Interim Specific Groundwater Criterion Support Document 1,1,1-Trifluoroethane (HFC-143a) *

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Summary
An interim specific ground water criterion of 5000 µg/L is derived for 1,1,1-trifluoroethane. The risk assessment is based on a NOAEL of 40,000 ppm, the highest exposure level administered, in a 90 day subchronic inhalation study in rats.

Physical and Chemical Properties (OECD, 2010, unless otherwise noted)

Chemical Name:	1,1,1-Trifluoroethane
CAS Number:	420-46-2
Common name:	HFC-143a
Synonyms:	Trifluoroethane; R-143a
Empirical Formula:	$C_2H_3F_3$
Structural Formula:	
Molecular Weight:	84
Form:	Clear, colorless gas
Odor:	Odorless
Melting Point:	-111.3◦C
Boiling Point:	-47.4◦C @101.3 kPa
Vapor Pressure:	12620-12720 kPa @ 25◦C
Water Solubility:	761 mg/L @ 25 ◦C
Octanol/Water Partition Coefficient:	Log K_{ow} = 1.74
Flammability:	7.1 – 16.1% @ 20-25 ◦C
Liquid density:	1.176 g/cm3 @ 50◦C (ECETOC)
Conversion factor:	1 ppm = 3.44 mg/m^3 (25° C, 1 atmosphere); (calculated using NIOSH, 2003)

Production and Use

1,1,1-trifluoroethane is commonly produced by the hydrofluorination of 1,1-dichloroethylene. Worldwide production of 1,1,1-trifluoroethane was estimated at 10,000 to 50,000 tons in the year 2006 (OECD, 2010). As reported in the most recent publically available data included in the Alternative Fluorocarbons Environmental Acceptability Study (AFEAS), the annual world-wide (exclusive of China and India) production of 1,1,1-trifluoroethane for 2007 was 18,325 metric tons (AFEAS, 2009). There are two identified production sites, one in the U.S. and one in France. It is produced at a purity of >99.9% and sold as a liquefied gas. 1,1,1-Trifluoroethane is mainly used in stationary air conditioning systems and commercial refrigeration (OECD, 2010).

Environmental Fate and Transport

Based on its octanol/water partition coefficient, water solubility, and vapor pressure, 1,1,1-trichlorofluorethane is expected to have a low potential for bioaccumulation, and to volatilize from surface water to air. Its half-life for photodegration is approximately 9,600 days (OECD, 2010).

Guidelines, Regulations, and Standards

No criteria or standards developed by other government agencies for 1,1,1-trifluoroethane in drinking water, ground water, surface water, or soil were located.

Pharmacokinetics and Metabolism

Absorption

1,1,1-Trifluoroethane is absorbed in rats by inhalation, as demonstrated by urinary excretion after inhalation exposure (OECD, 2010). Studies of absorption by other routes (e.g. oral, dermal) were not located.

Human studies have shown a rapid uptake of 1,1,1-trifluoroethane, reaching steady-state within a few minutes. Nine male volunteers were exposed to 500 ppm of 1,1,1-trifluoroethane for 2 hours during light physical exercise in an exposure chamber. At steady-state, the concentration in the blood was 3-10 μM (252-840 μg/L). Using physiologically based toxicokinetic modeling, it was estimated that 1.6% of the amount inhaled was absorbed (Gunnare et al., 2007).

Distribution

Distribution of 1,1,1-trifluoroethane has not been studied *in vivo*. In unpublished rat studies (Keller, 1994), partition coefficients between tissue and air were determined, as follows: 0.66 – blood : air, 1.13 – liver : air, 1.04 – fat : air, 0.99 – muscle : air.

Metabolism

Metabolism of 1,1,1-trifluoroethane was studied in male rats (3 per group) exposed by inhalation to 100, 390, 1040, 2050, 4800, or 40,000 ppm for 4-5 hours (Keller, 1994). In the 40,000 ppm group, the major urinary metabolite was trifluoroethanol, and the minor metabolites included the

glucuronide conjugate of trifluoroethanol, trifluroacetic acid, trifluoroacetaldehyde, and the urea conjugate of trifluoroacetaldehyde. No metabolites were detected in the urine from the 4800 ppm and lower groups.

