Freon™ 134a

Aerosol Propellant

Toxicity Summary For 1,1,1,2-Tetrafluoroethane (HFC-134a)

Technical Information

Summary

HFC-134a has very low acute toxicity by the inhalation route with a four-hour ALC in the rat of 567,000 ppm. As with other halogenated hydrocarbons, HFC- 134a is capable of sensitizing the beagle heart to epinephrine. In a two-week subchronic inhalation study, only very minor effects occurred in rats exposed to 100,000 ppm of HFC-134a. HFC-134a is not carcinogenic and not mutagenic in the Ames test; HFC-134a did not cause inverse mutations in Salmonella typhimurium or Escherichia coli. HFC-134a is not clastogenic to human male and female lymphocytes and did not induce chromosomal aberrations in Chinese hamster lung cells. The rate of metabolism of HFC-134a was found to be the same for human, rat, and rabbit microsome preparations. A 2-year inhalation study showed the incidence of Leydig cell hyperplasia and benign Leydig cell tumors to be significantly higher in the 50,000 ppm exposure level group compared to the controls. In a developmental study in rats, embryofetal toxicity occurred at an exposure level also toxic to the dams (340,000 ppm). The NOEL was 30,000 ppm.

Common Name

Hydrofluorocarbon (HFC)-134a

Hydrofluoroalkane (HFA)-134a

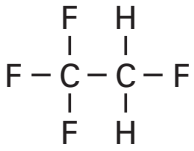
Chemical Name

Ethane, 1,1,1,2-tetrafluoro-

CAS Registry No.

811-97-2

Chemical Structure



Physical Properties

Form	Colorless gas
Molecular Weight	102.03
Boiling Point	-15 °F (–26.5 °C) at 736 mm Hg
Melting Point	-148 °F (–101 °C)
Density	1.21 g/mL (liquid under pressure)
Vapor Pressure	Gas at room temperature
Conversion Factors	1 mg/L = 238 ppm 1 ppm = 4.2 mg/m^3

Recommended Acceptable Exposure Limit (AEL)

1,000 ppm (8- and 12-hour TWA)

General Toxicity

HFC-134a, a gas at room temperature, has very low acute inhalation toxicity with a 4-hr ALC in the rat of 567,000 ppm (DuPont, 1979c). In a 2-wk inhalation study in rats, exposure to 100,000 ppm produced only an increased breathing rate. No pathological changes were noted (DuPont, 1979b). As with other halogenated hydrocarbons, HFC-134a is capable of sensitizing the beagle heart to epinephrine with a threshold at 75,000 ppm (DuPont, 1979a).

Male rats (5/group) were exposed to either air or 50,000 ppm HFC-134a 6 hr/day for 12 consecutive days. Body weights and liver weights were unaffected by the treatment. There were no differences in the rates of hepatic ß-oxidation. Total hepatic cyctochrome P-450 was not

affected. There were no biologically significant effects of exposure of rats to HFC-134a on serum cholesterol, trigylcerides, or hepatic enzymes (DuPont, 1995).

HFC-134a was administered for 1 hr daily to beagle dogs by a system for inhalation by face mask. In this 1-yr study, animals received air, air containing an additional 12% nitrogen, or air containing a nominal 12% HFC-134a for 376 or 377 days. 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 biochemistry, urine analysis, or post-mortem findings (Alexander et al., 1995).

The safety and tolerability of norflurane (1,1,1,2-tetrafluoroethane) in a pressurized metered-dose inhaler (MDI-A) was studied. A randomized, double blind, crossover, parallel group study was conducted in 16 healthy male subjects, ages 18-55 yr, who received 4 inhalations 4 times daily for 14 days or 8 inhalations 4 times daily for 14 days. No clinical significant changes occurred in blood pressure, heart rate, electrocardiograms, pulmonary function, hematology, or serum chemistry. One subject had elevated eosinophil counts throughout the study. Twenty-two adverse events related to the study propellant were recorded; the most frequent event was headache. It was concluded that the safety and tolerability of norflurane was demonstrated over 28 days of exposure in healthy subjects (Harrison et al., 1996).

Carcinogenic Potential

Groups of 80 male and 80 female rats were exposed 6 hr a day, 5 days a week, for 2 yr to 2500, 10,000, or 50,000 ppm of HFC-134a. No effects were seen on body weight, food consumption, or clinical signs of toxicity, and survival was not affected. Hematology, urinalysis, and blood chemistry were not different from controls. Histopathological examination revealed a significant increase in Leydig cell hyperplasia and a significant increase in the incidence of benign Leydig cell tumors in male rats exposed to 50,000 ppm of HFC-134a. The NOEL was 10,000 ppm (Zeneca, 1993).

Groups of 36 male and 36 female rats were administered by gavage 300 mg/kg/day of HFC-134a dissolved in corn oil, 5 days a week, for 52 weeks. When sacrificed at 125 weeks, no significant increase in the incidence of tumors of any organ was observed (Longstaff et al., 1984).

