TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO
EPA/600/8-88/041		PB88-178728/AS

4. TITLE AND SUBTITLE	5. REPORT DATE
Health Effects Assessment for Fully Halogenated Methanes	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES	

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
Public	Unclassified	
	20. SECURITY CLASS *(This page)* Unclassified	22. PRICE

EPA/600/8-88/041
June, 1987

HEALTH EFFECTS ASSESSMENT FOR FULLY HALOGENATED METHANES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with selected fully halogenated methanes. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to March, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-051. NTIS PB81-117624.

U.S. EPA. 1982. Errata for Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1986b. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for dichlorodifluoromethane. Online. (Verification date 7/22/85). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986c. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for trichlorotrifluoromethane. Online. (Verification date 7/8/85). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The RfD_{SO} estimated for trichlorofluoromethane (F-11) is 50 mg/day, which is based on a 6-week feeding study using rats (NCI, 1978). This study is weak in that the only endpoints examined were mortality and body weight depression. The RfD_O estimate for F-11, 20 mg/day, which has been verified by the U.S. EPA (1986b) as an ADI is based on a 2-year feeding study using rats (NCI, 1978). At the dose which was used to calculate the RfD_O, accelerated mortality was observed. This basis for RfD determination was accepted because an earlier RfD calculated from an inhalation study (U.S. EPA, 1980a) was less conservative. The RfD_{SI} and RfD_I estimates for F-11 are calculated from a 90-day inhalation study by Jenkins et al. (1970). The RfD_{SI} estimate for F-11 is 135.8 mg/day; when an additional uncertainty factor is applied the RfD_I estimate is 13.6 mg/day.

The RfD_{SO} estimate for dichlorodifluoromethane (F-12), 63 mg/day, is based on a 90-day feeding study using dogs (Clayton, 1967). The RfD_O (RfD) estimate for F-12 is 10 mg/day. This estimate, which has been verified by the U.S. EPA (1986a) as an RfD, is based on a 2-year feeding study using rats (Sherman, 1974). The RfD_{SI} and RfD_I estimates for F-12 were calculated from a 90-day inhalation study by Prendergast et al. (1967). The RfD_{SI} estimate is 33.8 mg/day; when an additional uncertainty factor is applied the RfD_I estimate for F-12 is 3.4 mg/day.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and John Helms (Office of Toxic Substances) was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Jacky Bohanon and Kim Davidson
Environmental Criteria and Assessment Office
Cincinnati, OH

TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ACTH	Adrenocortiocotropic hormone
ADI	Acceptable daily intake
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
FEL	Frank effect level
HA	Health advisory
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
LOAEL	Lowest-observed-adverse-effect-level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
SGPT	Serum glutamic pyruvic transaminase
SNARL	Suggested no adverse response level
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of dichlorodifluoromethane (F-12) and trichlorofluoromethane (F-11) are presented in Table 1-1.

In the troposphere, F-12 and F-11 remain stable and eventually diffuse into the stratosphere or are carried back to earth during the precipitation process (Callahan et al., 1979), where re-entry into the atmosphere by volatilization occurs. Once in the stratosphere these compounds are photolyzed by short wavelength UV light, releasing chlorine atoms that subsequently catalyze the destruction of ozone (Callahan et al., 1979).

The tropospheric lifetime of these compounds has been postulated to be ~20-30 years, which indicates that 40 to >90% of the tropospheric halomethanes will eventually reach the stratosphere (Callahan et al., 1979). In water, F-12 and F-11 will most likely volatilize to the atmosphere.

Based on the method of Lyman et al. (1982), the volatilization half-life from water 1 m deep has been calculated to be 5.7 hours for F-12 and 6.1 hours for F-11. The half-lives of these compounds in soil could not be located in the available literature. Based on their high vapor pressures, F-12 and F-11 are probably removed by volatilization from soil surfaces. An estimated K_{oc} value of 252 for F-12 suggests that slight adsorption to soil may occur (Swann et al., 1983), which would decrease the rate of volatilization. Adsorption of F-11 to soil should be less significant than F-12.

TABLE 1-1

Selected Chemical and Physical Properties and Environmental Fate of F-12 and F-11

Property	F-12	F-11	Reference
CAS number:	95-71-8	75-69-4	
Chemical class:	haloaliphatic compound	haloaliphatic compound	
Molecular weight:	120.92	137.38	
Vapor pressure:	4250 mm Hg at 20°C	687 mm Hg at 20°C	Verschueren, 1983
Water solubility:	280 mg/ℓ at 25°C	1100 mg/ℓ at 25°C	Verschueren, 1983
Log octanol/water partition coefficient:	2.16	2.53	Hansch and Leo, 1985
Bioconcentration factor:	26 (estimated)	49 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	252 (estimated)	127 (estimated)	Lyman et al., 1982
Half-life in			
Air:	14-21 years	30 years	Callahan et al., 1982
Water:	~6 hours (estimated)	~6 hours (estimated)	Lyman et al., 1982
Soil:	NA	NA	

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Quantitative data regarding the absorption of F-11 and F-12 following oral administration could not be located in the available literature. That F-11 and F-12 are absorbed from the gastrointestinal tract can be inferred from the observation of systemic toxicity following oral administration (Sections 3.1.1. and 3.2.1.).

2.2. INHALATION

In a study by Morgan et al. (1972), volunteers inhaled a known concentration of ^{38}Cl-labeled F-11 or F-12 in one breath and held that breath for 40 seconds. The subjects then exhaled through a charcoal trap and the amount of radioactivity exhaled was determined. The results showed that 45% of the concentration of inhaled F-11 was immediately exhaled, while 90% of inhaled F-12 was immediately exhaled.

A number of studies reviewed by U.S. EPA (1984a) indicated that F-11 and F-12 are readily absorbed. Because these studies do not quantitate absorption, details will not be presented. A general finding of these acute studies is that F-11 is absorbed to more readily than F-12.