Excretion
As discussed above, metabolites of 1,1,1-trifluoroethane are excreted in the urine in rats.

In male human volunteers exposed by inhalation to 500 ppm 1,1,1-trifluorethane for 2 hours, the concentration in plasma decreased rapidly when exposure was stopped. Using physiologically based toxicokinetic modeling, it was estimated that 1.2% of the total amount that was inhaled into the lung was exhaled unchanged after the exposure ended; this represents the amount that was absorbed into the body and excreted unchanged from the lungs. The mean urinary excretion of 1,1,1-trifluoroethane was measured as 0.0007% of the inhaled amount. The half-time for urinary excretion was 53 minutes (Gunnare et al., 2007).

Excretion by other routes (e.g. fecal) has not been studied.

Toxicity

Acute Toxicity

Oral
No oral studies of acute effects were located.

Inhalation
In a nose-only inhalation study, Charles River male rats (6 per group) exposed to 1,1,1-trifluoroethane concentrations of 97,000 or 540,000 ppm for 4 hours. The animals were observed during and immediately after exposure. They were then weighed and observed for clinical signs of toxicity during a 14-day post-exposure period (Brock et al., 1996). No mortality was observed following the 4-hr exposure, and the 4-hour inhalation LC50 was considered to be >540,000 ppm. During exposure, rats in both groups exhibited ocular and nasal discharges, but these are normally observed in nose-only exposure studies and were not attributed to compound exposure. Slight body weight losses (<10 g per rat) were observed in rats exposed to 97,000 ppm on the day following exposure. Moderate to severe weight losses (10 to >20 g per rat) were observed in rats exposed to 540,000 ppm 1,1,1-trifluoroethane. However, by 2 days after exposure and through the remainder of the 14-day observation period, normal weight gains were observed in all exposed rats from both groups (Brock et al., 1996).

Sprague-Dawley rats (5 per sex per group) were exposed nose-only to 0, 305,000, or 591,000 ppm 1,1,1-trifluoroethane for 4 hours; no mortality was observed at either concentration. Changes in respiratory pattern were observed for one male and one female exposed at 305,000 ppm and for one female exposed at 600,000 ppm. Peripheral vasodilatation was observed for one male and four females exposed at 591,000 ppm. No treatment related clinical signs were recorded during a 14-day post-exposure observation period. Macroscopic pathology and organ weight examinations did not reveal any treatment-related effect. Body weight and body weight gain appeared normal aside from a slight decrease noted on the day following the exposure,

which was attributed to the restraint system used. The 4-hour LC50 was greater than 600,000 (Cracknell, 1992).

Male Wistar rats were exposed by inhalation for 4 hours to concentrations of 5,500, 10,000, 16,000, 20,000, or 30,000 ppm. A significant decrease in liver glutathione was seen in rats exposed to concentrations of 10,000 ppm and above, but there was no change in glutathione disulfide levels in the liver, or glutathione levels in the lungs. There were no changes in serum levels of glutamate dehydrogenase, sorbitol denydrogenase, or lactate dehydrogenase; according to the authors, this indicated that tissue damage did not occur (Loizou et al., 1996).

In 9 male human volunteers exposed to 500 ppm for 2 hours there were no effects on electrocardiographic readings, and no supraventricular or ventricular extrasystoles were recorded. There were no effects of exposure related to irritation measured as ratings on a visual analog scale. Inflammatory markers including C-reactive protein, serum amyloid A protein, D-dimer, and fibrinogen as well as uric acid, were analyzed in plasma before and 1 day after exposure. Plasma fibrinogen was increased 1 day post-exposure in all 9 subjects, by 2.3% to 23%, with a mean increase of 11% ($p=0.0006$). No statistically significant increase was seen in other inflammatory markers or for uric acid. The mechanism for this increase in fibrinogen levels is unknown (Gunnare et al., 2007).

