

1,1,2,2-tetrafluoroethane (HFC-134) (2018)

I. IDENTIFICATION (Chemours, 2017)

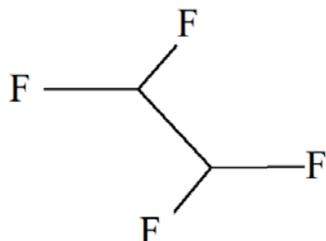
Chemical Name: 1,1,2,2-tetrafluoroethane

Synonyms: HFC-134

CAS Number: 359-35-3

Molecular Formula: C₂H₂F₄

Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES (Chemours, 2017; Chilworth Technology, 2016; Envigo CRS Limited, 2016a, 2016b)

Molecular Weight: 102.03 g/mol

Physical State and Appearance: Gas, colorless with a slight ether-like odor

Conversion Factors: 1 mg/m³ = 0.240 ppm (25°C (77°F) and 760 mm Hg); 1 ppm = 4.2 mg/m³ (25°C (77°F) and 760 mm Hg)

Melting Point: < -20°C (-4°F)

Boiling Point: -18.85°C (-1.93°F)

Vapor Pressure: 524.2 kPa (3932 torr; 73 psig) @ 25°C (77°F)

Vapor Density: 0.024 g/cm³

Flammability Limits: Not flammable

Flash Point: Not applicable

Autoignition Temperature: Not applicable

Specific Gravity: 1.302 g/cm³ @ 25°C (77°F)

Log K_{ow}: 2.5 at 40°C (104 °F)

Water Solubility: 6.5 g/L at 20°C (68 °F) and 760 mmHg

Stability: Stable under recommended storage conditions

Reactivity and Incompatibilities: Decomposes on heating. Not compatible with alkali metals alkaline earth metals, powdered metals, powdered metal salts.

III. USES (Chemours, 2017)

HFC-134 is used as a foam expansion agent and heat transfer fluid.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Lethality Data

Species	Route, Duration	LC ₅₀ (ppm)
Rat	Inhalation, 4-hr	> 244,000 (Haskell Laboratory, 2009a)
Rat	Inhalation, 4-hr	> 460,000 (Haskell Laboratory, 1991a)

2. Eye Irritation

The substance is a gas and has not been tested for eye irritation. However, in whole-body inhalation toxicity studies in rats with exposures up to 24.4% in air for 4 hours (Haskell Laboratory, 2009a) or up to 5% in air, 6-hours/day for 15 consecutive days, no signs of ocular irritation were observed (WIL Research Lab, 2015), including ophthalmological findings in long-term repeat dose studies (Haskell Laboratory, 1994).

3. Skin Absorption

The substance is a gas and has not been tested for dermal toxicity.

4. Skin Irritation

The substance is a gas and has not been tested for skin irritation. However, in whole-body inhalation toxicity studies in rats with exposures up to 24.4% in air for 4 hours (Haskell Laboratory, 2009a) or up to 5% in air, 6-hours/day for 15 consecutive days, no signs of dermal irritation were observed during clinical observations.

5. Skin Sensitization

The substance is a gas and has not been tested for skin sensitization.

6. Inhalation Toxicity

Two acute inhalation toxicity studies were conducted with HFC-134. No lethality was observed at any exposure concentration tested up to 460,000 ppm HFC-134 over a period of 4 hours. At exposure concentrations of 200,000 ppm and higher, the rats had no startle response to sound; 120,000 ppm is considered a NOAEL for anesthetic properties. The acute inhalation studies are described in detail below.

