# 2,3,3,3-Tetrafluoropropene

**Document History**
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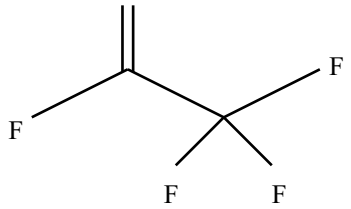
## I. IDENTIFICATION

Chemical Name: 2,3,3,3-tetrafluoropropene
Synonyms: HFO-1234yf
CAS Number: 754-12-1
UN/NA Number: 3161
Molecular Formula: C3H2F4
Structural Formula:




## II. CHEMICAL AND PHYSICAL PROPERTIES[1]

Physical State and Appearance: colorless gas
Odor Description: Slight
Molecular Weight: 114
Conversion Factor: 1 mg/m$^3$ = 0. 214 ppm (20°C and 760 mm Hg)
1 ppm = 4.66 mg/m$^3$
Melting Point: -152°C
Boiling Point: -30°C (-16°F) at 760 mm Hg
Vapor Pressure: 88 psia @ 21.1°C (70°F)
Vapor Density: 4.0 (relative to air = 1)
Saturated Vapor Concentration: not applicable; substance is a gas
Flammability Limits: 6.5–12.3% in air
Flash Point: not applicable; substance is a gas
Autoignition Temperature: 405°C (761°F)
Specific Gravity: 1.1 at 25°C (77°F) as compressed liquid
Solubility in Water: 198 mg/L at 25°C (77°F)
Stability: Normally stable; Avoid sources of ignition such as sparks, hot spots, welding flames and lighted cigarettes which may yield toxic and/or corrosive decomposition products.
Reactivity and Incompatibilities: Avoid contact with strong oxidizing agents or finely divided magnesium, aluminum, or other alloys.

## III. USES[1]

This substance is being developed as a low global-warming-potential refrigerant for mobile air conditioning. The material is currently used in the evaluation of mobile air conditioning systems, and thus, potential exposures are to employees in production facilities, testing laboratories and automobile manufacturing facilities.

## IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

Substance is a gas and has not been tested for toxicity by the oral route.

2. *Eye Irritation*

Substance is a gas and has not been tested for primary eye irritation. However, in a 4-week and a 13-week inhalation toxicity study with exposures up to 5% in air, 6-hours/day, 5 days/week, no signs of eye irritation were seen.[2,3]

3. *Skin Absorption*

No data available.

4. *Skin Irritation*

No primary dermal exposure studies were identified. Contact exposure to the liquid form of refrigerant gases can lead to rapid cooling of the skin with risk of frostbite.[4] High pressure liquid injection injury with subcutaneous freezing are possible near pinhole leaks of pressurized systems.

5. *Skin Sensitization*

No data available.

6. *Inhalation Toxicity*

a. A 4-hr acute inhalation study was conducted with 2 male and 2 female CD-1®

mice at an exposure concentration of 101,850 ppm. Post exposure observation time was 14 days. There was no mortality and no clinical or visible signs of toxicity. Gross necropsy observations did not show any abnormal findings. This was a non-GLP study.[5]

b. In a GLP study, two groups of 5 male and 5 female Sprague Dawley rats were exposed nose only to target concentrations of either 201,600 ppm or 405,800 ppm for 4 hours (oxygen added). The animals were held for a 14-day observation period. There were no clinical or visible signs of toxicity except for decreased breathing rates reported for 2 males and 2 females at 201,600 ppm and in all animals exposed to 405,800 ppm. Body weight gain was normal. There was no mortality and gross necropsy observations were unremarkable.[6]

