

**Public Health Goal for
1,1,2-TRICHLORO-1,2,2-TRIFLUOROETHANE
in Drinking Water**

Prepared by

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PREFACE

Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by

OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 4 mg/L (4 ppm) is developed for 1,1,2-trichloro-1,2,2-trifluoroethane (FC-113) in drinking water. FC-113 has a variety of uses, including degreasing and drying applications, as a refrigerant and as a cutting fluid. The compound is practically nontoxic when given in single doses either orally, dermally or by inhalation. Repeated short-term administration in several species did not reveal any distinctive toxicological effects. Cardiac sensitization was seen in certain species, particularly in the dog; this phenomenon has been reported at 1,200 ppm and higher. Chronic inhalation by rats of up to 20,000 ppm FC-113 did not cause any clear carcinogenic effect, although noncarcinogenic health effects such as an increase in liver weight occurred at doses as low as 2,000 ppm, the lowest dose tested. Mutagenicity assays are limited to the Ames *Salmonella* test and the dominant lethal assay in mice, both of which failed to demonstrate a significant mutagenic response. In one epidemiological study, workers exposed to 46 to 4,700 ppm FC-113 daily displayed no signs of toxicity. Although 45 ppm FC-113 in air can be detected, the taste or odor threshold for this chemical is greater than 300 ppm in tap water. No sensitive subpopulations were identified. There are no data suggesting increased sensitivity to FC-113 exposure in children or infants. Using the results of a chronic bioassay in rats, a PHG of 4 mg/L (4 ppm) is calculated for FC-113 in drinking water.

INTRODUCTION

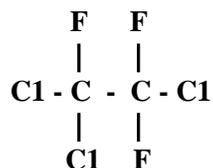
FC-113 is one of the most widely used chlorofluorocarbons. It was widely used in industrial applications such as a solvent for degreasing and dry cleaning, refrigerant, fire extinguisher component, chemical intermediate and blowing agent in foam production. Since 1996 it is no longer being produced in the United States (U.S.) although use of existing stocks is permitted. Emissions are declining as a result of the production ban.

This document is a revision and reassessment of a 1989 California Department of Health Services document (DHS, 1989) entitled *Proposed Maximum Contaminant Level: 1,1,2-Trichloro-1,2,2-trifluoromethane*. This 1989 report was based largely on a report prepared under contract to DHS (Risk Assessment Group, 1988). The 1989 DHS document calculated a Proposed Maximum Contaminant Level (PMCL) for FC-113 of 1.2 mg/L (1,200 ppb) in drinking water. Scientific literature newly available since the publication of the DHS (1989) evaluation was reviewed and any significant information was incorporated into the development of a PHG. Additional research reported since 1989 has been limited, with some new reports of human harm following accidental exposure, but little new experimental data. Exposure standards for FC-113 in drinking water or ambient air have not been developed by the U.S. Environmental Protection Agency (U.S. EPA).

CHEMICAL PROFILE

The physical and chemical properties of FC-113 are given in Table 1. Grayson (1979) reviewed the industrial synthesis of FC-113. It is a low boiling solvent used for dry-cleaning, as a refrigerant, in degreasing and drying applications, removal of solder flux and

application as a cutting fluid. FC-113 is not currently used as an aerosol propellant. It has the following chemical structure:



FC-113 (1,1,2-trichloro-1,2,2-trifluoroethane) has also been known variously as 1,1,2-trichloro-trifluoroethane, 1,2,2-trifluoro-1,1,2-trichloroethane, 1,1,2-trifluoro-1,2,2-trichloroethane, 1,1,2-trifluorotrichloroethane, 1,2,2-trichlorotrifluoroethane, TTE, trifluorotrichloroethane, trichlorotrifluoroethane and 1,2,2-trifluoro-1,1,2-trichloroethane. Trade names include Arklone 63, Arklone, Arklone P, F 113, FC-113, Freon 113, fluorocarbon 113, Forane 113, Freon 113 TR-T, Freon R 113, Freon TR-T, Frigen 113, Frigen 113 TR=T, Figen 113A, Genetron 113, Halocarbon 113, Hostron Precision Solvent Cleaner, Isotron T Solvent, R-113, Refrigerant 113, Ucon, Ucon 113 and Ucon Fluorocarbon 113 (HSDB, 1995).

