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Provisional Peer-Reviewed Toxicity Values for

Trichlorofluoromethane
(CASRN 75-69-4)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR TRICHLOROFLUOROMETHANE (CASRN 75-69-4)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. U.S. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3. Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

An RfD of 3×10^{-1} mg/kg-day for trichlorofluoromethane (also known as FC-11 or Freon 11) is available on IRIS (U.S. EPA, 2008). The assessment, verified 5-31-1985 and described in the Health Effects Assessment (HEA) for Fully Halogenated Methanes (U.S. EPA, 1987), is based on a duration-adjusted LOAEL of 349 mg/kg-day for decreased survival in rats in a National Cancer Institute (NCI, 1978) gavage cancer bioassay. The composite UF of 1000 included factors of 10 each for use of a LOAEL, interspecies extrapolation, and protection of sensitive populations. This RfD is also included in the Drinking Water Health Advisory list (U.S. EPA, 2006), which is based on a Drinking Water Health Advisory (DWHA) for trichlorofluoromethane (U.S. EPA, 1989), and in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997). The HEAST also lists a subchronic RfD of 0.7 mg/kg-day, described in the HEA (U.S. EPA, 1987), based on a duration-adjusted LOAEL of 714 mg/kg-day for decreased body weight and increased mortality in the 6-week range-finding study for the NCI (1978) cancer bioassay and a composite UF of 1000 (10 each for use of a LOAEL, interspecies extrapolation, and protection of sensitive populations). The HEA and DWHA are the only relevant documents included in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a). The Agency for Toxic Substances Disease Registry (ATSDR, 2008) has not developed a Toxicological Profile for trichlorofluoromethane. An Environmental Health Criteria Document for fully halogenated chlorofluorocarbons includes trichlorofluoromethane (WHO, 1990), but it did not derive toxicity values.

There is no RfC for trichlorofluoromethane on IRIS (U.S. EPA, 2008). The HEAST (U.S. EPA, 1997) lists a subchronic RfC and chronic RfC of 7 mg/m^3 and 7×10^{-1} mg/m^3, respectively, for trichlorofluoromethane derived in the HEA (U.S. EPA, 1987) from a subchronic inhalation study by Jenkins et al. (1970) using methods no longer supported by U.S. EPA. The critical effect was increased blood urea nitrogen (BUN) in exposed dogs at 1008 ppm (5746 mg/m^3). In a route-to-route extrapolation, the California Environmental Protection Agency (CalEPA, 1997) used this LOAEL as the basis for calculation of a Public Health Goal of 700 ppb in drinking water. At the time of the initial literature search (May 7, 2008), CalEPA

(2005) listed a chronic inhalation recommended exposure limit (REL) of 7×10^2 μg/m^3 for trichlorofluoromethane to protect against nervous system effects. However, this REL was eliminated when the table of RELs was updated on May 22, 2008. The American Conference of Governmental Industrial Hygienists (ACGIH, 2001, 2007) recommends a threshold limit value (TLV) ceiling of 1000 ppm (5600 mg/m^3) for trichlorofluoromethane to prevent acute cardiac sensitization in workers. The National Institute for Occupational Safety and Health (NIOSH, 2005) REL is also a ceiling level of 1000 ppm, while the Occupational Safety and Health Administration (OSHA, 2008) permissible exposure limit (PEL) is 1000 ppm as an 8-hour time-weighted average (TWA).

IRIS (U.S. EPA, 2008) does not contain a cancer assessment for trichlorofluoromethane, and neither does the HEAST (U.S. EPA, 1997). The HEA (U.S. EPA, 1987) assigned trichlorofluoromethane to U.S. EPA (1986) weight-of-evidence Group D—"Not classifiable as to human carcinogenicity"—based on the lack of data regarding the carcinogenic effect of the chemical in humans and insufficient evidence in animals. Trichlorofluoromethane is also classified as Group D in the DWHA list (U.S. EPA, 2006) based on the DWHA for trichlorofluoromethane (U.S. EPA, 1989). ACGIH (2007) has designated trichlorofluoromethane as A4—"Not classifiable as a human carcinogen." Trichlorofluoromethane is not included in the National Toxicology Program Report on Carcinogens (NTP, 2005). Results of the NCI (1978) bioassay were inconclusive for rats (due to low survival) and negative for mice. The carcinogenicity of trichlorofluoromethane has not been assessed by the International Agency for Research on Cancer (IARC, 2008).

Literature searches were conducted from 1960s through June 2009 for studies relevant to the derivation of provisional toxicity values for trichlorofluoromethane. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS, TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents (last 6 months).

