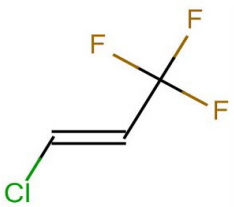
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

trans-1-Chloro-3,3,3-Trifluoropropene (1233zd(E))[2013]

I. IDENTIFICATION

Chemical Name: trans-1-Chloro-3,3,3-trifluoropropylene
Synonyms: HCFO-1233zd, 1233zd(E)
CAS Number: 102687-65-0
Molecular Formula: $C_3H_2ClF_3$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1]

Physical State and Appearance: Low boiling liquid
Odor Description: Slight
Molecular Weight: 130
Conversion Factor: 1 mg/m^3 = 0.190 ppm (20°C and 760 mm Hg), 1 ppm = 5.31 mg/m^3
Melting Point: < -90 °C
Boiling Point: 19°C (66°F)
Vapor Pressure: 1516 hPa @ 30°C
Vapor Density: 5.3 (relative to air = 1)
Saturated Vapor Concentration: Not applicable
Flammability Limits: Non flammable
Flash Point: Not applicable
Ignition Temperature: 380 °C at 986.8 - 1,035.9 hPa
Specific Gravity: 1.27 g/cm^3
Solubility in Water: 1.90 g/l
Stability: Normally stable. Avoid sources of ignition such as sparks and flames which may yield toxic and/or corrosive decomposition products
Reactivity & Incompatibilities: Incompatible with strong oxidizing agents, magnesium and aluminium

III. USES

Trans 1-chloro,3,3,3-trifluoropropene (HCFO-1233zd(E)) is a foam blowing agent, refrigerant and solvent.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Oral Toxicity

The substance is a low boiling liquid and has not been tested for oral toxicity.

2. Eye Irritation

The substance is a low boiling liquid and has not been tested for eye irritation. However, in whole body inhalation studies in rats (2 week exposure up to 20,000 ppm 6 hours/day, 5 days/week for 2 weeks) and rabbits (exposures up to 15000 ppm 6 hours/day, 7 days/week/ gestation days 6-28) no signs of ocular irritation were seen.[2,3]

3. Skin Absorption

No data

4. Skin Irritation

The substance is a low boiling liquid and has been tested for dermal irritation in three New Zealand rabbits. Due to the low boiling point, samples were cooled on ice prior to aliquots (0.5 ml) of sample being placed on the skin. Samples were then covered with a gauze patch and semi-occlusive dressing and secured with non-irritating tape for a 4-hour exposure. It is likely that the actual exposure to the material was less than 4 hours due to its low boiling point. Neither signs of effect from cooling the sample nor any signs of erythema or edema were observed at 1, 24, 48 or 72 hours following patch removal. The test substance is not considered to be a skin irritant.[4]

5. Skin Sensitization

No animal skin sensitization studies were available. Human patch tests have been conducted, see the human use section (Section V) for details.

6. Inhalation Toxicity

A Good Laboratory Practice (GLP) acute inhalation toxicity study was conducted with three groups (5/sex) of Sprague-Daw-

ley CD rats that were exposed nose-only to vapors of HCFO-1233zd(E) at levels of 96,000, 120,000 or 156,000 ppm for 4 hours. At termination, gross necropsy observations revealed red discoloration of the lungs. In addition, signs suggestive of CNS depression such as hunched posture, lethargy, piloerection and restlessness were reported. The 4-hour LC_{50} for HCFO-1233zd(E) was 118,200 ppm for males and 121,700 ppm for females. The combined 4-hour LC_{50} for males and females is 120,000 ppm. The difference between males and females was not significant. Based on these results, HCFO-1233zd(E) is considered practically nontoxic by the inhalation route of exposure.[6]

