UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: September 29, 2005

ACTION MEMORANDUM

SUBJECT: Inert Reassessment: Ethane, 1,1,1,2-Tetrafluoro-; CAS Reg. No.811-97-2

FROM: Pauline Wagner, Chief Pauline Wagner 9/29/05
Inert Ingredient Assessment Branch
Registration Division (7505C)

TO: Lois A. Rossi, Director
Registration Division (7505C)

I. FQPA REASSESSMENT ACTION

Action: Reassessment of one inert exemption from the requirement of a tolerance

Chemical: Ethane, 1,1,1,2-tetrafluoro-

CFR: 40 CFR part 180.910

CAS #: 811-97-2: Ethane, 1,1,1,2-Tetrafluoro-

Use Summary: 1,1,1,2-Tetrafluoroethane is used primarily as a refrigerant for 'high-temperature' refrigeration, such as domestic refrigerators and automobile air conditioners. Other potential uses include application in plastic foam blowing, as a solvent for special cleaning applications, as an aerosol propellant for medical inhalers, as an extraction solvent for food flavors and fragrances from plant materials, and as a fire extinguishant.

List Reclassification Determination: *The current List Classification for 1,1,1,2-tetrafluooroethane is 4B; it will retain its current Classification.*

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient 1,1,1,2-tetrafluoroethane and with the List reclassification determination as described above. I consider the one exemption established in 40 CFR part 180.910 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi, Director
Registration Division

9/29/05
Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
REVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 29, 2005

MEMORANDUM

SUBJECT: Reassessment of One Exemption from the Requirement of a Tolerance for 1,1,1,2-Tetrafluoroethane

FROM: Bipin Gandhi
Inert Ingredient Assessment Branch
Registration Division (7505C)

TO: Pauline Wagner, Chief Pauline Wagner 9/29/05
Inert Ingredient Assessment Branch
Registration Division (7505C)

Background

Attached is the science assessment for 1,1,1,2-tetrafluoroethane. The purpose of this document is to reassess one existing exemption from the requirement of a tolerance for residues of this inert ingredient when used in pesticide formulations as required under the Food Quality Protection Act (FQPA section 408). This assessment summarizes available information on use, physical/chemical properties, toxicological effects, environmental fate, ecotoxicity, and exposure profile of 1,1,1,2-tetrafluoroethane. In performing this assessment, the Agency has relied extensively upon information found on Toxnet SIS, a review performed by the World Health Organization (WHO, 1998) and selected primary literature.

Executive Summary

This report evaluates 1,1,1,2-tetrafluoroethane, a pesticide inert ingredient for which one exemption from the requirement of a tolerance exists for its residues when used in pesticide formulations as an aerosol propellant applied to growing crops or to raw agricultural commodities after harvest under 40 CFR §180.910.

1,1,1,2-Tetrafluoroethane is a gas under normal conditions. For toxicological endpoints, animal inhalation studies indicate that 1,1,1,2-tetrafluoroethane is low in acute and chronic toxicity. Reported inhalation LD_{50} values for rodents are above 700,000 ppm, and a NOAEL for subchronic inhalation exposures of 10,000 ppm (41,700 mg/m^3) was reported. Developmental effects have been reported in rodents and rabbits exposed via inhalation to 1,1,1,2-tetrafluoroethane, but only at concentrations of 50,000 ppm or higher. Oncogenicity data are limited to one inhalation study in which an increased incidence of benign Leydig cell adenomas were seen in male rats following exposure to 50,000 ppm of 1,1,1,2-tetrafluoroethane for 2 years; however, these tumors are commonly seen in this strain of rat. Genotoxicity tests on 1,1,1,2-tetrafluoroethane have reported negative results.

The results of an acute neurotoxicity study in rats indicate that inhalation exposure to 1,1,1,2-tetrafluoroethane concentrations of 40,000-140,000 ppm for up to 30 minutes induced dose-dependent neurobehavioral deficits ranging from reduced operant efficiency to apparent anesthesia. These exposure concentrations far exceed any level that would occur from the use of 1,1,1,2-tetrafluoroethane as a pesticide inert ingredient.

Exposure of 1,1,1,2-tetrafluoroethane is predominantly via the inhalation route because of the chemical's gaseous nature. No exposure through diet (food and drinking water) or dermal routes are anticipated.

In addition, the U. S. Food and Drug Administration has approved the use of 1,1,1,2-tetrafluoroethane as a propellant in drug inhalers and as an extraction solvent for food flavors and fragrances from plant materials (FDA, 2002).

