WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

AIHA® Guideline Foundation

1,3,3,3-Tetrafluoropropylene(2011)

I. IDENTIFICATION

Chemical Name: trans-1,3,3,3-tetrafluoropropylene
Synonyms: HFO-1234ze
CAS Number: 1645-83-6
UN/NA Number: NA
Molecular Formula: $C_3H_2F_4$
Structural Formula: trans-CHF=$CHCF_3$

II. CHEMICAL AND PHYSICAL PROPERTIES(1–7)

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: Not determined
Boiling Point: -19°C (-2°F)
Vapor Pressure: Gas with a boiling point of -19°C and therefore will have a vapor pressure of greater than 1 atmosphere at 20°C
Vapor Density: 4 (relative to air = 1)
Saturated Vapor Concentration: Not applicable (substance is a gas)
Flammability Limits: non flammable
Flash Point: Not applicable (substance is a gas)
Auto ignition Temperature: 368°C
Specific Gravity: 1.1 at 21.1°C (70°F) as compressed liquid
Solubility in Water: 0.373 g/L
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 & Incompatibilities: Avoid contact with strong oxidizing agents or finely divided magnesium, aluminum or other alloys.

III. USES

This substance is being developed as a low global warming potential foam blowing agent.

IV. ANIMAL TOXICITY DATA

Acute Toxicity and Irritancy

1. *Oral Toxicity*

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

2. *Eye Irritation*

   The substance is a gas and has not been tested for eye irritation. However, in 2-week, 4-week and 13-week inhalation toxicity studies with exposures up to 5%, 1.5% and 1.5% in air, respectively, 6-hours/day, 5 days/week, no signs of ocular irritation were seen.(2)

3. *Skin Absorption*

   No data

4. *Skin Irritation*

   The substance is a gas and has not been tested for dermal irritation. Typically, exposure to refrigerant gases can lead to cooling of the skin and frostbite.

5. *Skin Sensitazation*

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

Inhalation Toxicity

A GLP acute 4-hour inhalation toxicity study was conducted with three groups of 5 male and 5 female Sprague-Dawley CD rats that were exposed nose only to vapors of HFO-1234ze at levels of 0 (control), 100,000 or 207,000 ppm for 4 hours. The animals were held for a 14-day observation period. No mortality, no clinical signs of toxicity, no treatment-related changes to body weight, and no food consumption changes were observed. At termination, gross necropsy observations were normal and there were no treatment-

related or statistically significant differences in organ weights (kidneys, liver and lungs) or organ weight ratios. The 4-hour LC50 for HFO-1234ze is greater than 207,000 ppm. Based on these results, HFO-1234ze is considered practically nontoxic by the inhalation route of exposure.[3]

In an acute cardiac sensitization study, a group of 6 beagle dogs were exposed to vapors of HFO-1234ze at concentrations of 2%, 6% or 12% (20,000, 60,000 or 120,000 ppm). Exposures to each substance were conducted on different days; with at least a 2-day separation between the exposures. Initially a determination was made for the maximum level of epinephrine that would not cause a cardiac arrhythmia. The dogs were then exposed to the test substance for a total of 10 minutes. After the first five minutes of exposure, each dog received an injection of epinephrine at the predetermined maximum sub-arrhythmia dose. During the next five minutes of exposure, the dogs were monitored for the development of a cardiac arrhythmia. No arrhythmias or other signs of toxicity were induced in any of the dogs. Thus, it was concluded that exposure of dogs to a level of 12% (120,000 ppm) of either HFO-1234ze did not cause cardiac sensitization when challenged with epinephrine.[4]

Subacute Toxicity

A GLP 2-week inhalation toxicity study was conducted with four groups of 5 male and 5 female Sprague Dawley rats that were exposed nose only to vapors of HFO-1234ze at levels of 0 (control), 5000, 20,000 or 50,000 ppm for 6-hours/day, 5 days/week during a 2 week period, with a total of 10 exposure days. There were no treatment-related changes in clinical observations, body weight gain, food consumption or food conversion efficiency. Hematologic analysis, clinical chemistry analysis, organ weight measurements, and macroscopic and microscopic examination of the heart, liver and nasal passages revealed treatment-related effects in animals exposed to 20,000 and 50,000 ppm. The main effects were concentration-related and occurred in the heart (muscle fiber vacuolation and mononuclear cell infiltrates) and liver (hepatocellular vacuolation and mononuclear cell infiltrates) of animals exposed to 20,000 and 50,000 ppm and in the nasal passages (decreased goblet cell expression) of animals exposed to 50,000 ppm. Thus 5000 ppm was considered by the authors of the study to be the No Observed Effect Level (NOEL) for HFO-1234ze in this study.[2a]

