1, 1, 1, 2-TETRAFLUOROETHANE

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I. IDENTIFICATION

Chemical Name: 1, 1, 1, 2-Tetrafluoroethane
Synonyms: Tetrafluoroethane; HFC-134a; HFA 134a; Fluorocarbon 134a
CAS Number: 811–97–2
Molecular Formula: $C_2H_2F_4$
Structural Formula: CF_3CFH_2

II. CHEMICAL AND PHYSICAL PROPERTIES[1,2]

Physical State: Colorless gas
Molecular Weight: 102.03
Conversion Factors: 1 ppm = 4.24 mg/m^3
1 mg/m^3 = 0.24 ppm
Boiling Point: -26.2°C (-15°F) at 760 mm Hg
Vapor Pressure: 4268 mm Hg at 20°C (68°F); 5.6 atm at 20°C (68°F)
Odor Description: Faint ethereal odor
Flash Point: Nonflammable
Specific Gravity: 1.27 at 20°C (68°F)
Relative Density of Saturated Air: 4.2 (Displaces air)
Reactivity: Unreactive under most conditions
Stability: Stable under normal conditions.

III. USES AND VOLUME

Fluorocarbon 134a is a replacement for the current chlorofluorocarbons (CFCs). It is used as an aerosol propellant, refrigerant and air conditioning agent.

IV. TOXICOLOGY DATA

A. Acute Toxicity

1. *Oral Toxicity*

Because HFC-134a is a gas at room temperature, no data were located.

2. *Eye Toxicity*

Administration of HFC-134a (aerosol) to the eyes of rabbits resulted in only very slight irritation.[3]

3. *Skin Toxicity*

a. Skin Irritation

Slight irritation to intact skin of rabbits appeared following occlusive application of 0.5 mL (sprayed on gauze) for 24 hr.[3]

b. Skin Sensitization

Serial dermal application of 0.5 mL (sprayed on gauze) of HFC-134a to the backs of guinea pigs did not produce evidence of sensitization.[3]

4. *Inhalation*

Rat: 4-hr LC_{50} > 500,000 ppm[4]
30-min LC_{50} = 750,000 ppm[4]

In another 4-hour study[5] in rats, no toxic effects were seen at 81,000 ppm; lethargy and rapid respiration were noted at 205,000 ppm. At concentrations of 359,300 and 567,000 ppm (~20% O_2), toxic signs included lethargy, rapid respiration, salivation, weight loss and tearing. The lowest concentration that produced death was 567,000 ppm.

5. *Cardiac Sensitization*

The cardiac sensitization potential of HFC-134a was evaluated in Beagle dogs exposed to HFC-134a at various concentrations for approximately 5 minutes. The dogs were then given an intravenous injection of adrenalin and monitored for cardiac arrhythmias. The following results were obtained[6]:

EC_{50}:	270,000 ppm
Threshold for sensitization:	80,000 ppm
No-Observable-Effect Level:	50,000 ppm

B. Mutagenicity

1. *In vitro:*

HFC-134a was not active in the vapor phase Ames assay using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537, nor in *Escherichia coli* strain WP2uvrA, either in the presence or absence of an S9 metabolic activation system. Under similar conditions, it was also inactive in a chromosome aberration study using human lymphocytes and in an assay using *Saccharomyces cerevisiae* (yeast cells).[7]

2. *In vivo:*

HFC-134a was not active in a micronucleus assay in mice (15/sex/level) at exposure levels of 50,000, 150,000 or 500,000 ppm.[7] It was also negative in an unscheduled DNA synthesis assay in rats at exposure levels up to 100,000 ppm,[8] in a mouse dominant lethal study with exposures up to 50,000 ppm,[9] and in a rat bone marrow cytogenicity study with exposure levels up to 50,000 ppm.[10]

C. Metabolism

A study was conducted to investigate the potential metabolism of HFC 134a in male rats. The rats were exposed to C^{14}- radiolabeled HFC-134a by oral and inhalation routes, and excretion and distribution of the label were evaluated. No metabolism was seen following oral administration in corn oil, and only a slight increase in urinary fluoride was observed in the inhalation experiment. This increase indicated less than 1% of the dose was metabolized and could have come from an impurity or other sources. The greater part of radioactivity (~99%) was rapidly exhaled at termination of the exposure with only a trace remaining in some tissues such as liver and adrenal gland.[11]