Taking into consideration all available information on 1,1,1,2-tetrafluoroethane, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to 1,1,1,2-tetrafluoroethane when considering exposure through food/non-food commodities and all other nonoccupational sources of inhalation exposure for which there is reliable information. Therefore, it is recommended that the one (1) exemption from the requirement of a tolerance established for residues of 1,1,1,2-tetrafluoroethane when used as an aerosol propellant in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

1,1,1,2-Tetrafluoroethane (CAS Reg. No. 811-97-2, TFE; HFC 134a), a gaseous fluorocarbon, is being evaluated as part of EPA's tolerance reassessment process of inert ingredients. Commercially, 1,1,1,2-tetrafluoroethane is produced by the reaction of hydrogen fluoride with trichloroethylene in a closed system (WHO 1998). It is available as a liquefied gas and is supplied in a variety of pressurized containers. 1,1,1,2-Tetrafluoroethane is used primarily as a refrigerant for "high-temperature" refrigeration, such as domestic refrigerators and

automobile air conditioners. Other potential uses include application in plastic foam blowing, as a solvent for special cleaning applications, as an aerosol propellant for medical inhalers, as an extraction solvent for food flavors and fragrances from plant materials, and as a fire extinguishant in place of halons.

In performing this assessment, the Agency has relied extensively upon information found on Toxnet SIS, a review performed by the World Health Organization (WHO, 1998), and selected primary literature.

II Use Information

A. Pesticide Uses

The one tolerance exemption for 1,1,1,2-tetrafluoroethane being reassessed in this document is given in Table 1 below.

Table 1. Tolerance exemption

Tolerance Exemption Expression	40 CFR §	Use Pattern (Pesticidal)	Limits	CAS Reg. No./Name
1, 1, 1, 2 - Tetrafluoroethane	180.910[1/]	Aerosol propellant	- - -	811-97-2 Ethane, 1,1,1,2-tetrafluoro- (9CI)

1. Residues listed in 40 CFR §180.910 are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops or to raw agricultural commodities after harvest.

B. Other Uses

1,1,1,2-Tetrafluoroethane is used primarily as a refrigerant for 'high-temperature' refrigeration, such as domestic refrigerators and automobile air conditioners. Other potential uses include application in plastic foam blowing, as a solvent for special cleaning applications, as an aerosol propellant for medical inhalers, as an extraction solvent for food flavors and fragrances from plant materials, and as a fire extinguishant.

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of 1,1,1,2-tetrafluoroethane are given in Table 2 below.

TABLE 2. The physical and chemical properties (Toxnet SIS, 2005a and WHO, 1998)

Name/CAS Reg. No.	1,1,1,2-Tetrafluoroethane/811-97-2
Synonyms:	Norflurane R134a HFC 134A HFA 134A HCFC 134A TFE
Structure:	
Molecular formula:	$C_2H_2F_4$
Molecular weight	102.03
Form	Gaseous fluorocarbon
Odor:	Faint ether like odor
Boiling point:	-26° C@ 736 mm Hg
Melting point:	-101° C
Relative Vapor Density (air =1)	3.5
Vapor pressure:	4730 mm Hg at 25°C
Solubility	67 mg/L at 25°C (est) in water; >10% in ether
Partition Coefficient: log Kow	1.274 (est)

IV. Hazard Assessment

A. Hazard Profile

Much of the toxicity information available for 1,1,1,2-tetrafluoroethane presented in this profile is from the WHO (1998) report, from Toxnet SIS, and selected primary literature. Based on these references and sources there is sufficient information to conduct this assessment.

B. Toxicological Data

Acute toxicity

1,1,1,2-Tetrafluoroethane has low acute inhalation toxicity in laboratory animals. It is acutely lethal to rats only at very high inhalation exposure levels. The acute inhalation toxicity studies in laboratory animals are summarized in Table 3.

No central nervous system effects were observed in several inhalation studies in which rats were exposed to 50,000 ppm (208,500 mg/m^3) 1,1,1,2-tetrafluoroethane (Riley et al. as cited in Toxnet SIS). Contrary to this finding, a recent study by Ritchie et al. (2001) reported that exposure of rats to 1,1,1,2-tetrafluoroethane concentrations ranging from 40,000 ppm (166,800 mg/m^3) to 470,000 ppm (2,000,000 mg/m^3) for up to 30 minutes induced dose-dependent neurobehavioral effects.

In studies with rats high exposures to 1,1,1,2-tetrafluoroethane caused signs of pronounced CNS depression, such as lethargy, unresponsiveness, incoordination, respiratory distress, depression, and convulsions (Silber, 1979b, as cited in Toxnet SIS).

TABLE 3. Acute inhalation toxicity values of 1,1,1,2-tetrafluoroethane in laboratory animals

Species	Exposure	Effects/Comments	Reference
Rat	81,000 ppm (337,770 mg/m^3)	No effects	ECETOC, as cited in WHO (1998)
Rat	567,000 ppm (2.36x10^6 mg/m^3); 750,000 ppm (3.12 x10^6 mg/m^3);	4-hr lethal concentration 30-min LC_{50} (estim.)	Silber, 1979b, as cited in Toxnet SIS
Rat	>200,000 ppm (834,000 mg/m^3)	Depression of central nervous system.	Standring (personal communication), as cited in WHO (1998)
Dog	40,000 ppm (166,800 mg/m^3) 80,000 ppm (10 min) (333,600 mg/m^3) 160,000- 320,000 ppm (10 min) (667,200 mg/m^3 – 1,334,400 mg/m^3)	No effect on epinephrine-induced cardiac sensitization. Positive responses for cardiac sensitization. 50% effective concentration for cardiac sensitization.	Hardy et al., as cited in Toxnet SIS