A more recent study that quantifies absorption of F-11 in humans is presented by Angerer et al. (1985). Two women and one man were exposed to F-11 at an average concentration of 657±36 mℓ/m³ (~980 g/m³) for 150, 264 and 210 minutes, respectively. F-11 concentrations in the alveolar air and blood were determined. After 1 hour, the concentration of F-11 in the blood reached steady-state at an average alveolar air F-11 concentration of 537 mℓ/m³ (~800 g/m³). Pulmonary retention varied from 13.5-21.9% for the three volunteers, with the pulmonary ventilation rate of the volunteers equaling 9.4 ℓ/minute. The doses absorbed by the three individuals were

1.08, 1.35 and 1.88 g, correlating positively with the exposure time. The average F-11 blood concentration measured during the study was 2.8 mg/ℓ.

Brugnone et al. (1984) studied the absorption of F-11 and F-12 during occupational exposures. By measuring the differences in concentration between inhaled and exhaled air the investigators determined that 19% of inhaled F-11 is retained while 18% of F-12 is retained by the lungs.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. NCI (1978) studied the subchronic effects of F-11 in mice and rats in a preliminary dose range-finding study for a chronic toxicity and cancer study. Groups of five male and five female Osborne-Mendel rats and equal numbers of male and female B6C3F1 mice were treated by gavage with F-11 in corn oil 5 days/week for 6 weeks at doses of 0, 1000, 1780, 3160, 5620 and 10,000 mg/kg/day. Significant depression (26%) of body weight was observed in male rats receiving 1000 mg/kg/day, with at least one male rat dying in each dose group >1000 mg/kg/day. Female rats receiving 1780 mg/kg/day experienced a significant body weight depression (11%) with at least one death in each dose group >1780 mg/kg/day. Mice had no body weight depressions. Mortality began to occur at 5620 mg/kg/day in male mice and at ≥3160 mg/kg/day in female mice. Treated animals were not examined further.

In a 90-day feeding study described by Clayton (1967), male and female rats and male and female dogs received F-12 in the diet. Rats fed diets that provided 160-379 mg/kg bw/day did not show any effects on growth, behavior, hematological and SGPT values or in gross and microscopic appearance of an unspecified selection of organs and tissues. The only effect noted was a slight elevation of plasma alkaline phosphatase activity in females. Dogs fed 85-95 mg F-12/kg/day did not show any treatment-related effects.

3.1.2. Inhalation. Table 3-1 summarizes the subchronic inhalation studies of F-11 and F-12.

Stewart et al. (1978) studied health effects in humans following repeated exposures to F-11 or F-12. Eight male volunteers were exposed to 1000 ppm F-11 (5600 mg/m^3) or F-12 (4900 mg/m^3), 8 hours/day, 5 days/week for

TABLE 3-1

Subchronic Toxicity of Inhaled F-11 and F-12

Species	No./Sex	Compound	Exposure	Duration	Effects	Reference
Humans (age 18-46)	8/M	F-11	1000 ppm (5600 mg/m³)	8 hours/day, 5 days/week for 4 weeks	Statistically significant (p value not given), but minute and transient decrease in cognitive test performance	Stewart et al., 1978
Squirrel monkeys	9/M	F-11	~1.025% (58,000 mg/m³)	8 hours/day, 5 days/week for 6 weeks	A liver lesion was observed in one monkey, nonspecific inflammation of the lungs	Jenkins et al., 1970
Beagle dogs	2/M	F-11	~1.025% (58,000 mg/m³)	8 hours/day, 5 days/week for 6 weeks	Elevated serum urea nitrogen	Jenkins et al., 1970
Guinea pigs	8/M 7/F	F-11	~1.025% (58,000 mg/m³)	8 hours/day, 5 days/week for 6 weeks	Nonspecific inflammation of the lungs; mild discoloration of liver in ~25% of animals	Jenkins et al., 1970
Sprague-Dawley rats	8/M 7/F	F-11	~1.025% (58,000 mg/m³)	8 hours/day, 5 days/week for 6 weeks	Nonspecific inflammation of the lungs; mild discoloration of liver in ~25% of animals	Jenkins et al., 1970
Squirrel monkeys	8/M	F-11	~0.1% (5600 mg/m³)	continuous for 90 days	Nonspecific inflammation of the lungs	Jenkins et al., 1970
Beagle dogs	2/M	F-11	~0.1% (5600 mg/m³)	continuous for 90 days	Nonspecific inflammation of the lungs; elevated serum urea nitrogen	Jenkins et al., 1970
Guinea pigs	8/M 7/F	F-11	~0.1% (5600 mg/m³)	continuous for 90 days	Nonspecific inflammation of the lungs; mild liver discoloration	Jenkins et al., 1970
Sprague-Dawley rats	8/M 7/F	F-11	~0.1% (5600 mg/m³)	continuous for 90 days	Nonspecific inflammation of the lungs; mild liver discoloration	Jenkins et al., 1970
Beagle dogs	3/M 3/F	F-11	0.5% (28,000 mg/m³)	6 hours/day for 90 days	No signs of toxicity	Leuschner et al., 1983
Sprague-Dawley rats	20/M 20/F	F-11	1.0% (56,000 mg/m³)	6 hours/day for 90 days	No signs of toxicity	Leuschner et al., 1983
Humans (age 18-46)	8/M	F-12	1000 ppm (4900 mg/m³)	8 hours/day, 5 days/week for 4 weeks	No effects observed	Stewart et al., 1978

TABLE 3-1 (cont.)