c. In a study to evaluate cardiac sensitization potential, a group of 6 beagle dogs were exposed to concentrations of 20,000, 40,000 or 120,000 ppm of both HFO-1234yf. A total of six exposures were conducted, with at least a 2-day recovery period between exposures. Initially, a determination was made for the maximum concentration of epinephrine that would not cause cardiac arrhythmia (each dog served as its own control). Animals were administered a pre-exposure dose of epinephrine as a bolus injection approximately 5 minutes prior to exposure to the test material. The dogs were then exposed to the test compound for a total of 10 minutes. After the first five minutes of exposure, each dog received a challenge-dose injection of epinephrine at the pre-determined maximum sub-arrhythmia dose. During the next five minutes of exposure, the dogs were monitored for the development of cardiac arrhythmia. There were no arrhythmias, nor other signs of toxicity seen in any of these dogs immediately following exposure. Thus, it was concluded that the No-Observed-Effect-Level (NOEL) for HFO 1234yf was 120,000 ppm in this study. Neither material caused cardiac sensitization to epinephrine.[7]

B. Subacute Toxicity

In another GLP study, groups of 5 male and 5 female Sprague-Dawley rats were exposed, nose only, to HFO-1234yf at concentrations of 0 (control), 5000, 20,000 or 50,000 ppm 6 hours/day, 5 days/week for 2 weeks. There were no observed clinical or visible signs of toxicity, adverse effects on body weight gain, food consumption, or treatment-related changes in white blood cell parameters. While clinical chemistry analysis showed an increase in calcium levels at the mid- and high-exposure concentrations, these findings were not considered adverse. No abnormalities were observed in the analysis of organ weights, or macroscopic or microscopic examination of tissues, including a complete examination of tissues from the respiratory tract. The authors concluded that the No-Observed-Adverse-Effect-Level (NOAEL) for a 2-week exposure to HFO-1234yf was at least 50,000 ppm.[8]

C. Subchronic Toxicity

In a GLP study, groups of male and female Sprague-Dawley rats were exposed, nose-only, to HFO-1234yf at concentrations of 0 (control), 5000, 20,000 or 50,000 ppm for 6 hours/day, 5 days/week for 4 weeks. Five males and 5 females were used for the basic 4-week study, an additional 5 males and 5 females were used in the control and high concentration exposure groups for the 2-week recovery period, and additional male rats were used at all exposure concentrations for a unscheduled DNA synthesis study. There were no adverse effects on body weight gain, food consumption, or treatment-related changes in complete bood count parameters. While clinical chemistry analysis showed some variations, these variations did not occur in an exposure-related pattern, and thus, they were not considered treatment related. No adverse effects were observed relative to organ weights, or macroscopic or microscopic examination of tissues, including a complete examination of tissues from the respiratory tract. The authors concluded that the NOAEL for a 4-week exposure to HFO-1234yf was at least 50,000 ppm.[9]

In another GLP study, groups of 10 male and 10 female Sprague Dawley rats were exposed, nose-only, to HFO-1234yf at concentrations of 0 (control), 5000, 15,000 or 50,000 ppm for 6 hours/day, 5 days/week during a 14-week period. There were no observed clinical or visible signs of toxicity, adverse effects relative to body weight gain, food consumption, or complete blood count parameters. While clinical chemistry analysis showed some variations, these variations did not occur in an exposure-related pattern, and thus, they were not considered treatment related. There were no adverse findings in the analysis of organ weights, or macroscopic or microscopic examination of tis-

sues, including a complete examination of tissues from the respiratory tract. The authors concluded that the NOAEL for a 14-week exposure to HFO-1234yf was at least 50,000 ppm.[3]

D. Chronic Toxicity/Carcinogenicity

Gene expression changes were used to assess the carcinogenic potential of HFO-1234yf following exposure of female B6C3F1 mice and male F344 rats to concentrations of 10,000 or 50,000 ppm for 6 hrs/day, 5 days/wk for 13 weeks. The assessment was based on a comparison of the responses seen with HFO-1234yf to results from both positive (tetrafluoroethylene, 1-amino-2,4-dibromoanthraquinone, and Tris(2,3-dibromopropyl) phosphate) and negative (trichlorofluoromethane, iodoform, tetrafluoroethane and N-(1-naphthyl) ethylenediamine dihydrochloride) controls. Vehicle controls were also included. In addition, histopathological examination of selected tissues was conducted. No treatment-related histopathological lesions were observed, and statistical classification analysis predicted HFO-1234yf to be noncarcinogenic in both female mouse liver and male rat kidney. A variety of gene expression changes were observed in the male rat kidney without a dose response and therefore the significance is unclear.[10]