A GLP 4-week inhalation toxicity study was conducted with five groups of male and female Sprague Dawley rats were exposed nose only to vapors of HFO-1234ze at levels of 0 (control), 1000, 5000, 10,000 and 15,000 ppm for 6-hours/day, 5 days/week during a 4 week period, with a total of 20–21 exposure days. As an additional component of this study, at necropsy, liver cells from male rats in the control, 5000 and 15,000 ppm groups were evaluated in an Unscheduled DNA Synthesis Test and bone marrow from male rats in the control, 5000, 10,000 or 15,000 ppm groups was assessed in a Micronucleus Test. Results of these two mutagenicity tests are presented below under the heading Mutagenicity. No treatment-related changes were observed when clinical observations, body weight gain, food consumption or food conversion efficiency were evaluated. Although clinical chemistry analysis showed some variations, they did not appear in a concentration-related pattern and thus, they were not considered treatment-related. At necropsy, no treatment-related changes were found during macroscopic examination or in organ weights. Microscopic examination revealed very slight to moderate inflammation of the heart of male rats exposed to 15,000 ppm; two of which also showed muscle fiber vacuolation. Based on these results, 10,000 ppm was considered the No-Observed-Adverse-Effect Level (NOAEL) for a 4-week exposure to HFO-1234ze.[2b]

Subchronic Toxicity

A GLP 13-week inhalation toxicity study was conducted with four groups of 10 male and 10 female Sprague-Dawley rats that were exposed to vapors of HFO-1234ze at levels of 0 (control), 1,500, 5,000, or 15,000 ppm for 6 hours/day, 5 days/week during a 13-week period, with a total number of 63–64 exposure days. No treatment-related changes were observed when clinical observations, body weight gain, food consumption or food conversion efficiency were evaluated. Analysis of hematology parameters and clinical chemistry showed some slight variations at 15,000 ppm which may be treatment-related. At necropsy, no treatment-related gross changes were observed during macroscopic examination and no treatment-related organ weight changes were measured. However, microscopic examination revealed multifocal mononuclear cell infiltrates in the heart of both sexes at 15,000 ppm. Fibrosis was not observed. Based on these results, 15,000 ppm was considered a Low-Observed-Adverse-Effect Level (LOAEL) and 5000 ppm was considered the No-Observed-Effect Level (NOEL) for a 13-week exposure to HFO-1234ze.[2c]

Chronic Toxicity/Carcinogenicity

In vitro and in vivo genotoxicity test results presented below suggest that HFO-1234ze is not likely to be carcinogenic.

REPRODUCTIVE/DEVELOPMENTAL TOXICITY

Groups of 24 mated female rats were exposed nose only, to levels of 0 (control), 1500, 5000 or 15,000 ppm of HFO-1234ze for 6 hours/day on Days 6–19 of gestation. There was no mortality. No effect was seen on body weight or food consumption and clinical observations for all groups were unremarkable. There were no significant differences in fecundity index, number of corpora lutea and implantation sites, the number of live fetuses, the post implantation loss, or sex ratio of the pups. In the pups, there were no statistically significant differences in visceral or skeletal findings. In fact, it was interesting to note that in this study, there were a higher incidence of observations of delayed ossification seen in the control rats compared to the test substance exposed rats. This clearly was an example of random variation. It was concluded that the no-observed effect level was 15,000 ppm, the highest level tested.[5]