Species	No./Sex	Compound	Exposure	Duration	Effects	Reference
Squirrel monkeys	3/NR	F-12	0.084% (4136 mg/m³)	8 hours/day, 5 days/week for 6 weeks	Weight loss, nonspecific inflammation of lungs, heavy pigment deposits in liver, spleen and kidneys in one monkey	Prendergast et al., 1967
Beagle dogs	2/NR	F-12	0.084% (4136 mg/m³)	8 hours/day, 5 days/week for 6 weeks	Weight loss	Prendergast et al., 1967
New Zealand rabbits	3/NR	F-12	0.084% (4136 mg/m³)	8 hours/day, 5 days/week for 6 weeks	Nonspecific inflammation of the lungs	Prendergast et al., 1967
Hartley guinea pigs	15/NR	F-12	0.084% (4136 mg/m³)	8 hours/day, 5 days/week for 6 weeks	Nonspecific inflammation of the lungs, focal necrosis or fatty infiltration of the liver in several animals	Prendergast et al., 1967
Sprague-Dawley or Long Evans rats	15/NR	F-12	0.084% (4136 mg/m³)	8 hours/day, 5 days/week for 6 weeks	Nonspecific inflammation of the lungs	Prendergast et al., 1967
Squirrel monkeys	3/NR	F-12	0.081% (3997 mg/m³)	continuous for 90 days	Nonspecific inflammation of the lungs	Prendergast et al., 1967
Beagle dogs	2/NR	F-12	0.081% (3997 mg/m³)	continuous for 90 days	No changes observed	Prendergast et al., 1967
New Zealand rabbits	3/NR	F-12	0.081% (3997 mg/m³)	continuous for 90 days	Nonspecific inflammation of the lungs, weight gain depressed	Prendergast et al., 1967
Hartley guinea pigs	15/NR	F-12	0.081% (3997 mg/m³)	continuous for 90 days	Nonspecific inflammation of the lungs, slight-extensive fatty infiltration of hepatic cells; focal or submissive necrosis of liver in several animals	Prendergast et al., 1967
Sprague-Dawley or Long Evans rats	15/NR	F-12	0.081% (3997 mg/m³)	continuous for 90 days	Nonspecific inflammation of the lungs	Prendergast et al., 1967
Beagle dogs	3/M 3/F	F-12	0.5% (25,000 mg/m³)	6 hours/day for 90 days	No effects observed	Leuschner et al., 1983
Sprague-Dawley rats	20/M 20/F	F-12	1.0% (49,000 mg/m³)	6 hours/day for 90 days	No effects observed	Leuschner et al., 1983

4 weeks. The parameters examined were blood chemistries and hematologies, heart function, pulmonary function, neurological studies, electroencephalography, visual evoked response, ACTH stimulation and cognitive tests. No effects were observed in individuals exposed to F-12. The only effect observed in F-11 exposed individuals was a statistically significant, but minute and transient decrease in cognitive test performance. Because this decrease was not consistent, was transient, was not dose-related (in regard to total dose) and did not occur in subjects acutely exposed to the same concentrations for the same length of time, the authors concluded that this effect was not considered to be an adverse effect of exposure to F-11.

Jenkins et al. (1970) exposed squirrel monkeys, beagle dogs, guinea pigs and Sprague-Dawley rats to 58,000 mg/m³ F-11 8 hours/day, 5 days/week for 6 weeks. Compared with controls, effects noted in treated animals were elevated serum urea nitrogen in dogs (36 mg/100 mℓ exposed; 16.8 mg/100 mℓ controls), mild liver discoloration in ~25% of rats and guinea pigs, a liver lesion in 1/9 exposed monkeys and nonspecific inflammatory changes in lungs of rats, guinea pigs and monkeys. No other significant changes were observed in hematological or biochemical data or body weight.

Jenkins et al. (1970) also exposed squirrel monkeys, beagles, guinea pigs and rats to 5600 mg/m³ F-11 continuously for 90 days. The results observed were nonspecific inflammatory changes in the lungs of all species, elevated serum urea nitrogen levels in dogs (33 mg/100 mℓ exposed; 16.8 mg/100 mℓ controls) and mild liver discoloration in some rats and guinea pigs. One monkey, which died on day 78, had hemorrhagic lesions on the lung surface that were not directly attributed to exposure. About 50% of the monkeys used in the study were found to be infected with microfileria (Dipetalonema sp.). Hematological and biochemical data or body weight were not significantly affected.

Leuschner et al. (1983) exposed beagle dogs to 28,000 mg/m³ F-11 or 25,000 mg/m³ F-12, 6 hours/day for 90 days and rats to 56,000 mg/m³ F-11 or 49,000 mg/m³ F-12, 6 hours/day for 90 days. No signs of toxicity were observed in dogs or rats. The parameters examined were behavior, external appearance, food and water consumption, body weight, hematology, blood biochemistry, urinalysis and in dogs only, electrocardiography and circulatory function. At necropsy, organ weights were determined and histological examinations were completed in all dogs and in 10 rats/group/sex.

Prendergast et al. (1967) exposed squirrel monkeys, beagle dogs, rabbits, guinea pigs and rats to F-12 at 4136 mg/m³, 8 hours/day, 5 days/week for 6 weeks or to 3997 mg/m³ F-12 continuously for 90 days. The most severe effect observed was focal necrosis and fatty infiltration of the livers of guinea pigs, which was more severe in the continuously exposed guinea pigs compared with those that received intermittent exposures. Other effects observed in the animals exposed intermittently were nonspecific inflammation of the lungs in a number of guinea pigs, rats, rabbits and monkeys, weight loss in dogs and monkeys, heavy pigmentation in liver, spleen and kidney of one monkey and death of one rat. Continuously exposed rats, rabbits, monkeys and dogs showed a high incidence of lung congestion with inflammatory changes in the lungs, depressed body weight gain in rabbits and guinea pigs, and the deaths of 2/15 exposed rats and 1/15 guinea pigs.

Sayers et al. (1930) exposed monkeys, dogs and guinea pigs to F-12 at 1.1×10^6 mg/m³ for 7-8 hours/day, 5 days/week and 4 hours/day, 1 day/week for ~77 days (Sayers et al., 1930). Dogs experienced tremors and ataxia. Less severe tremors were also observed in monkeys. Tremors in both species lessened in severity after several weeks. Deaths of 10/26 exposed guinea

pigs and 6/26 controls were attributed to pneumonia. An initial increase in red blood cell count and hemoglobin was observed in several guinea pigs. In dogs and guinea pigs, the number of lymphocytes decreased slightly and the number of polymorphonuclear neutrophils increased slightly. An initial weight loss was also observed in exposed dogs and several guinea pigs.

3.2. CHRONIC

3.2.1. Oral. In the NCI (1978) study, F-11 was administered orally in corn oil to 50 male and 50 female Osborne-Mendel rats and equivalent numbers of male and female B6C3F1 mice, 5 days/week, with the exception of the high-dose groups of male mice, which initially contained 49 mice. Untreated and vehicle-treated controls consisted of 20 animals/sex/species. Treatments that were administered for 78 weeks were adjusted at 12 weeks (rats) and 7 weeks (mice) resulting in TWA doses of 488 and 977 mg/kg/day for low- and high-dose male rats, 538 and 1077 mg/kg/day for low- and high-dose female rats and 1962 and 3925 mg/kg/day for low- and high-dose mice of both sexes. These TWA doses are for treatment on 5 days/week and do not reflect expansion to daily treatment. No decrease in body weight was reported in rats. In male and female rats, dose-related early mortality was observed, which [although significant when compared with controls using the Tarone test ($p<0.001$)] was associated with murine pneumonia, which was observed in 88-100% of all rats. Low incidences (<20%) of pericarditis and pleuritis were observed in all treated groups of rats but not in controls. In mice, no statistically significant compound-related effect on body weight gain or clinical signs was observed. Based on the Tarone test, a significant ($p=0.009$) dose-related acceleration of mortality was observed in female but not male mice.