Table 1. Physical and Chemical Properties of FC-113 (HSDB, 1995)

CAS registry number	76-13-1
Molecular formula	C ₂ C1 ₃ F ₃
Molecular weight	187.38 g/mole
Description	Clear liquid (Chou <i>et al.</i> , 1978)
Boiling point	47.7°C
Melting point	-35°C (Grayson, 1979; Mackison, 1981)
Vapor pressure	336.1 mm Hg at 25°C
Specific gravity	1.56 (Mackison, 1981)
Octanol water partition coefficient (log ₁₀ K _{o/w})	3.16
Solubility	Practically insoluble in water (0.017% w/v at saturated pressure and 25°C), dissolves in ethanol and ether.
Conversion factor	7.79 mg/m ³ = 1.0 ppm; 0.1283 ppm = 1 mg/m ³
Odor	Similar to that of carbon tetrachloride (Mackison, 1981)
NIOSH No.	KJ 4000000

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Human exposure to FC-113 that is attributable to contamination of drinking water is difficult to assess in California because complete analytical data are not available for all water systems, although FC-113 has been found in at least eight locations in California ground water. In a survey of California drinking water wells, FC-113 concentrations of 0.5 to 2.5 ppb were noted in Kern County and Santa Clara County (DHS, 1986; 1988).

In calculating drinking water standards for public health protection, a value for daily water consumption must be assumed. For adults, a daily water consumption of 2 liters/day (2 L/day) is a default value; for children the default is 1 L/day. Volatile compounds in tap water also contribute to total exposures through inhalation and dermal contact from the use of water in showering, bathing, cooking, cleaning and other domestic uses. Consideration of the contribution of all sources of a volatile chemical exposure from drinking water results in an estimate of liter-equivalents per day (L_{eq}/day) which is used as an alternative to the default daily water consumption (L/day).

Using an exposure model to assess multipathway exposures from volatile substances in tap water (McKone, 1987), DHS (1989) estimated household inhalation (volatilized from showers and other water uses), ingestion and dermal (through bathing and washing) exposures to FC-113 in tap water in order to calculate L_{eq}/day values.

The mean estimate of total multipathway exposure from FC-113 in tap water was estimated as equal to that associated with ingestion of 8.0 L_{eq}/day . This was based on inhalation exposure estimates of 2.7 L/day for showering, 1.0 L/day for bathroom exposures and 0.7 L/day for other household uses. Dermal absorption was estimated to be equivalent to ingesting 2.0 L/day and ingestion exposures were estimated at 1.7 L/day.

The upper-bound estimate of total multipathway exposure from FC-113 in tap water was estimated as equal to that associated with ingestion of 30.2 L_{eq}/day . This was based on inhalation exposure estimates of 12.9 L/day for showering, 5.3 L/day for bathroom exposures and 3.7 L/day for other household uses. Dermal absorption was estimated to be equivalent to ingesting 4.6 L/day and ingestion exposures were estimated at 3.7 L/day.

It was assumed that the relative contributions percent of doses derived from oral, dermal and inhalation routes to the total dose remain constant over the range of FC-113 drinking water concentrations, and that the population is stationary.

METABOLISM AND PHARMACOKINETICS

Human

Three human subjects were studied for the amount of retention of FC-113 after inhalation. About 7 mg of radioactive labeled compound was inhaled once and the amount in exhaled air was measured during normal breathing. Over half of the inhaled FC-113 was exhaled immediately, with an average of 19.8% retained after 30 minutes (Morgan, 1972). Four men were exposed to 500 ppm for six hours/day over five days. The following week, they inhaled 1,000 ppm under the same conditions. Breath samples were collected before exposure each morning, and after exposure in the afternoon. A post-exposure breath sample was collected two days after the final exposure. During the week of exposure to 500 ppm, only 4 of 20 morning samples were above 1 ppm. During the week of exposure to 1,000 ppm, 14 of 20 morning samples were above 1 ppm. No upward trend in concentrations of afternoon samples was noted. Two days after cessation of exposure, only one sample had measurable FC-113 (1.5 ppm) (Reinhardt *et al.*, 1971). The absorption and excretion of FC-113 was determined via breath-holding experiments on humans using [$^{38}C1$] - labeled compounds. When the retention was plotted versus time in log-log form, the results could be correlated by a straight line, a power function of the form: $R(t) = A \exp[(-b)\log(t)]$, where A is the total amount absorbed, and R(t) is the amount remaining after

time t (minutes). For FC-113, the coefficient $b = 0.245$; $A \exp[(-0.245) \log(60)] = 0.3667$. The total excretion in breath after one hour was 63% of the original dose. The half-life is approximately 17 minutes. A urine sample taken one hour after inhalation showed an excretion rate of less than 0.01% per minute (Morgan, 1972).