Male and female rats were given a single 1-hour inhalation exposure to radiolabeled HFC-134a at an atmospheric concentration of 10,000 ppm. Of the inhaled dose, about 1% was recovered in urine, feces and expired air post-exposure indicating that excretion via the lungs is rapid. Of this 1%, approximately two-thirds was exhaled within 1 hour of the cessation of exposure as unchanged HFC-134a. The remaining radioactivity was exhaled as radiolabeled carbon dioxide or excreted in urine and feces as trifluoroacetic acid (TFA). Carbon dioxide was the major metabolite of HFC-134a accounting for 0.22 and 0.27% of the inhaled dose in the male and female rats, respectively. Urinary and fecal excretion accounted for 0.09% and 0.04% of the dose by both sexes, respectively. Total metabolism measured as the sum of the radioactivities in urine, feces, and as carbon dioxide amounted to 0.34 and 0.40% of the inhaled dose in male and female rats, respectively. There were no major sex differences in the rates, routes, or amounts of radiolabel excreted. Analysis of tissues at 5 days post-exposure showed a relatively uniform distribution of radioactivity. There was no evidence for a specific uptake of HFC-134a or a metabolite into any organ or tissue analyzed, including fat.[12]

Following administration of an inhaled dose of HFC-134a to human volunteers, trifluoroacetic acid was found at very low levels using a highly sensitive NMR spectroscopic method, suggesting that the metabolism of HFC-134a is minimal in man.[13] In another human study utilizing metered-dose inhalers, HFC-134a was reported to rapidly leave the body with an apparent half-life of only 5.1 minutes.[14-15] Similarly, another report states that only 10% of the administered dose of HFC-134a remained 10 minutes after termination of the exposure.[15-16] In addition, in one of the preceding studies[15] designed to collect PBPK model validation data in human volunteers, two subjects exposed to HFC-134a at 4000 ppm for several minutes reported unexpected changes in pulse rate and blood pressure. Additional testing was stopped. In view of the sample size and experimental design for the study, no conclusion or speculation about cause and effect was offered.

However, in a more recent study,[17] HFC-134a was not eliminated from the body as rapidly. In this investigation, 4 male and 4 female volunteers were exposed to 1000, 2000, 4000, or 8000 ppm of HFC-134a for one hour. No effects were seen on pulse rate, blood pressure, EKG, pulmonary function, serum chemistry, or clinical observations. Elimination of HFC-134a from the blood was biphasic, which was probably attributable to the pronounced distribution phase of HFC-134a into the fat compartment. The duration of the distribution equilibrium indicates that steady state was not reached at all concentrations after 60 minutes. The distribution phase of the elimination half-life for HFC-134a was approximately 9 minutes for females and 10 minutes for males. The terminal phase of the elimination half-life was approximately 43 minutes for females and 42 minutes for males. Note also in this study that 8 volunteers were exposed for1 hour to HFC-134a at concentrations as high as 8000 ppm without any adverse clinical effects, a result in direct contrast to an earlier observation[15] in two subjects exposed at 4000 ppm for several minutes.

D. Developmental and Reproductive Toxicity

Two teratology studies were conducted, one in rats and one in rabbits. In the rat study,[18] groups of

pregnant rats were exposed for 6 hours/day to levels of HFC-134a of 0, 30,000, 100,000, and 300,000 ppm on days 6 to 15 gestation. No teratogenic effects were observed in this study. Some growth retardation was observed at 300,000 ppm. In the rabbit study,[7] groups of pregnant white rabbits were exposed for 6 hours/day to levels of HFC-134a of 0, 2500, 10,000, and 40,000 ppm on days 7 to 19 of gestation. No treatment-related developmental toxicity effects were observed in this study.

The effects of HFC-134a on reproductive performance, development, and maturation were studied in rats. Male and female rats (the F_0 generation) were exposed nose-only to 2500, 10,000, or 50,000 ppm for 1 hour/day for 7 days/week starting 10 and 3 weeks before mating, respectively and continuing for 18 weeks (males) and to day 21 after delivery (females) to assess its effects on fertility. Selected F_0 dams were killed on gestational day 20 to examine the ovaries and uterine contents. F_0 males were sacrificed at 18 weeks for necropsy. Selected F_1 offspring were raised to maturity. The remaining F_0 females and F_1 offspring were killed on day 21 post-delivery and necropsied. The surviving F_1 rats were mated when 70 days old. The survival and development of the resulting F_2 offspring were evaluated. Additional female rats were exposed to 1800, 9900, or 64,400 ppm HFC-134a during days 17 to 20 of gestation and days one to 21 after delivery to assess the prenatal and postnatal effects of HFC-134a exposure (pre/postnatal study). Selected F_1 pups and the F_0 females were killed on day 21 post-delivery for necropsy. The remaining F_1 pups were mated when 84 days old. On gestational day 20, the F_1 females were killed for evaluation of the uteri and ovaries. Blood samples were collected periodically from selected animals during both studies and analyzed for HFC-134a. HFC-134a accumulated in the blood of the exposed animals in a concentration dependent manner and was rapidly eliminated. The mean biological half-life determined in the fertility and pre/postnatal study was 5.8 and 7 minutes, respectively. The only exposure-related effect seen was a slight statistical decrease in body weight gain in F_0 males exposed to 10,000 or 50,000 ppm, and cumulative weight gain in 50,000 ppm F_0 males in the fertility study. HFC-134a did not affect reproductive performance or maturation in either study.[19]

