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Provisional Peer-Reviewed Toxicity Values for

Dichlorodifluoromethane
(CASRN 75-71-8)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
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COMMONLY USED ABBREVIATIONS

BMC	Benchmark Concentration
BMD	Benchmark Dose
BMCL	Benchmark Concentration Lower bound 95% confidence interval
BMDL	Benchmark Dose Lower bound 95% confidence interval
HEC	Human Equivalent Concentration
HED	Human Equivalent 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 reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure (oral)
RfC	reference concentration (inhalation)
RfD	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
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR DICHLORODIFLUOROMETHANE (CASRN 75-71-8)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency'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) EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in 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 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 EPA IRIS Program. All provisional toxicity values receive internal review by a panel of 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 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

There is an RfD assessment for dichlorodifluoromethane (structure shown in Figure 1) on IRIS (U.S. EPA, 2009) in which a chronic RfD of 0.2 mg/kg-day is derived using a NOAEL from Sherman (1974) for reduced body-weight in rats exposed via diet for 2 years. The Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) also lists the chronic RfD of 0.2 mg/kg-day for dichlorodifluoromethane, citing a Drinking Water Health Advisory (DWHA) (U.S. EPA, 1987a) as the source. The HEAST (U.S. EPA, 1997) includes the chronic RfD from IRIS, as well as a subchronic RfD of 0.9 mg/kg-day that was derived in a Health Effects Assessment (HEA) (U.S. EPA, 1987b) using a NOAEL from Clayton (1967) for systemic effects in dogs exposed to dichlorodifluoromethane in the diet for 90 days. Other relevant EPA documents listed in the Chemical Assessments and Related Activities (CARA) database (U.S. EPA, 1994a, 1991) include an Ambient Water Quality Criterion Document (AWQCD) for halomethanes (U.S. EPA, 1982), which derived an Acceptable Daily Intake (ADI) of 0.8 mg/kg-day based on no effect in dogs exposed for 2 years (Sherman, 1974). Other oral toxicity values for dichlorodifluoromethane include an ADI of 0–1.5 mg/kg-day estimated by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (WHO, 1975); the derivation of this value is based on the same study and effect level as the chronic RfD on IRIS. WHO has also published an Environmental Health Criteria document on fully halogenated chlorofluorocarbons that includes dichlorodifluoromethane (WHO, 1990). Health assessments for dichlorodifluoromethane have not been conducted by ATSDR (2009) or CalEPA (2009a,b,c).

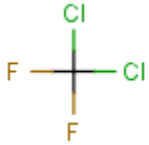

Figure 1. Chemical Structure of Dichlorodifluoromethane

There is no RfC assessment for dichlorodifluoromethane on IRIS (U.S. EPA, 2009). The HEAST (U.S. EPA, 1997) contains subchronic and chronic RfCs of 2 and 0.2 mg/m^3, respectively, that have been derived using outdated RfC methodology. These RfCs were converted for the HEAST from subchronic and chronic inhalation RfC values that were expressed in mg/kg-day (i.e., from an RfD_{SI} of 0.5 mg/kg-day and RfD_I of 0.05 mg/kg-day) in the HEA (U.S. EPA, 1987b) based on a subchronic inhalation LOAEL from (Prendergast et al., 1967) for liver pathology in guinea pigs. The American Conference of Governmental Industrial Hygienists (ACGIH, 2007, 2001) recommends a Threshold Limit Value-time-weighted average (TLV-TWA) of 1,000 ppm (4,950 mg/m^3) to minimize the potential for cardiac sensitization and systemic injury. A TWA limit of 1,000 ppm (4,950 mg/m^3) is similarly recommended by the National Institute for Occupational Safety and Health (NIOSH, 2005) as a Recommended Exposure Limit (REL) and promulgated by the Occupational Safety and Health Administration (OSHA) (2009) as a Permissible Exposure Limit (PEL).

There is no carcinogenicity assessment for dichlorodifluoromethane on IRIS (U.S. EPA, 2009) or in the HEAST (U.S. EPA, 1997), although the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) contains a Group D (not classifiable as to human carcinogenicity) cancer descriptor. The aforementioned ACGIH (2007, 2001) TLV-TWA for dichlorodifluoromethane is accompanied by an A4 carcinogenicity notation (not classifiable as a human carcinogen). The carcinogenicity of dichlorodifluoromethane has not been tested or evaluated by the National Toxicology Program (NTP, 2009, 2005) or the International Agency for Research on Cancer (IARC, 2009).

Literature searches were conducted for studies relevant to the derivation of provisional toxicity values for dichlorodifluoromethane. Databases searched include MEDLINE, TOXLINE (BIOSIS and NTIS), TOXCENTER, CANCERLIT, CCRIS, DART/ETIC, TSCATS/TSCATS 2, GENETOX, HSDB, RTECS, and Current Contents. The time period covered by most of the searches ranged from the 1960s through early January 2009, although some searches covered earlier years. No further references for this compound could be located following an updated literature search encompassing January through November 2009, in MEDLINE.