Subacute/subchronic Toxicity:

A 14-day inhalation toxicity study (Toxnet SIS) was conducted on 10 male rats/group. The rats were exposed to air or 100,000 ppm (417,000 mg/m^3) 1,1,1,2-tetrafluoroethane, 6 hours/day, 5 days/week (duration adjusted concentration = 74,500 mg/m^3). There were no compound-related changes in survival, body weight, hematology, blood chemistry, gross necropsy, or histopathology. The only clinical sign reported was an increased breathing rate during exposure. Focal interstitial pneumonitis was observed to the same extent in controls as in exposed rats. Increased urinary fluoride showed that the administered 1,1,1,2-tetrafluoroethane was absorbed and metabolized to a small extent. The NOAEL was 100,000 ppm and the LOAEL was not determined.

A 28-day inhalation toxicity study was performed by Riley et al. (Toxnet SIS) in which 16 rats/sex/group were exposed to target concentrations of 1000, 10,000, or 50,000 ppm (4170, 41,700, 208,600 mg/m^3, respectively), 6 hours/day, 5 days/week (duration adjusted concentrations = 745, 7450, or 37,250 mg/m^3, respectively). Except for lethargy on day 17 in males exposed to 50,000 ppm, there were no other compound-related clinical signs (including ophthalmic) or effects on food consumption, body weight gain, hematology, or urine composition. At 50,000 ppm, males showed mild interstitial pneumonitis (3/16 rats); and slight statistically-significant increases in alanine transaminase (12%), and in absolute kidney and liver weights (11 and 21%, respectively). At 10,000 ppm, males showed a statistically-significant (8%) increase in absolute liver weight. Relative liver weights were marginally increased in a dose-dependent manner. Absolute but not relative testicular weights of high-dose rats were increased by 2%. None of the organ changes were associated with histopathology, and none were seen in 90-day and chronic studies (see below). The NOAEL was 50,000 ppm and the LOAEL was not determined.

In a 90-day inhalation study (Toxnet SIS, 2005), 5-week old male and female Wistar-derived rats (20/sex/group) were exposed to 0, 2000, 10,000, or 50,000 ppm (0, 8340, 41,700, or 208,600 mg/m^3) 1,1,1,2-tetrafluoroethane (99.97% pure) for 6 hours/day, 5 days/week (duration adjusted concentrations = 0, 1500, 7500, or 37,500 mg/m^3). Ten animals per group were examined at the end of a 13-week exposure, and 10 were retained for a 4-week post exposure recovery period. There were no clinical signs of toxicity and no significant effects on body weight gain, food consumption, serum chemistry, hematology, or urinalysis parameters. A statistically-significant decrease in plasma triglycerides was observed in both sexes in the recovery group but not in the group examined after 13-week exposures, and appeared to be due to unusually high values in the control groups. A statistically-significant decrease (2.5% compared to controls) in absolute brain weight was noted in the 10,000 and 50,000 ppm females that were sacrificed after 90 days. However, re-analysis of the relative brain weight data showed that there was no statistically significant difference in either sex at any concentration. No other organ weight changes were noted. There were no significant microscopic changes attributable to exposure. The NOAEL was 50,000 ppm [NOAEL = 37,250 mg/m^3] and the LOAEL was not identified.

Genotoxicity:

The genotoxic potential of 1,1,1,2-tetrafluoroethane has been investigated in the following types of assays: a bacterial mutagenicity test; an *in vitro* mammalian cell cytogenetics study; an *in vivo* chromosomal aberration assay; a micronucleus study; an *in vivo* unscheduled DNA synthesis assay, and a dominant lethal study (Collins et al., 1995; WHO, 1998). 1,1,1,2-Tetrafluoroethane was not genotoxic in these assay systems. The results of the studies are presented in Table 4.