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure

A 38-year-old man who accidentally ingested a small amount of trichlorofluoromethane suffered multiple perforations of the stomach; the effects were presumed to result from the freezing action of the compound (Haj et al., 1980).

Inhalation Exposure

Stewart et al. (1975, 1978) exposed 8 male volunteers to 1000 ppm (5620 mg/m^3) trichlorofluoromethane 8 hours/day, 5 days/week, for a total of 18 exposures (3.5 weeks). The subjects served as their own controls, with comprehensive pre-exposure testing providing baseline measurements. The study authors recorded subjective symptoms before exposure and hourly until 5 hours after exposure was concluded for the day. They collected blood for serum chemistry (alkaline phosphatase [ALP], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], bilirubin, glucose, calcium, phosphorous, BUN) and hematology (complete blood count) before and after exposure; urinalysis (parameters not specified) was assessed at the same times. Other evaluations included electrocardiogram, pulmonary function (computerized spirometry

measurement), neurological evaluation (modified Romberg test and heel-to-toe test), electroencephalogram, visual evoked potentials, and cognitive tests (Flanagan coordination tests, Marquette time estimation test, and random number inspection test). The data showed no effects on any parameters other than the cognitive tests. Statistically significant decrements were observed in cognitive performance tests (data presented graphically, $p < 0.02$). The study authors described these effects as "minor and transient" and considered the significance of these effects to be questionable because similar effects were not observed in experiments wherein groups of male and female volunteers were acutely exposed to the same concentration (1000 ppm or 5620 mg/m^3) for up to 8 hours. However, as noted by the World Health Organization (WHO, 1990), several other studies have indicated a potential association between psychomotor impairment and chlorofluorocarbon exposure (Stopps and McLaughlin, 1967; Kehoe, 1943; Azar et al., 1972; Geller et al., 1977, all as cited by WHO, 1990), lending credence to the observed association with cognitive effects. In addition, higher concentrations of trichlorofluoromethane have resulted in neurological effects and/or brain histopathology in rats (Lester and Greenberg, 1950; Clayton, 1966; described below under "Other Studies"). Thus, the exposure concentration used in this study (5620 mg/m^3) is considered a LOAEL for mild effects on cognitive performance.

Animal Studies

Oral Exposure

Subchronic Studies—Both CalEPA (1997) and NRC (1980) discussed a 1-month study in mice (Kudo et al., 1971, as cited in CalEPA, 1997); this paper was published in Japanese and was not retrieved for this review. According to CalEPA (1997), mice (both sexes, but strain and number per sex not reported) were given trichlorofluoromethane at doses of 16.2, 54.5, or 218 mg/kg-day via daily oral administration (method not specified) for 1 month (Kudo et al., 1971, as cited in CalEPA, 1997). The toxicological evaluations were not described by CalEPA. The only effects reported in the summary were a slight decrease in food consumption and one case of liver cell vacuolation in the animals exposed to the highest dose. The available information is inadequate for the determination of effect levels.

CalEPA (1997) cited two oral studies that were not discussed in any other secondary references; efforts to obtain the original reports were not successful. In the first study, DuPont (1972, as cited in CalEPA, 1997) administered gavage doses of 0, 5, or 30 mg/mL trichlorofluoromethane in corn oil to albino ChR-CD rats (20/sex/group) for 90 days. The dosing frequency was 7 days/week for the first month and then 5 days/week for the remainder of the exposure period. CalEPA (1997) reported average daily doses of 41 to 73 mg/kg-day (low-dose group) and 245 to 450 mg/kg-day (high-dose group). Parameters monitored to assess toxicity included body weight, food intake, behavioral observations, hematology, and serum and urine chemistry (including BUN, ALP, creatinine, and AST). Upon sacrifice, half of the animals in each group were sacrificed for histopathology evaluation of unspecified tissues. CalEPA (1997) reported that there were no treatment-related differences in any of the parameters assessed.

An experiment with dogs was also conducted by DuPont (1972, as cited in CalEPA, 1997). Trichlorofluoromethane in corn oil was administered at doses of 0, 250, or 500 mg/mL via gelatin capsule to groups of dogs (4/sex/dose; strain not specified). CalEPA (1997) reported the average daily doses to be 40 to 69 mg/kg-day (low-dose group) and 170 to 346 mg/kg-day (high-dose group); the frequency of administration is not reported.

Toxicity in dogs was assessed using the same parameters assessed in rats. According to CalEPA (1997), there were no treatment-related effects. No other information on the DuPont studies is provided by CalEPA (1997); however, the studies were reported to contain "a number of shortcomings and inconsistencies," which CalEPA (1997) characterized as limiting their usefulness for risk assessment. The information available for these studies is inadequate for the determination of effect levels.