E. Subacute/Subchronic Toxicity

Rats were exposed to levels of 0, 1000, 10,000, or 50,000 ppm of HFC-134a 6 hr/day, 5 days/week, for 4 weeks. Slight changes were noted in liver, kidney, and testes weights at 50,000 ppm, but there was no evidence of histopathologic changes in these or other organs. Clinical observations, hematology, blood chemistry, and body weight gains were all normal.[20]

Groups of 10 male and 10 female mice were exposed nose-only, one hour a day, for a minimum of 28 consecutive days to75,000, 150,000, or 300,000 ppm of HFC-134a. There were no deaths or clinical signs directly related to HFC-134a. There were no effects on body weights, food consumption, hematology, or blood chemistry that could be attributed to exposure. The spleen weight of the 300,000 ppm males was increased compared to controls but in the absence of associated hematological or histopathological changes this finding was considered to have no toxicological importance. Gross and histopathological examination did not reveal any changes or lesions considered to be related to exposure to HFC-134a.[21]

In a subchronic study, rats were exposed to levels of 0, 5,000, 15,000, and 50,000 ppm of HFC-134a for 6 hr/day, 5 days/week for 13 weeks. The study involved complete clinical chemistry, hematology and histopathologic evaluation of more than 40 tissues/animal. No treatment-related effects were seen at any exposure level.[7]

Groups of 15 male and 15 female mice were exposed nose-only one hour a day, 7 days/week for a minimum of 13 weeks to 100,000, 250,000, or 350,000 ppm of HFC-134a. Two deaths occurred in the 350,000 ppm group that were thought to be compound related. Clinical signs, which included tremors and ataxia, were most evident in the 350,000 ppm group and appeared only occasionally at 250,000 ppm; no clinical signs of toxicity were seen at 100,000 ppm. In addition, there were no effects on body weight, food intake, ophthalmoscopy, or hematology. Gross and histopathological examinations did not reveal any lesions attributable to the HFC-134a exposure.[21]

Groups of 4 male and 4 female dogs were exposed one hour/day, 7 days/week to 15,000, 50,000, or 150,000 ppm for 13 weeks. There were no effects on body weight, food consumption, ophthalmoscopy, respiratory function, blood pressure, ECG, hematology, blood or urine chemistry. No exposure-related histopathological changes were seen. The most consistent clinical sign was salivation in the 50,000 and 150,000 ppm groups. Head shaking and tremor was observed almost exclusively in the 150,000 ppm group.[21]

F. Chronic Toxicity

The chronic toxicity/carcinogenicity potential of HFC-134a was evaluated in rats by daily

administration of oral doses of 300 mg/kg in corn oil for one year, followed by a 1-year additional observation period. No signs of toxicity or carcinogenicity were observed.[22]

Groups of 60 male and 60 female mice or rats were exposed to HFC-134a using snout-only inhalation exposure techniques for periods of one hour daily for at least 104 weeks. HFC-134a was delivered directly from cylinders at vapor concentrations of 2,500, 15,000, and 75,000 ppm for mice and from metered-dose inhalers at vapor concentrations of 2,500, 10,000, and 50,000 ppm for rats. Evidence of absorption (HFC-134a in blood) was found at each dose level and was dose-related. Neither species suffered treatment-related effects relative to survival, clinical signs, body weights, hematology or on the type, incidence, site or severity of gross lesions. There was no effect of treatment on the type, incidence, site or severity of neoplasms in mice or rats. Additionally, there were no non-neoplastic findings related to treatment in mice. HFC-134a was not oncogenic in rats or mice under these experimental conditions.[23]

HFC-134a was administered to Beagle dogs for 1 hour/day for one year by a system for inhalation by facemask at a nominal concentration of 120,000 ppm. HFC 134a was rapidly absorbed into and cleared from the blood. There were no treatment-related clinical signs or effects on body weight, food consumption, ophthalmoscopy, heart function, respiratory rate, pulse rate, hematology, blood chemistry, urine analysis or post-mortem findings. Under these experimental conditions, HFC-134a was considered to be nontoxic.[24]