REVIEW OF PERTINENT DATA

HUMAN STUDIES

Oral Exposure

No studies regarding the oral exposure of humans to dichlorodifluoromethane have been located.

Inhalation Exposure

Two volunteers were exposed to dichlorodifluoromethane (99.98% purity) at alternating concentrations of 1,000 (4,950 mg/m^3) and 10,000 ppm (49,500 mg/m^3) in 2.5-hour sessions, 3 times each over a 3-week testing period (Azar et al., 1972). Subjects were exposed to air for 2.5 hours on the days between dichlorodifluoromethane exposures (a total of six times). The subjects served as their own controls, with comprehensive preexposure testing providing baseline measurements. Physical examinations, including chest x-ray, electrocardiograms (EKG), hematology (hemoglobin [Hgb], hematocrit [Hct], complete white blood cell count [WBC]), and

clinical chemistry (alkaline phosphatase [ALP], aspartate aminotransferase [AST, formerly SGOT], alanine aminotransferase [ALT, formerly SGPT], lactic acid dehydrogenase [LDH]; total bilirubin, cholesterol, protein, and lipids; creatinine, glucose, blood urea nitrogen [BUN], uric acid) were performed 1 week before the start of the experiment and 1 week following completion of the experiment. During exposure, volunteers were monitored for clinical signs of toxicity and subjected to continuous EKGs and a battery of psychomotor testing. Endpoint tidal volume measurements were taken 15 minutes pre- and postexposure (every minute for 15 minutes; at 2 and 4 hours). No signs of toxicity were reported, and all clinical chemistry and hematology parameters were within normal limits (data not shown). Subjects scored slightly lower (7%) on psychomotor tests during exposure to 49,500 mg/m^3, but not 4,950 mg/m^3, dichlorodifluoromethane.

Azar et al. (1972) also described the results of an unpublished study by Kehoe (1943). This study also included two subjects, one exposed to 4% (198,000 mg/m^3), 6% (297,000 mg/m^3), 7% (347,000 mg/m^3), and 11% (545,000 mg/m^3) dichlorodifluoromethane for periods of 80, 80, 35, and 11 minutes, respectively, and another exposed to 4% for 14 minutes followed immediately by 2% (99,000 mg/m^3) for 66 minutes. At 4%, the subjects experienced a generalized tingling sensation, humming in the ears, apprehension, altered electroencephalogram (EEG), decreased psychological test scores, and slurred speech. These effects increased in intensity with exposure level. At 11%, the study authors reported observing a marked decrease in consciousness and amnesia in the subjects within 10 minutes, preceded and accompanied by significant cardiac arrhythmia. No further details of this study are available.

Stewart et al. (1978) exposed eight male human subjects to 1,000 ppm (4,950 mg/m^3) of dichlorodifluoromethane (99.9% purity) for 8 hours/day, 5 days/week, for up to 4 weeks. Subjects were volunteers who were all Caucasian males that ranged in age from 18 to 46 years. The subjects served as their own controls, with comprehensive preexposure testing providing baseline measurements. Subjective symptoms were recorded before exposure and hourly until 5 hours after exposure. Blood was collected for hematology (complete blood cell count) and serum chemistry (ALP, AST, LDH, bilirubin, glucose, calcium, phosphorus, BUN) before and after exposure, and urinalysis (fluoride excretion) was assessed at the same time. Other evaluations included heart function (EKGs and systolic time interval measurements), pulmonary function (computerized spirometry measurement), adrenocorticotropic hormone (ACTH) stimulation, neurological evaluation (modified Romberg test and heel-to-toe test), EEG, visual evoked potentials, and cognitive tests (Flanagan coordination tests, Marquette time estimation test, and random number-inspection test). No untoward symptoms or clinical signs of illness were observed. Clinical chemistry and hematology parameters remained within normal limits for exposed subjects (data not shown); neither heart nor pulmonary function was compromised (data were shown only for pulmonary function). Individuals repeatedly exposed to dichlorodifluoromethane showed normal evoked responses, cognitive test performances, and ACTH stimulation responses (data not shown). Because a wide range of endpoints are evaluated and no adverse physiological effects are reported, a duration-adjusted NOAEL of 1,179 mg/m^3 is identified for the 4-week exposure in this study. No studies examining the effects of longer-term inhalation exposure in humans were located.

Additional studies (Emmen, 2000; Harrison et al., 1996; Antti-Poika et al., 1990) that examined effects related to exposure to fluorocarbon mixtures that included dichlorodifluoromethane were not evaluated for this review.