Acute cardiac sensitization potential was evaluated according to the method described by ECETOC.[7] A group of 6 beagle dogs were exposed to vapors of HCFO-1233zd(E) at concentrations of 25,000, 35,000 or 50,000 ppm. Each exposure level was evaluated on a different day 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 pre-determined maximum sub-arrhythmia dose. During the next five minutes of exposure, the dogs were monitored for the development of a cardiac arrhythmia. No signs of cardiac sensitization were observed in any of the dogs. However, at 35,000 ppm dogs exhibited tremors and excessive salivation that made it impossible to conduct the electrocardiogram (ECG) monitoring. At 50,000 ppm only two dogs were exposed and no ECG measurements were obtained. One dog exhibited convulsions and one dog exhibited tremors which interfered with the ECG data. Based on these findings the threshold for general toxicity (not cardiac sensitization) was 35,000 ppm and the NOEC was 25,000 ppm.[8]

B. Subacute Toxicity

A GLP 2-week inhalation toxicity study was conducted with four groups (5/sex) of Sprague Dawley rats exposed to HCFO-1233zd(E). In this study, groups of rats were exposed to vapors of HCFO-1233zd(E) 6 hours/day, 5 days/wk for 2 weeks. The exposure levels were 0 (control), 2,000, 7,500 or 20,000 ppm. There was no mortality, nor effects on body weight, body weight change or food consumption. Differences from controls in hematology parameters were limited to an increase in prothrombin time in high level females only and the number of neutrophils and monocytes in high level males only. A significant increase was seen in the serum levels of two liver enzymes, alanine transaminase (ALAT) and aspartate (ASAT) in 20,000 ppm males, along with a slight increase in ASAT (high level females). Females in the mid- and high-level exposure groups showed an increase in blood glucose concentrations. Both males and females in the high-level group showed increases in urea levels. While histopathological examination of the kidney and liver did not show evidence for treatment-related effects, these observations could be suggestive of the beginning of effects on these organs. It should be noted that the livers in the 20,000 ppm females did show increases in hepatocellular vacuolation. A decrease in the spleen weight was seen in the 20,000 ppm males, but not the females. This finding did not appear to be significant. Histopathological changes in the heart were seen in the 20,000 ppm males and females and the 7,500 ppm males. These findings were described as multifocal mononuclear cell infiltrates and were slight to moderate in the 20,000 ppm males, very slight to slight in the 20,000 ppm females and very slight in the 7,500 ppm level males.[2] The NOEC is 2,000 ppm.

A GLP 4-week inhalation toxicity study was conducted with five groups (5/sex) of Sprague Dawley rats. They were exposed nose only to vapors of HCFO-1233zd(E) at levels of 0 (control), 2,000, 4,500, 7,500 or 10,000 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, 7,500 and 10,000 ppm groups were evaluated in an Unscheduled DNA Synthesis Test, and bone marrow from male rats in the control, 4,500, 7,500 and 10,000 ppm groups was assessed in a Micronucleus Test. Results of these two mutagenicity tests are presented below under the heading Mutagenicity (Section F1 and F2). No treatment-related abnormalities were seen during clinical examinations. There were no effects on body weight, body-weight gain or food consumption. Unlike the 2-week study, no significant effects were observed in hematology. A statistically significant increase was seen in potassium levels at the two highest exposure levels in the males. This was not seen in the females. Urinalysis met normal parameters. Gross necropsy observations were normal. In the opinion of the study director, treatment-related findings in the heart similar to those seen in the preceding 2-week study were not seen. However, 4 of 5 female rats exposed to 10,000 ppm presented with focal cardiac infiltrates that were considered to be very slight in contrast to 1 of 5 control female rats. As noted in a subsequent peer-review of the cardiac tissues, the severity (minimal to slight) and location of these effects (apex) were consistent with spontaneous lesions known to occur in rats.[9] The incidence in the treated male rats was similar to controls. Based on the slight increase in potassium levels at 7,500 and 10,000 ppm, the NOEC was 4,500 ppm.[10]

