

**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

**INTEROFFICE COMMUNICATION**

TO: File for 1,1,2-trichloro-1,2,2-trifluoroethane (CAS #76-13-1)

FROM: Anne Kim, Air Quality Division, Toxics Unit

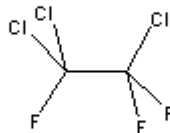
SUBJECT: Screening Level Derivation

DATE: March 22, 2006

**The initial threshold screening level (ITSL) for 1,1,2-trichloro-1,2,2-trifluoroethane is 19140  $\mu\text{g}/\text{m}^3$  based on a 24-hour averaging time.**

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2005), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration or reference dose for 1,1,2-trichloro-1,2,2-trifluoroethane. The molecular weight of 1,1,2-trichloro-1,2,2-trifluoroethane is 187.4 g. The molecular structure of 1,1,2-trichloro-1,2,2-trifluoroethane is shown in Figure 1.

**Figure 1**



This compound was initially evaluated by AQD staff in 1992 using interim procedures to derive an impact of 76700  $\mu\text{g}/\text{m}^3$  and 110000  $\mu\text{g}/\text{mg}^3$  with an 8-hour and 24-hour averaging time, respectively. 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113) was then again reviewed in 2002, and a screening level of 2700  $\mu\text{g}/\text{m}^3$  based on an annual averaging time was proposed. This chemical is being re-reviewed to finalize an ITSL for CFC-113.

## **Background**

CFC-113 is a colorless liquid that vaporizes rapidly at room temperature. CFC-113 is used as a solvent, degreaser, dry cleaning agent, and refrigerant. Humans may be exposed to CFC-113 during manufacture, use, or in spill accidents. (Woollen et al., 1990; Trochimowicz et al., 1988; Voge, 1989)

## **Animal Toxicity**

A study conducted by Vainio et al. (1980) exposed male Wistar rats to 0, 200, 1000, or 2000 ppm CFC-113 vapor five days/week, six hours/day for 1 or 2 weeks. There were at least ten rats in each dose group (N was not specified in the study report). At least five rats of each dose group was sacrificed after one week of exposure, and another set of at least five rats from each dose group was sacrificed after two weeks of exposure to CFC-113. Morphological and biochemical analyses were conducted using samples from the animals' livers and kidneys. All effects occurred in doses 200 ppm and above. The adverse effects observed included decrease in CYP450 content, increase of smooth endoplasmic reticulum with vacuolization, increase in number of autophagosome vacuoles, and other histopathological and biochemical changes. In the 200 ppm group, the level of CYP450 normalized in the second week, so the authors established 200 ppm, the lowest exposure dose level, as the NOAEL.

Another two-week study was conducted in male Wistar rats using concentrations of 0, 200, 1000, or 2000 ppm of CFC-113 (Savolainen et al., 1980). Exposure occurred five days per week, six hours per day. Of the 15 rats in each group, five were sacrificed after one week of exposure, another five after two weeks, and the remaining five were observed for another seven days. Changes in levels of NADPH-diaphorase, brain glutathione, and cerebral RNA were found in the 2000 ppm dose group. In addition, the five rats withdrawn from exposure for a seven-day observation period continued to show a decrease in cerebral RNA levels (other effects normalized). The authors concluded that effects seen in rats exposed to 2000 ppm CFC-113 raises concern for humans. The NOAEL of this study is 1000 ppm.

Leuschner (1976) exposed 40 Sprague-Dawley rats to 10000 ppm CFC-113 six hours per day for three months (another 40 rats served as control). Many endpoints were examined during exposure and after: behavior and external appearance, intake of food and drinking water, body weight gain, hematology, clinical biochemistry, macroscopic autopsy, and tissue sections for histology. There were no observed differences between rats exposed to 10000 ppm CFC-113 and control. Thus, based on evidence of no effects resulting from CFC-113 exposure, the NOAEL was set at 10000 ppm.