Sherman (1974) fed groups of four male and four female beagle dogs (1-2 years of age) diets containing F-12 that provided 8 mg/kg bw/day for 2 years. No meaningful differences were observed in food consumption, body weight, hematology, urinalysis and biochemistry measurements.

Sherman (1974) also studied the effects of F-12 in rats that were dosed by intragastric intubation for up to 2 years. Groups of 21 female and 11 male CD rats were utilized. Males received 11-27 or 130-273 mg/kg/day F-12 in corn oil. Females received 11-25 or 128-242 mg/kg/day. Dose ranges for each group were estimated by the author. Two vehicle control groups were included, each consisting of 11 males and 21 females. After 3 months the rats were mated. No F-12 was given to pregnant females between days 18 or 19 of gestation and day 5 of lactation. Groups of 50 male and 50 female offspring received nothing, corn oil, or F-12 at the low or high dose. The results showed a somewhat depressed body weight gain and food efficiency in female rats receiving 131-273 mg F-12/kg/day. No differences in food consumption or mortality between exposed and control groups were noted. No compound-related changes in hematology, urinalysis, clinical chemistry and histopathological examinations were noted at either dose level.

3.2.2. Inhalation. Pertinent data regarding the effects of chronic inhalation exposure to F-11 and F-12 could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. No pertinent data regarding teratogenic and other reproductive effects associated with oral exposure to F-11 were located in the available literature. In the chronic oral study using rats treated with 11-27 or 131-273 mg/kg/day F-12 for up to 2 years, no abnormalities were observed in fertility, gestation, viability and lactation or upon histopathological examination (Sherman, 1974). Rats (male and female) received

on the average ~15 or 150 mg F-12/kg/day in corn oil by gavage. Dosing was discontinued from days 18 or 19 of gestation until day 5 of lactation. The experiment was continued for 3 generations.

Culik and Sherman (1973) treated pregnant Charles River rats (25-27/group) by gavage with 2 mℓ corn oil containing an average of 0, 16.6 or 170.9 mg F-12/kg on gestation days 6-15. F-12 administration did not affect maternal weight gain, the numbers of implantation sites or viable fetuses, mean fetal body weight or fetal crown-rump length. No major abnormalities were observed in live fetuses, and the numbers of minor defects in offspring of treated days were similar to those of controls.

3.3.2. Inhalation. In a study by Paulet et al. (1974), groups of 10 pregnant rabbits and 20 pregnant Wistar rats were exposed to a mixture of F-11 and F-12 in air for 2 hours/day on days 4-16 of gestation (rat) or days 5-20 of gestation (rabbits). The mixture was at ~200,000 ppm (~1 kg/m^3) with the proportion of F-12:F-11 at 9:1. Half of the animals were sacrificed on day 20 (rats) or day 30 (rabbits) of gestation. The remaining animals were allowed to deliver. No treatment-related adverse effects on maternal or fetal body weights, number of implantations, resorptions, fetuses, stillbirths or the number of pups surviving at 1 and 4 weeks were observed. No abnormalities were observed in treated litters; however, the method of fetal examination was not stated.

3.4. TOXICANT INTERACTIONS

At relatively high concentrations, epinephrine has been shown to alter the sensitivity of the heart to F-11. In a study by Belej et al. (1974), anesthetized rhesus monkeys (1.8-2.7 kg) with tracheas cannulated for artificial respiration were exposed to F-11 in air for 5 minutes and then to

room air for 10 minutes. The minimal concentrations of F-11 causing cardiotoxicity were 5% (280,000 mg/m³) for cardiac arrhythmia and 2.5% (140,000 mg/m³) for depression of myocardial contractility associated with hypotension. When epinephrine was infused (intravenously) the minimal F-11 concentration causing arrhythmia was reduced to 2.5%. Tachycardia also appeared when F-11 was given while epinephrine was infused. The minimal concentration of F-11 required to cause arrhythmia was further reduced to 0.5% (28,000 mg/m³) when epinephrine infusion was accompanied by coronary artery occlusion.

Neither epinephrine infusion nor coronary artery occlusion reduced the concentration of F-12 required to cause cardiac arrhythmia in rhesus monkeys (Belej et al., 1974). In the normal heart, a 10% (495,000 mg/m³) concentration of F-12 in air was required to cause cardiac arrhythmia.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenic potential of F-11 or F-12 in humans could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. NCI (1978) conducted a carcinogenicity bioassay for F-11 in which groups of male and female Osborne-Mendel rats and male and female B6C3F1 mice were orally dosed with F-11 in corn oil. Rats received TWA doses as follows: males, 488 or 977 mg/kg/day; females, 538 or 1077 mg/kg/day, 5 days/week for 78 weeks. Mice received TWA doses of 1962 or 3925 mg/kg/day (both sexes) on the same dosing schedule as the rats. There were 20 untreated and vehicle-treated controls per sex per species (see Section 3.2.1.). There was no significant positive association between tumor incidence in rats surviving $\geq$52 weeks and F-11 exposure. These results were inconclusive, however, because of high early mortality in male and female rats; an inadequate number of rats survived long enough to be at risk for late-developing tumors. The results in mice showed no statistically significant increase in tumor incidence and no unusual tumors were found.

In a 3-generation study of F-12 using rats, Sherman (1974) analyzed tumor incidences. F-12 did not cause an increase in tumor incidence in CD male and female rats treated by gavage with 11-27 (average ~15) or 131-273 (average ~150) mg F-12/kg/day in corn oil.

4.2.2. Inhalation. Maltoni et al. (1982) exposed groups of 90 male and 90 female Sprague-Dawley rats to F-11 and F-12 at concentrations of 0, 0.1 or 0.5% (F-11:5600, 28,000 mg/m^3; F-12:4900, 25,000 mg/m^3) 4 hours/day, 5 days/week for 104 weeks. Exposed rats were examined only for brain tumors (ependymomas, gliomas and meningiomas), but incidences did not differ significantly from controls.