C. Subchronic Toxicity

A GLP 13-week inhalation toxicity study was conducted with four groups (10/sex) of Sprague Dawley rats that were exposed nose-only to vapors of HCFO-1233zd(E) at levels of 0 (control), 4,000, 10,000 or 15,000 ppm for 6 hours/day, 5 days/week during a 13-week period, for 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 clinical chemistry parameters showed some slight variations at 15,000 ppm which may be treatment-related. Elevation in AST and ALT were observed in high level males only. 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 hearts of all rats at 15,000 ppm, 7 of 10 males at 10,000 ppm and 1 male at 4,000 ppm. Fibrosis was not observed. Based on these results 4,000 ppm was considered a LOAEC.[9] However, the cardiac tissues were peer-reviewed by an outside board certified veterinary pathologist. The peer-review expert considered the cardiac lesion in the one male at 4,000 ppm not to be adverse based on its location (apex of heart) and its similarity to spontaneous lesions seen in this strain of rat.[11,12] Thus the 4,000 ppm level in this study was considered to be the NOAEC.

D. Chronic Toxicity

No chronic toxicity studies have been conducted on this material.

E. Reproductive/Developmental Toxicity

Groups of 24 mated female Wistar rats were exposed nose-only to levels of 0 (control), 4,000, 10,000 or 15,000 ppm of HCFO-1233zd(E) 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, the number of corpora lutea, the number of 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. A statistically significant increased incidence in dilated urinary bladders, a visceral anomaly, was observed in fetuses of dams exposed to 15,000 ppm. This effect may not be relevant as corresponding kidney abnormalities or increased amniotic fluid, were not observed. It was concluded that the NOEC was 10,000 ppm.[13]

An inhalation prenatal developmental toxicity study of HCFO-1233zd(E) in rabbits was conducted. Four groups of time-mated female New Zealand rabbits (22/group) were exposed by whole-body inhalation to 0 (control), 2,500, 10,000 or 15,000 ppm HCFO-1233zd(E) 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 HCFO-1233zd(E) to pregnant rabbits did not cause maternal or developmental toxicity in this study.[3]

In a 2-generation reproductive toxicity study, groups of 19 Wistar rats were exposed to HCFO-1233zd(E) by nose-only or whole-body inhalation for 6 hours/day, 5 days/week during premating, and daily during mating, gestation and lactation at concentrations of 2,000, 5,000 or 15,000 ppm. No female exposures occurred between gestation Day 19 and lactation Day 4. Mortality occurred in females at the high dose (15,000 ppm) in both the F0 and F1 generations. Two females in the F0 generation were found dead on lactation Days 16 and 17. One female in the F1 generation was found dead on lactation Day 19. Histological evaluation of these animals revealed no obvious cause of death.

There were no other compound related findings in either F0 or F1 generations, including clinical observations, body weights, food consumption, estrus cycles, sperm parameters, mating or fertility, gestation, lactation, parturition, sexual maturation, organ weights, and macroscopic and microscopic evaluations, specially relative to the cardiac lesion seen in the preceding 90-day study, no such microscopic lesions were seen in this strain of rat exposed up to 15,000 ppm.

The NOEC for parental toxicity was considered to be 5,000 ppm and was based on the mortality observed in the high-dose females at 15,000 ppm.

The NOEC for fertility and development was considered to be 15,000 ppm because no adverse effects on fertility, reproduction or development of the offspring were observed.[14]

F. Genotoxicity/Mutagenicity

1. In vitro

A GLP Ames assay was conducted with HCFO-1233zd(E) which involved exposure of bacterial cells *S. typhimurium* TA 1535, TA1537, TA 98, TA 100 and E. coli WP2 uvrA with and without S-9 metabolic activation. Exposure levels of up to 76% (plus 19% O_2 and 5% CO_2) were used. HCFO-1233zd(E) did not induce a response in any strain tested with or without metabolic activation.[15]