TABLE 4. Genotoxicity of 1,1,1,2-tetrafluoroethane in *in vitro* and *in vivo* assays			
Test system	***Concentration/Test procedure***	***Results***	***Reference***
Salmonella typhimurium, reverse mutation (Ames assay)	0, 5-100% (v/v) for 24 or 72 hr with or without S-9 in five strains: TA 98, TA 100, TA 1535, TA 1537, and TA1538.	Negative.	Collins et al., 1995
Escherichia coli strain WP2 UVRA	0, 5-100% (v/v) for 24 or 72 hr with or without S-9 mix.	Negative.	Collins et al., 1995
Cytogenetics assay in human lymphocytes, *in vitro*	0, 5-100% (v/v) for 72 or 96 hr, with (6 hr) or without S-9 mix (24 or 48 hrs).	Negative. Reduced mitotic index was not seen at 72 hr, but occurred at 96 hr at ≥75% TFE. No statistically or biologically significant increase in chromosomal aberrations either in the presence or absence of S-9.	Collins et al., 1995
Cytogenetics assay in Chinese hamster lung (CHL) cells, *in vitro*	0, 4-100% (v/v) for 72 or 96 hr, with (6 hr) or without S-9 mix (24 or 48 hrs).	Frequency of chromosomal aberrations was very low in the negative controls, whereas induction was clearly observed in the positive control groups. No further details were available.	Collins et al., 1995
Mouse micronucleus assay	Groups of 15 mice/sex/group exposed at concentrations of 50,000 ppm (5 or 6 hr), or 150,000 ppm (6 hr) with or without S-9 mix. Positive controls (5/sex) treated with cyclophosphamide. Sacrifice at 24, 48, and 72 hr.	Negative, and the number of normochromatic erythrocytes with micronuclei did not increase. The ratio of polychromatic/ normochromatic erythrocytes in both male and female mice remained unaffected by the treatment.	Collins et al., 1995
Unscheduled DNA synthesis in rat hepatocytes (thymidine incorporation)	0, 50,00, or 100,000 ppm via inhalation for 6 hr without activation.	Negative. At both concentrations the mean net nuclear grain count was clearly less than zero and the percentage of cells in repair less than 20. TFE therefore resulted in a clearly negative response at 10%, a concentration which would result in significantly lower oxygen concentration availability to treated animals.	Collins et al., 1995
Dominant lethal study in rat	No details available.	Negative.	Hodge et al., as cited in WHO

Reproductive toxicity

Daily 1-hr inhalation exposure of random bred albino AHA strain rats (30/sex/dose) to 0, 2500, 10,000, or 50,000 ppm (0, 10,425, 41,700, or 208,500 mg/m^3) 1,1,1,2-tetrafluoroethane (99.3%) during gametogenesis, mating, and post-mating periods had no exposure-related

adverse effects on the fertility of rats. The results of a dominant lethal study revealed no effect on fertility of male rats (WHO, 1998).

Developmental toxicity:

In an inhalation developmental toxicity study by Lu (Toxnet SIS), pregnant rats (11 controls and 6/dose group) were exposed for 6 hours/day on gestation days 6-15 to 30,000, 100,000, or 300,000 ppm 1,1,1,2-tetrafluoroethane (125,200, 417,200, or 1,252,000 mg/m^3, respectively). Rats exposed to 100,000 ppm showed a decreased response to sound based on observations of the animal's response to tapping on the side of the chamber. Rats exposed to 300,000 ppm showed no response to sound, and exhibited severe tremors and incoordination which were completely reversed 1 hour post-exposure. The animals exposed to 300,000 ppm consumed less than those in the other groups and body weight gain was significantly less. These differences were not present by gestation day 21 (6 days postexposure). Statistically-significant increases in fetal effects at 300,000 ppm included reduced mean fetal weights (2.4 vs 3.7 g in controls), increased average percent malformed fetuses/litter (5.4 vs 1.5; not statistically-significant), and average percent fetuses with variations/litter (93.4 vs 44.8). This study established a maternal and fetal NOAEL of 100,000 ppm ([417,200 mg/m^3] and LOAEL of 300,000 ppm [1,252,000 mg/m^3).

In an inhalation developmental toxicity study by Hodge et al. (Toxnet SIS), 29-30 rats/group, exposed for 6 hours/day on GD 6-15 to target concentrations of 1,000, 10,000, or 50,000 ppm 1,1,1,2-tetrafluoroethane (4170, 41,700, or 208,600 mg/m^3, respectively) showed no significant clinical signs of toxicity, and reproductive parameters were not impaired, including numbers of implantations, corpora lutea, resorptions, post implantation loss, and live fetuses. Mean fetal weights of the 50,000 ppm rats was slightly but significantly reduced ($p<0.01$), although litter weight and gravid uterine weight were not affected. Skeletal development of these fetuses was slightly retarded, as indicated by increased incidence of unossified or partially ossified bones. The maternal NOAEL was 50,000 ppm, [208,600 mg/m^3, and the developmental NOAEL and LOAEL were 10,000 ppm [41,700 mg/m^3] and 50,000 ppm [208,600 mg/m^3], respectively.

In a preliminary rabbit inhalation developmental study by Wiekramaratne (Toxnet SIS), 10 animals/group, were exposed to 5,000, 20,000, or 50,000 ppm (21,000, 84,000, and 210,000 mg/m^3, respectively) 1,1,1,2-tetrafluoroethane for 6 hours/day on days 7-19 of gestation. In the group exposed to 50,000 ppm 1,1,1,2-tetrafluoroethane, one animal died and one aborted, and the dams showed statistically-significant increases in pre-implantation losses (26% vs 6% in unexposed controls). Also observed were a reduced number of fetuses, reduced litter and gravid uterine weight, and increased fetal weight. In comparison with controls, the number of live fetuses from 50,000 ppm dams (45 vs 58 in controls) and litter weight (244.0 g vs 369.3 g) were decreased, and fetal weight was increased (43.4 g vs 38.2 g). In the group exposed to 50,000 ppm, there was a slight loss of body weight during GDs 7-10, compared with weight gains of 40-50 g in other groups. Weight gains during gestation were not different in any other exposed

groups. No external abnormalities were seen. The maternal and developmental LOAEL was 50,000 ppm and the respective NOAELs were 20,000 ppm.