E. Reproductive/Developmental Toxicity

Groups of 25 pregnant Sprague Dawley rats were exposed, nose-only, to HFO-1234yf at concentrations of 0 (control), 5000, 20,000 or 50,000 ppm for 6 hrs/day on Days 6–19 of gestation. During the course of the study, there were variations in maternal body weight, body-weight gain and food consumption. However, these differences did not follow an exposure-related pattern and were ultimately viewed by the authors over the entire period of gestation as not representing a treatment-related effect. There were no differences in the number of implantation sites, pre- and post-implantation losses, live and dead fetuses, resorptions, or ratio of male to female pups between the test groups and the controls. No treatment-related external or visceral abnormalities were observed. There was a high frequency of skeletal variations and delayed ossification in both treated groups and controls. There were apparent concentration effects in litter incidence for some skeletal regions, but not others. The overall pattern of delayed ossification was not considered by the authors to represent a treatment-related adverse effect. Since the usual pattern for delayed ossification in mammalian development is that it resolves as the pup matures and these types of effects are often secondary to maternal stress, the delayed ossification was not considered by the authors to be an adverse developmental effect.[11,12] The authors concluded "no adverse maternal and developmental effects were observed in rats after inhalation for 6 hours with HFO-1234yf during GD 6–19 at a concentration up to 50,000 ppm."[13]

In a pilot rabbit developmental toxicity study, groups of 12 pregnant rabbits were scheduled to be exposed to concentrations of 0 (control) 2500, 10,000 or 50,000 ppm 6 hrs/day, daily from Day 6–28 of gestation. By Day 14 of gestation, 9 of 12 rabbits had died in the 50,000 ppm exposure group and subsequent exposures at this concentration were discontinued. By Day 21 of gestation, 5 of 12 rabbits had died in the 10,000 ppm exposure concentration group and subsequent exposures at this concentration were also discontinued. There were no deaths or apparent adverse effects at 2500 ppm in the dams. Evaluation of the pups from the surviving does in all exposure groups did not reveal any evidence of developmental toxicity or effects on survival.[13]

Following completion of the pilot study, an OECD 414 Guideline study was conducted using groups of 24 pregnant rabbits exposed to concentrations of 0 (control), 2500, 4000, 5500 and 7500 ppm. Again the exposures were 6 hours/day, from Days 6–28 of gestation. The full series of exposures were conducted on all groups. Six of 24 rabbits died in the 7500 ppm exposure concentration group and 2 of 24 died in the 5500 ppm exposure concentration group. There were no deaths in the 4000 or 2500 ppm groups or in the controls. No other indications of maternal toxicity were observed, and no changes in clinical observations, (e.g., mean body weight gain deficits and decreases in food consumption), as well as maternal organ histopathology for the 2500 and 4000 ppm exposure groups. There were no differences in intrauterine growth and survival and external fetal morphology were not affected by the maternal test substance exposures. There were no significant differences in survival of pups or litter size in any treatment group. External and skeletal evaluation of all pups from the 4000 ppm exposure concentration group and one half of the pups from the control, 2500 ppm and 7500 ppm exposure concentration groups was completed. No significant developmental effects were seen in the pups from any exposure group. As the complete evaluation was conducted on the dams and pups at 4,000 ppm, and there were no effects on any parameter in either adults or pups, it can be concluded that the no-observed-effect-level for maternal and pup toxicity is at least 4000 ppm.[14]