A GLP chromosome aberration test was conducted with cultured human lymphocytes that were exposed to vapor levels of HCFO-1233zd(E) up to 50,000 ppm, with and without S-9 metabolic activation. The objective of this study was to assess the potential of HCFO-1233zd(E) to induce chromosome aberrations in human lymphocytes cultured *in vitro*. Cultures were grown in the absence (3-hour treatment with 18-hour recovery or 21-hour treatment) or presence (3-hour treatments with 18-hour recovery) of rat S-9 metabolic activation. HCFO-1233zd(E) did not cause a positive response either in the absence or presence of S-9 metabolic activation. It was concluded that HCFO-1233zd(E) showed no evidence of increasing the frequency of structural chromosome aberrations under the conditions of this test.[16]

2. *In vivo*

In a bone marrow micronucleus study a group of 10 male mice were exposed to a level of 50,000 ppm of HCFO-1233zd(E) for 4 hours. Both positive and negative controls were included. At 24 and 48 hours after the exposure, bone marrow was collected from the femurs of 5 mice and evaluated for the presence of micronucleated polychromatic erythrocytes. It was concluded that the test material did not induce chromosomal damage or damage to the mitotic spindle apparatus (micronuclei) in the target bone marrow cells. Thus it was concluded that HCFO-1233zd(E) was not active in this assay.[17]

A rat micronucleus test was an added procedure to the 4-week inhalation toxicity study (described above), in which groups (5/sex) of Sprague-Dawley rats were exposed nose-only to vapors of HCFO-1233zd(E) at levels of 0 (control), 2,000, 4,500, 7,500 or 10,000 ppm 6 hours/day for 5 days/week. At necropsy, bone marrow from 5 male rats in the control, 7,500 and 10,000 ppm groups was used in the Micronucleus Test. At the highest concentration tested (10,000 ppm), no damage to chromosomes or increased incidence of micronuclei was observed in the bone marrow cells of male rats.[10]

An unscheduled DNA synthesis test was also included in the 4-week inhalation toxicity study (described above) in which groups (5/sex) of Sprague-Dawley rats were exposed nose only to vapors of HCFO-1233zd(E) at levels of 0 (control), 2,000, 4,500, 7,500 or 10,000 ppm 6 hours/day, 5 days/week during a 4-week period. At necropsy, liver cells from male rats in the control, 7,500 and 10,000 ppm groups were used in the unscheduled DNA synthesis test. At the highest concentration tested (10,000 ppm), no unscheduled DNA synthesis was observed in the liver cells of male rats.[10]

G. Metabolism/Pharmacokinetics

The biotransformation of HCFO-1233zd(E) and kinetics of metabolite excretion with urine were assessed *in vitro* and in animals after inhalation exposure. To characterize biotransformation in vitro, liver microsomes from rats, rabbits and humans were incubated with HCFO-1233zd(E). Male Sprague Dawley rats and female New Zealand White rabbits were exposed by inhalation to 2,000, 5,000 or 10,000 ppm of HCFO-1233zd(E) for 6 hours and urine was collected for 48 hours after the end of the exposure. Urine samples and microsomal incubation supernatants were analyzed for metabolites using 19F-NMR, LC-MS/MS and GC/MS.

S-(3,3,3-trifluoro-trans-propenyl)-glutathione was identified as predominant metabolite of HCFO-1233zd(E) in rat, rabbit and human liver microsomes in the presence of glutathione. Products of the oxidative biotransformation of HCFO-1233zd(E) were only minor metabolites when glutathione was present. In rats, both 3,3,3-trifluorolactic acid and N-acetyl-(3,3,3-trifluoro-trans-propenyl)-L-cysteine were observed as major urinary metabolites. 3,3,3-Trifluorolactic acid was not detected in the urine of rabbits exposed to HCFO-1233zd(E). Several minor metabolites formed by alternative reactions of S-(3,3,3-trifluoro-trans-propenyl)-glutathione were also excreted. Quantitation showed rapid excretion of both metabolites with urine $T_{1/2}$ of less than 6 hours in both species. Based on metabolite recovery in urine and estimated doses of HCFO-1233zd(E) received by inhalation, the extent of biotransformation of HCFO-1233zd(E) was determined as approximately 0.01% of received dose in rabbits and approximately 0.002% in rats. Based on metabolite structures, HCFO-1233zd(E) undergoes both oxidative biotransformation and glutathione conjugation at very low rates. The very low extent of biotransformation and the rapid excretion of metabolites formed are consistent with the very low potential for toxicity of HCFO-1233zd(E) in mammals. This metabolic profile is very similar to the tetrafluoro analog, HFO-1234ze.[18]