A GLP acute inhalation study was conducted according to OECD test guideline 403. Groups of 5 male and 5 female CrI:CD[®](SD) rats were exposed to a mean vapor concentration of 244,000 ppm HFC-134 via whole-body inhalation exposure for a single, 4-hour period. No deaths occurred during the exposure or the 14-day recovery period. The rats quickly became inactive, and had no startle response throughout the 4-hour exposure. Approximately 15 minutes after the exposure ended, the rats appeared to recover. Seven of 10 rats lost from 0.3% to 3.7% of their initial body weight the morning after the exposure. One female rat continued to display slight (1.7 to 2.3%) body weight losses on post exposure days 2 and 3 and then displayed normal weight gain throughout the remainder of the 14-day recovery period. There were no other body weight losses or adverse clinical signs of toxicity observed in any rats in this study. No test substance-related gross lesions were found in the study. Under the conditions of this study, the 4-hour LC₅₀ was greater than 244,000 ppm (Haskell Laboratory, 2009a).

In a non-GLP, non-guideline acute inhalation toxicity screen, groups of 6 male CrI:CD[®]BR rats were exposed to 120,000, 200,000, 380,000, or 460,000 ppm HFC-134 via nose-only inhalation exposure for a single, 4-hour period. No deaths occurred during the exposure or the 14-day recovery period. Clinical signs of toxicity observed during exposures to 380,000

and 460,000 ppm HFC-134 included rapid breathing and no response to a tail pinch or to tapping on the exposure chamber. In addition, rats exposed to 200,000 ppm HFC-134 showed no response to tapping on the chamber. In the 460,000-ppm exposure group, 2 of 6 rats exhibited nasal discharge and 4 of 6 rats exhibited wet fur immediately following exposure; however, these signs are considered normal in restrained rats. All rats had slight to moderate body weight losses 1 day following exposure, losing between 1% and 6% of initial body weight. By 2 days following exposure, all rats had resumed weight gains and, except for some transient body weight losses in individual rats, exhibited a pattern of normal body weight gain throughout the remainder of the recovery period. Under the conditions of this study, the approximate lethal concentration (ALC) of HFC-134 was greater than 460,000 ppm, the highest concentration tested (Haskell Laboratory, 1991a).

A GLP cardiac sensitization study was conducted using a titrated epinephrine challenge study design. One group of 6 male Beagle dogs was exposed via muzzle-only inhalation exposure to 50,000, 75,000, or 100,000 ppm HFC-134. Each animal had a minimum of 24 hours of separation between exposures. Each dog served as its own control. Baseline responses to epinephrine challenge doses were collected for each animal prior to exposure to the test substance and a predetermined challenge dose was established during this baseline period. An individual response (up to approximately 10 unifocal ectopic beats) to adrenaline alone was targeted up to a maximum of 12 µg/kg. The dogs were then individually dosed with the first pre-determined dose of adrenaline. Five minutes later, they were exposed to the test substance for a total of approximately 10 minutes. After the first five minutes of exposure, each dog received a challenge injection of epinephrine. During the next five minutes of exposure, the dogs were monitored for the development of a cardiac arrhythmia. There were no arrhythmias at 75,000 ppm, and two of the 6 dogs displayed multifocal ventricular ectopic activity lasting approximately 2 seconds followed by several ectopic beats at 100,000 ppm. Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for cardiac sensitization was 75,000 ppm and the lowest-observed-adverse-effect level (LOAEL) was 100,000 (Huntingdon Research Centre, 1994).

B. Subacute Toxicity

1. Inhalation

A 28-day GLP inhalation toxicity study was conducted using a method that was similar to and generally aligned with OECD

test guideline 412. Four groups of male and female CrI:CD[®]BR rats (10/sex) were exposed to 0, 2000, 10,000, or 50,000 ppm HFC-134 via whole-body inhalation for 6 hours per day, 5 days per week for a 4-week period. All animals survived until the termination of the study and were sacrificed by design.