NCI (1978) conducted a dose range-finding study of trichlorofluoromethane in rats and mice (NCI, 1978). Groups of Osborne-Mendel and B6C3F1 mice (5/sex/species/dose) were given trichlorofluoromethane via gavage at doses of 0, 1000, 1780, 3160, 5620, or 10,000 mg/kg-day, 5 days/week, for 6 weeks. Survival and body-weight gain were the only parameters monitored in the dose range-finding study. In rats, at least one death occurred in each male group exposed to ≥1780 mg/kg-day and each female group exposed to ≥3160 mg/kg-day. Body weight was significantly reduced (26% less than controls) in male rats exposed to 1000 mg/kg-day; in females, body weight was reduced (11%) at 1780 mg/kg-day. Among mice, deaths occurred in males exposed to doses ≥5620 mg/kg-day and in females exposed to doses ≥3160 mg/kg-day. No body-weight changes occurred in mice exposed to doses below those causing mortality. No other dose-response information is provided in the study. This study identifies a FEL of 1000 mg/kg-day for marked body-weight reduction in male rats, and a FEL of 3160 mg/kg-day for mortality in female mice.

Chronic Studies—NCI (1978) administered trichlorofluoromethane in corn oil to Osborne-Mendel rats (50/sex/dose) and B6C3F1 mice (50/sex/dose). Untreated and vehicle control groups (20/sex/species) were maintained. The test material was administered via gavage 5 days/week for 78 weeks. Doses were adjusted at Week 12 in rats and at Week 7 in mice; the authors estimated TWA doses of 488 and 977 mg/kg-day for male rats, 538 and 1077 mg/kg-day for female rats, and 1962 and 3925 mg/kg-day in mice of both sexes. The author-supplied time-weighted doses reflect doses administered 5 days/week; they were not adjusted to reflect continuous (e.g., 7 days/week) exposure. After exposure was terminated, rats were observed for 28 to 33 weeks, and mice were observed for 13 weeks. Daily observations for mortality were conducted, and body weight, food consumption, clinical signs, and palpable tissue masses were assessed weekly for the initial 10 weeks and monthly for the remainder of the study. Upon death, humane sacrifice, or terminal sacrifice, all animals were necropsied; comprehensive histopathology evaluations (29 tissues) were performed on all animals.

In rats, a statistically significant ($p < 0.001$) dose-related increase in mortality (relative to the vehicle control group) occurred in both males and females (NCI, 1978), with deaths occurring as early as Week 4 of treatment in the high-dose females and Week 15 in other treated groups. The authors reported that chronic murine pneumonia was evident in 88 to 100% of all rats and that this infection probably contributed to the early mortality. Signs of illness, including hunched appearance and labored respiration, occurred at higher frequency than in controls at both doses during the beginning of the study; frequencies of these effects were similar to controls for the remainder of the study. Gross necropsy and histopathology examinations revealed pleuritis and pericarditis in treated, but not control rats. Tumor incidences were not significantly higher in exposed male or female rats; however, NCI (1978) concluded that inadequate numbers of rats survived long enough to be at risk from late-developing tumors. The U.S. EPA (IRIS RfD derivation, verified 5-31-1985) identified the low dose (488 mg/kg-day in male rats) as a LOAEL for accelerated mortality, pleuritis, and pericarditis.

In mice, NCI (1978) documented a statistically significant ($p = 0.009$) dose-related acceleration of mortality in females but not in males. Based on graphical presentation of the survival data, the earliest deaths in female mice occurred between Weeks 7 and 15 in both treated groups, while no control female deaths occurred until around Week 37. The pneumonia observed in rats was not observed in mice. The study authors reported no treatment-related effect on body weight or the incidence of clinical signs or nonneoplastic or neoplastic pathology. NCI (1978) concluded that, despite the increased mortality in females, enough male and female mice survived through study termination for assessment of late-developing tumors. The low dose (1962 mg/kg-day) represents a LOAEL for early mortality in females.