Animal

Male Wistar rats were exposed via inhalation to 200, 1,000 or 2,000 ppm FC-113 for six hours/day, five days/week for two weeks. Five animals from each exposure group were tested after one or two weeks, and five from each group were tested seven days after the end of exposure along with the control group. Results are the mean of five rats \pm S.D. Analysis of brain samples showed the following accumulations after one week exposure to 200, 1,000 or 2,000 ppm FC-113: 5.4 ± 2.1 nmol/g, 23.4 ± 6.1 nmol/g and 46.6 ± 22.2 nmol/g, respectively. After two weeks of exposure, brain samples from exposed rats showed 5.8 ± 1.7 nmol/g, 23.7 ± 5.0 nmol/g and 40.6 ± 25.0 nmol/g, respectively. Perirenal fat samples also showed a dose-dependent accumulation of FC-113 between one and two weeks after exposure. However, after a withdrawal period of seven days, no fluorocarbon was detected in either tissue (Savolainen and Pfaffli, 1980).

Male Fischer 344 rats were exposed to FC-113 in a recirculating chamber in an attempt to measure metabolism *in vivo* using the gas uptake method. Uptake of FC-113 could not be accurately measured using this method. Authors concluded that large concentrations were needed to produce modest blood levels, due to the very small partition coefficient of FC-113 (Anderson *et al.*, 1980).

Four beagle dogs (unanesthetized) were exposed to FC-113 via inhalation for 10 minutes at concentrations of 0.1%, 0.5% or 1.0%. Mean blood concentrations after five minutes of exposure were: 0.1% FC-113, 2.6 $\mu\text{g/mL}$ arterial and 1.5 $\mu\text{g/mL}$ venous; 0.5% FC-113, 12.5 $\mu\text{g/mL}$ arterial 4.9 $\mu\text{g/mL}$ venous; 1.0% FC-113, 18.0 $\mu\text{g/mL}$ arterial and 12.1 $\mu\text{g/mL}$ venous. Blood levels increased rapidly during the first five minutes of exposure and then more slowly or not at all during the remaining five minutes. At the end of the 10 minutes exposure, the concentrations decreased sharply during the first few minutes followed by a slower decline. Arterial concentrations were generally higher than venous levels during exposure, while the reverse was true after exposure. Tissue uptake of parent FC-113 compound occurs during exposure followed by release into venous blood after the exposure ends (Trochimowicz *et al.*, 1974). Guinea pigs were injected with 3 mL/kg FC-113 for 20 successive days and then exposed to 4 to 5% vapor for one hour. FC-113 values immediately after exposure were highest in the fat; moderate in the brain, liver and kidneys; somewhat lower in the lung, heart, spleen and muscle; and lowest in the blood. Freon content in the blood and organs decreased gradually with time (Furuya, 1980). Shortly after exposure of rats and guinea pigs, FC-113 content decreased in the following order: fat, brain, liver, kidney, heart, lung, muscle and blood (Furuya, 1979).

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

FC-113 is practically nontoxic when given in single oral doses to mammals. Oral LD₅₀ values for various species are: 43,000 mg/kg for rats, 17,000 mg/kg for rabbits (AIHA, 1968) and \geq 92,000 mg/kg for dogs. The approximate lethal dose given to the rabbit by dermal application is 11,000 mg/kg (Clayton, 1967). The intraperitoneal LD₅₀ in mice was reported to be 8,600 mg/kg (Aviado and Belej, 1974).

Inhalation four-hour LC₅₀ values in rats range from 38,500 to 68,000 ppm (Du Pont, 1985). In one report it was stated that the inhalation LC₅₀ to mice was twice the concentration required to produce anesthesia in 50% of the animals (Burn *et al.*, 1959). Inhalation of 10% FC-113 in air by rats for four hours was lethal (Aviado and Belej, 1974), but inhalation of 1% for two hours caused only disturbances in equilibrium.