In another study by the same authors (Wiekramaratne 1989b as cited in Toxnet SIS), New Zealand rabbits (28/group) were exposed via inhalation 6 hours/day on GDs 7-19 to target levels of 0, 2500, 10,000, or 40,000 ppm 1,1,1,2-tetrafluoroethane (0, 10,400, 41,700, 166,900 mg/m^3). All dams survived, and no compound-related clinical signs were observed. Dams exposed to 10,000, or 40,000 ppm gained significantly less weight than controls between GD 7 and 19 (during the exposure), but body weights at GD 30 were not different from controls (97% of control weight in both groups). The weight gains during GD 7-19 were 260, 222, 190, and 162 g in the control, 2500, 10,000, and 40,000 ppm groups, respectively. Historical data were available on weight gain in rabbits used as controls in nine studies from the same laboratory during a 2.5 year period. The mean weight gains for the controls averaged 224 g and there was no trend over time. Exposure to 10,000 and 40,000 ppm caused statistically-significant increased incidences of nonossified seventh lumbar transverse processes. Increased incidence of partially ossified pelvic pubes also was seen in the same exposure groups, but was significant only at 10,000 ppm. These findings were not statistically significant on a litter basis. None of the approximately 75 other skeletal variations reported were significantly different, and the total incidence of minor variations was not affected by exposure. The fetal defects were not considered to be biologically-significant. The study defined a developmental NOAEL of 40,000 ppm and the NOAEL was not determined. For maternal toxicity, a LOAEL of 40,000 ppm [166,900 mg/m^3] and a NOAEL of 10,000 ppm [41,700 mg/m^3] were identified.

Neurotoxicity:

Acute neurobehavioral effects in rats following inhalation exposure to 1,1,1,2-tetrafluoroethane were investigated by Ritchie et al. (2001). Male Wistar rats were exposed to various concentrations of 1,1,1,2-tetrafluoroethane ranging from 40,000 to 470,000 ppm for up to 30 min while performing in either a rotarod/motorized running wheel apparatus or in an operant chamber. The relative neurobehavioral toxicity of difluorodichloroethane and 1,1,1,2-tetrafluoroethane was assessed by comparing both gross motor system incapacitation and more subtle changes in ability to perform an operant discrimination task. The results indicate that exposure to 1,1,1,2-tetrafluoroethane or difluorodichloroethane concentrations from 40,000 ppm to 470,000 ppm, for up to 30 min induced dose-dependent neurobehavioral effects. 1,1,1,2-Tetrafluoroethane was shown to induce deficits more rapidly and at lower concentrations when compared to difluorodichloroethane. The LOAEL was 40,000 ppm and the NOAEL was not determined.

Ritchie et al. (2001) reported that transient tremors occurred in laboratory animals at 1,1,1,2-tetrafluoroethane concentrations >99,000 ppm, lethargy and rapid respiration at 205,000 ppm, and additional CNS effects at a concentration of 750,000 ppm. The LC_{50} in rats was reported to be over 700,000 ppm (no further details were provided).

Carcinogenicity:

A 2-year inhalation study was conducted with 1,1,1,2-tetrafluoroethane in Wistar-derived rats (Collins et al., 1995; Toxnet SIS) in which groups of 85 rats/sex were exposed (whole-body) to 0, 2500, 10,000, or 50,000 ppm 1,1,1,2-tetrafluoroethane (99.8% pure; 0, 10,400, 41,700, and 208,600 mg/m^3, respectively), 6 hours/day, 5 days/week (duration adjusted concentration = 1860, 7450, or 37,250 mg/m^3, respectively). Interim results through 52 weeks were also reported (Collins et al., 1995; Toxnet SIS). The animals were observed for clinical signs of toxicity at least once daily and several times during exposure. Body weight and food consumption were monitored weekly during the first 14 weeks and biweekly, thereafter. Hematological, clinical chemistry, and urinalysis evaluations were conducted on 10 rats/sex/group at 14, 27, 52, and 104 weeks. After 1 year, 10 rats/sex/group were sacrificed and examined for gross pathology and histopathology of over 40 tissues, including nose, trachea, and lung. The remaining animals were examined after 104 weeks of exposure.