Dermal
Testing using dermal exposure was not conducted because the compound is a gas at room temperature.

Short Term and Subchronic Toxicity

Oral
No oral short term or subchronic studies are available.

Inhalation
In an initial 4-week nose-only inhalation study, four groups of 10 male and 10 female rats were exposed 6 hours/day, 5 days/ week at concentrations 0, 2000, 10,000, or 40,000 ppm. Decreases in mean body weights of male rats exposed to 2000, 10,000, or 40,000 ppm were observed periodically during the study with no changes in food consumption in male rats. There were no body weight changes in female rats. No significant changes in organ weights were noted within the treatment groups.

In all of the groups of male rats exposed to 1,1,1-trifluoroethane, there were degenerative changes in the testes (eosinophilic debris within the lumen of the seminiferous tubules) (Brock et al. et al., 1996). Tubular structure and germ cell necrosis were not prominent. In the epididymides, decreased sperm cell density and increased exfoliated germ cell debris were correlated with the severity of the testicular damage. These effects occurred in 7 to 8 of the 10 rats per group, and were minimal to mild, in the 10,000 and 40,000 ppm. In the 2000 ppm group, they were seen in 3 of 10 rats and were very slight. It was noted that during the study, there were problems with the proper fit of the conical restraining devices used in nose-only

exposure studies, and that high temperature conditions occurred in the 1,1,1-trichloroethane exposure chambers on several occasions.

Brock et al. (1996) state that stresses such as those the high temperatures experienced by the exposed rats in the nose-only study are known to have adverse effects on the testes and fertility of both rats and humans (Van Demark and Fre, 1970). Since there were concerns that the testicular effects seen in the nose only study were related to these stresses, the entire study was repeated in male rats using whole body exposures under normal chamber conditions and without restraints. No adverse testicular effects or clinical signs were seen at any exposure level in this second 4 week study, nor in the 90 day study (below). Based on these results, the authors considered the testicular effects seen in the nose-only study to be an artifact of the exposure systems, and the authors state that 40,000 ppm was the NOAEL for 4 week exposure (Brock et al., 1996).

In a 90-day whole-body inhalation study, male and female rats (20 per sex per exposure level) were exposed for 6 hours/day, 5 days/ week, to 0, 2000, 10,000, or 40,000 ppm. Changes in body weight observed throughout the study occurred inconsistently and did not exhibit a dose-response relationship. No changes in food consumption were observed. These changes were not considered to be compound-related. There were no clinical signs of toxicity, effects on organ weight, or adverse gross or microscopic pathology changes. Beta-oxidation, a measure of peroxisome proliferation, was not affected. Since there was no evidence of toxicity at any exposure concentration, the NOAEL for rats exposed up to 90 days was considered to be 40,000 ppm (Brock et al., 1996).

Neurological Toxicity

No studies have been conducted that specifically examine the effects of 1,1,1-trifluoroethane on the nervous system. No neurological conditions were noted in the self-evaluations by human male volunteers exposed to 1,1,1-trifluoroethane (Gunnare et al., 2007).

Chronic Toxicity and Carcinogenicity

Oral

In a limited study evaluating the carcinogenicity of 1,1,1-trifluoroethane, rats (36 per sex) were dosed for one year by gavage 5 days a week with 1,1,1-trifluoroethane dissolved in corn-oil at a single dosage of 300 mg/kg body weight. There was a non-dosed control group (32 per sex) and a vehicle control group (40 per sex). Four other fluorocarbons were also tested at 300 mg/kg/day in this study. No range finding studies were conducted prior to the chronic study to determine the appropriate dose range, including the maximum tolerated dose. The animals were then observed until week 125 with detailed necropsy at termination (Longstaff et al., 1983).

