WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

cis-1,1,1,4,4,4-Hexafluoro-2-butene (1336mzz-Z)(2014)

I. IDENTIFICATION

Chemical Name: cis-1,1,1,4,4,4-hexafluoro-2-butene
Synonyms: HFO-1336mzz-Z; HFO-1336mzz(Z); (Formacel® 1100)
CAS Number: 692-49-9
Molecular Formula: C4H2F6
Structural Formula:

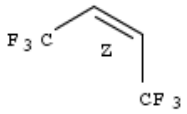

Fig. 1.Double bond geometry as shown.

II. CHEMICAL AND PHYSICAL PROPERTIES(1)

Physical State and Appearance: Low boiling liquid
Odor Description: Odorless
Molecular Weight: 164.05 g/mol
Conversion Factor: 1 mg/m^3 = 0.149 ppm (25 °C and 760 mm Hg); 1 ppm = 6.7 mg/m^3
Melting Point: -90.5 °C (-131°F)
Boiling Point: 33°C (91°F)
Vapor Pressure: 453 torr (5.93 psig) @ 20 °C
Vapor Density: 6.03 kg/m^3 (0.377 lb/ft^3) @ 30 °C and 1 atm; 11.7 kg/m^3 (0.729 lb/ft^3) @ 50°C and 1 atm
Saturated Vapor Concentration: 597,000 ppm @ 20 °C and 1 atm
Flammability Limits: Non-flammable
Flash Point: Not applicable (non-flammable)
Ignition Temperature: None
Specific Gravity: 1.38 g/mL @ 20 °C
Solubility in Water: 3.834 g/L @ 25 °C
Stability: Stable under recommended storage conditions
Reactivity & Incompatibilities: No reactivity at room temperature and thermally stable up to 400°C. Not compatible with strong acids and strong bases.
Partition Coefficient (Kow): 2.3

III. USES

Cis 1,1,1,4,4,4-hexafluoro-2-butene (HFO-1336mzz-Z) is a foam-blowing agent, refrigerant, fire extinguishant and solvent.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity

1. Lethality Data

No data are available for acute lethality.

2. Eye Irritation

HFO-1336mzz-Z has not been tested for eye irritation because it would evaporate at body temperature. However, in whole body inhalation studies using HFO-1336mzz-Z in vapor form conducted in rats and rabbits revealed no signs of ocular irritation.

3. Skin Absorption

No data are available for skin absorption. The low boiling point of the chemical would complicate studies of dermal absorption.

4. Skin Irritation

A GLP skin irritation study with New Zealand White rabbits was conducted in accordance with OECD test guideline 404.(2) An aliquot of 0.5 ml of HFO-1336mzz-Z was applied to a 6 cm^2 area of the shaved skin of 3 rabbits and the application site was covered with a gauze square, which was held in place with non-irritating tape and covered with a semi-occlusive dressing. The rabbits were dermally exposed to HFO-1336mzz-Z for 4 hours after which the substance was removed. Due to the low boiling point of this chemical, the extent of exposure may have been limited. Test sites were evaluated according to the Draize scale criteria at approximately 60 minutes, and 24, 48 and 72 hours after test substance removal and no dermal irritation was noted at any time point. Under the conditions of this study HFO-1336mzz-Z was not considered a skin irritant.(3)

5. Skin Sensitization

No data are available for skin sensitization.

6. Acute Inhalation Toxicity

A GLP acute (approximate lethal concentration (ALC)) inhalation toxicity study was conducted with one group of 4 male Crl:CD(SD) rats that were exposed whole-body for a single, 2-hour period to vapors of HFO-1336mzz-Z at 21,000 ppm.[4] The test atmosphere was generated by flash evaporation and concentrations were measured by gas chromatography. The animals were weighed and observed for clinical signs of toxicity during a 14-day recovery period. No rats died following exposure to HFO-1336mzz-Z or during the recovery period. Irregular respiration was observed during exposure as well as a slight body weight loss (0.31% - 4.6%) on the day after exposure, followed by normal weight gain for the remainder of the recovery period. Under the conditions of this study, the 2-hour ALC for HFO-1336mzz-Z was greater than 21,000 ppm.[4]