There were no exposure-related effects on survival, clinical signs, food consumption, body weight, behavior, or ocular characteristics. In males, slight concentration-related decreases were noted in hemoglobin, hematocrit, RBCs, and WBCs after 14 weeks (but not after 17, 53, or 104 weeks). Slightly elevated plasma glucose was noted in males at week 14, but not in succeeding weeks, and in females at week 27 (but not at week 53 or 104). No gross or histopathological effects were noted in hemoglobin, hematocrit, RBCs, and WBCs after 14 weeks (but not after 17, 53, or 104 weeks). Slightly elevated plasma glucose was noted in males at week 14, but not in succeeding weeks, and in females at week 27 (but not at week 53 or 104). No gross or histopathological changes were observed in the 10 animals sacrificed at 52 weeks. The only treatment-related effects after 104 weeks of exposure were in the testes. A statistically-significant increase in absolute and relative testes weight was found at terminal sacrifice (n = 75, relative weights were 0.6, 0.59, 0.61, and 0.66 in the 0, 2500, 10,000, or 50,000 ppm groups, respectively). In addition (as reported in WHO, 1998), in the surviving rats there were dose-related increased incidences of Leydig (interstitial) cell hyperplasia and benign Leydig cell adenomas in the testes. The incidence of Leydig cell hyperplasia in the control, low-, mid-, and high-dose groups was 27/85, 25/79, 31/85, and 40/85 (32%, 32%, 37%, and 47%, respectively). The incidence of Leydig cell adenomas was 9/85, 7/79, 12/85, and 23/85 (11%, 9%, 14% and 27%), respectively. Hyperplasia was observed in most animals with Leydig cell tumors. In the high-dose group, the incidence of Leydig cell adenomas was significantly ($p<0.05$) increased above controls. At 10,000 ppm, the incidences of Leydig cell adenomas and hyperplasia were within the range of historical controls (4%-19%). This study established a LOAEL of 50,000 ppm [37,250 mg/m^3] and a NOAEL of 10,000 ppm [7450 mg/m^3].

Following the finding of Leydig cell tumors in rats, Barton et al. (1994) conducted a mechanistic study to investigate the underlying mechanism for the formation of Leydig cell tumors in rats. In this study, the endocrine function was measured in a groups of males rats exposed to 0, 10,000, 30,000 and 100,000 ppm 1,1,1,2-tetrafluoroethane, 6 hr/day for 16 weeks. The basal LH (luteinising hormone) levels and the levels following stimulation with LHRH

(luteinising hormone releasing hormone) were measured. There were no increases in LH levels either basally or following stimulation. At 100,000 ppm, a small increase in testosterone secretion and a concomitant rise in progesterone secretion were noted. The authors concluded that slight increase in testosterone secretion is consistent with enhanced Leydig cell function. However, such changes are reversible and of no concern for the pharmaceutical use of 1,1,1,2-tetrafluoroethane. The lack of qualitative change in androgen biosynthesis indicated that Leydig cells do not secret increased amounts of androgen precursors after exposure to 1,1,1,2-tetrafluoroethane. The NOAEL was 30,000 ppm.

In another 2-year inhalation study by Alexander et al. (WHO, 1998), daily, 1 hour, nose-only exposure at concentrations up to 50,000 ppm (208,500 mg/m^3) in HanIbm rats (60/sex/group) and up to 75,000 ppm (312,750 mg/m^3) in $B_6C_3F_1$ mice (60/sex/group) caused no exposure-related increase in neoplastic or non-neoplastic findings. In a similarly designed study, 1-year exposure to 120,000 ppm (500,400 mg 1,1,1,2-tetrafluoroethane /m^3) did not induce tumors in dogs. There were no toxicologically-significant effects as indicated by clinical signs, body weight, food consumption, physical examination, hematology, blood biochemistry, organ weight, or examination for major organ lesions.

Table 5 Summary of the sub-chronic toxicity, reproductive toxicity, development toxicity, carcinogenicity and neurotoxicity.

Table 5. Summary of Toxicological Data for 1,1,1,2-Tetrafluoroethane

Assessment Type	Study	NOAEL/LOAEL
Subchronic – Rats/males/ 14 days	Inhalation – 417,000 mg/m^3/6hrs/5 days/wk	NOAEL = 417,000 mg/m^3 LOAEL = Not determined
Subchronic – 16/rats/28 days	Inhalation – 4170, 41,700, 208,600 mg/m^3/6hrs/5 days/wk	NOAEL = 208,600 mg/m^3 LOAEL = Not determined
Subchronic – Wistar rats/90 days	Inhalation – 0, 8340, 41,700, 208,600 mg/m^3/6hrs/5 days/wk	NOAEL = 208,600 mg/m^3 LOAEL was not determined
Reproductive Toxicity – Reproductive Toxicity - Albino rats	Inhalation – 0, 10,425, 41,700 or 208,500 mg/m^3	NOAEL = 208,500 mg/m^3
Developmental Toxicity – Rats/6 hours a day on gestation days (GD) 6-15	Inhalation – 125,400, 417,200, 1,252,000 mg/m^3	NOAEL (maternal) = 417,200 mg/m^3 LOAEL = 1,252,000 mg/m^3
Developmental Toxicity – Rats/6 hours a day on GD 6-15	Inhalation – 4,170, 41,700,108,600 mg/m^3	NOAEL (maternal) =208,600 mg/m^3 LOAEL(maternal)= not determined NOAEL (developmental) = 41,700mg/m^3 LOAEL (developmental) =208,500 mg/m^3
Developmental Toxicity - rabbit/d hours GD days 7-19	Inhalation - NOAEL (maternal) = 417,200 mg/m^3 LOAEL = 1,252,000 mg/m^3	LOAEL (developmental and maternal) = 210,000mg/m^3 LOAEL = (developmental and maternal) =