Groups of 60 male and 60 female B6C3F1 mice or Hanlbm Wistar rats were exposed to HFC-134a using snout-only inhalation exposure techniques for periods of 1 hr daily for at least 104 weeks. HFC-134a was delivered directly from cylinders at vapor concentrations of 2500, 15,000 and 75,000 ppm for mice and from metered-dose inhalers at vapor concentrations of 2500, 10,000, and 50,000 ppm for rats. Neither species suffered treatment-related effects on survival, clinical signs, body weights, hematology nor 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. There were no non-neoplastic findings related to treatment in mice. HFC-134a was considered not to be oncogenic (Alexander and Libretto, 1995).

Mutagenic Potential

HFC-134a was not mutagenic in the Ames Salmonella assay or in the yeast Saccharomyces cerevisiae, either in the presence or absence of an activation system (Litton, 1976). Additionally, HFC-134a was negative in a cell transformation assay with baby hamster kidney fibroblasts (Longstaff et al., 1984). HFC-134a was also negative in the UDS assay in cultured rat hepatocytes (ICI, 1990a), negative in a mouse micronucleus assay (Hoechst, 1989), and was not clastogenic to cultured human lymphocytes (ICI, 1990b).

Developmental Toxicity

Groups of pregnant rats were exposed to 30,000, 100,000, or 300,000 ppm of HFC- 134a for 6 hr a day on days 6-15 of gestation. Signs of maternal toxicity included reduced response to sound, reduced food consumption, and reduced body weight gain in the rats exposed to 100,000 and 300,000 ppm. Embryotoxicity occurred only in the 300,000 ppm group and was expressed as a significant decrease in fetal body weight and an increase in variations. No teratogenic response was found (DuPont, 1981).

Groups of pregnant rabbits were exposed to 2500, 10,000, or 40,000 ppm of HFC- 134a for 6 hr a day on days 7-19 of gestation. Maternal toxicity, characterized by reduced body weight gain and reduced food consumption, was seen in the 10,000 and 40,000 ppm groups. No embryo/feto toxicity was seen in any of the HFC-134a exposed groups (ICI, 1989).

Reproductive Toxicity

HFC-134a was administered to AHA rats by snout-only inhalation for 1 hour daily to assess the effects of treatment on reproduction and development. In the fertility study, rats were exposed to atmospheres of 2500, 10,000 or 50,000 ppm HFC-134a throughout gametogenesis, mating, pregnancy, and lactation. In a peri- and post-natal study, rats were exposed to HFC-134a from days 17 to 20 of pregnancy and days 1 to 21 post-partum to atmospheres of 1800, 9900, or 64,400 ppm. The only treatment-related effect was a slight reduction in body weight gain of males of the treated parental generation at 50,000 ppm (fertility study). In neither study, were there any adverse effects of HFC-134a on the reproductive performance of treated animals or on the development, maturation, or reproductive performance of up to two successive generations (Alexander et al., 1996).

Male Sprague-Dawley rats (25/group) were exposed 6 hours/day to atmospheres containing 0, 10,000, 30,000, or 100,000 ppm. Males were treated for 11 weeks prior to mating, through to termination after approximately 18 weeks of treatment. The first 9 weeks of treatment were nose-only; thereafter, the animals were exposed by a whole-body system. Assessments included LH levels, androgen release from the testes, and biosynthesis. At 100,000 ppm, there was a small increase in testosterone secretion and biosynthesis. At this level, there was also a concomitant rise in progesterone secretion, when the testis was incubated with human chorionic gonadotropin, without any qualitative change in androgen biosynthesis. There were no changes observed at 10,000 or 30,000 ppm (Inveresk Research International, 1994).

No effects on reproduction were seen in groups of male mice exposed 6 hours a day for 5 days to 1000, 10,000, or 50,000 ppm of HFC-134a and then mated with unexposed female mice (ICI, 1979).

Metabolism

In a metabolism study, rats were exposed to 10,000 ppm of radio-labeled HFC-134a for one hour. Total radioactivity in the expired air, urine, and feces amounted to approximately 1% of the inhaled dose. Of this, approximately two-thirds was exhaled within one hour of the cessation of exposure as unchanged HFC-134a. Carbon monoxide and trifluoroacetic acid were the only metabolites detected (ICI, 1991).

The potential oxidative metabolite of HFC-134a, trifluoroacetic acid (TFA), was studied in human urine following inhalation dosing with HFC-134a. TFA is the only fluorinated species observed in the urine samples and only at very low levels, indicating that the oxidative route of metabolism can occur in vivo in man; but, this metabolism is minimal in terms of percentage of administered dose (Monte et al., 1994).

Male rats were exposed to atmospheres of 10,000, 25,000, or 50,000 ppm HFC-134a for up to 6 hours. Urinary metabolites were trifluoroacetic acid (TFA), trifluoroacetaldehyde hydrate (TFAA-H2O), urea adduct (TFAA-urea), trifluoroethanol (TFE), and ß-glucuronide (TFE-glu). Metabolites in the plasma and testes immediately following exposure were TFA, TFA-H2O, and TFE. TFA was the major metabolite at all exposure levels, then TFAA (TFAA-H2O + TFAA-urea), and finally TFE (TFE + TFE-glu). The rate of metabolic excretion into urine was TFAA>TFE>TFA. Total HFC-134a metabolized was 454, 891, and 962 nmol/250 g rat at 10,000, 25,000, and 50,000 ppm, respectively (Green et al., 1997).

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