A second GLP acute inhalation study was conducted according to OECD test guideline 403.[5,6] One group of 5 male and 5 female Crl:CD(SD) albino rats were exposed nose-only to vapors of HFO-1336mzz-Z for 4 hours at a concentration of 102,900 ppm, the highest achievable vapor concentration. Mean temperature and relative humidity of the exposure atmosphere were 25 °C and 41%, respectively. Mortality, clinical observations, body weights and body weight changes were evaluated over a 14-day post-exposure observation period. Necropsies were conducted on all animals. None of the animals died during the exposure or the 14-day post-exposure observation period. The 4-hr LC50 for HFO-1336mzz-Z was greater than 102,900 ppm. Clinical observations immediately following exposure included tremors and rales. There were no toxicologically significant clinical signs during the 14-day post-exposure observation period, and all animals were considered clinically normal one day following the exposure. There were no remarkable changes in body weight. The only macroscopic finding noted during the scheduled necropsy was clear fluid contents in the uterus for 1 female. However, this finding was considered spurious and not related to the test substance exposure. Based on these results, HFO-1336mzz-Z is considered to have very low acute toxicity by the inhalation route of exposure.[5]

The cardiac sensitization potential of HFO-1336mzz-Z was evaluated under GLP conditions.[7] A group of 6 beagle dogs was exposed muzzle-only for approximately 31 minutes (following a 2-minute exposure to air) to vapors of the substance at concentrations of 12,500, 25,000 or 50,000 ppm. Each dose was evaluated in the animals with a minimum of 48 hours between each exposure and each dog served as its own control. Three days prior to exposure, baseline response to the epinephrine challenge doses were collected for each animal. Animals were then administered predetermined increasing doses of epinephrine (2, 4, 6 and 8 µg/kg) as bolus injections via an appropriate vein beginning approximately 5 minutes following exposure to the test substance. Epinephrine challenge bolus injections were administered a minimum of 3 minutes apart or until the electrocardiogram (ECG) of the animal returned to its normal baseline rhythm. Cardiac sensitization was observed in 5 animals following exposure to 50,000 ppm of the test substance and in 4 animals following exposure to 25,000 ppm of the test substance. There were no signs of cardiac sensitization noted in animals that were exposed to 12,500 ppm of the test substance. During the exposure to 50,000 ppm of substance, multiple premature ventricular contractions were noted at 17 seconds post-dose, followed by ventricular tachycardia leading into ventricular fibrillation and the subsequent death of 1 animal. Following the 50,000 ppm exposure, intermittent tremors were noted in 2 animals and pale extremities were noted in 3 animals. After exposure to 25,000 ppm, intermittent tremors were noted for 1 animal. Consequently, the no-observed adverse effect level (NOAEL) and lowest-observed adverse effect level (LOAEL) for cardiac sensitization in epinephrine-challenged dogs were 12,500 ppm and 25,000 ppm, respectively.[7]

B. Subacute Toxicity

A 5-day inhalation range-finding study was conducted to evaluate potential toxic effects of the test material when administered via nose-only exposure to rats for 5 consecutive days. Four groups (5/sex) of Crl:CD(SD) rats were exposed nose-only to 0 (control), 1000, 10,000 or 50,000 ppm of HFO-1336mzz-Z for 6 hours per day. There were no test substance-related clinical observations, effects on coagulation or serum chemistry parameters or macroscopic findings. Non-adverse, statistically significant differences from control on hematology parameters included lower absolute reticulocyte counts in the 10,000 and 50,000 ppm group males. Red cell mass (red blood cells, hemoglobin and hematocrit) was higher in the 10,000 and 50,000 ppm group males, while red cell mass was lower in the 50,000 ppm group females. Reduced body weight gain, reduced food consumption and degeneration of the olfactory epithelium, neutrophilic infiltration and luminal cellular debris in the nasal cavity were observed at the 10,000 and 50,000 ppm exposure levels. The NOAEL was 1,000 ppm.[8]