		84,000mg/m^3
Carcinogenicity - Wistar rats/2 year study	Inhalation – 0, 10,400, 41,700, 208,600 mg/m^3	NOAEL = 37,250 mg/m^3 LOAEL = 7450 mg/m^3
Carcinogenicity - rats/6 hours day for 16 weeks	Inhalation – 0, 41,700, 125,100, 417,000 mg/m^3	NOAEL = 125,000 mg/m^3 LOAEL = Not Reported
Carcinogenicity - rats Daily 1hour/ nose only	Inhalation - 208,500 mg/m^3	No adverse reported
Carcinogenicity – mice	Inhalation – 312,750 mg/m^3	No adverse reported
Carcinogenicity – Dog /1 year	Inhalation – 500,400 mg/m^3	No adverse reported
Neurotoxicity - Rats	Inhalation 125,000, 1,959,900 mg/m^3	NOAEL = not determined LOAEL = 125,000mg/m^3

C. Metabolism And Pharmacokinetics:

Ellis M. K. et al. (1993) investigated the metabolic fate and disposition of 1,1,1,2-tetrafluoroethane in rats following a single inhalation exposure. "Wistar-rats of both sexes were exposed in an inhalation chamber to an atmosphere of 10,000 parts per million 1,1,1,2-tetrafluoroethane (HFC134a) (containing some carbon-14 labeled HCF134a to give a specific activity of 6.9 to 12.4 microCuries per millimole) for 1 hour (hr). Urine and feces were collected at 6 hr intervals for 24 hr, and at 24 hr intervals for 5 days. Exhaled air was subjected to charcoal adsorption. At the end of the period, rats were sacrificed, and total carcass radioactivity as well as tissue distribution of radioactivity were assessed. Results showed that of the inhaled HCF134a, about 1% was recovered in exhaled air, urine, and feces, and of this the majority of the HCF134a (about 66%) was eliminated in the exhaled air within 1hr of the end of exposure. The main metabolite was carbon-dioxide, and it accounted for 0.27% and 0.22% of the inhaled doses in females and males, respectively. Urinary and fecal excretion accounted for 0.09% and 0.04% of the doses, respectively, in both sexes. At the end of day five, only about 0.15% of the dose remained in the carcass. The overall metabolism was calculated to be 0.37% of the inhaled dose. Residues accounted for 13.4% and 11.1% of total radioactivity recovered from males and females, respectively. The authors conclude that there are no significant sex differences in the absorption, distribution, metabolism, and excretion of 1,1,1,2-tetrafluoroethane (HFC134a) in the rat, and that the metabolic profile is consistent with a single metabolic pathway."

Liver microsomes from male Fischer 344 rats were incubated with 1,1,1,2-tetrafluoroethane (1.5, 7.5, 17.7, 24.2, 45.1 and 69.1%) at 37 for 15 minutes; in addition, either carbon monoxide (CO) was added or NADP was omitted from the incubation. Defluorination was similar at both 24.2 and 45.1% concentrations of 1,1,1,2-tetrafluoroethane: approximately 103 ng/mg protein/15 minutes. Addition of CO or NADP reduced the amount of fluoride ion produced 17 ng/mg/15 minutes and 9 ng/mg/15 minutes respectively. The study author concluded that 1,1,2-tetrafluoroethane undergoes an oxidative rather than a reductive defluorination (Olson et al., 1990 as cited in EPA/OPPTS review by L. Keifer dated June 2, 1992).

A comparison study demonstrated that the oxidation of 1,1,1,2-tertafluoroethane is catalyzed by cytochrome P-450IIE1 in rats. The Agency concluded from the results of the two studies that small amounts of 1,1,1,2-tetrafluoroethane may undergo oxidative defluorination in vitro with the same rate of metabolism similar in rats and humans when normalized to nmol of cytochrome P-450 (EPA/OPPTS review by L. Keifer dated June 2, 1992).

D. Special Considerations for Infants and Children:

1,1,1,2-Tetrafluoroethane has very low toxicity for all endpoints, with effects seen only at very high concentrations (NOAEL range from 41,700 – 417,000 mg/m^3). Based on this information there is no concern, at this time, for increased sensitivity to infants and children to 1,1,1,2-tetrafluoroethane when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization/Drinking Water Considerations

1,1,1,2-Tetrafluoroethane is expected to partition almost exclusively to the atmosphere. Aqueous discharges would be expected to volatilize, with half-lives of days to a few weeks. 1,1,1,2-Tetrafluoroethane is not soluble in water. It is not expected that 1,1,1,2-tetrafluoroethane will accumulate in biota (log K_{ow} = 1.06) or adsorb to soil or sediment (log $K_{oc} \approx 1.5$). The overall estimated lifetime of 1,1,1,2-tetrofluoroethane in the troposphere is 14.6 years. 1,1,1,2-Tetrafluoroethane is not expected to be present in drinking water as a result of its use as a pesticide inert ingredient.