Transient and non-dose response related body weight changes were observed throughout the exposure period. No statistically significant, test substance-related adverse effects were observed in clinical or neurobehavioral observations nor on blood or urine clinical chemistry parameters, hematology parameters, organ weights, or macroscopic and microscopic pathology assessments. No adverse effects were noted in the reproductive systems of either males or females and no adverse exposure-related macroscopic, weight, or histopathological changes were noted in the respective reproductive organs. Under the conditions of this study, the NOAEL for HFC-134 in male and female rats was 50,000 ppm (Haskell Laboratory, 1994).

2. Oral

No data available. Substance is a gas.

C. Subchronic Toxicity

1. Inhalation

No subchronic toxicity data are available for HFC-134, however, a robust toxicity database exists for a similar substance, 1,1,1,2-tetrafluoroethane (CAS 811-97-2; HFC-134a) which includes repeated dose inhalation toxicity. As noted in Appendix 1, HFC-134 and HFC-134a exhibit similar physical/chemical characteristics and a similar toxicology profile. As such, toxicology data for HFC-134a will be used to provide information for those endpoints for which no data is available for HFC-134. Several repeated dose inhalation toxicity studies have been conducted with HFC-134a including a GLP 90-day subchronic and 2-year carcinogenicity studies (ECETOC, 2006).

A 90-day GLP inhalation toxicity study was conducted with HFC-134a using a method that was similar to and generally aligned with OECD test guideline 413 wherein four groups of male and female Alpk:APfSD (Wistar-derived) rats (20/sex) were exposed via whole-body inhalation to 0, 2000, 10,000, or 50,000 ppm HFC-134a. The animals were exposed for 6 hours/day, 5 days/week over a 13-week period. Ten males and 10 females from each group were sacrificed in week 14 following their last exposure, and the remaining animals were sacrificed in week 18 following a 4-week recovery phase. There were no mortalities and all animals remained in good clinical condition throughout the study. Transient and non-dose

response related changes in body weight and food consumption were observed throughout the exposure period. There were no test substance-related adverse findings in ophthalmology, hematology, blood or urine clinical chemistry, urinalysis, organ weight, or macroscopic parameters. In addition, microscopic examination did not reveal any histopathological changes attributable to HFC-134a exposure. Under the conditions of this study, the NOAEL was 50,000 ppm (ICI Central Toxicology Laboratory, 1992a)

2. Oral

No data available. Substance is a gas.

D. Chronic Toxicity/Carcinogenicity

No chronic toxicity studies have been conducted with HFC-134.

A two-year inhalation toxicity study was conducted with HFC-134a according to OECD test guideline 453 wherein four groups of male and female Alpk:APfSD (Wistar-derived) rats (85/sex) were exposed 6 hours a day, 5 days a week, to 0, 2500, 10,000, or 50,000 ppm HFC-134a via whole-body inhalation. Ten rats of each sex from each exposure group were designated for interim sacrifice after 52 weeks with the remainder continuing to terminal sacrifice after 104 weeks. No adverse effects were observed on body weight, food consumption, ophthalmological, or clinical signs of toxicity, or survival. No test substance-related adverse effects on hematology, urinalysis, urine chemistry, or blood chemistry were observed. There were no adverse treatment-related macroscopic or microscopic findings after 52 weeks of exposure (interim sacrifice). After the full two years of exposure, 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. These findings occurred late in life and were not associated with increased mortality. Additional studies have since been conducted (ECETOC, 2006). suggesting a similar mechanism to other compounds which explains why Leydig cell tumors are commonly found in rats and are not considered to be relevant for humans (Cook et al., 1999; Steinbach, 2015). Under the conditions of this study, the NOAEL was 10,000 ppm in male rats and 50,000 ppm in female rats (Zeneca Central Toxicology Laboratory, 1993).

E. Reproductive/Developmental Toxicity

A GLP prenatal developmental study was conducted according to OECD test guideline 414 wherein five groups of 22 time-mated nulliparous female CrI:CD[®](SD) rats were exposed to 0,

1000, 5000, 10,000 and 50,000 ppm HFC-134 via whole-body inhalation for 6 hours per day beginning on gestation day (GD) 6 up to and including GD 20. There were no adverse test substance-related effects of the test substance on maternal animals, on intrauterine growth or survival, or on fetal morphology at any exposure concentration. Under the conditions of this study, the NOAEL for maternal and fetal effects was 50,000 ppm (WIL Research Laboratories Inc., 2015).