4.3. OTHER RELEVANT DATA

F-11 was negative for base-pair substitutions and frame-shift mutations in the presence or absence of a metabolic activating system when tested with Salmonella typhimurium strains TA1535 and TA1538 and Escherichia coli K-12 (Uekleke et al., 1976, 1977). Longstaff et al. (1984) found both F-11 and F-12 to be nonmutagenic with and without S-9 activation in Salmonella typhimurium strains TA100 and TA1535, and the compounds did not transform BHK21 cells. F-11 and F-12 were also shown to be negative for forward mutations in the Chinese hamster ovary/hypoxanthine guanine phosphoribosyl transferase assay with or without metabolic activation (Krahn et al., 1979). Van't Hof and Schairer (1982) found F-12 to be negative in a mutagenicity test using a Trandescantia hybrid.

4.4. WEIGHT OF EVIDENCE

There was no evidence in the available literature indicating that F-11 or F-12 are carcinogens. An oral NCI (1978) bioassay of F-11 was inconclusive in rats because of high early mortality and negative in mice. Orally administered F-12 did not cause an increase in tumors in CD rats in a 3-generation study (Sherman, 1974). Inhalation of F-11 or F-12 did not cause an increased incidence of brain tumors in exposed rats. Mutagenicity assays support the carcinogenicity studies; F-11 and F-12 were negative in mutagenicity assays in bacteria and mammalian cells (see Section 4.3.).

Because of the lack of sufficient evidence concerning the carcinogenic potential of F-11 and F-12, these compounds can be placed in EPA Group D, not classified (U.S. EPA, 1986a). Although IARC has not classified F-11 and F-12 as to their carcinogenicity to humans, an IARC classification of Group 3 (i.e., cannot be classified) seems most appropriate.

5. REGULATORY STANDARDS AND CRITERIA

The U.S. EPA (1982) has recommended water quality criteria for F-11 and F-12. The criterion for F-11, 12 mg/ℓ, was based on an RfD of 24 mg/day or 0.35 mg/kg/day (U.S. EPA, 1982) calculated from an NCI (1978) oral study that defined a rat LOAEL of 488 mg/kg, 5 days/week, which was associated with accelerated mortality, and an uncertainty factor of 1000. This RfD has been verified by U.S. EPA (1986c) and rounded to 20 mg/day (0.3 mg/kg/day). The criterion for F-12 of 28 mg/ℓ was based on an RfD of 56.0 mg/day (0.8 mg/kg/day) (U.S. EPA, 1982). This RfD was calculated from a 2-year oral study using dogs (Sherman, 1974), which defined a NOAEL of 80 mg/kg/day; an uncertainty factor of 100 was applied (U.S. EPA, 1982). The RfD of 56.0 mg/day has recently been replaced by a verified RfD of 10 mg/day (0.2 mg/kg/day) based on an oral chronic rat NOEL of 15 mg/kg/day (Sherman, 1974) and an uncertainty factor of 100 (U.S. EPA, 1986b).

The NAS (1980) has determined a SNARL for F-11 for a 70 kg adult of 88 mg/ℓ for 1-day exposure and 8.0 mg/ℓ for 7-day exposure. The F-12 SNARL for 1-day exposure of a 70 kg adult is 350 mg/ℓ, while the 7-day SNARL is 150 mg/ℓ (NAS, 1980). A chronic SNARL of 5.6 mg/ℓ for F-12 has also been calculated (NAS, 1980).

The ACGIH (1985) has adopted a ceiling TLV of 1000 ppm (~5600 mg/m^3) for F-11. The ACGIH (1985) TWA-TLV for F-12 is 1000 ppm (~4950 mg/m^3). OSHA (1985) has set the PEL for both F-11 and F-12 at 1000 ppm (F-11, ~5600 mg/m^3; F-12, ~4950 mg/m^3).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). The only subchronic oral study of F-11 available was the range-finding experiment for a chronic cancer study by NCI (1978). Mice and rats were dosed by gavage with the corn oil vehicle or 1000, 1780, 3160, 5620 or 10,000 mg/kg/day of F-11, 5 days/week for 6 weeks followed by 2 weeks of observation. Male rats showed a 26% depression in body weight at 1000 mg/kg/day and at least one death/group at the higher dose levels. Female rats showed no effects at 1000 mg/kg/day; body weight depressions but no deaths occurred at 1780 mg/kg/day. Mice had no effects at doses <5620 mg/kg/day. Because the only endpoints studied were body weight and mortality, the LOAEL of 1000 mg/kg/day for rats from this study alone is a weak basis for determining an RfD_{SO}. However, these data are supported by the available chronic data (see Section 6.2.1.).

An RfD_{SO} can be estimated from the LOAEL of 1000 mg/kg/day (NCI, 1978) by multiplying the LOAEL by 5/7 days to convert to daily exposure, and by dividing by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for interspecies variability, 10 for deriving an RfD_{SO} from a LOAEL). The calculated RfD_{SO} for F-11 is 0.714 mg/kg/day, or 50 mg/day for a 70 kg human.

The 90-day feeding study by Clayton (1967) is the only oral toxicity study of appropriate duration from which to determine an RfD_{SO} for F-12. In this study, oral administration of 160-379 mg/kg/day of F-12 to male and female rats produced no effects on behavior, growth, hematology, SGPT activity and the gross and microscopic appearance of tissues and organs. The only effect observed was a slight elevation of plasma alkaline phosphatase activity. Dogs were orally dosed with F-12 at 84-95 mg/kg/day (~90

mg/kg/day) for 90 days. This treatment did not produce any clinical signs of toxicity and no changes were detected in blood and urine tests or in histological examinations. Because the data for dogs provide a more clearly defined NOAEL, these data will be used to calculate an RfD_{SO}.

An RfD_{SO} can be estimated from the dog NOAEL of 90 mg/kg/day (Clayton, 1967) by dividing by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for intraspecies variability). The calculated RfD_{SO} for F-12 is 0.9 mg/kg/day, or 63 mg/day for a 70 kg human.