Mortality was not increased in the rats treated with 1,1,1-trifluoroethane. Body weight in the male rats dosed with 1,1,1-trifluoroethane was significantly decreased ($p<0.05$) between weeks 28 and 88. The numerical body weight data are not provided.

In this study, only the incidence of neoplasms was reported, and non-neoplastic gross or histological pathology findings were not reported. Blood or urine was not evaluated for clinical

chemistry parameters in this study. Numerical data on the incidence of neoplasms are not presented, and the results provided are limited to the following statement that refers to 1,1,1-trifluoroethane and two of the of the other fluorocarbons that were tested (Longstaff et al., 1984): "No significant increase in the incidence of neoplasms in any organ was observed. In most organs, the incidence of neoplasms was small. In the mammary gland of females, pituitary gland of males, and the skin of males, there were no significant increases in the incidences of neoplasms as a result of treatment and the incidences observed were similar to that expected for the strain of rat used. No increased incidence in pancreatic acinar cell adenomas or carcinomas was observed between corn-oil treated and untreated control groups."

Due to its limited design and the limited results presented, the only conclusion that can be made from the information presented is that chronic oral exposure to 1,1,1-trifluoroethane significantly decreased body weight in male rats, and that no increased incidence of neoplasms was detected in groups of 36 male and female rats. It should be noted that larger groups of animals (e.g. 50 per sex) are normally used in chronic studies conducted by NTP.

Inhalation
A chronic inhalation study of 1,1,1-trifluoroethane has not been conducted.

Reproductive and Developmental Toxicity

No reproductive toxicity study, such as a two generation study, has been performed for 1,1,1-trifluoroethane.

In a rat developmental toxicity study, pregnant females (approximately 25 per group) were exposed whole-body to 1,1,1-trifluoroethane concentrations of 0, 2000, 10,000, or 40,000 ppm for 6 hours daily on gestation day 6 through 15. No adverse clinical signs were noted at any exposure level or biologically significant effects on body weights, body weight gains, or food consumption were noted (Brock et al., 1996).

In the rat, the incidence of reproductive parameters and the incidence of malformations were unaffected by exposure to 1,1,1-trifluoroethane. However, the mean percentage (on a per litter basis) of visceral variations due to retarded development was significantly increased at all exposure levels. The mean % of visceral variations per litter in the control, low, medium, and high groups (respectively) were 1.6, 10.5, 8.7, and 10.0%. The occurrence of specific types of visceral variations (# of fetuses, followed by # of litters in parentheses) in the 0, 2000, 10,000, and 40,000 ppm groups, respectively were: Patent ductus arteriosis: 0, 0, 5(1), and 1(1). Small papilla: 3(3), 19(11), 10(8), 13(8). The mean percent per litter of combined visceral, skeletal, and external variations was increased in all exposure groups, and was statistically significantly increased in the high exposure group. The mean percent per litter of combined variations in the control, low, medium, and high exposure groups was 7.9, 12.8, 12.6, and 16.7%, respectively. The increased incidence of variations was attributable to only visceral and skeletal variations. Data on skeletal variations are not provided, and no external variations were observed in any group (Brock et al., 1996).

Brock et al. (1996) state that the increase in variations is due to an unusually low incidence of variations in the control group, and that the incidence of variations seen in the treated groups is within the range seen historically in controls in inhalation studies in the laboratory. It is stated that the mean historical incidence of variations in controls is 10.5% and the range is 6.8 to 16.2%. Based on this, the authors concluded that the increased incidence of variations was unrelated to compound exposure. However, it is not clear from the information provided by the authors if this mean and range for historical incidence data refer to total variations or visceral variations, for which a significant increase was seen in all exposed groups in this study. Without this specific information, it is not possible to evaluate their comparisons to historical control incidence.

In a rabbit developmental toxicity study, pregnant females (24 per group) were exposed whole-body to 1,1,1-trifluoroethane concentrations of 0, 2000, 10,000, or 40,000 ppm for 6 hours daily on gestation day 6 through 18. No adverse clinical signs were noted at any exposure level or biologically significant effects on body weights, body weight gains, or food consumption were noted (Brock et al., 1996).