Signs of FC-113 intoxication in rats exposed to concentrations in excess of the four-hour LC₅₀ were tonic convulsions, pronounced tremor followed by unresponsiveness, polypnea and pallor. The lungs were congested and edematous (Du Pont, 1985). At the higher concentrations, cardiac arrhythmias occurred. In another study, no rats, out of an unspecified number, died when exposed to 28,100 ppm for two hours (Philadelphia Naval Shipyard, undated, as cited by Du Pont, 1985).

When anesthetized Swiss mice inhaled 5 or 10% FC-113 for six minutes, only one of the three mice exhibited cardiac arrhythmias at the highest dose level. However, when mice were challenged with 6 mg/kg epinephrine and were exposed to 5 or 10% FC-113 in air, all of the animals at the highest concentration developed arrhythmia and one of three animals at the 5% level developed arrhythmia (Aviado and Belej, 1974). Inhalation by guinea pigs of 20% FC-113 in air for two hours induced narcosis (Aviado and Belej, 1974). Exposure to 39,100 ppm FC-113 for two hours induced congestion in rat liver and kidney (Du Pont, 1985).

Inhalation of 11,000 to 13,000 ppm by dogs for six hours caused emesis, lethargy and central nervous system (CNS) disturbances (tremor, nervous twitching). Within 15 minutes of cessation of exposure, the animals appeared normal (ACGIH, 1986).

Simultaneous exposure to the insecticide synergist, piperonyl butoxide, failed to influence the toxicity of FC-113 in rats (Desoile *et al.*, 1975) particularly in the beagle dog. Concentrations as low as 1,200 ppm in the beagle dog and 2,400 ppm in the rat have been reported to produce cardiac sensitization (Du Pont, 1985). This phenomenon is related to acute inhalation of high concentrations of FC-113 and it is potentiated by epinephrine administration (Clark and Tinston, 1973), but endogenous epinephrine has not been considered sufficient to produce sensitization in dogs even at 12,000 ppm FC-113 (ACGIH, 1986).

Instillation of 0.1 mL FC-113 into the conjunctival sac in rabbits produced a mild corneal opacity and slight conjunctivitis within 24 hours. The rabbit eyes appeared normal within 48

hours of treatment (AIHA, 1968). Duprat *et al.* (1976) considered FC-113 a "non-irritant" to eyes or skin.

Inhalation of 1,500 ppm by two male volunteers for 2.75 hours failed to affect their performance on a variety of psychomotor tests, but evidence for decreased performance was noted after exposure to 2,500 ppm. Inhalation of 3,500 or 4,500 ppm clearly reduced test results, but within 15 minutes of cessation of exposure, objective and subjective (somnia, loss of concentration) signs of FC-113 intoxication had subsided (Stoppa and McLaughlin, 1967). Intubation of one liter (20,000 mg/kg) of cold FC-113 produced immediate, transient cyanosis. The only objective signs reported after recovery were severe rectal irritation and diarrhea which persisted for three days (Clayton, 1966).

Using *in vitro* preparations, FC-113 was reported to increase acetylcholinesterase activity in the frog heart vagus ($ED_{50} = 160$ ppm) (Young and Parker, 1975). Alarie *et al.* (1975) reported that *in vitro* ventilation of rat lungs with FC-113 caused alveolar instability and atelectasis.

Subchronic Toxicity

Six rats were exposed two hours daily, five days a week for 12 months to 12,000 ppm of FC-113. One rat died of intestinal occlusion, a second died after 17.5 months with a tumor of the left kidney. Lung and kidney lesions were observed which were not clearly attributable to exposure to FC-113 (Desoile *et al.*, 1968).

An unspecified number of rats were exposed to 100 ppm of FC-113, 18 hours each day for 16 days. There were no deaths or other signs of toxic effects. An unspecified number of rats were exposed to 250 or 500 ppm of FC-113, seven hours each day for 30 days. Body weight gain depression and pale livers at the 500 ppm level were the only signs of toxicity. An unspecified number of rats were exposed to 2,500 or 5,000 ppm of FC-113, seven hours each day for 30 days. There was no mortality, but at 5,000 ppm weight gain depression and pale livers were observed (Clayton, 1967).

Groups of four male and four female rats were exposed to FC-113 at varying concentrations and durations of exposure. At 5,000 ppm for 4.5 hours, there was no effect. At 60,000 ppm for one hour, slight anesthesia was observed. After removal from the exposure chambers the animals rapidly returned to normal (Gage, 1957).