6.1.2. Inhalation (RfD_{SI}). A number of subchronic F-11 inhalation studies are summarized in Table 3-1. The study by Leuschner et al. (1983) is not useful for risk assessment. The study did not define thresholds of toxicity in rats or dogs, although transformed doses from this experiment were higher than those in the multispecies experiment by Jenkins et al. (1970) in which adverse effects were noted. Transformed doses were calculated in the following manner: mg/kg/day = mg/m^3 x (hours exposed/24 hours) x (days exposed/7 days) x inhalation rate (m^3/day) x 1/body weight (kg). [Inhalation rates were calculated using formulas from U.S. EPA (1986d): inhalation rate for dogs = $0.92/2.11\ (BW)^{0.9}$ and inhalation rate for guinea pigs = $0.98/2.11\ (BW)^{0.9}$.] In the study by Jenkins et al. (1980), squirrel monkeys, dogs, guinea pigs and rats were exposed to F-11 at 58,000 mg/m^3, 8 hours/day, 5 days/week for 6 weeks or to 5600 mg/m^3 continuously for 90 days. Dogs continuously exposed to F-11 had nonspecific inflammation of the lungs and increased serum urea nitrogen levels (33 mg/100 mℓ exposed, 16.8 mg/100 mℓ control). The dogs were exposed to a transformed dose of ~1940 mg/kg/day that was calculated using the body weight (9.9 kg) provided by the investigators. Increased serum urea nitrogen levels were observed only in dogs at 1940 mg/kg, which can be

considered to be a LOAEL. This LOAEL is a more appropriate basis for an RfD_{SI} than the LOAEL of 381 mg/kg/day in humans associated with minutely decreased cognitive test performance (Stewart et al., 1978) because the dog study was a longer term experiment and a more comprehensive evaluation of criteria of toxicity was performed. An RfD_{SI} of 1.94 mg/kg/day or 135.8 mg/day for a 70 kg human can be calculated from the LOAEL of 1940 mg/kg/day by dividing the transformed dose by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for individual variability, 10 for deriving an RfD_{SI} from a LOAEL).

The study of F-11 exposure in humans by Stewart et al. (1978) indicates that an RfD_{SI} of 135.8 mg/day for a 70 kg human should be protective. Stewart et al. (1978) exposed male volunteers to F-11 at 5600 mg/m³, 8 hours/day, 5 days/week for 4 weeks (381 mg/kg/day). The only effect was a minute decrease in cognitive test performance. An RfD_{SI} calculated from this exposure would be 266.7 mg/day which is slightly higher but in close agreement with the RfD_{SI} calculated from the dog LOAEL.

Prendergast et al. (1967) exposed squirrel monkeys, beagle dogs, rabbits, guinea pigs and rats to F-12 at 4136 mg/m³ for 8 hours/day, 5 days/week for 6 weeks or to 3997 mg/m³ continuously for 90 days. Guinea pigs were found to be more susceptible to F-12 than the other species. Focal necrosis and fatty infiltration of the liver were found in both exposure protocols, with an increase in the incidence and severity in animals exposed continuously (1941.6 mg/kg/day; bw = 0.584 kg) compared with those exposed intermittently (482.3 mg/kg/day; bw = 0.632 kg). Using 482.3 mg/kg/day as a LOAEL, an RfD_{SI} of 0.482 mg/kg/day or 33.8 mg/day for a 70 kg human can be calculated by dividing the transformed dose by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for intraspecies variability, 10 for deriving an RfD_{SI} from a LOAEL).

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). The U.S. EPA (1982, 1986c) RfD for F-11 of 0.344 mg/kg/day or 24.4 mg/day is based on the lowest dose tested (488 mg/kg/day) in the NCI (1978) chronic oral study in which a dose-related acceleration of mortality was observed in male and female rats. The increase in mortality became apparent in low-dose rats as early as week 15 and in high-dose females as early as week 4. According to NCI (1978), murine pneumonia, which was observed in 88-100% of rats in all groups, appeared to be a factor in early mortality. The preferential acceleration of mortality among treated groups may have been a result of F-11 lowering the resistance to pneumonia.

A previous determination of the RfD, calculated from a subchronic inhalation study (Jenkins et al., 1970), was less conservative. The new RfD of 24.4 mg/day has been verified by U.S. EPA (1986c) as the best estimate of an RfD for F-11 and rounded to 20 mg/day for a 70 kg human.

The U.S. EPA (1986b) RfD for F-12 was based on a 2-year oral study in rats by Sherman (1974) in which male and female CD rats received ~15 or ~150 mg/kg/day of F-12 by gavage. The only effects observed were depressed body weight gain and food efficiency in high-dose female rats. The low dose (~15 mg/kg/day) was therefore used as a NOEL to calculate the RfD. The RfD of 0.15 mg/kg/day or 10 mg/day for a 70 kg human, was calculated using an uncertainty factor of 100.

CSs for oral exposure to F-11 and F-12 are listed in Table 6-1. A CS for F-11 was calculated from the NCI (1978) study in which accelerated mortality was observed in rats at 348.6 mg/kg/day. A human MED of 4172 mg/day was calculated by multiplying 348.6 mg/kg/day by the cube root of the ratio of the rat body weight (0.35 kg, estimated from graphic data provided

TABLE 6-1

Composite Scores for the Toxicity of F-11 and F-12 by Oral Exposure

Compound	Species/ Strain	Sex	Exposure Dosage	Human MED (mg/day)	RV_d	Effect	RV_e	CS	Reference
F-11	rats/ Osborne-Mendel	M+F	348.6 mg/kg/ day by gavage 5 days/week, 78 weeks, 28-33 weeks observation	4172.7	1	accelerated mortality	10	10	NCI, 1978
F-12	rats/CD	F	150 mg/kg/day by gavage, for 2 years	1795	1	depressed body weight gain and food efficiency	4	4	Sherman, 1974

by investigators) to the reference human body weight and by 70 kg. This MED corresponds to an RV_d of 1. The effect that occurred at this dose, accelerated mortality, corresponds to an RV_e of 10 and the CS, the product of RV_e and RV_d, for F-11 equals 10.