The blood:air partition coefficient for HFCO-1233zd(E) was determined for rats, rabbits and humans (see table below). As seen in the table below, the blood:air partition coefficient is lower for humans than for rats or rabbits. Therefore, at equivalent exposure concentrations the dose delivered to the systemic circulation of humans is less than half as much as a rat.[19]

Tissue Type	Blood:Air Partition Coefficient * (mean ± standard deviation)
Human Whole Blood, Female	0.586 ± 0.085
Human Whole Blood, Mixed	0.602 ± 0.026
Rabbit Whole Blood	0.897 ± 0.076
Rat Whole Blood	1.49 ± 0.218

*n=10

A PB/PK model was also developed using the structure and function of the physiological model jointly developed by the U.S. Environmental Protection Agency (U.S. EPA), industry and the US Department of Defense scientists. Using this model, the rat NOAEC of 4,000 ppm for 6 hours/day, 5 days/week for 28 days would be equivalent to a concentration of approximately 10,000 ppm in humans exposed for 8 hours/day, 5 days/week for 28 days.[20]

V. HUMAN USE AND EXPERIENCE

HCFO-1233zd(E) was also evaluated for skin sensitization in a human repeated insult patch test (RIPT) under semi-occlusive conditions. One hundred six (106) subjects completed the study. HCFO-1233zd(E) was applied to a semi-occlusive patch which was immediately placed on the skin. The patch was removed from the skin 24 hours later. Subjects were evaluated for irritation at the site of exposure 24–48 hours following patch removal. The induction phase consisted of 9 exposures (3 times a week for 3 weeks). Following a 1–2 week rest period, the subjects were challenged to a single exposure to HCFO-1233zd(E) applied to a fresh area of skin for 24 hours in the same manner described above. Subjects were evaluated for skin irritation at 24 and 48 hours following patch removal. No evidence of skin irritation or skin sensitization was observed in any of the subjects.[5]

VI. RATIONALE

HCFO-1233zd(E) is a non-flammable, low-boiling liquid (BP = 19°C) with a relatively high vapor pressure (1516 hPA@30°C). It is rapidly absorbed into the bloodstream by inhalation, quickly achieves a steady-state concentration, is not metabolized to any significant extent, and then rapidly exits the body by the inhalation route.

This fluorocarbon has low acute inhalation toxicity potential as shown by a 4-hour LC_{50} in rats of 120,000 ppm (v/v) and no evidence of cardiac sensitization at levels as high at 35,000 ppm in dogs. However, general toxicity in this study was observed at 35,000 ppm but not at 25,000 ppm or below. On a repeated exposure basis, it is also low in toxicity. Sprague-Dawley rats exposed 6 hours/day, 5 days/week for 90 days showed no adverse effects during exposure at inhaled levels as high as 15,000 ppm. Following exposure, histopathology was unremarkable except for multifocal mononuclear cell infiltrates in ventricular cardiac tissue – in all rats at 15,000 ppm, in 7 of 10 males at 10,000 ppm but not in 10 of 10 females, and not in 9 of 10 males or 10 of 10 females at 4,000 ppm. However, there was one similar lesion seen in a male rat at 4,000 ppm but it was less severe, located in the apex of the heart, similar to lesions seen spontaneously in this strain of rat, and therefore was not considered to be treatment-related. Hence, the NOAEC for this 90-day study was considered to be 4,000 ppm. Subsequently, in a 2-generation inhalation reproduction study in another strain of rat (Wistar), male and female parental rats exposed at < 15,000 ppm for 11 weeks or longer showed no histopathological cardiac lesions. Tissues were examined by a board certified veterinary pathologist expert. He indicated two distinct patterns of lesions in the hearts. Spontaneous lesions in rat hearts are located primarily in the apex and adjacent sections. Whereas, test article induced changes were observed in the ventricular free wall, heart base or atria. The severity also tended to be more severe in treatment-related lesions.