Another three-month study was conducted in 15 male and 15 female CD rats (Schneider et al., 1979). The rats were exposed to 0, 7500, 12500, or 17500-20000 ppm CFC-113 six hours per day, five days per week. On the 19<sup>th</sup> exposure, the highest concentration of 17500 ppm was increased to 20000 ppm ("in order to enhance the likelihood of producing clinical abnormalities" [Schneider et al., 1979]). Five rats from each group were sacrificed on the 30<sup>th</sup> day of exposure and the rest were terminated after 63 exposures for pathological examination. Increased lung weights corresponding to multi-focal granulomatous interstitial pneumosis was found in the 17500-20000 ppm dose group. The pneumosis was not considered to be a direct effect of CFC-113 exposure, but the increase in intensity of the granulomatous interstitial pneumonia corresponding with increased lung weights could not be dismissed. No other clinical observations, gross autopsy results, or histological changes were considered to be CFC-113 exposure related. The exposure dose of 12500 ppm may be a potential NOAEL for this study.

A chronic inhalation study available was conducted by Trochimowicz et al. (1988). One hundred male and 100 female CrI:CDBR rats in each group were exposed to 0, 2000, 10000, or 20000 ppm CFC-113 six hours per day, five days per week for two years. Body weights were recorded, appearance and behavior were noted, and urine and blood samples were analyzed throughout the duration of the study. Ten male and ten female rats from each group were sacrificed after 12 months of exposure, and the remaining rats were sacrificed after 24 months. Tissues were examined macroscopically and microscopically. A slight significant decrease in body weight gain was observed in the 10000 and 20000 ppm dose groups. A small number of tumors were found; however, the authors emphasized the occurrence of tumors being within normal historical background levels. Furthermore, tumors were not dose-dependent or from the same cell type, so the authors concluded that the tumors were not CFC-113 exposure related. Based on the body weight gain differences, the authors established 2000 ppm as the NOAEL. The reliability of this experiment's results, however, is questionable. After six months of sampling, a housing mistake between control and 2000 ppm males occurred, and a new group of controls was designated. In addition, all groups were infected by *Corynebacterium kutscheri* in the second year of the study which caused a tuberculosis-like infection. For treatment purposes, exposure ceased for 14 exposures (during week 61-63) and tetracycline was given via drinking water.

A reproductive study was conducted by Tinston et al. (1981). Male rats were exposed to CFC-113 vapors for ten weeks before being introduced to female rats that were exposed to CFC-113 vapors for three weeks. Both male and female rats were exposed to concentrations of 0, 5000, or 12500 ppm CFC-113 six hours per day, five days per week. During the time of pairing, the exposure continued six hours per day, and now, seven days per week. Half of the females (sub-group A) continued to be exposed until day 20 of gestation. This group was allowed to litter and their offspring were observed for four weeks – at which point both the dam and pup populations were sacrificed and discarded without necropsy. The other half of females (sub-group B) discontinued CFC-113 exposure starting from gd 0 and were sacrificed between gd 17 and gd 20 to examine uterine contents and record the number of live and dead fetuses and number of resorptions.

Results from the pre-pairing period: Male rats exposed to 5000 ppm CFC-113 had significantly decreased body weight gains and female rats exposed to 5000 ppm CFC-113 had significantly increased body weight gains, both compared to control. The male and female rats in the 12500 ppm group, however, had body weight gains that were comparable to that of control, so no significance is attached to these body weight gain differences observed.

Results from the pairing period: The rats exposed to CFC-113 showed positive signs of mating earlier than control rats, but it was not a statistically significant finding. The investigators concluded that “there were no statistically significant differences in pregnancy or coital success rates between the rats exposed to CFC-113 and the controls” (Tinston et al., 1981).

Results from the post-pairing period (sub-group A): There were no statistically significant differences evident between exposed and control rats.

Results from the post-pairing period (sub-group B): A dose-related decrease in the number of corpora lutea implantations and mean number of fetuses occurred, where the reductions in only the highest exposure group was statistically significant compared to control numbers.

Results from the post partum period (sub-group A): Pups from parents exposed to 5000 ppm CFC-113 had statistically higher body weight values compared to control. The eye opening and completion of pinna detachment and hair growth occurred statistically earlier compared to

control in pups whose parents were exposed to 5000 ppm CFC-113. The pups from the 12500 ppm group did not exhibit either of these differences so the investigators concluded that the effects seen in the 5000 ppm group bore no toxicological significance.