In the rabbit, there was a slight increase (not statistically significant) in the incidence of combined malformations (mean % per litter) in the 2000 and 40,000 ppm groups. The mean percentage of offspring with malformations per litter was 3.1, 8.2, 3.4, and 7.1% in the control, high, medium, and low dose groups, respectively. The increased incidence was primarily related to increased skeletal malformations (anomalies in the ribs such as extra sites of ossification, and vertebral anomalies). The percentage incidence of skeletal malformations per litter was 1.5, 7.5, 3.4, and 6.3%, respectively. No clear dose-response was apparent in either the types or numbers of malformations, and the incidence was within the historical control range for total malformations (Brock et al., 1996).

Genotoxicity/Mutagenicity

1,1,1-Trifluoroethane was positive in the Ames assay both with and without metabolic activation using the two *Salmonella typhimurium* strains TA1535 and TA100 (Longstaff et al., 1983). In these studies, bacteria were exposed to varying concentrations of 1,1,1-trifluorethane in closed vessels for 48 hours. The maximum effective concentration for a mutagenic response was 50% in both strains. In later studies, two separate Ames assays with and without metabolic activation in 4 or 5 strains of *S. typhimurium* and one strain of *E. coli* were negative. In this study, the bacteria were exposed on plates to 1,1,1-trifluoroethane in air at concentrations of 3.5% to 100% in closed vessels at 37^{O}C for 48 hours (Brock et al., 1996).

1,1,1-Trifluoroethane was negative for cytotoxicity and cell transformation in baby hamster kidney (BHK21) cells with metabolic activation (Longstaff et al., 1983). *In vitro* clastogenic activity was determined with human lymphocytes, exposing the isolated cells to concentrations up to 3.5%. No statistically significant increases in chromosomal aberrations were observed at any of the concentrations tested, with or without metabolic activation (Brock et al., 1996). In the *in vivo* micronucleus study, male and female mice were exposed to 1,1,1-trifluoroethane at concentrations of 2000, 10,000, and 40,000 ppm for 6 hours/day on 2 consecutive days. No clinical signs of toxicity were evident during the exposures or after the exposures. No

statistically significant increase in micronucleated polychromatic erythrocytes in bone marrow, and no significant decrease in polychromatic erythrocytes in peripheral blood was observed in either male or female mice at any sacrifice interval (Brock et al., 1996).

Development of Toxicity Factor

Choice of Appropriate Carcinogenicity Descriptor

Based on the USEPA (2005) Guidelines for Carcinogen Risk Assessment, the available data on 1,1,1-trifluoroethane suggests that it is most appropriate to consider it as Not Likely to Be Carcinogenic to Humans for the purposes of risk assessment.

Derivation of Reference Dose

Several of the studies and endpoints discussed above were considered as the basis for the Reference Dose for 1,1,1-trifluoroethane.

The increased incidence of variations in the inhalation developmental study (Brock et al., 1996) was considered as a possible basis for the RfD. In this study, visceral variations were significantly increased at all exposure levels, and total variations (including visceral, skeletal, and external variations) were significantly increased at the highest exposure level. The authors discounted the relevance of these observations by stating that the incidence of variations in the control group was below historical control incidence in the laboratory, and that the incidence in the exposed groups was within the historical controls range. However, it is unclear from the information provided whether the authors compared the incidence of **visceral** variations to the historical control incidence of **visceral** variations or to the historical incidence of **total** variations. The historical incidence database is not available to clarify this uncertainty, and these uncertainties preclude the use of this endpoint as the basis for risk assessment. Additionally, there was a suggestion of increased incidence of malformations, particularly skeletal malformation, in rabbits, but it was not statistically significant and there was not a clear dose-response for this effect. Although the data are suggestive in both species that 1,1,1-trichloroethane exposure increased the incidence of variations, for these reasons, the developmental variations were not used as the basis for the RfD.