ANIMAL STUDIES

Oral Exposure

Subchronic Studies—In a 90-day study written as a brief summary, mixed-sex groups of rats (unspecified number and strain) were administered dichlorodifluoromethane (purity not specified) at 0 or 160–380 mg/kg-day (individual doses not specified) via gavage as vegetable oil solutions (Waritz, 1971; Clayton, 1967). Endpoints evaluated included clinical signs, body-weight, hematology, serum enzymes (ALP and ALT), urinalysis (fluoride excretion), gross pathology, and histopathology. Data regarding mortality or body-weight are not reported; however, it is reported that no rats exhibited clinical signs of toxicity. Hematological parameters were not affected by treatment (data not shown); urinary fluoride levels and ALP activity were slightly higher (but within normal limits) in treated rats than in the controls at 30, 60, and 90 days (data not shown). The study authors did not consider the increase in ALP activity observed in treated rats to be indicative of hepatic damage because livers isolated from these animals were histopathologically within control limits.

In the same report, the study authors also assessed toxicity in mixed-sex groups of dogs (unspecified number and breed) administered dichlorodifluoromethane at 0 or 84–95 mg/kg-day (individual doses not specified) in the diet (Waritz, 1971; Clayton, 1967). The same toxicological parameters that were assessed in rats were also assessed in dogs. The study authors reported that dichlorodifluoromethane treatment did not elicit clinical signs of toxicity, and no hematological, urine analytical, or histopathological changes were apparent (data not shown). Although no adverse effects are reported in rats or dogs, these studies are limited in that data are presented qualitatively, and little information regarding sample size, control conditions, and administered doses is available. These limitations preclude the identification of reliable effect levels for these studies.

Chronic Studies—Weanling Charles River CD rats (50/sex/dose) from dams exposed during gestation were administered dichlorodifluoromethane (purity not reported) via gavage at 0, 0.2, or 2% in corn oil 7 days/week for 6 weeks and 5 days/week thereafter for 2 years (Sherman, 1974). The compound was administered in volumes calculated to approximate the intakes expected from dietary concentrations of 0, 300, or 3,000 ppm. The study authors estimated the average daily doses over the course of the 2-year study to be 0, 15, or 150 mg/kg-day in both male and female rats. Two control groups, each consisting of 50 males and 50 females, were used. Throughout the study, rats were monitored regularly for signs of clinical toxicity or mortality. Body weight and food consumption data were recorded weekly for the first 6 months, bi-weekly up to 1 year, and monthly thereafter. Body-weight gain, food consumption, and food efficiency were tabulated every 3 months (quarterly) throughout the duration of the 2-year bioassay. Hematological analyses (Hgb, Hct, RBC, total and differential WBC) and urine analyses (pH, color, appearance, 24-hour volume, presence of occult blood and bilirubin, solute concentration, creatinine, and semiquantitative measures of sugar, protein, and urobilinogen) were performed on 10 rats/sex/dose at 1, 3, 9, 12, 18, and 24 months. Blood collected from an additional 10 rats/sex/dose at the same time intervals was used to assess serum chemistry (ALP, ALT, and total bilirubin). Six rats/sex/group were sacrificed at 1 year; the

remaining rats were sacrificed at 2 years. Fluoride content in the femur and dichlorodifluoromethane content of various tissues (including adrenals, blood, bone marrow, brain, heart, kidney, liver, muscle, and fat) were analyzed in some animals at the 1- and 2-year sacrifice. Following sacrifice, all test animals were necropsied, and organ weights (adrenals, brain, heart, lungs, liver, spleen, kidney, testis, stomach, and pituitary) were recorded. Comprehensive histopathological examinations (of 33 tissues) were performed.

The study authors reported that survival was similar between the treated and control rats, and observed no clinical findings related to exposure (Sherman, 1974). Feed consumption was similar in treated and control groups; however, female rats had slightly lower levels of food efficiency (statistical analyses not performed). Based on data presented graphically, mean body-weight of rats administered the high-dose of dichlorodifluoromethane appeared lower than that of the controls throughout most of the study. However, for low- and high-dose males, mean body-weight gains were within 10% of controls at all interim sampling time points up to the terminus of study at Day 728. For high-dose females, reductions in mean body-weight gains of >10% compared to the control groups are apparent in every quarter through to terminus of study at Day 728. At the conclusion of the first quarter (Day 91), which represents a subchronic duration in rats, body-weight gain in high-dose dichlorodifluoromethane-treated females is 11.5% lower than controls (Table 1). In the low-dose group females, mean body-weight gain did not vary significantly (i.e., >10%) from controls. No dose-related changes in hematology, serum chemistry, urinalysis, organ weights, or histopathology are evident in any treatment group; however, the data are reported only as mean values without standard deviations or standard errors, and no statistical analyses are reported. Based on the first quarter (0–3 month) data from the Sherman (1974) 2-year study, a subchronic NOAEL of 15 mg/kg-day and LOAEL of 150 mg/kg-day are identified based on a reduction in mean body-weight gain in female rats.