6.2.2. Inhalation (RfD_I). There were no chronic inhalation studies available for either F-11 or F-12. Therefore, RfD_I values will be estimated from RfD_{SI} values by applying an additional uncertainty factor of 10 to the RfD_{SI} value. By this method, the RfD_I for F-11 is 0.194 mg/kg/day or 13.6 mg/day for a 70 kg human, and the RfD_I for F-12 is 0.0482 mg/kg/day or 3.4 mg/day for a 70 kg human.

CSs for inhalation exposure to F-11 and F-12 are listed in Table 6-2. Because the data for both compounds were obtained from subchronic studies an additional uncertainty factor of 10 was used when calculating human MEDs.

Since subchronic inhalation studies of F-11 used relatively high exposure concentrations, all MEDs would correlate to an RV_d value of 1. Inflammation of the lungs was observed in all animal species tested. Other lesions also occurred in dogs and guinea pigs. In dogs, elevated serum urea nitrogen was observed and guinea pigs had mild discoloration of the liver (Jenkins et al., 1970). In both species, an RV_e of 4 was chosen, based primarily on the more severe effect of inflammation in the lungs, and the CSs, calculated as the product of the RV_d and RV_e, are also 4. All inhalation CS values calculated were less than the oral CS so they will not be discussed further.

The data from which CSs for F-12 were calculated were obtained from Prendergast et al. (1967). The MED calculated for guinea pigs exposed intermittently to F-12 (Prendergast et al., 1967) correlates to an RV_d of 1.3. The remaining MEDs correlate to RV_ds of 1. The most severe effects

TABLE 6-2

Composite Scores for the Toxicity of F-11 and F-12 by Inhalation Exposure

Compound	Species/ Strain	Sex	Exposure Dosage (mg/kg/day)	Human MED (mg/day)*	RV_d	Effect	RV_e	CS	Reference
F-11	beagle dogs	M	1940 continuous for 90 days	7075	1	Elevated serum urea nitrogen inflammation of the lungs	4	4	Jenkins et al., 1970
F-11	guinea pigs	M+F	2841 continuous for 90 days	3833	1	Mild liver discoloration, inflammation of the lungs	4	4	Jenkins et al., 1970
F-12	Hartley guinea pigs	NS	482.3, 8 hours/ day, 5 days/week for 6 weeks	650.6	1.3	Nonspecific inflammation of the lungs, focal necrosis and fatty infiltration of the liver	6	7.8	Prendergast et al., 1967
F-12	New Zealand rabbits	NS	530.5, 8 hours/ day, 5 days/week for 6 weeks	1256.2	1	Nonspecific inflammation of the lungs	4	4	Prendergast et al., 1967
F-12	Hartley guinea pigs	NS	1941.6 continuous for 90 days	2619.2	1	Inflammation of the lungs, slight-extensive fatty infiltration of hepatic cells, several animals-focal or submassive necrosis of the liver	7	7	Prendergast et al., 1967
F-12	New Zealand rabbits	NS	2174.4 continuous for 90 days	5149.1	1	Weight gain depressed, nonspecific inflammation of the lungs	4	4	Prendergast et al., 1967

*MED = Exposure Dose x [weight animal/70 kg (human reference weight)]$^{1/3}$ x 70 kg x 1/10 an additional uncertainty factor of 10 is used to extrapolate from subchronic data to chronic

NS = Not specified

were observed in guinea pigs (focal necrosis and fatty infiltration of the liver). These effects increased in incidence and severity from the intermittent exposures to the continuous exposure. The effects from the intermittent exposures correspond to an RV_e of 6, while the effects from the continuous exposure correspond to an RV_e of 7. The highest CS value, 7.8, is from guinea pigs exposed intermittently; the effects, although similar to those seen with continuous exposure, occurred at a lower transformed dose.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Chronic oral cancer studies of F-11 and F-12 (NCI, 1978; Sherman, 1974) did not result in any increased tumor incidences. The data base is considered inadequate to assess the carcinogenic potential of these compounds; therefore, an oral q_1^* cannot be calculated.

6.3.2. Inhalation. The data base is considered inadequate to assess the carcinogenic potential of these compounds; therefore, an oral q_1^* cannot be calculated.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment, adopted by ACGIH with intended changes for 1985-1986. Cincinnati, OH. p. 15, 32.

Angerer, J., B. Schroder and R. Heinrich. 1985. Exposure to fluorotrichloromethane (F-11). Int. Arch. Occup. Environ. Health. 56: 67-72.

Belej, M.A., D.G. Smith and D.M. Aviado. 1974. Toxicity of aerosol propellants in the respiratory and circulatory systems. IV. Cardiotoxicity in the monkey. Toxicology. 2: 381-395.

Brugnone, F., L. Perbellini and P. Apostoli. 1984. Blood concentration of solvents in industrial exposure. Coll. Med. Leg. Toxicol. Med. 125: 165-168.

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-related environmental fate of 129 priority pollutants. Vol. II. U.S. EPA, Washington, DC. EPA 440/4-79-029B.

Clayton, W.J., Jr. 1967. Fluorocarbon toxicity and biological action. Fluorine Chem. Rev. 1(2): 197-252.

Culik, R. and H. Sherman. 1973. Teratogenic study in rats with dichlorodifluoromethane (Freon 12), Haskell Laboratory Report No. 206-273, Courtesy of DuPont de Numours, Inc. 10 p.

Hansch, C. and A.J. Leo. 1985. MedChem Project Issue No. 26, Pomona College, Claremont, CA.

Jenkins, L.J., R.A. Jones, R.A. Coon and J. Siegal. 1970. Repeated and continuous exposures of laboratory animals to trichlorofluoromethane. Toxicol. Appl. Pharmacol. 16: 133-142.

Krahn, D.F., F.C. Borsky and K.T. McCooey. 1982. CHO/HGPRT mutation assay. Evaluation of gases and volatile liquids. In: Genotoxic Effects of Airborne Agents. Environ. Sci. Res. 25: 91-103.

Leuschner, F., B.W. Neumann and F. Huebscher. 1983. Report on subacute toxicological studies with several fluorocarbons in rats and dogs by inhalation. Arzneim.-Forsch. 33(10): 1475-1476.

Longstaff, E., M. Robinson, C. Bradbrook, J.A. Styles and I.F.H. Purchase. 1984. Genotoxicity and carcinogenicity of fluorocarbons. Assessment by short-term in vitro tests and chronic exposure in rats. Toxicol. Appl. Pharmacol. 72: 15-31.