A GLP 4-week inhalation toxicity study was conducted with four groups of male and female Crl:CD(SD) rats according to OECD test guideline 412.[9] The animals were exposed nose-only to 0 (control), 2500, 5000 or 10,000 ppm of HFO-1336mzz-Z for 6 hours/day, 5 days/week for a 4-week period. The control and 10,000 ppm groups each consisted of 20 rats per sex and the 2500 and 5000 ppm groups each consisted of 10 rats per sex. On the day following the 20th exposure, 10 animals/sex were euthanized and subjected to necropsy. The remaining 10 animals/sex from the control and the 10,000 ppm groups were necropsied following a 15-day non-exposure recovery period. All animals survived to the scheduled necropsies. There were no test material-related effects on coagulation or urinalysis parameters, ophthalmic, macroscopic or microscopic findings, or on respiratory tract tissues. Reduced body weight, reduced body weight gain and reduced food consumption were observed at the 5000 and 10,000 ppm exposure levels. In male rats, there was an increase in serum albumin (12.2% over control) and total protein (9.4% over control) at the 3-week point, but at recovery, these protein parameters were lower than controls. The NOAEL was 2500 ppm, based on the effects on body weight and food consumption.[10]

C. Subchronic Toxicity

A GLP OECD test guideline 413[11] 13-week inhalation toxicity study was conducted with four groups of 20/sex Crl:CD(SD) rats that were exposed whole-body to 0, 500, 1500 or 10,000 ppm of HFO-1336mzz-Z.[12] The animals were exposed for 6 hours/day, 5 days/week during a 13-week period, for 63 total exposures. After the exposure period, a group of 10 rats/sex from each exposure level fasted, and then blood and urine samples were collected, and were sacrificed one day post-exposure for anatomical pathology evaluation including microscopic tissue evaluation. Following a month recovery period, groups of 10 rats/sex were sacrificed after blood and urine collection for clinical pathology, and were submitted for gross and histopathology tissue evaluation. There were no test substance-related adverse effects in the ophthalmology examinations or the clinical or anatomical pathology parameters at any exposure concentration. Non-adverse test substance-related microscopic findings were observed in the anterior nose, teeth and femur of rats exposed to HFO-1336mzz-Z. Test substance-related mucous cell hyperplasia of the respiratory epithelium was observed in 0/10, 0/10, 4/10 and 9/10 males from the 0, 500, 1500 and 10000 ppm groups, respectively. Following the 1-month recovery period test substance-related mucous cell hyperplasia of the respiratory epithelium was not observed. Mucous cell hyperplasia is a very common, adaptive response and one that is subjectively identified, especially in cases where the effect is minimal to mild, and it is related to production and release of protective mucous substances in response to irritation. The effect was reported as minimal, not associated with injury of the respiratory epithelium, was completely reversible and was judged as non-adverse per normal histopathological interpretation practices.[13]

Incomplete decalcification of enamel in the incisor teeth was observed in 0/10, 2/10, 3/10 and 6/10 males from the 0, 500, 1500 and 10000 ppm groups, respectively. The incomplete decalcification referred to in the study report did not represent an *in vivo* effect of bone or tooth decalcification, rather, it was a histological processing artifact, and refers to a tissue processing phenomenon that indicates that metabolism of the parent material includes production of some free fluoride. In these studies, there was histologic evidence that in some of the exposed groups, the laboratory process of acid decalcification in some bone and the incisor teeth was not complete. The significance of potential fluoride exposure to teeth and bone was assessed based upon the presence or absence of clinical and/or microscopic changes suggestive of injury or loss of function in these tissues. Since there were no changes in the enamel-forming cells of the tooth or in general dentition of affected animals, the incomplete decalcification of enamel in the incisor teeth in males was considered non-adverse.

Incomplete decalcification of bone trabeculae in the femur was observed in 10/10 males rats from all exposure levels and in 6/10, 10/10 and 10/10 females in the 500, 1500 and 10000 ppm groups, respectively. The discussion related to incomplete decalcification of the teeth, applies equally to the bone. Since the incomplete decalcification of bone trabeculae was not associated with morphological changes in osteoblasts or osteoclasts, it was considered non-adverse.