1,1,1,2-Tetrafluoroethane is not soluble in water, therefore, it is not expected to be present in surface or ground water.

V. Exposure Assessment:

Exposure of 1,1,1,2-tetrafluoroethane to the general population is solely via the inhalation route because of its gaseous nature, therefore no oral or dermal exposure assessment is required. However, since there are no inhalation toxicity endpoints, further inhalation exposure assessment for 1,1,1,2-tetrafluoroethane is not necessary.

VII. Aggregate Exposures

In examining aggregate exposure, FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For 1,1,1,2-tetrafluoroethane, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to 1,1,1,2-tetrafluoroethane as an inert ingredient in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to 1,1,1,2-tetrafluoroethane and any other substances and this material does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that 1,1,1,2-tetrafluoroethane, has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/

IX. Human Health Risk Characterization

For toxicological endpoints, animal inhalation studies indicate that 1,1,1,2-tetrafluoroethane is low in acute and chronic toxicity. Reported LD_{50} values in rodents are above 700,000 ppm, and for subchronic exposures a NOAEL of 10,000 ppm (41,700 mg/m^3) was reported. Developmental effects have been reported in rodents and rabbits exposed to 1,1,1,2-tetrafluoroethane, but only at concentrations of 50,000 ppm or higher. Oncogenicity data are limited to one study in which an increased incidence of benign Leydig cell adenomas were seen in rats following exposure to 40,000 ppm 1,1,1,2-tetrafluoroethane for 2 years. However, these tumors are commonly seen in this strain of rat. Genotoxicity tests on 1,1,1,2-tetrafluoroethane have given negative results.

The Food and Drug Administration has approved the use of 1,1,1,2-tetrafluoroethane as a propellant in drug inhalers and as an extraction solvent for food flavors and fragrances from plant materials (FDA, 2002).

Exposure of 1,1,1,2-tetrafluoroethane is predominantly via the inhalation route because of the chemical's gaseous nature. No exposure through diet (food and drinking water) or dermal routes are anticipated.

While inhalation exposures are possible, toxicity of this chemical is very low for all endpoints. Human are not expected to exposed to such high level of 1,1,1,2-tetrafluoroethane when it is used in pesticide formulations.

Taking into consideration all available information on 1,1,1,2-tetrafluoroethane, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to 1,1,1,2-tetrafluoroethane when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is concluded that the exemption from the requirement of a tolerance established for residues of 1,1,1,2-tetrafluoroethane in/on raw agricultural commodities can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

Based on the information submitted above, 1,1,1,2-tetrafluoroethane partitions almost exclusively to air and is not soluble in water. Therefore, there are no concerns for risks to nontarget organisms. No hazard expected to environment or to ecosystem.

References

Barton, S.J., P. McDonald, and J. Sandow. 1994. HFC 134a: Study of the effects on testicular endocrine function after inhalation exposure (6 h per day). Unpublished study, Report No. 7955. Study performed by Inveresk Research International, Tranent, Scotland. Submitted to U.S. EPA under TSCA Section 8D on 09/14/1994. Doc. # 86940001897, Microfiche #. OTS0557487.

Collins, M. S., G. M. Rusch, Sato, F., Hext, P.M., and R.E. Millischer. 1995. 1,1,1,2-Tetrafluooethane: Repeat exposure inhalation toxicity study in the rat, developmental toxicity in the rabbit, and genotoxicity in vitro and in vivo. Fund. Appl. Toxicol. 25:271-280.

Ellis, M. K., L. A. Gowans, T. Green, R.J. N. Tanner. 1993. Metabolism Fate and Disposition of 1,1,1,2-Tetrafluoroethane (HFC134a) in Rats following a Single Exposure by Inhalation. Xenobiotica. 23(7): 719-729.

Food and Drug Administration. 2002. Agency Response Letter GRAS Notice No. GRN 00082. June 5, 2002.

Keifer, Leonard C., 1992. Review of metabolism studies with HFC-134a. U. S. Environmental Protection Agency. Office of Pesticides and Toxic Substances. June 2, 1992.

Ritchie, G. D., E. C. Kimmel, Bowen, L. E., Reboulet, J. E., J. Rossi III. 2001. Acute neurobehavioral effects in rats from exposure to HFC 134a or CFC 12. Neurotoxicology 22:233-248.

Toxnet SIS. 2005. National Library of Medicine, National Institute of Health. http://www.toxnet.nlm.nih.gov.

WHO. 1998. 1,1,1,2-Tetrafluoroethane. Concise International Chemical Assessment Document 11. Published under joint sponsorship of the United Nations Environmental Programme, the International Labor Organisation, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals. World Health Organization, Geneva, Switzerland.