Sherman (1974) also administered dichlorodifluoromethane (purity not specified) to Beagle dogs (4/sex/dose) at 0, 300, or 3,000 ppm in the diet for 2 years. The doses were estimated by the study authors to be 0, 8, or 80 mg/kg-day in both male and female dogs. Dogs were monitored daily for mortality and clinical signs of toxicity, and body weights were recorded weekly. Endpoints evaluated to assess toxicity included hematology (Hgb, Hct, RBC, total and differential WBC), clinical chemistry (ALP, ALT, BUN, glucose, cholesterol, creatinine, total protein, albumin-globulin ratios), and urinalysis (pH, color, appearance and sediment analysis; osmolality, creatinine, blood, acetone, bilirubin, and fluoride content; and semiquantitative tests for sugar, protein, and urobilinogen). After 1 year of continuous feeding, one dog/sex from the control group and one dog/sex from the high-dose group were sacrificed; the remaining dogs were sacrificed at 2 years. The study authors analyzed fluoride content in the femur and dichlorodifluoromethane content of various tissues (including adrenals, blood, bone marrow, brain, heart, kidney, liver, muscle, and fat) in all animals at the 1- and 2-year sacrifice. After treatment for 2 years, three 24-hour urine samples were collected from three dogs/sex/group to measure total 17-ketosteroid (i.e., adrenal cortical steroid hormone) levels. All animals were necropsied, and organ weights (adrenals, brain, heart, thymus, lungs, liver, spleen, kidney, testis, stomach, and pituitary) were recorded. Comprehensive histopathological examinations (35 tissues) were performed. Complete microscopic examinations were performed on the organs and tissues of dogs in the control and high-dose groups.

Table 1. Average Weight Gain of Male (M) and Female (F) Charles River CD Rats Fed Dichlorodifluoromethane for 3 Months[a]

Treatment Group[b]	Months on Test	Starting Weight	Weight at end of Quarter	Weight Gain	% Change compared to controls
Control[c]	0–3	M: 133 g	M: 527 g	M: 394 g	
		F: 111 g	F: 293 g	F: 182 g	
Low-dose (15 mg/kg-day)	0–3	M: 122 g	M: 518 g	M: 396 g	M: + 0.5 %
		F: 105 g	F: 278 g	F: 173 g	F: - 5.0 %
High-dose (150 mg/kg-day)	0–3	M: 130 g	M: 486 g	M: 356 g	M: - 9.6 %
		F: 115 g	F: 276 g	F: 161 g	F: - 11.5 %

[a]Data presented are first-quarter interim sample values from the 2-year study (Sherman, 1974).
[b]50 rats/sex/group, except for the controls where n = 100 rats/sex.
[c]Values are means of two separate concurrent control groups.

The study authors observed no treatment-related deaths or clinical signs of toxicity (Sherman, 1974). No differences in body weight or food consumption were apparent between the control and treated groups (statistical analysis not performed). No significant changes or abnormal trends were observed in hematology, serum chemistry, or urinalysis results (data presented as means without standard deviations or statistical analyses). Fluoride content of the femur was not increased in treated dogs; however, low levels of dichlorodifluoromethane were detected in the fat and bone marrow of high-dose animals after treatment for 2 years. Although the study authors reported no significant changes in organ weights, some values exhibited moderate variability that did not correlate with body-weight (no statistical analyses were performed). The study authors considered the limited histopathological findings (including interstitial lymphoid nodules, lymphoid cells, renal pelvis, and subpleural fibrosis) to be age related, and, consequently, not dose related. A NOAEL of 80 mg/kg-day (the high-dose level) is identified in dogs.

No significant changes in tumor incidence related to dichlorodifluoromethane treatment were found in any dose group (rats or dogs) during the 2-year studies (Sherman, 1974). The rat study is considered an adequate bioassay of carcinogenicity because it includes a large sample size that received histopathological evaluation, it includes the maximum tolerated dose (MTD), and it is of sufficient duration to detect the production of tumors. However, the dog study is not considered adequate as a cancer bioassay since group sizes are small, the MTD is not achieved, and the duration of the experiment may not have been long enough to detect tumors with long latency periods.

Reproductive/Developmental Studies—Groups of 11 male and 21 female Charles River CD rats were administered 0, 0.2, or 2% dichlorodifluoromethane (unspecified purity) via gavage as corn oil solutions for 7 days/week (first 6 weeks) or 5 days/week (thereafter) for a 15-week premating period and throughout mating, gestation, and lactation, except from gestational day (GD) 18 to postnatal day (PND) 4, for three generations (Sherman, 1974). The compound was administered in volumes calculated to approximate the intakes expected from dietary concentrations of 0, 300, or 3,000 ppm. Average daily doses were estimated to be approximately 0, 15, or 150 mg/kg-day by the author. Two vehicle-only control groups, each containing 11 males and 21 females, were used. Endpoints evaluated included body weights of F3 rats, reproductive indices in all generations (fertility, gestation, viability, and lactation), and histopathology in F3 offspring after 4 weeks of untreated postweaning observation.