Inhalation Exposure

Subchronic Studies—Clayton (1966) reported the previously unpublished results of three experiments with trichlorofluoromethane. In the first, several species of laboratory animals were exposed to trichlorofluoromethane (purity not specified) at a concentration of 4000 ppm (22,500 mg/m^3). Groups of rats (6/sex), mice (4/sex), and guinea pigs (2 males), along with 1 male rabbit, were exposed for 6 hours each day, for 28 days. Following exposure, the animals were observed for a 15-day recovery period. It is not clear whether concurrent control groups were maintained; no data on control animals are reported. Mortality, body weight, hematology (erythrocyte count, leukocyte count, hemoglobin, and hematocrit, in rats only), and histology (organs and tissues not specified) were monitored. No effects were observed on any of these parameters (data not shown). In other experiments reported by this author, several species were exposed to trichlorofluoromethane 3.5 hours/day for 20 days. In these experiments, two cats, three guinea pigs (sex of these species not reported), and 5 male rats were exposed to 25,000 ppm (140,500 mg/m^3), while two dogs (sex not reported) were exposed to 12,500 ppm (70,200 mg/m^3). No effects were observed on body weight, hematological parameters (erythrocyte count, total and differential leukocyte count, hemoglobin, and hematocrit), or on urinalysis (protein and sediment). The study authors reported that there were no pathology changes to the liver, kidneys, heart, lungs, or spleen; it is not clear whether this refers to gross or microscopic pathology. The information presented in this report is inadequate for the definition of effect levels—especially in the absence of control data.

Jenkins et al. (1970) exposed several species of animals to nominal trichlorofluoromethane concentrations of 0 or 1000 ppm (5620 mg/m^3) via whole-body inhalation continuously for 90 days. They used Sprague-Dawley rats (8 males and 7 females per group), Princeton-derived guinea pigs (8 males and 7 females per group), Beagle dogs (2 males/group), and squirrel monkeys (9 males/group). The study authors observed all animals daily for clinical or behavioral signs of toxicity. Body weight and hematology (hemoglobin [Hgb], microhematocrit, and total leukocyte count) were assessed before and after the experiment. At sacrifice at the end of the exposure period, serum levels of urea nitrogen and alanine aminotransferase (ALT) were measured in all animals. Liver samples were collected from rats and guinea pigs for measurement of ALP and tyrosine aminotransferase. ALP and creatinine were also measured in serum from these species. Liver function, as assessed by bromosulfophthalein retention, was assessed in dogs. In rats and guinea pigs, 24-hour urinary excretion of fluoride was measured. The study authors performed histological examinations on the heart, lung, liver, spleen, and kidney (all species); brain and spinal cord (dogs and monkeys); and adrenal and thyroid (dogs only). They also subjected tissues from all dogs and monkeys to histopathologic examination, while tissues from half of the rats and guinea pigs were examined.

The average measured concentration of trichlorofluoromethane was 1008 ± 44 ppm (5660 mg/m^3). Jenkins et al. (1970) reported no deaths among the rats, and the data showed that body weight was not affected by exposure. There were no statistically significant effects on hematology, serum, or liver chemistry, or 24-hour fluoride excretion in rats. Upon necropsy, the study authors grossly observed mild liver discoloration in about one-fourth of rats, and they reported one male rat as having an enlarged right kidney (no further details reported). No treatment-related effects on survival, body weight, hematology, serum chemistry, or urinary excretion of fluoride were observed in guinea pigs; however, about one-fourth of the animals were reported to exhibit liver discoloration (no further details reported). In dogs, the study authors documented no treatment-related effects on survival, body weight, hematology, liver function, or gross necropsy. Levels of BUN were significantly increased in exposed dogs (2-fold higher than controls; $p \leq 0.01$ by *t*-test performed for this review); there were no other serum chemistry changes in dogs. On Day 78 of the experiment, one monkey died. Necropsy showed hemorrhagic lesions on the lung surface of the monkey. The study authors considered the death unrelated to exposure. The authors indicated that, in about 50% of the monkeys, they detected microfilarial (*Dipetalonema* sp.) infections in the abdomens; the significance of this infection is uncertain. The study authors reported that microscopic examination revealed "nonspecific inflammatory changes" in the lungs of all species, mild vacuolar changes in the liver of guinea pigs, and focal degeneration of the renal tubular epithelial cells in rats; no further details (or incidences) are provided. The study authors concluded that none of the histopathology effects could be related to exposure. A LOAEL of 5660 mg/m^3 is identified for dogs based on increased BUN; this same concentration is a freestanding NOAEL for the other species.

Jenkins et al. (1970) also assessed the effects of discontinuous exposure to nominal concentrations of 0 or 10,000 ppm (0 or 56,200 mg/m^3) 8 hours/day, 5 days/week, for 6 weeks. The species, group sizes and sexes, and toxicity evaluations were the same as for the continuous exposure experiment described above. The concentration of trichlorofluoromethane was measured to be 10,250 ± 100 ppm (57,600 mg/m^3). As in the continuous exposure experiment, the BUN levels were statistically significantly increased in exposed dogs (2.2-fold higher than controls; $p \leq 0.01$ by *t*-test performed for this review). The study authors also reported the following effects: mild discoloration, characterized as a darkening of the tissue, of the liver in rats and guinea pigs (incidence reported to be about one-fourth of these animals), a single grossly-observed liver lesion (2 mm × 4 mm in size) in one monkey; focal myocytolysis in one rat; focal nonspecific myocarditis in two rats; and nonspecific inflammatory changes of the lungs in guinea pigs, rats, and monkeys (incidences not reported). As with the continuous exposure experiment, the study authors concluded that none of the histopathology effects could be related to exposure. A LOAEL of 57,600 mg/m^3 is identified for dogs based on increased BUN; this same concentration is a freestanding NOAEL for the other species.