An inhalation range-finding prenatal developmental toxicity study of HFO-1234ze in rabbits was conducted for the purpose of determining appropriate exposure concentrations for a definitive prenatal developmental toxicity study. Four groups of time-mated female New Zealand rabbits (6/group) were exposed by whole-body inhalation to 0 (control), 1500, 5000 or 15,000 ppm HFO-1234ze for 6 hours/day during gestation days 6 to 28. All animals survived to the scheduled necropsy on Gestation Day 29. No signs of maternal toxicity were observed. Intrauterine growth and survival were unaffected by maternal exposure to all exposure levels. No external fetal malformations or developmental variations were found. It was concluded that inhalation exposures up to 15,000 ppm HFO-1234ze to pregnant rabbits did not cause maternal or developmental toxicity in this pilot study.[6]

A GLP inhalation prenatal developmental toxicity study of HFO-1234ze in rabbits was conducted. Four groups of time-mated female New Zealand rabbits (22/group) were exposed by whole-body inhalation to 0 (control), 1500, 10,000 or 15,000 ppm HFO-1234ze for 6 hours/day during Gestation Days 6 to 28. All animals survived to the scheduled necropsy on gestation day 29. No signs of maternal toxicity were observed. Intrauterine growth and survival were unaffected by maternal exposure to all exposure levels. It was concluded that inhalation exposures up to 15,000 ppm HFO-1234ze did not cause maternal toxicity in this study. Also, there were no effects on pup live birth, sex ratio or malformations. The NOEL for exposure of pregnant rabbits to HFO-1234ze for both does and pups was 15,000 ppm.[7]

GENOTOXICITY/MUTAGENICITY

In Vitro

An assay screen was conducted with the bacteria Salmonella typhimurium (strains TA1535, TA1537, TA98, and TA100) and Escherichia coli (strain WP2 uvrA) both with and without metabolic activation from a rat liver preparation. Each strain was exposed to a single exposure level of 5% (50,000 ppm) HFO 1234ze. Under the conditions of this assay, HFO-1234ze did not induce any evidence of mutagenic activity.[8]

A GLP Ames assay was conducted with HFO-1234ze which involved exposure of bacterial cells TA 1535, TA1537, TA 98, TA 100 and WP2 uvrA both with and without S-9 metabolic activation. Exposure levels of up to 76% (plus 19% O_2 and 5% CO_2) were used. HFO-1234ze did not induce a response in any strain tested either without or in the presence of metabolic activation.[9]

A GLP Chromosome Aberration Test was conducted with cultured human lymphocytes that were exposed to vapors levels of HFO-1234ze up to 76%, both with and without S-9 metabolic activation. Under the conditions of this test, HFO-1234ze was not actively mutagenic (not clastogenic).[10]

In Vivo

A Mouse Micronucleus Assay was conducted following a single 4-hour exposure to 29,208 ppm HFO-1234ze. At 48 and 72 hours after exposure, peripheral blood smear samples were obtained from 5 male and 5 female exposed mice, as well as from negative and positive control animals. It was concluded that a 4-hour exposure to 29,208 ppm HFO-1234ze did not cause chromosome damage in the peripheral blood of exposed mice.[11]

A second Micronucleus Assay was conducted with 10 male and 10 female CD-1 mice that were exposed by nose-only inhalation to 103,300 ppm HFO-1234ze for 4 hours. At 24- and 48-hours after exposure, bone marrow cells from 5 mice per sex per interval were collected and analyzed for

the presence of micronuclei. No signs of toxicity were observed during or after exposure. It was concluded that HFO 1234ze was non-genotoxic at a level of 103,300 ppm, as it did not cause an increase in micronuclei or evidence of bone marrow cell toxicity in mice.[3]

A rat Micronucleus Test was an added procedure to the 4-week inhalation toxicity study (described above), in which groups of male and female Sprague-Dawley rats were exposed nose only to vapors of HFO-1234ze at levels of 0 (control), 1000, 5000, 10,000 or 15,000 ppm 6-hours/day, 5 days/week during a 4-week period. At necropsy, bone marrow from male rats in the control, 5000, 10,000 or 15,000 ppm groups was used in the Micronucleus Test. At the highest concentration tested (15,000 ppm), no damage to chromosomes or increased incidence of micronuclei was observed in the bone marrow cells of male rats.[2b]