A prenatal developmental toxicity screening study was conducted wherein groups of 7 pregnant CrI:CD[®]BR rats were exposed to 0, 2000, 10,000, or 50,000 ppm HFC-134 via whole-body inhalation for 6 hours per day beginning on gestation day (GD) 7 up to and including GD 16. During the in-life portion of the study, body weights, food consumption, and clinical observations data were collected. On GD 22, each female was euthanized and subjected to a gross examination of the thoracic and abdominal viscera. Implantation types (live and dead fetuses, and resorptions) and their relative positions were recorded. Live fetuses were weighed, sexed, and examined for external alterations. No test substance-related statistically significant adverse effects on maternal or fetal body weights or external fetal malformations were observed at any exposure concentration. Additionally, there were no statistically significant test substance-related effects on intrauterine survival at any exposure concentration. Under the experimental conditions employed in this study, the NOAEL for maternal and fetal effects was 50,000 ppm (Haskell Laboratory, 2009b).

Reproductive toxicity has not been evaluated for HFC-134 but no effects were observed on the reproductive organs in the 28-day inhalation toxicity study (Haskell Laboratory, 1994).

Data for the similar substance, HFC-134a (see Appendix 1) can be used to further support the evaluation of HFC-134. In a fertility study to assess the effects of treatment on reproduction and development, male and female AHA (a Glaxo strain having both Sprague-Dawley and Wistar origins) rats were exposed to atmospheres of 2500, 10,000 or 50,000 ppm HFC-134a via nose-only inhalation for 1 hour daily throughout gametogenesis, mating, pregnancy and lactation. Exposures were for 10 and 3 weeks prior to mating for the males and females, respectively. Exposures continued during the mating period. The males were further exposed until week 18 of exposure and then euthanized. Fourteen of the 30 pregnant F0 females were exposed until day 19 post coitum and terminated the next day (day 20 post coitum) for examination of their uterine contents and ovaries. The remaining F0 females were further exposed until day 20 post coitum, at which time exposures were suspended to allow

parturition to occur. Exposure of these F0 females recommenced at the same concentrations on day 1 post-partum until day 21 post-partum, at which time the dams were terminated and the male and female F1 pups separated. The only treatment-related effect was a slight reduction in body weight gain of males of the treated parental generation at 50,000 ppm. There were no adverse effects of HFC-134a on the reproductive performance, development, or maturation of treated animals up to two successive generations. The NOAEL for reproductive and developmental toxicity was 50,000 ppm, the highest exposure level tested (Alexander et al., 1996).

In a dominant lethal assay, four groups of 15 male CD1 mice were exposed via whole-body inhalation to 1000, 10,000 or 50,000 ppm HFC-134a for 6 hours/day for 5 consecutive days. A group of 30 male CD1 mice were exposed to air only and served as the negative control group and two groups of 15 male CD1 mice were exposed orally to one of two positive control substances. After the last exposure, each male was housed with 2 virgin females for 4 consecutive nights. Further matings with new females were conducted at weekly intervals for a total of 8 times. Fifteen days after being paired with the males (about 75% of the way through gestation), the females were euthanized and their uteri were examined for numbers of live implantations, early deaths, and late deaths. There were no adverse clinical observations noted at any time during the exposure period. The study indicated that HFC 134a did not affect male fertility or cause mutagenic effects through sperm (ICI Central Toxicology Laboratory, 1979)