In summary, the only adverse effects observed were a decrease in the mean number of corpora lutea and a decrease in the mean number of implantations and fetuses, both of which were from the 12500 ppm group. The investigators discussed the historical control data for mean values of corpora lutea counts found in their lab and other labs that had used rats from the same source. The researchers stated that “the values obtained in this study could be considered to be within the overall range for this strain of rat” (Tinston et al., 1981). In addition, they pointed out that the control values from this study were at the higher end of the historical range, which indicates that the, perhaps perceived, significant difference between the high dose group and control may, in fact, be fallacious. EPA, after evaluating this reproductive study, concluded there were no significant adverse effects (WHO, 1990).

Despite the suggestion that effects were found to be within historical control values, the authors concluded that “the reduction in the number of corpora lutea in the 12500 ppm group could be considered as a possible effect...[and] 5000 ppm could be considered as a ‘no-effect’ level” (Tinston et al., 1981).

Ward, in 1983 (secondary reference), exposed 24 pregnant rats to 0, 5000, 12500, and 250000 ppm CFC-113 six hours per day on gestational days 6-15 (inclusive) (EPA, 1983). Maternal toxicity was observed in the 25000 ppm group; maternal body weight gain and food consumption was lower than those of control. There was an increase in the incidence of extra ribs in the pups examined from all exposure groups. The investigators, however, concluded that CFC-113 is not teratogenic because the abnormality increase was within historical control background levels. Thus, based on decreased weight gain and decreased food consumption in the 25000 ppm group, the potential NOAEL may be set at 12500 ppm.

### **Human Toxicity**

A human study was conducted in seven male volunteers exposed to concentrations of CFC-113 for 4 hours (Woollen et al., 1990). Exposure concentrations were 1980, 4100, or 7630 mg/m<sup>3</sup> CFC-113. Samples were taken during and after exposure to measure levels of CFC-113 in the blood and breath. Low levels of CFC-113 were found in the blood indicating low solubility of CFC-113 in blood. The blood/air and fat/air partition coefficients were determined to be  $0.41 \pm 0.06$  and  $59 \pm 1.2$  at a concentration of 1 ug/mL. Using these results, the fat/blood coefficient was estimated to be 146.

Rasmussen et al. (1988), through a cross-sectional clinical study, followed 99 workers involved in degreasing using halogenated hydrocarbons. All workers were subjected to occupation medical checkups, clinical neurological and psychological examinations. Three of 23 workers employed in a factory that used CFC-113 for degreasing showed signs and symptoms of psychoorganic syndrome after 2 ½ to 4 ½ years of heavy CFC-113 exposure. All three cases showed evidence of psychoorganic syndrome to only a slight degree.

An occupational study conducted by Imbus and Adkins (1972) evaluated the effects of CFC-113 exposure in persons working at the Kennedy Space Center. Fifty exposed workers were randomly selected and found to be exposed, on average, to a mean concentration of 699 ppm (ranging from 46 to 4700 ppm) of CFC-113 vapors six hours per day for 2.77 years. Another set of fifty randomly-selected unexposed workers were examined for control purposes. All study subjects were examined thoroughly via complete history, complete physical examination,

electrocardiogram test, visual profile, audiometry, blood chemistry, urinalysis, chest x-ray examination, and timed vital capacity (TVC) test. Comparing results between the two groups of workers showed no changes or any biologically and statistically significant differences.

The EPA evaluated a few human studies in the HAD for CFC-113 (1983): A study conducted by Triebig and Burkhardt (1978, secondary reference) obtained case histories from ten women and three men and performed blood chemistry, urinalysis, and breath analysis before and after the one-week exposure period. Inhalation of occupational exposure levels of CFC-113 in the 13 subjects revealed no adverse effects.

In another study, four male volunteers were exposed to 500 ppm CFC-113 during the first week and 1000 ppm during the second week of the study (Reinhardt et al., 1971, secondary reference). Exposure occurred three hours in the morning and in the afternoon, five days per week for two weeks in an environmental chamber. Psycho-motor tests were conducted before and after each exposure level – test scores showed no adverse effect. Clinical tests, including hematology, blood chemistry, and urinalysis, were performed before each exposure level and three days after the final exposure – labs were unremarkable. Subjective impressions were recorded – no adverse observation or equilibrium unbalance was noted. The investigators concluded that CFC-113 is not retained in tissue 48 hours after repeated exposure.