An unspecified number of male Wistar rats was exposed to 200, 1,000 or 2,000 ppm FC-113 for six hours daily, five days/week for one or two weeks. After one to two weeks of treatment, there was proliferation and vacuolization of the smooth endoplasmic reticulum of the liver at the mid and high exposure levels. Hepatic drug metabolizing enzyme activities decreased in a dose-dependent manner. FC-113 was found to bind to cytochrome P_{450} and this effect was increased by phenobarbital pretreatment (Vainio *et al.*, 1980).

The American Industrial Hygiene Association (AIHA, 1968) summarized a series of studies in rats inhaling 5,000 ppm, seven hours/day, five days/week for 30 days. Decreased weight gain and mild histopathologic changes in the liver were observed. Inhalation of 25,000 ppm, 3.5 hours/day for 20 days by rats failed to induce biochemical or histologic changes which could be attributed to FC-113 exposure.

An unspecified number of rabbits were exposed to 11,000 ppm of FC-113, two hours/day, five days/week for 4 to 37 weeks. Signs of intoxication reported were emphysema and inflammatory bronchitis which may have been associated with age of the animals (Desoile *et al.*, 1968). Application of 5 g/kg FC-113 daily for five days to rabbit skin elicited slight histologic changes in the liver and signs of damage to the treated epidermis (AIHA, 1968).

Fifty rats, 40 mice, 8 dogs and 4 monkeys were exposed to FC-113 continuously for 14 days. There were no deaths nor were there any adverse findings such as clinical signs, hematological values, clinical chemistry parameters, electroencephalograms, body weights or changes in organ to body weight ratios (Carter *et al.*, 1970, cited by Du Pont, 1985). When guinea pigs or rats were exposed to FC-113 at 25,000 ppm or cats and dogs at 12,500 ppm for 3.5 hours each day for 20 days, there was no mortality nor sign of toxicity (Clayton, 1967). Dogs, guinea pigs and rats were exposed to 5,100 ppm and guinea pigs were exposed to 25,000 ppm of FC-113 for 70 hours, 3.5 hours/day, five days/week for four weeks. There was no evidence of damage in the heart, lungs, liver, kidneys or spleen (Humpfner, 1973).

Three beagle dogs per sex were exposed to 5,000 ppm FC-113 in air for six hours daily for 90 days. A control group of three male and three female dogs was exposed to an air flow without FC-113. Similarly, 20 rats per sex were exposed to 10,000 ppm for six hours/day for 90 days. No adverse effects were noted by the authors in either species at these doses (Leuschner *et al.* 1983).

A summary of available subchronic and chronic inhalation and ingestion studies with FC-113 is tabulated in U.S. EPA's health assessment document for 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-113) (U.S. EPA, 1983) and in Sax and Lewis (1986).

Reproduction and Developmental Toxicity

Groups of 24 pregnant rats were exposed to 0, 5,000, 12,500 or 25,000 ppm FC-113 in air, six hours/day on days 6 to 15 of gestation. The control group was exposed to air only. Except for one maternal death and one abortion at the highest concentration, there was no indication of maternal toxicity. Based upon evaluation of the standard fetal parameters for teratogenicity, there was no evidence of an embryotoxic or teratogenic effect (Du Pont, unpublished data cited by U.S. EPA, 1983).

Groups of 12 pregnant rabbits were exposed to 0, 2,000 or 20,000 ppm FC-113 in air for two hours daily on days 6 to 14 of gestation. Decreased body weight gain in the high-dose group was considered evidence of maternal toxicity. In the high-dose group there were one maternal death, one fetal death and one pup was delivered prematurely on day 29. No remarkable variations were observed in the external soft tissue or in the skeletons of the fetuses (Du Pont, unpublished data cited by U.S. EPA, 1983).

In a second study conducted in the same year (1967), groups of eight rabbits received 0 (distilled water), 1 or 5 g/kg-day of FC-113 orally by stomach tube on days 8 through 11 of gestation. There was a dose-dependent increase in mortality. Four animals died in the high-dose group, accompanied by body weight loss and reduction in food and water consumption. Pregnancy rates were low in all dose groups. Among 32 live fetuses evaluated, there were no remarkable anatomical changes. Because of the high maternal toxicity and small

number of animals used in this study, the study is inadequate as an assessment of the teratogenic potential of FC-113 (Du Pont, unpublished data, cited in U.S. EPA, 1983).