Treatment-related reduced body weight gain and reduced food consumption were observed at the 10,000 ppm exposure level. Following the month recovery period, both male and females from the 10,000 ppm exposure group demonstrated body weights that were similar to the control group, indicating that the test substance-induced reductions in body weight parameters were reversible. Clinical signs of toxicity (abnormal gait, aggressive behavior, ear twitching, hyperactivity, low posture, tremors, and hyperactivity) were observed in 1-3 male rats exposed to 10,000 ppm and began toward the end of the exposure period (test day 77).

Based on the test substance-related reductions in body weights, food consumption, and food efficiency in both males and

females exposed to 10,000 ppm, the NOAEL for this study was 1500 ppm.[12]

A second 13-week GLP (OECD test guideline 413) [11] inhalation toxicity study was conducted with five groups (10/sex) of Crl:CD(SD) rats that were exposed whole-body to 0, 3000, 4000, 5000 or 7500 ppm.[14] The objective of this study was to refine the NOAEL, and to evaluate potential clastogenic effects of the test material in a satellite micronucleus assay. The animals were exposed for 6 hours/day, 5 days/week during a 13-week period for a total of 65 exposures. There were no test substance-related adverse findings in ophthalmology, clinical observations, clinical pathology, organ weights, or gross pathological evaluations at any exposure level.

Microscopic findings were observed in the teeth and femur/knee joints of all exposed male and female rats. These changes included incomplete decalcification of enamel in the distal region of the upper incisors. The incomplete decalcification referred to in the study report did not represent an *in vivo* effect of bone or tooth decalcification, rather, it was a histological processing artifact, and refers to a tissue processing phenomenon that indicates that metabolism of the parent material includes production of some free fluoride. The significance of potential fluoride exposure to teeth and bone was assessed based upon the presence or absence of clinical and/or microscopic changes suggestive of injury or loss of function in these tissues. Since there were no changes in the enamel-forming cells of the tooth or in general dentition of affected animals, the incomplete decalcification of enamel in the incisor teeth in males was considered non-adverse.

Incomplete decalcification of bone trabeculae in the femur was also observed in all exposed males and in females exposed to 7500 ppm. However, since the incomplete decalcification of bone trabeculae was not associated with morphological changes in osteoblasts or osteoclasts in the affected animals, it was considered non-adverse.

No test substance-related changes in body weight, food consumption or food efficiency were observed in females at any exposure concentration. In males, test substance-related adverse effects on body weight and food consumption were observed at 7500 ppm. The NOAEL for this study was 5000 ppm in male rats and 7500 ppm in female rats.[14]

D. Chronic Toxicity/Carcinogenicity

No chronic toxicity studies have been conducted with this material.

E. Reproductive/Developmental Toxicity

In a GLP prenatal developmental study, groups of 22 time-mated nulliparous female Crl:CD(SD) rats were exposed 6 hours/day to HFO-1336mzz-Z by whole-body inhalation beginning on gestation day (GD) 6 through GD 20 according to OECD test guideline 414.[15] Exposure concentrations were 0 (control), 500, 1500 or 10,000 ppm. No maternal, embryo, or fetal lethality or fetal structural malformations or variations were observed at any exposure concentration. Test substance-related and adverse maternal toxicity was evident at 10,000 ppm and was demonstrated as reduced body weights, body weight gains, and food consumption. In addition, there was an increased incidence of pallor among dams at 10,000 ppm. Test substance-related and adverse developmental toxicity was evident at 10,000 ppm as a statistically significant reduction (16%) in mean fetal body weight. The NOAEL for maternal and fetal effects was 1500 ppm.[16]