No effects on reproductive capabilities were reported (Sherman, 1974). Treated rats did not vary significantly from controls in number of pregnancies, litter size, fetal viability at birth, pup growth and survival, or gross pathology in pups (data reported as mean values without standard deviations or statistical analyses). A NOAEL of 150 mg/kg-day (the highest dose tested) is identified for reproductive and developmental toxicity (parental and pup) in rats.

In a developmental toxicity study available only as a brief summary (Culik and Sherman, 1973, as cited in U.S. EPA 1987a,b), pregnant Charles River rats (25–27/dose) were administered dichlorodifluoromethane (purity not specified) at 0, 17, or 171 mg/kg-day via gavage as corn oil solutions on GDs 6–15. Endpoints evaluated included maternal food intake and body weight; number of implantations, resorptions, and live fetuses/litter; fetal body weight and length; and external, skeletal, and soft-tissue abnormalities. Dichlorodifluoromethane

administration reportedly did not affect maternal weight gain, the numbers of implantation sites or viable fetuses, mean fetal body-weight, or fetal crown-rump length (data not shown). The study authors detected no major abnormalities in live fetuses, and reported that minor defects in the offspring of treated rats were similar to those of controls. Although reporting of the data is limited, a NOAEL of 171 mg/kg-day for maternal and developmental toxicity in rats is identified.

Inhalation Exposure

Subchronic Studies—Sprague-Dawley rats (20/sex/dose) were exposed via whole-body inhalation chambers to dichlorodifluoromethane (>99% pure) at 0 or 10,000 ppm (approximately 49,500 mg/m^3) for 6 hours/day, 7 days/week for 90 days (Leuschner et al., 1983). The study authors monitored rats regularly for mortality, clinical signs of toxicity, body weight, and consumption of food and water. Endpoints evaluated to assess toxicity included hematology (Hgb, Hct, RBC, total and differential WBC, reticulocytes, platelets, 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 [BSP]); sight, hearing, and dental examinations; 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, urinalysis, sight, hearing, or dentition were observed (data not shown). In addition, no histological alterations attributable to dichlorodifluoromethane exposure were observed. Areas of focal alveolar over-inflation and an intraalveolar accumulation of macrophages in the lungs were noted, but the study authors did not consider them to be related to exposure because these changes were also detected, to the same degree, in control animals. This study identifies a duration-adjusted NOAEL of 12,375 mg/m^3 in rats.

Leuschner et al. (1983) also assessed effects in purebred Beagle dogs exposed (3/sex/group, whole-body) to 0 or 5,000 ppm (25,000 mg/m^3) dichlorodifluoromethane (>99.9% purity) for 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 (phenolsulfonphthalein [PSP]); glycogen in heart, liver and muscle; blood pressure; and EKG. No treatment-related effects were observed on any of the parameters (data not shown). A duration-adjusted NOAEL of 6,250 mg/m^3 is identified in dogs from these data.

Prendergast et al. (1967) exposed Sprague-Dawley or Long-Evans rats (n = 15, sex unspecified), Hartley guinea pigs (n = 15, sex unspecified), New Zealand white rabbits (n = 3, sex unspecified), Beagle dogs (n = 2), and squirrel monkeys (n = 3) via whole-body inhalation chambers to dichlorodifluoromethane (99% purity) at 836 ppm (4,136 mg/m^3) 8 hours/day, 5 days/week, for 6 weeks (intermittent exposure) or at 808 ppm (3,997 mg/m^3) continuously for 90 days (continuous exposure). The study authors maintained the control animals (304 rats, 314 guinea pigs, 48 rabbits, 34 dogs, and 57 monkeys) in the exposure chambers without contaminant, and monitored all animals regularly for mortality and clinical signs of toxicity. Body weights were recorded prior to exposure, at monthly intervals, and at study termination. Hematology assessments conducted prior to and following exposure, included Hgb, Hct, and

total and differential WBC counts. A comprehensive histopathological analysis of the liver, kidney, heart, lung, and spleen was also performed.

The study authors noted that one rat died after intermittent exposure to dichlorodifluoromethane, but were uncertain whether this death was related to exposure (Prendergast et al., 1967). No rats exhibited clinical signs of toxicity, and no hematological differences between control animals and treated animals are apparent (data presented as mean values; statistical analyses were not performed by study authors). Gross examination revealed that several rats, including controls, had varying degrees of lung congestion (incidence not reported). Histopathological examinations detected nonspecific inflammatory changes in the lungs of both experimental and control animals (incidence not reported). The duration-adjusted exposure concentration of 985 mg/m^3 is a NOAEL in rats with intermittent exposure in this study.