Chronic Toxicity and Carcinogenicity

Groups of 100 male and 100 female Crl: CDR (SD) BR rats were administered 0, 2,000 \pm 100, 10,000 \pm 500 or 19,900 \pm 1,000 ppm FC-113 vapor (v/v \pm SD) five days/week, six hours/day over two years. Body weights, appearance and behavior, mortality and clinical chemical parameters were monitored regularly during the study period. Ten rats per sex in each group were sacrificed by design after one year, and all rats at the end of the two-year study period and rats found dead or sacrificed *in extremis* were subjected to histopathological evaluation. There were decreases in mean body weight gains among female rats in the 10,000 ppm dose group and rats of both sexes in the 20,000 ppm dose group. There were transient decreases in serum glucose levels in male rats at 20,000 ppm. Increased urinary excretion of fluoride was observed in both male and female rats in the 10,000 and 20,000 ppm groups. The study was complicated by the development of a tuberculosis-like infection (*Corynebacterium kutscheri*) in rats in the second year of the study, which resulted in 18 to 35% infection-related mortality in the males and 5 to 8% mortality in the females. However, an adequate number of survivors was available for pathological assessment. Pathological evaluation did not show evidence of an oncogenic effect at any dose level. The no-observed-adverse-effect-level (NOAEL) in this study was determined to be 2,000 ppm by the authors, although a statistically significant increase in relative liver weights was reported for male rats in all exposure groups (Du Pont, 1985; Trochimowicz *et al.*, 1988). For the purpose of PHG development, 2,000 ppm was considered a lowest-observed-adverse effect-level (LOAEL) based on a significant increase in liver weight.

Neonatal Swiss mice (52 per group) received a solution of FC-113 subcutaneously. The animals received 0.1 mL FC-113 (19%) in tricaprylin on days one and four after birth and 0.2 mL on days 14 and 21. There were four groups: group one received solvent control only, group two received 10% FC-113 in the solvent, group three received 5% of the synergist piperonyl butoxide in the solvent and group four received a mixture of FC-113 (19%) and piperonyl butoxide (5%). Piperonyl butoxide was chosen for study because it was used as a synergist in several aerosol cans. Dose levels were 0.1 and 0.2 mg as a 10% solution of FC-113; the total dose received was 0.6 mL and the animals were observed for one year after the final injection of 0.2 mL on day 21. There was no indication of a synergistic effect of piperonyl butoxide to the increase in mortality. There was some indication of an increase in hepatomas with the compound and synergist together (group four) compared to the control (17% compared to 8%) in the males. Hepatomas were found after 51 weeks in male mice receiving both piperonyl butoxide and FC-113. The incidence of hepatomas was 17% of those at risk given piperonyl butoxide and FC-113 together, as compared to a 5% risk in male mice administered FC-113 alone. No hepatomas were observed in the female mice. The incidence of malignant lymphomas in female mice was 4% after combined treatment, 5% in female mice receiving FC-113 alone compared to no incidence of malignant lymphomas in female mice administered subcutaneous injections of piperonyl butoxide or vehicle alone. Only one case of lymphoma was documented in the 48 male mice receiving the vehicle only and one instance of mammary carcinoma was observed in female mice injected with FC-113. The numbers were insufficient for statistical evaluation (Epstein *et al.*, 1967).

Genotoxicity

In the Ames *Salmonella* assay, FC-113 was found to be nonmutagenic in strains TA 1535, TA 1536, TA 1537 and TA 1538 both with or without S9 activation (Simmon *et al.*, 1977). In a dominant lethal assay in mice, FC-113 was found not to be mutagenic when administered by the intraperitoneal route at 100 or 200 mg/kg (Epstein *et al.*, 1972).

Toxicological Effects in Humans

Four human volunteers were exposed to atmospheric concentrations of 500 to 1,000 ppm FC-113 for six hours/day, five days/week (three hours in the morning and three hours in the afternoon). Clinical observations, laboratory tests, subjective impressions, electrocardiographic monitoring and measurement of psychomotor reactions did not reveal any adverse effect (Reinhardt *et al.*, 1971).

Two male subjects were experimentally exposed to 1,500, 2,500, 4,000 and 4,500 ppm FC-113 for two hours 45 minutes. Four psychomotor tests were administered during the exposure period. Exposures to 1,500 ppm were without consistent observable effect, while 2,500 ppm was considered to be associated with slight adverse effects on performance. Exposures to 2,500 ppm or more were associated with loss of concentration, drowsiness and dizziness upon lateral head shaking. These effects resolved within 15 minutes of leaving the exposure chamber (Stoppa and McLaughlin, 1967).

