)

3000 ppm (14,220 mg/m^3): 5-minute STEL

VIII. REFERENCES

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