A study conducted by Stopps and McLaughlin (1967, secondary reference) subjected two healthy males to 1500, 2500, 3500, 4000, and 4500 ppm CFC-113 for 2 ¾ hours in an environmental chamber. Four psychomotor tests were used to identify adverse effects from CFC-113 exposure. “Slight but definite impairment of psychomotor performance” was not observed until subjects were exposed to 2000 ppm CFC-113 (EPA, 1983). The higher CFC-113 exposure concentrations caused complaints of loss of task concentration, drowsiness, heaviness (without ache) in the head, and dizziness following lateral movement of the head. These effects disappeared fifteen minutes after exiting the chamber.

EPA also evaluated the study conducted by Imbus and Adkins (1972), presented above, and used this study as the source of the critical effect to develop a RfD, 30 mg/kg/day (IRIS, 2006).

### **Discussion**

Use of Imbus and Adkins’ (1972) study is ideal because the route of exposure is inhalation and, since the study was conducted in humans, there is less uncertainty involved than when extrapolating from animal data to humans. The EPA, using this same human inhalation study, determined a RfD and not a RfC (the RfC methodology was finalized in 1994 – nine years after this RfD was established in 1985). Nevertheless, because it would be inappropriate to convert a RfD, which was determined from an inhalation study, back into inhalation units, and because a RfC can be derived directly from the human inhalation study, a RfC was determined following EPA’s RfC derivation guidelines (EPA, 1994) (shown in Figure 1 below).

Figure 1. Calculation of RfC using Imbus and Adkins' study – NOAEL = 699 ppm

**Conversion of concentration units from ppm to mg/m<sup>3</sup>:**  

$$X \text{ mg/m}^3 = \frac{\text{ppm} * \text{MWT}}{24.45}$$

$$X \text{ mg/m}^3 = \frac{699 \text{ ppm} * 187.4 \text{ g}}{24.45}$$

$$X \text{ mg/m}^3 = 5358 \text{ mg/m}^3$$

**Calculation of LOAEL<sub>[HEC]</sub>:**  

$$\text{NOAEL}_{[\text{HEC}]} (\text{mg/m}^3) = \text{NOAEL} (\text{mg/m}^3) * (\text{MVho/MVh}) * 5 \text{ days}/7 \text{ days}$$
 NOAEL<sub>[HEC]</sub> = the NOAEL dosimetrically adjusted to an ambient human equivalent concentration  
 NOAEL = occupation exposure level (time-weighted average)  
 MVho = human occupational default volume for an 8-hour occupational exposure (10 m<sup>3</sup>)  
 MVh = human ambient default volume for a 24-hour continuous exposure (20 m<sup>3</sup>)

$$\text{NOAEL}_{[\text{HEC}]} (\text{mg/m}^3) = 5358 \text{ mg/m}^3 * (10 \text{ m}^3/20 \text{ m}^3) * (5 \text{ days}/7 \text{ days})$$

$$\text{NOAEL}_{[\text{HEC}]} (\text{mg/m}^3) = 1914 \text{ mg/m}^3$$

**Calculation of RfC:**  

$$\text{RfC} = \frac{\text{NOAEL}_{[\text{HEC}]}}{\text{UF}}$$
 NOAEL<sub>[HEC]</sub> = defined above  
 UF = uncertainty factor

> UFs that apply: 1) variation in sensitivity among members of the human population = 10  
 2) extrapolation from sub-chronic to chronic = 10

$$\text{RfC} = \frac{1914 \text{ mg/m}^3}{10 * 10}$$

$$\text{RfC} = 19.14 \text{ mg/m}^3 = 19140 \text{ ug/m}^3$$

The reproductive study conducted by Tinston et al. (1981) did show significant adverse effects in rats exposed to CFC-113 vapors. Although the authors discussed in length reasons for discounting the significance of the decreased corpora lutea numbers, a RfC will be derived based on this endpoint. First, there was a dose-response-related decrease in corpora lutea numbers with only the highest dose group, 12500 ppm, being statistically significantly different from control. Second, the point the investigators make about the values being within historical control background numbers does not outweigh the fact that there were significant differences between the exposed and *concurrent* controls. The RfC derived from the reproductive study is shown in Figure 2 below.