Two epidemiological studies have been reported. A group of 50 workers were exposed about six hours per day for an average of 2.77 years to an environment which contained from 46 to 4,700 ppm of FC-113. The mean concentration was 699 ppm. The only subjective complaint was dry skin. Six of the workers exposed to FC-113 had a history of respiratory disorders which the authors could not relate to occupational exposure. There were no other remarkable effects reported (Imbue and Adkins, 1972).

Ten women and three men had occupational exposures to FC-113 from 1 to 14 years (mean of nine years) and 6 to 21 years (mean of 11 years), respectively. Average daily ambient levels were measured and were between 23 and 62 ppm. During a one-week observation period, the females were exposed for one 3.5 to 5.8 hour work-day and the males were exposed for brief periods. No abnormal findings were reported from blood and urine analyses (Triebig and Burkhardt, 1978).

During a seven-year interval, the U.S. Navy recorded 38 Freon-related exposures resulting in harm, including 16 chemical burns and 22 inhalation injuries. FC-113 was one of the implicated substances. The problem was associated with unsafe use in small, closed and unventilated areas (Voge, 1989). Two deaths resulted from occupational exposure to FC-113 in small enclosed spaces. One incident involved a worker in a small degreasing tank and the other resulted from a large shipboard FC-113 release.

A case report of an elderly male who developed hypochromic anemia and colitis after exposure to FC-113 was reported by Hoshika *et al.* (1989), although the original article was unavailable for review.

An anesthetized patient was accidentally administered approximately one liter of cold FC-113 into the stomach. Immediate and transient cyanosis was observed, but the patient survived and

severe rectal irritation and diarrhea lasting three days were the only adverse effects noted (Clayton, 1966)

FC-113 appears to be metabolically inert and of low toxicity in humans and experimental animals. Cardiac effects appear to be limited to relatively high inhalation exposure levels. Most of the toxicology studies are from exposure by inhalation including a chronic study which failed to demonstrate a carcinogenic response; only minimal effect on relative liver weight was observed at 2,000 ppm. Available data do not provide any evidence of teratogenic effects. No information is available on other potential reproductive effects.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

There is inadequate human dose-response information available on which to base the calculation of a PHG for FC-113. Therefore, an NOAEL for FC-113 was derived from an animal study.

FC-113 cardiac toxicity appears to be limited to relatively high inhalation exposure levels. Most of the toxicology studies in laboratory animals are from exposure by inhalation including a chronic study which failed to demonstrate a carcinogenic response; only minimal effect on relative liver weight was observed at 2,000 ppm. Available data do not provide evidence of teratogenic activity and no information is available on other potential reproductive effects.

The most appropriate study for the determination of the PHG for FC-113 is a two-year toxicity study conducted in rats (Du Pont, 1985). In this study, the lowest dose tested (2,000 ppm or 15,400 mg/m³) of exposure to FC-113 for five days/week, six hours/day was considered by the researchers as an NOAEL, although this dose was associated with a slight but statistically significant increase in liver weights among male rats. For the purpose of calculating a PHG, 2,000 ppm was considered to be a mild LOAEL because of increased liver weights in all exposure groups. However, due to the lack of any histopathological evidence, this effect was considered a mildly toxic effect for the purposes of calculating a PHG.

At the 10,000 and 20,000 ppm level, the main effects noted were slight decreases in body weight gain. The magnitude of this effect was less than 10% in the 10,000 ppm group, but greater than 10% in the 20,000 ppm. The biological significance of deficits in body weight gain of less than 10% has been questioned.

Carcinogenic Effects

No evidence of carcinogenicity was noted in a two-year inhalation study with rats (Du Pont, 1985).