F. Genotoxicity/Mutagenicity

1. *In vitro*

A GLP Bacterial Reverse Mutation Assay (Ames) assay with HFC-134 was conducted according to OECD test guideline 471 using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA* both in the presence and absence of an Aroclor-induced rat liver S9 activation system. The assay was performed in two phases, using the desiccator method, a modification of the plate incorporation method. The first phase, the initial toxicity-mutation assay, was used to establish the dose-range for the confirmatory mutagenicity assay and to provide a preliminary mutagenicity evaluation. The second phase, the confirmatory mutagenicity assay, was used to evaluate and confirm the mutagenic potential of the test substance. The dose levels tested in the initial toxicity-mutation assay were 1.4, 2.8, 6.9, 14, 21, 28 and 37 mmol/L. The test system was exposed to the test substance for 24±1 hours. No positive mutagenic responses

were observed with any of the tester strains in either the presence or absence of S9 activation. Neither precipitate nor toxicity was observed. In the confirmatory mutagenicity assay, the test system was exposed to the test substance for 48 to 72 hours. The exposure period was increased based on the lack of toxicity observed in the initial toxicity-mutation assay. The dose levels tested were 6.9, 14, 21, 28 and 37 mmol/L. No positive mutagenic responses were observed with any of the tester strains in either the presence or absence of S9 activation. No precipitate was observed. Toxicity was observed beginning at 28 or at 37 mmol/L. Under the conditions of this study, HFC-134 exhibited no mutagenic responses in either the presence or absence of metabolic activation (BioReliance Corporation, 2015).

A second (earlier) GLP Ames assay with HFC-134 was conducted according to OECD test guideline 471 using *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535 both in the presence and absence of an Aroclor-induced rat liver S9 activation system. The assay was conducted via the plate incorporation method where the test system was exposed to HFC-134 in glass exposure chambers. Cell cultures were exposed to atmospheres up to 100% HFC-134. Under the conditions of this study, HFC-134 exhibited no mutagenic responses in either the presence or absence of metabolic activation (Haskell Laboratory, 1991c).

A GLP *in vitro* mammalian chromosome aberration assay with HFC-134 was conducted according to OECD test guideline 473 using cultured human peripheral blood lymphocytes both in the presence or absence of an Aroclor-induced rat liver S9 activation system. Human peripheral blood lymphocytes were stimulated into division in culture then treated with HFC-134 in glass exposure chambers. Selection of appropriate test substance exposure concentrations and harvest times for the chromosome aberration trials were based upon a cytotoxicity trial which assessed cell-cycle delay. Two separate chromosome aberration trials were conducted where cell cultures were exposed to atmospheres up to 100% HFC-134 and where appropriate concurrent vehicle and positive controls were included. Metaphases from treated cultures (together with appropriate vehicle and selected positive control cultures) were subjected to detailed examination for the presence of chromosomal aberrations using light microscopy. No statistically significant increases in the incidence of aberrant metaphases in either the absence or presence of S9 mix were observed in either chromosome aberration trial. Mitotic indices were not appreciably depressed at any concentration of HFC-134 tested. Under the conditions of this study, HFC-134 was not

clastogenic in either the presence or absence of metabolic activation (Haskell Laboratory, 1991b).

A GLP *in vitro* mammalian gene mutation assay with HFC-134 was conducted according to OECD test guideline 476 using cultured Chinese hamster ovary cells both in the presence or absence of an Aroclor-induced rat liver S9 activation system. In this assay, HFC-134 was evaluated for its ability to induce forward mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus. The substance was evaluated in a preliminary dose range-finding assay at concentrations of 0.391, 0.781, 1.56, 3.13, 6.25, 12.5, 25.0, 50.0 and 100% (v/v, in air) with and without S9 (the highest concentration evaluated was the limit dose for this assay). No visible precipitate was observed by the end of treatment, and the test substance did not have an adverse impact on the pH of the cultures. Based on these results, HFC-134 was evaluated in the definitive mutagenicity assay at concentrations of 6.25, 12.5, 25.0, 50.0, 75.0 and 100% (v/v, in air) with and without S9. No significant increases in mutant frequency, as compared to the concurrent vehicle controls, were observed at any concentration evaluated with or without S9. In contrast, the positive controls induced a significant increase in mutant frequency. Under the conditions of this study, HFC-134 was not mutagenic in either the presence or absence of metabolic activation (BioReliance Corporation, 2014).