In a GLP prenatal developmental study, groups of time-mated female New Zealand White rabbits were exposed 6 hours/day to HFO-1336mzz-Z by whole-body inhalation beginning on gestation day (GD) 7 through GD 28 according to OECD test guideline 414.[15] Exposure concentrations were 0 (control), 2500, 5000, 7500 or 15,000 ppm. Due to limitations on the numbers of animals that could be placed into exposure chambers, the study was conducted in 2 phases (12 animals were exposed per phase). However, due to excessive toxicity during phase 1, no animals were exposed to the test substance at 15,000 ppm in phase 2. No test substance-related macroscopic findings were noted for any females at the scheduled gestation day 29 necropsy. No embryo or fetal lethality or fetal structural malformations or variations were observed at any exposure concentration. Test substance-related maternal moribundity as a result of impaired use of hind limbs, increased respiration, hypoactivity, tonic convulsions, labored respiration, prostration, and/or a pale body were observed at 7500 and 15,000 ppm. Test substance-related mean body weight losses or reduced mean body weight gains with corresponding reduced mean food consumption were noted for females in the 15,000 ppm group. Test substance-related reduced fetal body weight reductions were observed at 15,000 ppm. The NOAEL for maternal effects was 5000 ppm and the NOAEL for fetal effects was 7500 ppm.[17]

A 2-generation pilot study was conducted in order to determine the optimal intermediate and high exposure concentrations for a subsequent multi-generation reproduction toxicity study. Groups of 30 male and 30 nulliparous and non-pregnant female Crl:CD(SD) rats were exposed to 0, 1500, 5000 or 8500 ppm of

substance via whole-body inhalation for 6 hours per day for 7 days per week. After approximately 2 weeks of exposure, body weight, body weight gain, food consumption, and/or food efficiency were statistically significantly reduced in males at 1500 ppm and above, and in females at 5000 ppm and above. Clinical signs of toxicity were observed in males exposed to 8500 ppm during the second week of exposure (hyperactive on multiple days, lethargic on 2 days, convulsions on 1 day, and stained fur on multiple days). Since the exposure concentrations exceeded the maximum tolerated concentration, exposures of all of the female rats and 8500 ppm male rats were discontinued, and 3 additional male groups were added by reassigning a subset of control group males. For the remainder of the study, 10 males per group were exposed to 0, 500, 1500, 3000 or 5000 ppm for 6 hours per day, 7 days per week, and one group of 5000 ppm males were exposed for 5 days per week for 25 days (in addition to the previous 17 days of exposure as described above for rats in the 1500 and 5000 ppm groups). Statistically significantly reduced body weight and body weight gain occurred at 1500 ppm and above. Food consumption was significantly reduced at 3,000 ppm and above. There were no clinical signs of toxicity at any exposure concentration in the study once the exposure adjustments were made. The lack of body weight and clinical toxicity at the 5000 ppm level following adjustment of the exposure period from 7 days/week to 5 days/week demonstrates that the 13-week, 5 day/week exposure (i.e. the normal workplace exposure) is the correct study design for establishing the point of departure in derivation of the WEEL value. The NOAEL based on statistically significantly reduced body weight and body weight gain in male rats was 500 ppm.[18]

F. Genotoxicity/Mutagenicity

1. In Vitro

A GLP Bacterial Reverse Mutation Assay (Ames) assay with HFO-1336mzz-Z was conducted according to OECD test guideline 471[19] using *Salmonella* strains TA98, TA100, TA1535, and TA1537 and E. coli strain WP2 uvrA either in the presence or absence of Aroclor-induced rat liver S9. The maximum concentration tested was 5000 µg/plate. Under the conditions of this study, HFO-1336mzz-Z did not exhibit mutagenic responses in the presence or absence of metabolic activation.[20]

A GLP chromosome aberration assay was conducted according to OECD test guideline 473[21] with cultured human peripheral blood lymphocytes that were exposed to HFO-1336mzz-Z up to 1640 µg/mL (without metabolic activation) or up to 1200 µg/mL (with metabolic activation). The cells were treated for 4 and 20 hours without metabolic activation or for 4 hours in the presence of metabolic activation. All cells were harvested 20 hours after treatment initiation. Based on the findings of this study, it was concluded that HFO-1336mzz-Z was negative for the induction of structural and numerical chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation.[22]