In a chronic inhalation study, groups of 85 male and 85 female rats were exposed to 2500, 10,000, and 50,000 ppm of HFC-134a six hours per day, five days a week, for two years. At the one-year interim sacrifice, no evidence of compound-related toxicity was seen. At the end of the study, when compared to controls, there were no toxicologically significant differences in survival, body weight, clinical chemistry (with exception of occasional small increases in urinary fluoride in the 10,000 an 50,000 ppm groups), hematology, or organ weights (with exception of the testes). While the rate of tumor incidence was generally comparable between the control and HFC-134a exposed groups, the incidence of Leydig cell hyperplasia and benign Leydig cell tumors was statistically significantly higher in the 50,000 ppm exposure level group compared to the controls. Mean testicular weight was also higher in the 50,000 ppm exposure group compared to the controls. There was no statistically significant excess of Leydig cell tumors, hyperplasia, or altered testis weight at the lower concentrations of HFC-134a tested. On the basis of results from this study, the no-observed effect level (NOEL) for rats exposed chronically to HFC-134a was 10,000 ppm.[7]

On the basis of the increased incidence of Leydig cell tumors at 50,000 ppm, the NOEL for rats exposed chronically to HFC-134a was 10,000 ppm. However, these Leydig cell tumors at 50,000 ppm are judged to have little biological relevance to man for several reasons. Tumor formation was limited to a single tissue in a single species, suggesting that mechanisms involved in the observed tumorigenesis are specific to male rats. Whatever the mechanism, it is epigenetic in nature since HFC-134a is not mutagenic in *in vitro* or in *in vivo* tests. Also, no other chemical that induces Leydig cell tumors in rats has been shown to be carcinogenic in humans, or even to produce adverse testes effects in humans as shown by the negative results from several epidemiology studies.[25]

In addition, several of the most well-understood mechanisms for Leydig cell tumor formation indicate that rats would be particularly sensitive to agents that induce tumors of this type,[26] although the biological understanding is not sufficient to demonstrate with complete certainty the mechanism by which HFC-134a acts. Nevertheless, the weight of evidence suggests that at HFC-134a concentrations relevant to occupational exposure, the Leydig cell tumor findings are not a suitable basis for assessing human health risk.

V. HUMAN USE AND EXPERIENCE

Since production of HFC-134a has been limited prior to 1995, no information has been reported on human use and experience. Since 1991, the AIHA OEL for HFC-134a has been 1000 ppm (8-hour time-weighted average).[27]

VI. RATIONALE

HFC-134a, a gas at room temperature, is very low in acute toxicity by the inhalation route with a 4-hour LC_{50} in rats greater than 500,000 ppm. Similar to many halocarbons and hydrocarbons, it is capable of sensitizing the Beagle dog heart to epinephrine. A 5-minute exposure to HFC-134a followed by an epinephrine challenge caused cardiac sensitization in 50% of the test dogs at 270,000 ppm; the threshold concentration for sensitization was 80,000 ppm. The major toxicological effect of HFC-134a at high concentrations (i.e., >10% v/v) is anesthesia. In subchronic (90-day) inhalation toxicity studies, only very minor CNS effects occurred in rats, mice and dogs at

concentrations > 50,000 ppm. HFC-134a was not carcinogenic in rats in an oral gavage chronic study at 300 mg/kg, or in a 2-year chronic inhalation study (1 hr/day exposures) in rats (≤50,000 ppm) and mice (≤75,000ppm). When rats were exposed to HFC-134a by inhalation for 6 hours/day, 5 days/week for 2 years, 10,000 ppm was the NOEL for the study and 50,000 ppm produced only Leydig cell hyperplasia and benign Leydig cell tumors, rodent-specific effects of little or no relevance to humans.

Relative to mutagenic potential, *in vitro* studies showed no evidence of point mutations (*Salmonella typhimurium*) or chromosome aberrations (human lymphocytes) and *in vivo* studies showed no potential for clastogenicity (cytogenetics, dominant lethal, UDS). In developmental toxicity studies, HFC-134a was not teratogenic in rats (≤300,000 ppm) or rabbits (≤40,000 ppm). In metabolism studies in both animals and humans, HFC-134a was shown to be metabolized to little (<1%) or no extent and was rapidly eliminated from the body within minutes following exposure. The preceding data suggest that a Occupational Exposure Level (OEL) of 1000 ppm is still appropriate for HFC-134a. This value should provide an adequate margin of safe-ty to protect against CNS effects (e.g., dizziness, nausea, anesthesia), cardiac sensitization and any other type of systemic injury. A 1000 ppm OEL limit has been in effect since 1991 and a review of the toxicolog-ical literature since that time supports that value.

VII. RECOMMENDED OEL

1000 ppm (4240 mg/m^3): 8-hour time-weighted average (TWA)

VIII. REFERENCES

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