Figure 2. Calculation of RfC using Tinston et al.'s study – NOAEL = 5000 ppm

**Conversion of concentration units from ppm to mg/m<sup>3</sup>:**

$$X \text{ mg/m}^3 = \frac{\text{ppm} * \text{MWT}}{24.45}$$

$$X \text{ mg/m}^3 = \frac{5000 \text{ ppm} * 187.4 \text{ g}}{24.45}$$

$$X \text{ mg/m}^3 = 38000 \text{ mg/m}^3$$

**Calculation of NOAEL<sub>[ADJ]</sub>:**

$$\text{NOAEL}_{[ADJ]} \text{ (mg/m}^3\text{)} = E \text{ (mg/m}^3\text{)} * D \text{ (hrs/24 hrs)} * W \text{ (days/7 days)}$$

NOAEL<sub>[ADJ]</sub> = the effect level obtained with an alternate approach, adjusted for duration of experimental regimen

E = experimental concentration level

D = number of hours exposed/24 hours

W = number of days of exposure/7 days

$$\text{NOAEL}_{[ADJ]} = 38000 \text{ mg/m}^3 * (6 \text{ hrs/24 hrs}) * (7 \text{ days/7 days})$$

$$\text{NOAEL}_{[ADJ]} = 9500 \text{ mg/m}^3$$

**Calculation of NOAEL<sub>[HEC]</sub>:**

$$\text{NOAEL}_{[HEC]} \text{ (mg/m}^3\text{)} = \text{NOAEL}_{[ADJ]} \text{ (mg/m}^3\text{)} * \text{RGDR}_r$$

NOAEL<sub>[HEC]</sub> = the effect level obtained with an alternate approach, dosimetrically adjusted to an HEC

NOAEL<sub>[ADJ]</sub> = defined above

RGDR<sub>r</sub> = the regional gas dose ratio; a dosimetric adjustment factor for respiratory tract region, r (in this case extrarrespiratory – ER)

**Calculation of RGDR<sub>ER</sub>:**

$$\text{RGDR}_{ER} = \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

(H<sub>b/g</sub>)<sub>A</sub>/(H<sub>b/g</sub>)<sub>H</sub> = the ratio of the blood:gas (air) partition coefficient of the chemical for the laboratory animal species to the human value.

\*Although human data (blood:gas partition coefficient = 0.41; Woollen et al., 1990) is available, there is no animal data. In the absence of data on the ratio of the blood:gas (air) partition coefficients, it is assumed that (H<sub>b/g</sub>)<sub>A</sub>/(H<sub>b/g</sub>)<sub>H</sub> equals 1.

$$\text{NOAEL}_{[HEC]} \text{ (mg/m}^3\text{)} = 9500 \text{ mg/m}^3 * 1$$

$$\text{NOAEL}_{[HEC]} \text{ (mg/m}^3\text{)} = 9500 \text{ mg/m}^3$$

**Calculation of RfC:**

$$\text{RfC} = \frac{\text{NOAEL}_{[HEC]}}{\text{UF}}$$

NOAEL<sub>[HEC]</sub> = defined above

UF = uncertainty factor

> UFs that apply: 1) variation in sensitivity among members of the human population = 10

2) extrapolation from animal data to humans = 3

3) extrapolation from sub-chronic to chronic = 10

$$\text{RfC} = \frac{9500 \text{ mg/m}^3}{10 * 3 * 10}$$

$$\text{RfC} = 32 \text{ mg/m}^3 = 32000 \text{ ug/m}^3$$

The human occupational study conducted by Imbus and Adkins (1972) will be used to determine the initial threshold screening level (ITSL). Although the human inhalation study did not test for reproductive endpoints, the RfC derived from this study (19140 ug/m<sup>3</sup>) is lower than the RfC based on reproductive effects (32000 ug/m<sup>3</sup>) and should be protective of all toxic endpoints, including reproductive toxicity.

### **Derivation of Screening Level**

The RfC calculation based on the human occupational study resulted in a value of 19140 ug/m<sup>3</sup>. Pursuant to Rule 232(1)(a), the ITSL is equal to the RfC; therefore, the ITSL for CFC-113 is 19140 ug/m<sup>3</sup> based on a 24-hour averaging time.

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