Prendergast et al. (1967) noted that two rats died following continuous exposure, but were uncertain whether the deaths were related to dichlorodifuoromethane exposure. Consistent with results obtained from intermittent exposure, there are no clinical signs of toxicity and no hematological differences between control and treated animals (data presented as mean values; statistical analyses were not performed by study authors). Both experimental and control animals were reported to have lung congestion and nonspecific inflammatory changes in the lungs (incidence not reported). No other histopathological variations were found. The exposure concentration of 3,997 mg/m^3 is a NOAEL in rats with continuous exposure in this study.

No guinea pigs died as the result of intermittent exposure to dichlorodifluoromethane (Prendergast et al., 1967). The mean percentage of body-weight gain in treated guinea pigs is about 40% less than control animals over the course of the experiment (data presented as mean percentages weight gain, no statistical analyses were performed by the study authors). The study authors suggested that this effect may be due, at least in part, to higher starting weights of treated guinea pigs compared to the controls. Hematological data showed no treatment-related effects. Histopathological examinations revealed varying degrees of lung congestion and nonspecific inflammatory changes to the lungs of both experimental and control animals (incidence not reported). Treated (but not control) guinea pigs also exhibited focal necrosis and fatty infiltration of the liver (incidence not reported). The duration-adjusted exposure level of 985 mg/m^3 is a LOAEL for intermittent exposure in guinea pigs based on liver effects and a reduction in body-weight gain.

One death occurred as a result of continuous exposure of guinea pigs to dichlorodifluoromethane, but it is uncertain whether this death was chemical-related (Prendergast et al., 1967). Consistent with the results obtained from repeated exposure, guinea pigs subjected to continuous exposure exhibited a reduction (~40%) in the mean percentage of body-weight gain over the course of the study compared to control animals (mean data presented without standard deviations or statistical analyses). The data showed that hematological parameters for treated guinea pigs were within the normal range. Several experimental and control animals had lung congestion and nonspecific inflammatory changes in the lungs (incidence not reported). Focal necrosis and fatty infiltration of the liver was reported in all treated animals. Liver damage was more severe than in guinea pigs subjected to intermittent

dichlorodifluoromethane exposure. The exposure concentration of 3,997 mg/m^3 is a LOAEL for continuous exposure in guinea pigs based on liver effects and a reduction in body-weight gain.

In rabbits, neither intermittent nor continuous treatment to dichlorodifluoromethane affected survival, and no clinical signs of toxicity were apparent (Prendergast et al., 1967). The only significant finding was that treated rabbits exhibited a reduction in body-weight gain of about 50% with respect to controls with repeated exposure (data presented as mean percentage of weight gain, analyses not performed by study authors). When exposed to dichlorodifluoromethane continuously for 90 days, the difference in body-weight gain was more apparent, with treated animals gaining about 83% less than control animals. No other treatment-related effects were reported. Duration-adjusted LOAEL values of 985 mg/m^3 and 3,997 mg/m^3, based on a reduction in body-weight gain in rabbits from the intermittent or continuous exposures, respectively, are identified for these studies.

Additional studies examined the effects of intermittent and continuous exposure to dichlorodifluoromethane in Beagle dogs and squirrel monkeys (Prendergast et al., 1967). No clinical signs of toxicity were reported. However, body-weight gains were significantly reduced by 10–20% compared to control animals in intermittently-exposed dogs and monkeys; in contrast, in continuously-exposed animals, body-weight gains were increased compared to controls (data presented as mean percentage of weight gain). Similar to the experiments conducted in rats, guinea pigs, and rabbits, both experimental and control animals (dogs and monkeys) showed congestion and nonspecific inflammatory changes to the lungs (incidence not reported). Though the very small sample sizes used for these experiments are a considerable limitation, a duration-adjusted LOAEL value of 985 mg/m^3 (intermittent exposure) and a NOAEL of 3,997 mg/m^3 (continuous exposure) for reduced body-weight gain are identified in dogs and monkeys exposed for up to 90 days.

Sayers et al. (1930) exposed mixed-sex groups of guinea pigs (26/group), dogs (2/group), and monkeys (2/group) to dichlorodifluoromethane (whole body) at 0 or 200,000 ppm (989,000 mg/m^3) for 7–8 hours/day for 5 days/week, or 4 hours/day, 1 day/week, for up to 12 weeks. The study authors monitored animals regularly for mortality, clinical signs of toxicity, and changes in body-weight. Hematology parameters (Hgb, RBC, WBC [total and differential]) were evaluated in 10 guinea pigs/group and in all dogs and monkeys every 7–10 days. Complete autopsies were performed at spontaneous time of death, at the termination of the study, or after a 30-day postexposure observation period. During the first week of exposure to 20% dichlorodifluoromethane, guinea pigs experienced signs of nasal irritation; dogs and monkeys exhibited tremors and ataxia. These signs were diminished following exposure. Mortality in guinea pigs (6/26 control animals and 10/26 treated animals) was attributed to pneumonia. No dogs or monkeys died. Weight gain and hematological parameters reportedly remained within normal limits for all animals (data not shown). Autopsy revealed no pathological variations attributable to dichlorodifluoromethane exposure. Small samples sizes, limited data reporting, and the poor condition of the animals (i.e., pregnancies and pneumonia in guinea pigs and tuberculosis in monkeys) are limitations of this study and preclude the identification of effect levels.