CALCULATION OF PHG

A public health-protective concentration (C) for FC-113 in drinking water (in mg/L) can be calculated using the general equation for noncarcinogenic endpoints:

$$\text{PHG} = \frac{\text{NOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{Leq/day}} = \text{mg/L}$$

where,

NOAEL	=	No-observed-adverse-effect-level (in mg/kg-day, see following discussion)
BW	=	Adult male body weight (70 kg)
RSC	=	Relative source contribution of 40% (0.4)
UF	=	Uncertainty factor of 300 (3-fold for LOAEL to NOAEL conversion, 10-fold for inter-species variation, 10-fold for human variability)
Leq/day	=	Volume of water consumed daily (8.02 or 30.2 Leq/day) based on data presented in DHS (1989) for inhalation, ingestion and dermal exposures from FC-113 in tap water

To convert the LOAEL for liver weight effects from inhalation exposure to an NOAEL for drinking water, a time-weighted mean daily exposure was first calculated assuming that 50% (0.5) of inspired fluorocarbon was absorbed. At the LOAEL of 15,400 mg/m³ (15.4 mg/L), the rat respiratory minute volume is 0.65 L/minute/kg (Guyton, 1947) and the total daily exposure duration is six hours. Anderson. (1983) reported a daily respiratory volume of 0.64 m³/kg-day for a rat.

$$\frac{15.4 \text{ mg/L} \times 0.65 \text{ L/min/kg} \times 6 \text{ h/day} \times 60 \text{ min} \times 5 \text{ days/week} \times 0.5}{7 \text{ days/week}}$$

= 1,287 mg/kg-day

The OEHHA default uncertainty factor used when extrapolating from valid results of long-term studies in animals to humans and when human data of appropriate exposure duration are not available is 100, in accordance with U.S. EPA practice (*Fed. Regis.* 50:46946, November 13, 1985). For this assessment, an additional uncertainty factor of three was used to extrapolate a mild LOAEL to an NOAEL. A relative source contribution (RSC) of 40% was used (instead of the common 20% default) because tap water is expected to be a major exposure source, compared to other sources such as food, soil, and ambient air. The tap water also provides extensive additional exposure from inhalation resulting from other uses of water in the home.

Therefore,

$$C_{\text{mean}} = \frac{1,287 \text{ mg/kg} \times 70 \text{ kg} \times 0.40}{300 \times 8.02 \text{ Leq/day}}$$

= 14.97 mg/L = 15 mg/L (rounded) = 15 ppm.

Or,

$$C_{\text{conserv}} = \frac{1,287 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.40}{300 \times 30.2 \text{ Leq/day}}$$

= 3.98 mg/L = 4 mg/L (rounded) = 4 ppm.

Two public health-protective concentrations (C) were calculated for FC-113 in drinking water; 4 and 15 mg/L (4 and 15 ppm). (Note: Refer to the section on Environmental Occurrence and

Human Exposure for derivation of the mean [8.02] and conservative [30.2 Leq/day] dose estimates.) The value of 4 mg/L (4 ppm) is the PHG for FC-113 in drinking water.

RISK CHARACTERIZATION

Exposures to FC-113 occur via the inhalation, ingestion and dermal routes of exposure. Contamination of drinking water wells has occurred and the volatility of this chemical can lead to substantial exposures via inhalation and dermal contact as well as drinking water ingestion. Production of FC-113 in the U.S. ceased in 1996, and exposures are expected to decline as the use of FC-113 is phased out. In general, reports or adverse effects associated with human exposure to FC-113 have been relatively few and as use and emissions of FC-113 decline, the potential for human harm will also lessen. No sensitive populations were identified. There are no data suggesting increased sensitivity for infants and children.

Major uncertainties in the dose-response assessment and the derivation of the PHG include the lack of adequate human health effects data and limited metabolism, genotoxic, reproductive and lifetime exposure studies. There are uncertainties regarding the relative contribution of water-borne exposures as compared with inhalation and other routes of exposure.

OTHER REGULATORY STANDARDS

The California Maximum Contaminant Level (MCL) for FC-113 is 1.2 mg/L (1.2 ppm) in drinking water. The U.S. Environmental Protection Agency (U.S. EPA) has not developed a Maximum Contaminant Level (MCL).

U.S. EPA has not developed Health Advisories specifically for FC-113 in drinking water. U. S. EPA has developed an oral reference dose of 30 mg/kg-day (U. S. EPA, 1997).

The Occupational Safety and Health Administration's (OSHA's) standard for workplace exposure to FC-113 is 1,000 ppm averaged over an eight-hour work shift. A short-term exposure limit of 1,250 ppm is recommended by the American Conference of Governmental Industrial Hygienists (ACGIH). The Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) designated spent halogenated solvents, such as FC-113, as a hazardous material under the Hazardous Materials Transportation Act (40 CFR 172.101, October 1, 1981).

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