Leuschner et al. (1983) exposed male and female Sprague-Dawley rats (20/sex/group, whole body) to 0 or 10,000 ppm (0 or 56,200 mg/m^3) trichlorofluoromethane (>99.9% pure) for 6 hours/day, 7 days/week, for 90 days. The parameters monitored to assess toxicity included hematology (hemoglobin; erythrocyte, total and differential leukocyte, reticulocyte, and platelet counts; hematocrit; methemoglobin; clotting time; and Heinz bodies); clinical chemistry (AST, ALT, ALP, glucose, BUN, total protein, bilirubin, lipids, cholesterol, electrolytes, calcium, chloride, uric acid, creatinine, and protein); urinalysis (color, specific gravity, protein, glucose, bilirubin, hemoglobin, ketone bodies, pH, and sediment analysis); liver function (bromosulfophthalein retention) sight, hearing, and dental examinations; and organ weights

(11 organs, not specified) and histological examinations of 27 tissues including the lungs (on 10 rats/sex/group). No significant changes in body-weight gain, hematology, clinical chemistry, urine composition, sight, hearing, or dentition were observed (data not shown). In addition, no histological alterations attributable to trichlorofluoromethane exposure were observed. Areas of focal alveolar over-inflation and an intraalveolar accumulation of macrophages were observed to the same extent in the exposed and control groups. This study identifies a freestanding NOAEL of 56,200 mg/m^3.

Leuschner et al. (1983) also assessed the effects in purebred Beagle dogs exposed (3/sex/group, whole body) to 0 or 5,000 ppm (0 or 28,100 mg/m^3) trichlorofluoromethane (>99.9% pure) 6 hours/day, 7 days/week, for 90 days. The same toxicological parameters that were assessed in rats were also assessed in dogs, with the following additional evaluations: free cholesterol, triglycerides, phosphatides, and fatty acids in serum; renal function; glycogen in heart, liver, and muscle; blood pressure; and electrocardiogram. No treatment-related effects were observed on any of the parameters (data not shown). A freestanding NOAEL of 28,100 mg/m^3 is identified from these data.

Chronic Studies—In a chronic-duration study focused on assessing carcinogenicity, trichlorofluoromethane (99.95% purity) was administered by inhalation (whole body) to Sprague-Dawley rats (90/sex/group) and Swiss mice (60/sex/group) at 1000 or 5000 ppm (5620 or 28,100 mg/m^3) 4 hours/day, 5 days/week, for 104 weeks (rats) or 78 weeks (mice) (Maltoni et al., 1988). Control groups of rats (150/sex) and mice (90/sex) were maintained concurrently. Animals were observed until spontaneous death. All animals underwent full necropsy, and histological examinations were performed on an extensive collection of organs and tissues. In rats, survival and body weight were comparable between control and treated groups (data not shown). In mice, survival of control animals was lower than that of exposed animals. The body weight of mice was not affected by treatment (data not shown). The study authors reported no other information on nonneoplastic findings for either species. The data showed that trichlorofluoromethane did not induce statistically significant differences in the incidence of total benign or malignant tumors when compared with groups of unexposed rats or mice. Concentration-related increases in the incidences of lung adenomas, leukemias, and total tumors were observed in treated female mice, but the increases were not statistically significant. In high-dose female mice, the study authors documented a statistically significant difference in the incidence of mammary tumors in comparison with controls (6/60 vs. 1/90 controls, *p*-value not reported), even after the data were adjusted for reduced control survival. However, the study authors reported that the incidence observed in the high-dose group (10%) was within the range observed in control mice in other experiments conducted in their laboratory (2.0−15.2%).