A two-generation inhalation reproduction study (OECD 416) in rats is also in progress at the time of publication of this OEL document. The study is using exposure concentrations of 50,000, 15,000, 5000 and 0 (control) ppm. F1-generation female animals were exposed, nose-only, until the end of the pre-mating period for 6 hours/day and 5 days/week, and daily during mating and up to Gestation Day (GD) 19 for 6 hours/day. From Day 5 of lactation onwards, F1-generation females were exposed daily 6 hours/day to HFO-1234yf by whole body exposure until sacrifice on or shortly after Day 21 of lactation. The results from the first generation are available. No maternal effects, effects on reproductive performance, or effects on fetal bone ossification or rib development were seen. There was a delay in sexual maturation of a few days in the female rats but not the males and there was an increase in the number of female pups with a corresponding decrease in the number of male pups at 15,000 and 50,000 ppm. Neither effect was statistically significant at 15,000 ppm. A clear NOAEL was seen at 5000 ppm.[15]

F. Genotoxicity/Mutagenicity

A GLP Ames assay was conducted involving exposure of *Salmonella typhimurium* (TA 1535, TA 1537, TA 98, and TA 100) and *E. coli* (WP2 uvrA) both in the presence and absence of S-9 metabolic activation. Exposure concentrations of up to 76% (plus 19% $O_2$ and 5% $CO_2$) were used. At exposure concentrations of 20% and above a two-fold increase in mutations was seen with TA 100 and WP2 uvr2 in the presence of S-9. All other cell lines were inactive.[16]

In a second GLP study, cultured human lymphocytes were exposed to concentrations up to 76%, both in the presence and absence of S-9 metabolic activation. Under the conditions of this test, HFO-1234yf was not active (not clastogenic) in this assay.[17]

In a GLP micronucleus study, mice were exposed to concentrations of up to 200,000 ppm of HFO-1234yf. Bone marrow cells were collected and analyzed for the presence of micronuclei. Under the conditions of this assay HFO 1234yf did not produce chromosomal damage or damage to the mitotic spindle apparatus in bone marrow cells.[2]

As an additional component in the 4-week GLP study[9] described earlier where groups of male and female Sprague Dawley rats were exposed, nose-only, to HFO-1234yf at concentrations of 0 (control), 5000, 20,000 or 50,000 ppm for 6-hours/day, 5 days/week for 4 weeks. A micronucleus assay was conducted on these rats and additional male rats were included at all exposure concentrations for a unscheduled DNA synthesis study. There was no evidence of genotoxicity or in either the micronucleus or unscheduled DNA synthesis assay.[9]

Based on the preceding *in vitro* and *in vivo* studies, the overall weight-of-evidence suggests that HFO-1234yf is not genotoxic.

G. Metabolism/Pharmacokinetics

The blood/air partition coefficient (PC) for human, rat and rabbit blood was measured using published methodology. There was not a significant difference in partition coefficients between male (0.035) or female (0.038) humans. The PC for rabbit blood (0.072) was similar to that of rat blood (0.076), and it was determined based on physiologically-based pharmacokinetic (PBPK) modeling that the concentration of HFO-1234yf in human blood would be only 50% of the concentration in either rat or rabbit blood under the same exposure conditions.[18] In a study to evaluate the physiologically-based toxicokinetics (PBTK) using modeling, exposures were simulated for adult female humans exposed by inhalation to a concentration of 400 ppm HFO-1234yf for 1, 14, or 28 days for varying daily time periods. Model predicted blood levels of HFO-1234yf were compared to those from rat and rabbits. The ratios of animal/human area under the concentration-time curve (AUC) for rabbit/human and rat/human are summarized in the following table:

The comparison of rabbit AUC for 6 hours (one study day) of exposure at the NOAEL was 19 times higher than the human AUC for 6 hours of exposure. This ratio increased to a value of 26 when rabbit AUC for 7 days of exposure for 6 hours/day was compared with the human AUC for 5 days of exposure (one work week) for 6 hours/day. As summarized in the table, the resulting rat AUC/human AUC ratios range between 188 and 349, depending on the assumed length of daily human exposure.[19] Therefore, at equivalent exposure concentrations the dose delivered to the systemic circulation of humans would be half of that delivered to a rabbit.[20]

## V. HUMAN USE AND EXPERIENCE

As HFO-1234yf is a new product, there is no history of human use.