An Unscheduled DNA Synthesis Test was also included in the 4-week inhalation toxicity study (described above), in which groups of male and female Sprague-Dawley rats were exposed nose only to vapors of HFO-1234ze at levels of 0 (control), 1000, 5000, 10,000 or 15,000 ppm 6-hours/day, 5 days/week during a 4-week period. At necropsy, liver cells from male rats in the control, 5,000 and 15,000 ppm groups were used in the Unscheduled DNA Synthesis Test. At the highest concentration tested (15,000 ppm), no unscheduled DNA synthesis was observed in the liver cells of male rats.[2b]

Metabolism/Pharmacokinetics

HFO-1234ze did not undergo any measurable metabolism when rats were exposed to levels up to 5% HFO-1234ze for a single 4-hour period.[12]

Statistical analysis of rodent gene expression changes were conducted as part of the comprehensive toxicological assessment of HFO-1234ze. This was not a guideline study, was not GLP compliant, and is not accepted as a validated method by the regulatory authorities; however, it was conducted to provide additional information. Potential gene expression changes in liver, kidney and lung tissue were assessed following exposure of female B6C3F1 mice and male F344 rats to levels of 5000 and 15,000 ppm HFO-1234ze 6-hrs/day, 5 days/wk for 13 weeks. The assessment was based on the results from a comparison of the responses seen with HFO-1234ze to 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.

Statistical classification analysis predicted HFO-1234ze to be noncarcinogenic in both female mouse liver and male rat kidney. A positive response was seen with the female mouse lung. These findings had a statistical probability of selecting true negatives of 100% for kidney, 99.2% for liver and 83% for lung. The probability for a true positive being identified was 90% for the kidney, 97.2% for the liver and only 71.3% for the lung. There was no dose response relationship with respect to changes in gene expression. Furthermore, as only a limited number of genes were altered, it was concluded that for the female mouse lung, the number of genes altered was too small to perform a meaningful gene ontology enrichment analysis. No treatment related histopathological lesions were observed in the liver or kidney[13] and only 1/10 mice in both exposure groups showed mild irritation in the lung.[5,14] The weight of evidence suggests that HFC-1234ze is not likely to be carcinogenic. This conclusion is supported by the lack of mutagenic activity in all mammalian cell studies, the lack of significant metabolic activity, the lack of systemic toxicity and the lack of significant lesions in the livers, kidneys and lungs in any of the studies.

V. HUMAN USE AND EXPERIENCE

As HFO-1234ze is a new product; there is no history of human use.

VI. RATIONALE

There was no lethality seen in dogs exposed for 4 hours at concentrations up to 207,000 ppm and dogs exposed at levels up to 120,000 ppm did not develop cardiac arrhythmias. The NOEL was 5000 ppm in the 2-week, 4-week and 13-week studies. No treatment-related changes were observed in clinical observations, body weight gain, and food consumption or food conversion efficiency. In addition, no treatment-related gross changes were observed at necropsy or during macroscopic examination and no treatment-related organ weight changes were measured for any dose level. In the 4-week study, 10,000 ppm was considered the NOAEL and microscopic examination revealed very slight to moderate inflammation of the heart of male rats (only) exposed to 15,000 ppm; two rats also showed muscle fiber vacuolation. In the 13-week study, analysis of hematology parameters and clinical chemistry showed some

slight variations and microscopic examination revealed multifocal mononuclear cell infiltrates in the heart of both sexes at 15,000 ppm although fibrosis was not observed. The Low-Observed-Adverse-Effect Level (LOAEL) in this study was considered to be 15,000 ppm. Rabbits showed no signs of maternal toxicity at the highest doses tested (15,000 ppm) in both a pilot and full reproductive/developmental studies. Intrauterine growth and survival were unaffected by maternal exposure to all exposure levels. It was concluded that inhalation exposures of pregnant rabbits at concentrations up to 15,000 ppm HFO-1234ze did not cause maternal toxicity, effects on pup live birth, sex ratio, or external malformations.[8] Providing for uncertainty for interspecies variation and uncertainty for interspecies variation, 800 ppm as an 8-hour TWA should be protective of workers. This is also approximately 20-fold below the NOEL for reproductive and developmental effects.

VII. RECOMMENDED WEEL® GUIDE

800 ppm as an 8-hour TWA

VIII. REFERENCES

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