Other Studies

Toxicokinetics

WHO (1990) reviewed the available toxicokinetic data on trichlorofluoromethane; no newer toxicokinetic studies were identified in the literature search. There are no data on the toxicokinetics of trichlorofluoromethane after oral exposure in any species. Radiolabelling studies have been used to estimate the absorption of inhaled trichlorofluoromethane to be about 82% in humans and 77% in dogs (as reviewed by WHO, 1990 and CalEPA, 1997). Available in vivo data suggest little or no metabolism of inhaled trichlorofluoromethane in humans or in dogs; most of the compound is rapidly eliminated unchanged via exhaled air (reviewed by WHO, 1990). After inhalation exposure to radiolabelled trichlorofluoromethane, only traces of

radioactivity are recovered in the urine or feces (reviewed by WHO, 1990). Wolf et al. (1978), an in vitro study, suggests that rat liver microsomes could dechlorinate trichlorofluoromethane to dichlorofluoromethane (Wolf et al., 1978); however, there are currently no in vivo data to support this finding.

Acute/Short-term Toxicity

In an acute inhalation study, Clayton (1966) exposed three male rats to 12,000 ppm (67,416 mg/m^3) trichlorofluoromethane 4 hours/day for 10 days, followed by an 11-day recovery period. It is unclear whether a control group was used. The rats exhibited a slight tachypnea and an increase in tidal volume, as well as slight muscle twitching, during exposure. The authors reported that there was a rapid recovery from these effects after exposure was terminated. Histological examination revealed neuronal edema and neuroglia vacuolization in the brain, edema and emphysema in the lungs, vacuolation of cells in the liver, and increased hematopoiesis in the spleen. The significance of these findings is uncertain considering the lack of control data.

Neurotoxicity

Lester and Greenberg (1950) observed neurological changes in rats exposed to high concentrations of trichlorofluoromethane for 30 minutes. Groups of white rats (strain, sex, and group size not reported) were exposed to 5, 6, 7, 8, 9, 10, 15, 20, 30, or 50% by volume (v/v) trichlorofluoromethane (equivalent to concentrations of 281, 337, 393, 449, 506, 562, 843, 1124, 1685, or 2809 g/m^3). No changes in postural, righting, or corneal reflex were observed at 281 g/m^3, but altered postural reflex was observed in rats exposed to 337 g/m^3 and higher concentrations. At exposures ≥449 g/m^3, a change in righting reflex was noted. Rats exposed to ≥506 g/m^3 became completely unconscious, and those exposed to higher concentrations died during the exposure period.

Kyrklund et al. (1988) measured the lipid and fatty acid composition in the cerebral cortex of male Sprague-Dawley rats exposed continuously for 30 days to trichlorofluoromethane at a concentration of 580 ppm (3260 mg/m^3). Body and brain weights were also assessed at study termination. There were no treatment-related changes in body or brain weight, or in brain lipid or fatty acid composition.

Genotoxicity

Trichlorofluoromethane was not mutagenic, with or without metabolic activation, in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538 or *Escherichia coli* WP2 uvrA (Araki et al., 1994; Longstaff et al., 1984; Greim et al., 1977; Uehleke et al., 1977; Zeiger et al., 1987), or Chinese hamster ovary cells (Krahn et al., 1982). Negative results were also obtained for trichlorofluoromethane in a BHK21 mammalian cell mutagenicity test (Longstaff et al., 1984; WHO, 1990). All of these studies were conducted using test systems appropriate for volatile chemicals.

DERIVATION OF A PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD FOR TRICHLOROFLUOROMETHANE

Subchronic p-RfD

The database for subchronic oral exposure to trichlorofluoromethane is very limited. There were three oral studies that were described by secondary sources (Kudo et al., 1971 and two unpublished studies conducted by DuPont, 1972, both as cited by CalEPA, 1997). The first (Kudo et al., 1971, as cited by CalEPA, 1997) was a 1-month mouse study published in Japanese and was not retrieved for this review. Efforts to obtain the unpublished studies (subchronic gavage studies in rats and dogs, DuPont, 1972, as cited by CalEPA, 1997) were not successful. Based on the information provided by CalEPA, none of these three studies document clearly adverse effects. While additional efforts to obtain these studies might yield reliable effect levels, it is not clear that any of them would support the derivation of a subchronic p-RfD. The only other oral study of subchronic duration is a dose range-finding study conducted by NCI (1978) in which mortality and body weight were the only parameters assessed. This study cannot support the derivation of a subchronic p-RfD.