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York. p. 4-9, 5-5, 15-13, 15-21.

Maltoni, C., A. Ciliberti and D. Carretti. 1982. Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. Ann. NY Acad. Sci. 381: 216-249.

Morgan, A., A. Black, M. Walsh and D.R. Belcher. 1972. Absorption and retention of inhaled fluorinated hydrocarbon vapors. Int. J. Appl. Radiat. Isotop. 23: 285-291.

NAS (National Academy of Sciences). 1980. Drinking Water and Health. Vol. 3. National Academy Press, Washington, DC. p. 101-104, 166-168.

NCI (National Cancer Institute). 1978. Bioassay of Trichlorofluromethane for Possible Carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 106. 46 p. [Also published as DHEW(NIH)78-1356]

OSHA (Occupational Safety and Health Administration). 1985. OSHA Occupational Standards. Permissible Exposure Limits. 29 CFR 1910.1000.

Paulet, G., S. Desbrousser and E. Vidal. 1974. Absence d'effetteratogene des fluorocarbones chez le rat et le lapin. [Absence of teratogenic effects of fluorocarbons in the rat and rabbit]. Arch. Mal. Prof. Med. Trav. Secur. Soc. 35: 658-662. (Fre.)

Prendergast, J.A., R.A. Jones, L.J. Jenkins and J. Siegal. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10: 270-289.

Sayers, R.R., W.P. Yant, J. Chornyak and J.W. Shoaf. 1930. Toxicity of dichlorodifluoromethane. Department of Commerce, U.S. Bureau of Mines Report, Report of Investigation (RI) 3013.

Sherman, H. 1974. Long-term feeding studies in rats and dogs with dichlorodifluoromethane (Freon 12 Food Freezant). Haskell Laboratory Report No. 24-74. Unpublished, courtesy duPont de Nemours Co.

Stewart, R.D., P.E. Newton, E.D. Baretta, A.A. Herrmann, H.V. Forster and R.J. Soto. 1978. Physiological response to aerosol propellants. Environ. Health Perspect. 26: 275-285.

Swann, R.L., D.A. Laskowski, P.J. McCall, K. VanderKuy and H.J. Dishburger. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Res. Rev. 85: 17-28.

Uehleke, H., H. Greim, M. Kramer and T. Werner. 1976. Covalent binding of haloalkanes to liver constituents, but absence of mutagenicity on bacteria in a metabolizing test system. Mutat. Res. 38: 114.

Uehleke, H., T. Werner, H. Greim and M. Kramer. 1977. Metabolic activation of haloalkanes and tests in vitro for mutagenicity. Xenobiotica. 7(7): 393-400.

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-051. NTIS PB-81-117624.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 49347-49357.

U.S. EPA. 1982. Errata for Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1983. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986a. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

U.S. EPA. 1986b. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for dichlorodifluoromethane. Online. (Verification date 7/22/85). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986c. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for trichlorotrifluoromethane. Online. (Verification date 7/8/85). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986d. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

Van't Hof, J. and L.A. Schairer. 1982. Trandescantia assay system for gaseous mutagens. A report of the U.S. Environmental Protection Agency. Gene-Tox. Program. Mutat. Res. 99(3): 303-315.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., New York. p. 484, 676.

APPENDIX A

Summary Table for F-11

	Species	Experimental Exposure/Dose	Effect	Reference Dose[a] (RfD_S or RfD)	Reference
Inhalation					
RfD_{SI} (formerly AIS)	beagle dogs	5600 mg/m³ continuously for 90 days (1940 mg/kg/day)	Elevated serum urea nitrogen, inflammation of the lungs	135.8 mg/day	Jenkins et al., 1970
RfD_I (formerly AIC)	beagle dogs	5600 mg/m³ continuously for 90 days (1940 mg/kg/day)	Elevated serum urea nitrogen, inflammation of the lungs	13.6 mg/day[b]	Jenkins et al., 1970
Oral					
RfD_{SO}	Osborne-Mendel rats	1000 mg/kg/day, 5 days/week for 6 weeks, 2 weeks observation (714.3 mg/kg/day)	Body weight depression	50 mg/day	NCI, 1978
RfD_O	Osborne-Mendel rats	488 mg/kg/day, 5 days/week for 66 weeks, 33 weeks observation (348.6 mg/kg/day)	Acceleration of mortality	20 mg/day	NCI, 1978
Maximum					
CS	rat	348.6 mg/kg/day, 5 days/week for 78 weeks (RV_d=1)	Acceleration of mortality (RV_e=10)	10	NCI, 1978

[a]Reference doses are mg/day for a 70 kg human

[b]The RfD_S was divided by an additional uncertainty factor to extrapolate from subchronic to chronic exposure.

APPENDIX B

Summary Table for F-12

	Species	Experimental Exposure/Dose	Effect	Reference Dose[a] (RfD_S or RfD)	Reference
Inhalation					
RfD_{SI} (formerly AIS)	guinea pigs	4136 mg/m³, 8 hours/day, 5 days/week for 6 weeks (482.3 mg/kg/day)	Nonspecific inflammation of the lungs, several animals-focal necrosis or fatty infiltration of the liver	33.8 mg/day	Prendergast et al., 1967
RfD_I (formerly AIC)	guinea pigs	4136 mg/m³, 8 hours/day, 5 days/week for 6 weeks (482.3 mg/kg/day)	Nonspecific inflammation of the lungs, several animals-focal necrosis or fatty infiltration of the liver	3.4 mg/day[b]	Prendergast et al., 1967
Oral					
RfD_{SO}	beagle dogs	90 mg/kg/day for 90 days	NOAEL	63 mg/day	Clayton, 1967
RfD_O	CD rats	15 mg/kg/day by gavage for 2 years	NOAEL	10 mg/day	Sherman, 1974
Maximum					
CS	guinea pigs	4136 mg/m³ (482.3 mg/kg/day) 8 hours/day, 5 days/week for 6 weeks (RV_d=1.3)	Inflammation of the lungs, focal necrosis and fatty infiltration of the liver (RV_e=6)	7.8	Prendergast et al., 1967

[a]Reference doses are mg/day for a 70 kg human exposure.

[b]The RfD_S was divided by an additional uncertainty factor to extrapolate from subchronic to chronic exposure.