## VI. RATIONALE

The primary point of departure for the OEL is the mortality seen in the adult pregnant rabbits at 5500 ppm.

**Evaluation of safety margin for repetitive human exposure to HFO-1234f based on repetitive animal exposure at the NOAEL**

| Exposure concentration (mg/L) | Days of exposure | Human AUC | Animal AUC | Animal AUC/ Human AUC | Notes |
|---|---|---|---|---|---|
| human: 400 ppm<br>rabbit: 4,000 ppm (NOAEL) | 1 | 0.42 | 8.04 | 19 | [1] |
| | 14 | 4.26 | 112.76 | 26 | [2] |
| | 28 | 8.52 | 225.58 | 26 | [2] |
| | 1 | 0.56 | 8.04 | 14 | [3] |
| | 14 | 5.67 | 112.76 | 20 | [4] |
| | 28 | 11.33 | 225.58 | 20 | [4] |
| Human: 400 ppm<br>rat: 50,000 ppm (NOAEL) | 1 | 0.42 | 106.1 | 250 | [1] |
| | 14 | 4.26 | 1487.9 | 349 | [2] |
| | 28 | 8.52 | 2975.0 | 349 | [2] |
| | 1 | 0.56 | 106.1 | 188 | [3] |
| | 14 | 5.67 | 1487.9 | 263 | [4] |
| | 28 | 11.33 | 2975.0 | 263 | [4] |

[1] Human exposure for 6 hrs per day, rabbit or rat exposure for 6 hrs per day
[2] Human exposure for 6 hrs per day and 5 days per week, rabbit or rat exposure for 6 hrs per day and 7 days per week
[3] Human exposure for 8 hrs per day, rabbit or rat exposure for 6 hrs per day
[4] Human exposure for 8 hrs per day and 5 days per week, rabbit or rat exposure for 6 hrs per day and 7 days per week

PBTK modeling shows that the rabbit uptake is twice that of humans, indicating that this concentration in rabbits is higher than the equivalent human concentration. There was a clear no observed effect level at 4,000 ppm for both maternal and potential developmental effects in rabbits. No mortality was seen at these same concentrations of exposure in rats, indicating that the rabbit is the more sensitive species. For example, in the 4-hour acute toxicity study in rats, no mortality was seen at 405,800 ppm and in several repeat-exposure inhalation studies no treatment-related toxicity was seen at the highest concentration tested, 50,000 ppm. However, there were deaths in rabbits at 5500 and 7500 ppm and 10,000 ppm in the developmental toxicity studies, HFO-1234yf did not induce developmental effects at concentrations below those that induced maternal effects. No developmental effects were observed at a concentration of 4,000 ppm in rabbits and no adverse treatment-related reproductive or developmental effects were observed at 5000 ppm in rats. Thus, the point of departure based on general systemic toxicity in rabbits is expected to protect against potential reproductive and developmental effects as well.

## VII. RECOMMENDED OEL

500 ppm as an 8-hour TWA

## VIII. REFERENCES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Literature searches performed: Computer searches according to the WEEL AOP "Literature Search Protocol" and of Toxicology Data Bank, MEDLINE, HAZARD- LINE, TOXLINE and CANCERLINE databases, MicroMedex/TOMES, MEDITEXT®, HAZARDTEXT®, CHRIS, Fisher/Acros MSDS, Dolphin MSDSs, HSDB®, LOLI®, ERG2000, New Jersey Hazardous Substance Fact Sheet, OHM/TADS, RTECS®, POISINDEX®