Chronic Studies—In long-term carcinogenicity bioassays, dichlorodifluoromethane (99.98% purity) was administered by inhalation (whole-body) to Sprague-Dawley rats

(90/sex/group) or Swiss mice (60/sex/group) at 1,000 or 5,000 ppm (4,900 or 25,000 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. Body-weight of mice was not affected by treatment (data not shown). No other information on nonneoplastic findings is reported for either species. No treatment-related differences in the incidence of malignant tumors or the total number of benign and malignant tumors (including brain tumors, mammary tumors, leukemias, pheochromocytomas, and pheochromoblastomas) are reported in rats. In mice, significant increases are reported in the total number of tumors for males and females, pulmonary adenomas in males and females at the high dose, and leukemias in males and low-dose females. However, when the study authors applied the log rank test to account for age-related trends, they found no statistically significant increases over control levels in the incidence of any tumor type in male or female mice.

Reproductive/Developmental Studies—In a developmental study, groups of 10 pregnant Wistar rats or rabbits (strain not specified) were exposed to a 9:1 mixture of dichlorodifluoromethane and trichlorofluoromethane at 200,000 ppm (approximately 989,000 mg/m^3) for 2 hours/day on GDs 4–16 (rats) or 5–20 (rabbits) (Paulet et al., 1973). The study authors sacrificed half of the animals at GDs 20 (rats) or 30 (rabbits); the remaining animals were permitted to deliver. Evaluations performed included maternal body weights, numbers of implantations, resorptions, and live fetuses; fetal development abnormalities, and birth weight and perinatal survival of pups. No treatment-related changes are apparent in any of these parameters (data reported as mean values without standard deviations or statistical analyses). The exposure level of 200,000 ppm (989,000 mg/m^3) is identified as a NOAEL for developmental effects in rats and rabbits for the tested mixture.

OTHER STUDIES

Short-term Studies

Taylor and Drew (1975) exposed New Zealand white rabbits (4 males/dose) to dichlorodifluoromethane (purity not reported) at a concentration of 0 or 100,000 ppm (494,500 mg/m^3) for 6 hours/day for 29 days. Endpoints evaluated to assess toxicity included body weight, respiratory rate, cardiac output, other cardiac responses (including mean arterial pressure [MAP], rate of change in left ventricle pressure [LV dP/dt], left ventricle systolic pressure [LVP], and left ventricle end diastolic pressure [LVEDP]), and histopathology (four tissues). The study authors reported that body weight, respiratory rate, and histopathology of the heart, lung, liver, and kidney were similar among experimental and control animals (data not shown). No significant changes in cardiac responses (MAP, LV dP/dt, LVP, and LVEDP) were detected; however, cardiac output was 16% higher in the dichlorodifluoromethane-exposed group than the control group (data not shown). Although this difference was not statistically significant ($p > 0.1$), it is possible that biologically significant effects on cardiac output could not be detected due to the small sample size.

Genotoxicity

A limited amount of information is available on the genotoxicity of dichlorodifluoromethane. Dichlorodifluoromethane did not induce reverse mutations in *Salmonella typhimurium* strains TA1535, TA98, TA1537, or TA100 or *Escherichia coli* WP2*uvr*A when tested with or without metabolic activation (Araki et al., 1994; Longstaff, 1988; Longstaff et al., 1984; Russell et al., 1980). However, treatment with dichlorodifluoromethane (50%) plus oxygen (50%) significantly increased the mutation rate in *Neurospora crassa* (Stephens et al., 1971). Dichlorodifluoromethane was not mutagenic in a *Tradescantia* assay (Van't Hof and Schairer, 1982). Dichlorodifluoromethane was not cytotoxic or mutagenic in a Chinese hamster ovary HGPRT assay in the presence or absence of metabolic activation (Krahn et al., 1982), and dichlorodifluoromethane tested negative in a cell transformation assay in BHK21 cells with metabolic activation (Longstaff, 1988). In vivo, dominant lethal mutations were not induced in the F3B generation of Charles River rats exposed for three generations to dichlorodifluoromethane at doses of up to 150 mg/kg-day (Sherman, 1974).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RFD VALUES FOR DICHLORODIFLUOROMETHANE

SUBCHRONIC p-RFD

The subchronic studies in rats and dogs are described only as brief summaries by their original authors (i.e., Waritz, 1971; Clayton, 1967); they presented insufficient information on study methods and results to identify effect levels. The remaining database for oral toxicity to dichlorodifluoromethane includes chronic, reproductive and developmental toxicity studies from a single report (Sherman, 1974) and is summarized in Table 2.