In other inhalation toxicity studies, this fluorocarbon was not teratogenic in rats and rabbits (NOECs of >10,000 ppm) and had no adverse effects on male or female reproduction in rats at < 15,000 ppm. In addition, it was not mutagenic in a variety of *in vitro* and *in vivo* studies. Finally, based on pharmacokinetic studies using rat and human tissue, blood:air partition coefficients, and PBPK modeling, the very low metabolic activity of this fluorcarbon was confirmed and investigators concluded that rats absorb twice as

much chemical into their bloodstream as humans exposed at the same inhaled level.

Utilizing the 4,000 ppm NOAEC based on cardiac infiltration observed in rats from the 90-day inhalation study, a 10-fold total uncertainty factor for extrapolation would yield a 400 ppm WEEL (8-hour, TWA). However, since the pharmacokinetic data clearly shows that rats would absorb more than twice as much fluorocarbon as humans at the same exposure level, a WEEL value of 800 ppm should be protective.

VII. RECOMMENDED WEEL GUIDE

800 ppm as an 8-hour TWA

VII. REFERENCES

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(2) Subacute (2-week) Inhalation Toxicity Study with HCFO-1233zd(E) in rats. 2008. TNO Study 8157, 15 December, TNO Quality of Life, Zeist, The Netherlands conducted for Honeywell International, ref. MA-RR-08-4253.

(3) HCFO-1233zd Embryo-Fetal Toxicity Study In Rabbits via Whole-Body Inhalation Exposure. 2010. Huntingdon Life Sc. Report 09-4348 2 September, Huntingdon Life Science, East Millstone, NJ conducted for Honeywell International, MA-RR-10-4311.

(4) 1233zd(E) Acute dermal irritation in rabbits. 2012. MB Research Report, 31 May, Report MB-12-20766.03 conducted for Honeywell International ref MA-RR-12-4342.

(5) Repeated Insult Patch Study. 2012. TKL Research Study Number 103122. July 3, MA-RR-12-4343.

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(7) ECETOC. 2009. Evaluation of Cardiac Sensitization Test Methods, Technical Report No. 105. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium.

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(9) Peer review of hearts from inhalation toxicity studies with various fluorocarbons. 2011. Environmental Pathology Laboratories, Sterling VA, conducted for Honeywell International, ref MA-RR-11-4335.

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(12) Lack of Toxicological Significance of Myocardial Lesion in Rat B0022 Exposed to 4,000 ppm HCFO-1233zd(E). 2013. Environmental Pathology Laboratories, Sterling VA, conducted for Honeywell International, March.

(13) HCFO-1233zd(E) Embryo-fetal Toxicity Study in Rats via Inhalation. 2009. TNO Study 8965, 18 September, TNO Quality of Life, Zeist, The Netherlands conducted for Honeywell International, ref. MA-RR-10-4294.

(14) Two-generation reproduction study by inhalation with 1233zd(E) in Wistar Rats. 2012. TNO Triskelion, Ziest, The Netherlands conducted for Honeywell International, 3 December, ref MA-RR-12-4355.

(15) Bacterial Reverse Mutation Test with 1233zd(E). 2011. BioReliance Study AC12HE.502700.BTL, 11 January, conducted for Honeywell International, ref. MA-RR-08-4247.

(16) HCFO-1233zd *In Vitro* Mammalian Chromosome Aberration Test In Human Lymphocytes. 2010. Huntingdon Life Sc. Report NBJ0048, 21 June, Huntingdon Life Sciences, Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England conducted for Honeywell International, MA-RR-10-4307.

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(18) Schmidt T, Bertermann R, Rusch G, Tveit A, Dekant W. 2013. Biotransformation of trans-1-chloro-3,3,3-trifluoropropene (trans-HCFO-1233zd). Toxicol Appl Pharmacol (e-pub Feb 18, 2013).

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