In the chronic oral study in which rats were exposed to 300 mg/kg/day for 52 weeks, the authors reported that body weight was significantly ($p<0.05$) decreased in males from weeks 28 to 88 (Longstaff et al., 1983). This time period extends to 36 weeks after exposure ended. No data or discussion is provided on the magnitude of the body weight decrease. Despite the statistical significance of the body weight decrease, if the magnitude of the decrease was, in fact small (e.g. <10%), it would not necessarily be considered an adverse effect. Thus, in the absence of these data, this endpoint cannot be used as the quantitative basis of the RfD. However, consideration of the decreased body weight observed by Lonstaff et al. (1983) should not be entirely dismissed because it occurred in the only oral study conducted on the compound, which was also the only chronic study that has been conducted.

The NOAEL of 40,000 ppm from the subchronic rat inhalation study (Brock et al., 1996) is selected as the basis for the Reference Dose. This was also the highest concentration used in the rat and rabbit developmental studies (Brock et al., 1996).

The inhalation NOAEL can be converted to an oral NOAEL by multiplying by the default daily inhalation volume, 20 m^3/day and body weight, 70 kg, and adjusting for the fact that exposure occurred for 5 of 7 days per week, 6 of 24 hours per day, as follows:

40,000 ppm = 137,000 mg/m^3

$$\frac{137{,}000\ mg/m^3 \times 20\ m^3/day \times 6\ hrs/24\ hrs \times 5/7\ days\ per\ week}{70\ kg} = 7000\ mg/kg/day$$

The uncertainty factors applied to derive the Reference Dose are:

10 – Interspecies, to account for animal-to-human variability
10 – Intraspecies variability, to protect sensitive subpopulations
10 – Subchronic-to-chronic
10 – Database insufficiency - to account for lack of two-generation reproductive study, and for insufficient data to evaluate the potential for decreased body weight from chronic exposure

The total UF is 10,000

RfD = 7,000 mg/kg/day/10,000 = 0.7 mg/kg/day.

Derivation of Interim Specific Ground Water

New Jersey ground water criteria are based on the assumptions for chronic drinking water exposure.

The interim specific criterion is derived as follows:

$$\frac{0.7\ mg/kg/day \times 70\ kg \times 0.2}{2\ L} = 5\ mg/L = 5000\ \mu g/L$$

Where:
0.7 mg/kg/day = RfD
70 kg = assumed body weight of adult
2 L/day = assumed daily drinking water ingestion volume
0.2 = Relative Source Contribution factor to account for non-drinking water exposures

Discussion of Uncertainties

This interim specific ground water criterion was developed using risk assessment approaches generally used by USEPA and NJDEP. These approaches are based on reasonable, but health protective, assumptions and approaches. Uncertainties in this risk assessment are common to all risk assessments based on animal data, including the assumption that effects observed in experimental animals are relevant to humans and that effects observed at higher levels can be used to develop health-based criteria for environmental exposures to lower levels. Uncertainties specific to this risk assessment relate to deficiencies in reporting of data leading to the inability to sufficiently evaluate the potential for 1,1,1-trifluoroethane to cause developmental variations in rats and to cause decreased body weight in male rats after oral exposure, due to the inadequate presentation of information relevant to these endpoints in the publications in which these effects were observed. An additional uncertainty in this risk assessment is route-to-route extrapolation of inhalation data to develop an oral Reference Dose. However, the endpoints of concern for 1,1,1-trifluoroethane are not related to the point of entry, and no data are available to suggest that absorption, metabolism, distribution, or excretion differ between inhalation or oral exposure.

Confidence in this assessment

Due to the availability of only a single chronic duration study, which included only a single dose level which had not been determined to be the Maximum Tolerated Dose, and to deficiencies in the reporting of data in that study, as well as data reporting deficiencies in the key developmental study and the lack of a study of reproductive effects, the confidence in this assessment is judged to be low.

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