2. In Vivo

A GLP rat micronucleus test was included as part of the 13-week inhalation toxicity study (described above), in which five groups (10/sex) of male and female Crl:CD(SD) rats were exposed whole-body to 0, 3000, 4000, 5000 or 7500 ppm of substance. The animals were exposed for 6 hours/day, 5 days/week during a 13-week period for a total of 65 exposures. Five animals per sex per exposure concentration had blood collected following the fourth exposure, after approximately 4 weeks of exposure and at the time of final sacrifice for micronucleus evaluation according to OECD test guideline 474.[23] At the highest concentration tested (7500 ppm), no effect on the number of micronucleated polychromatic erythrocytes was observed.[14]

G. Metabolism/Pharmacokinetics

There is evidence of fluoride ion release from HFO-1336mzz-Z in the subchronic inhalation studies. Skeletal changes in rats following repeated exposure to HFO-1336mzz-Z are most likely due to fluoride release and binding to bone. Fluoride changes in bone can be beneficial at low levels (strengthening bone, preventing dental caries and osteoporosis) or adverse at higher exposures causing skeletal fluorosis and renal failure in several cases.[24–27]

V. HUMAN USE AND EXPERIENCE

HFO-1336mzz-Z is a new chemical and not in general use.

VI. RATIONALE

HFO-1336mzz-Z is a nonflammable, low-boiling liquid (BP = 33°C) with a relatively high vapor pressure (453 torr @ 20°C). Workplace exposures would likely occur via the inhalation route. The 4-hour LC_{50} in rats of >102,900 ppm (v/v) indicates that the substance has low acute inhalation toxicity. The NOAEL for cardiac sensitization in dogs was 12,500 ppm. Cardiac sensitization was noted in 4 of 6 dogs following exposure to 25,000 ppm. HFO-1336mzz-Z was not a dermal irritant in the rabbit following 4 hours of exposure. HFO-1336mzz-Z is a substance with a low order of repeated dose toxicity. During 13-week repeated inhalation exposure studies

in rats, no significant adverse effects were noted at 5000 ppm in either sex.

In two inhalation pre-natal developmental toxicity studies, no evidence of embryo/fetal lethality or fetal structural malformations or variations was observed in rats or rabbits. The NOAEL for maternal and fetal effects in rats was 1500 ppm and the NOAELs for maternal and fetal effects in rabbits were 5000 and 7500 ppm, respectively. In a pilot/tolerability study in rats conducted to determine the optimal exposure concentrations for a subsequent multi-generation reproduction toxicity study, the NOAEL based on statistically significantly reduced body weight and body weight gain in male rats was 500 ppm. HFO-1336mzz-Z was not mutagenic or clastogenic in a variety of *in vitro* and *in vivo* studies.

Although three repeated exposure studies (3 weeks or longer duration) had NOAELs ranging from 500-1500 ppm based on body weight reductions, these studies are not appropriate for establishing a point of departure for the WEEL derivation. One of these studies was a non-GLP screen (pilot) for a 2-generation reproductive study in which animals were exposed for 7 days/week and two of these studies were GLP, guideline studies (rat prenatal developmental and 90-day inhalation) which had a NOAEL of 1500 ppm, based on reduced body weight at the next highest exposure concentration of 10000 ppm, which represented a large gap between exposure concentrations. Skeletal fluorosis, based on evidence of fluoride ion release from HFO-1336mzz-Z, may be possible at higher exposure levels. The key study for use as the WEEL derivation point of departure was a rat GLP 90-day (13-week) inhalation study that was conducted to refine the NOAEL. In that key study, the NOAEL was 5000 ppm in male rats based on reduced body weight, and 7500 ppm in females (highest concentration tested).

The NOAEL of 5000ppm based on reduced male body weight in the 13-week rat inhalation toxicity study was selected as the point of departure for derivation of the WEEL value. The inhalation NOAEL was adjusted by application of appropriate uncertainty factors to account for interindividual variability. A WEEL value of 500 ppm is expected to provide an acceptable margin of safety for potential adverse health effects in workers exposed to airborne HFO-1336mzz-Z. The WEEL is also protective against skeletal fluorosis, which may be possible at higher exposure levels because of HFO-1336mzz-Z metabolism.

VII. RECOMMENDED WEEL

8-Hour Time Weighted Average: 500 ppm (3350 mg/m^3)

VIII. REFERENCES

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