2. *In vivo*

No data available for HFC-134, the following *in vivo* genotoxicity data are available for HFC-134a

A GLP mouse micronucleus assay was conducted according to EPA guideline "In vivo mammalian bone marrow cytogenetic test: micronucleus assay. HG-Chromo-Micronuc, August 1982". Following a single 6-hour exposure to 0, 50,000, 150,000, or 500,000 ppm HFC-134a via whole-body inhalation in groups of male and female NMRI mice (5/sex). At 24, 48, or 72 hours after the exposure period, the animals were euthanized and bone marrow erythrocytes samples were prepared for each animal, as well as from negative and positive control animals. The incidence of micronucleated polychromatic erythrocytes in the bone marrow was not statistically significantly different from controls. The ratio of poly- to normo-chromatic cells remained unaffected by the treatment with HFC 134a. Under the conditions of this study, HFC-134a did not induce micronuclei in bone marrow cells of the NMRI mouse and was concluded not to be mutagenic (Hoechst Aktiengesellschaft, 1989).

A GLP Unscheduled DNA Synthesis Test was conducted according to OECD test guideline 486 wherein groups of 4-5 male Alpk/APfSD Wistar-derived rats were exposed for a single 6-hour period to 0, 10,000, 50,000, or 100,000 ppm HFC-134a via whole-body inhalation. Immediately following the exposure, hepatocytes were prepared from the rats. No unscheduled DNA synthesis was observed in the cells at any concentration analyzed up to and including 100,000 ppm HFC-134a. Under the conditions of this study, HFC-134a was negative for the induction of DNA repair (ICI Central Toxicology Laboratory, 1992b).

G. Metabolism/Pharmacokinetics

No data are available for HFC-134. A similar fluorocarbon, HFC-134a is rapidly absorbed and equilibrates with tissues following inhalation exposure. HFC-134a is quickly eliminated from the blood via expired air with a half-life of a few minutes.

V. HUMAN USE AND EXPERIENCE

No data available for HFC-134 as it is a new chemical in commerce. However, HFC-134a is used as a propellant for pressurized metered dose inhalers (pMDI) used by asthmatics.

VI. RATIONALE

HFC-134 has very low acute inhalation toxicity, did not induce cardiac sensitization at concentrations up to 75,000 ppm, was not genotoxic *in vitro* and did not cause developmental or maternal toxicity. In the 4-week inhalation toxicity study no toxicity was observed and the NOAEL was 50,000 ppm, the highest exposure level tested (Haskell Laboratory, 1994). Based on data for a similar material (HFC-134a), HFC-134 is not expected to be extensively metabolized or cause genetic toxicity or carcinogenicity.

The WEEL for HFC-134 is based primarily on the NOAEL from the subacute 4-week inhalation toxicity study in rats. The point of departure is 50,000 ppm, the highest concentration tested in this study (Haskell Laboratory, 1994). This is also the NOAEL and the highest exposure level tested in the developmental toxicity study. The subacute inhalation NOAEL was adjusted to account for inter-individual variability, subacute to chronic duration, animal to human extrapolation, daily duration of exposure, and residual uncertainty. In addition, the lack of adverse effects noted in the toxicology studies for HFC-134a was considered. The WEEL value of 1000 ppm is expected to provide a significant margin of safety against the

production of any potential adverse health effects in workers exposed to HFC-134.

VII. RECOMMENDED WEEL GUIDE

8-Hour Time-Weighted Average (TWA): 1000 ppm

VII. REFERENCES

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