Chronic p-RfD

A chronic oral RfD of 3×10^{-1} mg/kg-day for trichlorofluoromethane is available on IRIS (U.S. EPA, 2008).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR TRICHLOROFLUOROMETHANE

Table 1 summarizes the data available for use in the derivation of subchronic and chronic p-RfCs for trichlorofluoromethane. To provide a common basis for comparing the studies, the effect levels from each study are adjusted to equivalent continuous exposure concentrations. The adjusted animal NOAELs and LOAELs were then converted to human equivalent concentrations ($NOAEL_{HEC}$ and $LOAEL_{HEC}$) using the appropriate dosimetric adjustment (U.S. EPA, 1994b) and as further described below. As an extrarespiratory effect (increased BUN) was observed in the only animal study that identified a LOAEL (Jenkins et al., 1970), trichlorofluoromethane was treated as a Category 3 gas, and the ratio of blood:gas partition coefficients was used to make the dosimetric adjustment for all of the studies. A blood:gas partition coefficient for trichlorofluoromethane in humans was identified (0.87; Abraham et al., 2005), but values for other species were not. In the absence of chemical-specific blood:gas partition coefficients for the relevant species, the default ratio of 1.0 is used. The equation used to calculate the $LOAEL_{HEC}$ is as follows:

$$LOAEL_{HEC} = (LOAEL_{ADJ}) \times [(H_{b/g})_{ANIMAL} \div (H_{b/g})_{HUMAN}]$$

where

$(H_{b/g})_A \div (H_{b/g})_H$ = animal-to-human blood:air partition coefficient ratio

Table 2 shows the $NOAEL_{HEC}$ and $LOAEL_{HEC}$ values calculated for each of the studies.

Table 1. Summary of Inhalation Noncancer Dose-Response Information

Species	Sex	Exposure Concentration (mg/m^3)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses	Comments	Reference
Human volunteers	M	5620	8 hr/d, 5 d/wk, for 2−4 wk	NA	5620	Small decrements in cognitive performance	LOAEL	Stewart et al., 1975, 1978
Rat, guinea pig	M/F	0, 5660, (continuous) or 57,600 (discontinuous)	24 hr/d for 90 d (continuous) or 8 hr/d, 5 d/wk, for 6 wk (discontinuous)	0, 5660, (continuous) or 57,600 (discontinuous)	NA	None		Jenkins et al., 1970
Rat	M/F	0, 56,200	6 hr/d, 7 d/wk for 90 d	57,600	NA	None		Leuschner et al., 1983
Monkey	M/F	0, 5660, (continuous) or 57,600 (discontinuous)	24 hr/d for 90 d (continuous) or 8 hr/d, 5 d/wk, for 6 wk (discontinuous)	0, 5660, (continuous) or 57,600 (discontinuous)	NA	None	One monkey died in the continuous experiment; authors considered the death unrelated to exposure.	Jenkins et al., 1970
Dog	M	0, 5660, (continuous) or 0, 57,600 (discontinuous)	24 hr/d for 90 d (continuous) or 8 hr/d, 5 d/wk, for 6 wk (discontinuous)	NA	5660 (continuous) 57,600 (discontinuous)	Increased BUN	LOAEL	Jenkins et al., 1970
Dog	M/F	0, 28,100	6 hr/d, 7 d/wk, for 90 d	28,100	NA	None		Leuschner et al., 1983

Table 2. Calculation of Human Equivalent Concentrations

Study	Species	Effect	Effect Level (mg/m^3)	Duration-Adjusted Effect Level[a] (mg/m^3)	Dosimetric Adjustment[b]	Human Equivalent Concentration[c] (mg/m^3)
Stewart et al., 1975, 1978	Human	None	NOAEL = NA LOAEL = 5620	$NOAEL_{ADJ}$ = NA $LOAEL_{ADJ}$ = 1338	NA[d]	NOAEL = NA LOAEL = 1338
Jenkins et al., 1970, continuous exposure	Rat, Guinea pig	None	NOAEL = 5660 LOAEL = NA	$NOAEL_{ADJ}$ = 5660 $LOAEL_{ADJ}$ = NA	1.0	$NOAEL_{HEC}$ = 5660 $LOAEL_{HEC}$ = NA
Jenkins et al., 1970, discontinuous exposure	Rat, Guinea pig	None	NOAEL = 57,600 LOAEL = NA	$NOAEL_{ADJ}$ = 13,700 $LOAEL_{ADJ}$ = NA	1.0	$NOAEL_{HEC}$ = 13,700 $LOAEL_{HEC}$ = NA
Leuschner et al., 1983	Rat	None	NOAEL = 56,200 LOAEL = NA	$NOAEL_{ADJ}$ = 14,100 $LOAEL_{ADJ}$ = NA	1.0	$NOAEL_{HEC}$ = 14,100 $LOAEL_{HEC}$ = NA
Jenkins et al., 1970, continuous exposure	Monkey	None	NOAEL = 5660 LOAEL = NA	$NOAEL_{ADJ}$ = 5660 $LOAEL_{ADJ}$ = NA	1.0	$NOAEL_{HEC}$ = 5660 $LOAEL_{HEC}$ = NA
Jenkins et al., 1970, discontinuous exposure	Monkey	None	NOAEL = 57,600 LOAEL = NA	$NOAEL_{ADJ}$ = 13,700 $LOAEL_{ADJ}$ = NA	1.0	$NOAEL_{HEC}$ = 13,700 $LOAEL_{HEC}$ = NA
Jenkins et al., 1970, continuous exposure	Dog	Increased BUN	NOAEL = NA LOAEL = 5660	$NOAEL_{ADJ}$ = NA $LOAEL_{ADJ}$ = 5660	1.0	$NOAEL_{HEC}$ = NA $LOAEL_{HEC}$ = 5660
Jenkins et al., 1970, discontinuous exposure	Dog	Increased BUN	NOAEL = NA LOAEL = 57,600	$NOAEL_{ADJ}$ = NA $LOAEL_{ADJ}$ = 13,700	1.0	$NOAEL_{HEC}$ = NA $LOAEL_{HEC}$ = 13,700
Leuschner et al., 1983	Dog	None	NOAEL = 28,100 LOAEL = NA	$NOAEL_{ADJ}$ = 7030 $LOAEL_{ADJ}$ = NA	1.0	$NOAEL_{HEC}$ = 7030 $LOAEL_{HEC}$ = NA

[a]Adjusted to equivalent continuous exposure concentration based on exposure regimen shown in Table 1 as in the following equation: $NOAEL_{ADJ}$ = NOAEL × exposure hours/24 hr × exposure days/7 d
[b]Ratio of blood:gas partition coefficients
[c]Calculated as shown in this equation: $NOAEL_{HEC}$ = NOAEL × dosimetric adjustment
[d]No dosimetric adjustment is necessary for the human study

Subchronic p-RfC

As shown in Table 2, the LOAEL (1338 mg/m^3) calculated for the human study by Stewart et al. (1975, 1978) was one-fourth the value of the only other $LOAEL_{HEC}$ (5660 mg/m^3). The remaining studies identify freestanding $NOAEL_{HEC}$ values (generally in other species) that exceeded the two $LOAEL_{HEC}$ values. Because the study used only a single exposure concentration, benchmark dose modeling of the data is not possible. For the subchronic p-RfC derivation, the LOAEL of 1338 mg/m^3 from the human study (Stewart et al., 1975, 1978) is divided by a UF of 1000 to derive a **subchronic p-RfC** as shown below:

Subchronic p-RfC = LOAEL ÷ UF
= 1338 mg/m^3 ÷ 1000
= **1 mg/m^3**

The composite UF of 1000 consists of the following:

- A 10-fold UF is used for protection of sensitive individuals in the absence of information to determine potentially susceptible populations.
- A UF of 10 is applied for use of a LOAEL.
- A database UF of 10 is used for database limitations. The database lacks reproductive, developmental, and comprehensive neurobehavioral toxicity studies.

Confidence in the key study (Stewart et al., 1975, 1978) is medium-to-low. The study assessed sensitive toxicological endpoints and was well documented. However, the exposed group consisted of only eight male volunteers, only a single exposure concentration was used, and the study duration was less than 1 month. Confidence in the database is low because it includes limited subchronic studies in several species and a chronic study in two species focusing on carcinogenicity. The database lacks reproductive, developmental, and comprehensive neurobehavioral toxicity studies. Low confidence in the subchronic p-RfC follows.

Chronic p-RfC

Due to the brevity of available studies and insufficient justifications for considering long-term effects, no chronic value is developed.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR TRICHLOROFLUOROMETHANE

Weight-of-Evidence Descriptor

Under the U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, there is "*Inadequate Information to Assess the Carcinogenic Potential of Trichlorofluoromethane*." There are no human data on the potential carcinogenicity of trichlorofluoromethane. The one chronic oral bioassay of this compound (NCI, 1978) provides no evidence of carcinogenicity in mice, and is inconclusive in rats because inadequate numbers survived long enough to be at risk from late-developing tumors. The chronic inhalation study by Maltoni et al. (1988) indicates a statistically significant increase over controls in the incidence of mammary carcinomas in Swiss mice exposed to 5000 ppm of trichlorofluoromethane; however, the incidence is within the range observed in control mice from other

experiments conducted in the same laboratory. Trichlorofluoromethane gave negative results in the available tests of genotoxicity, which include tests of mutagenicity in bacterial and mammalian cells in vitro.

Quantitative Estimates of Carcinogenic Risk

Human cancer data are lacking, and the available animal data are inadequate to assess potential carcinogenicity, precluding the derivation of a p-OSF and a p-IUR for trichlorofluoromethane.

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