The chronic rat study (Sherman, 1974) includes quarterly tabulation (i.e., every 3 months) of average body-weight gains. In female rats, compared to controls, dichlorodifluoromethane exposure was associated with a significant (i.e., >10%) reduced body-weight gain in every quarter from initiation to terminus of study. For the first quarter, which entailed Days 0–91 of the study, a subchronic LOAEL of 150 mg/kg-day and NOAEL of 15 mg/kg-day are identified based on a reduction in body-weight gain in females (Sherman, 1974). Although NOAELs are also available from the studies for systemic toxicity in dogs (Sherman, 1974), reproductive toxicity in rats (Sherman, 1974), and developmental toxicity in rats (Culik and Sherman, 1973), these occurred at higher dichlorodifluoromethane doses.

The subchronic NOAEL of 15 mg/kg-day, identified from the subchronic-duration interim-sampling time point (0–3 months) in female rats (Sherman, 1974), is selected as the most appropriate point of departure (POD) for derivation of the subchronic p-RfD. Benchmark dose (BMD) modeling is not possible as the data were reported by the study authors as means without variability. The female rat NOAEL of 15 mg/kg-day has been divided by a composite UF of 300 to derive a **subchronic p-RfD** for dichlorodifluoromethane as follows:

Subchronic p-RfD = NOAEL ÷ UF
= 15 mg/kg-day ÷ 300
= 0.05 or 5×10^{-2} mg/kg-day

Table 2. Summary of Oral Noncancer Dose-Response Information for Dichlorodifluoromethane

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Charles River CD rat 50/sex/group	Administered via gavage in corn oil 7 days/week for the first 6 weeks and 5 days/week thereafter for 2 years. Approximate average daily doses of 0, 15, or 150 mg/kg-day	chronic: 15 subchronic: 15	chronic: 150 subchronic: 150	Reduction in body-weight (females)	Basis for the chronic RfD assessment on IRIS. Body-weight gain reductions of >10% were apparent at every quarterly sampling point throughout the duration of the 2-year study. No significant changes in tumor incidence were observed.	Sherman, 1974
Beagle dog 4/sex/group	0, 300, or 3,000 ppm (0, 8, or 80 mg/kg-day) in the diet for 2 years	80	NA	NA	No significant changes in tumor incidence were observed.	Sherman, 1974
Charles River CD rat, three-generation reproductive study (11 M, 21 F/group)	Administered via gavage in corn oil 7 days/week for the first 6 weeks and 5 days/week thereafter through premating, mating, gestation and lactation (except GD 18 – PND 4). Approximate average daily doses of 0, 15, or 150 mg/kg-day	150	NA	NA		Sherman, 1974
Charles River CD rat 25–27 females/group	0, 17, or 171 mg/kg-day via gavage on Days 6–15 of gestation.	171	NA	NA	Unpublished study available only as a brief summary in secondary reviews.	Culik and Sherman, 1973, as cited in U.S. EPA, 1987a,b

The composite uncertainty factor (UF) of 300 is composed of the following UFs:

- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient.
- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
- UF_L: A factor for extrapolation from a LOAEL to a NOAEL is not applied because the point-of-departure used in the derivation of a subchronic p-RfD is a NOAEL.
- UF_D: The database for oral exposure to dichlorodifluoromethane consists of inadequate subchronic toxicity studies in two species (only brief summaries available), a chronic toxicity study in two species, a multigeneration reproductive toxicity study, and a developmental toxicity study in one species available only as a brief summary. A factor of 3 ($10^{0.5}$) is applied for database inadequacies, as data for evaluating developmental toxicity are insufficient (no data in a second species, incomplete reporting of the available study).

Confidence in the principal study (i.e., Sherman, 1974) is high. An adequate number of animals have been used, the treatment regimen spans early-life, subchronic, and chronic durations, and appropriate endpoints are thoroughly evaluated. The only negative aspect of this study is that data are presented without measures of variation or statistical analyses. Confidence in the database is medium. Long-term oral toxicity studies are available in two species (rats and dogs) (i.e., Sherman, 1974), and a multigeneration reproductive toxicity study in rats (i.e., Sherman, 1974) is also available. However, developmental toxicity data are limited to one study in one species (i.e., Culik and Sherman, 1973) available only as a brief summary from secondary sources. All of the critical oral toxicity studies were conducted by the same researchers. Taken together, these studies establish medium confidence in the derived subchronic p-RfD.

CHRONIC RFD

IRIS (U.S. EPA, 2009) lists a chronic RfD of 0.2 mg/kg-day for dichlorodifluoromethane based on the 2-year NOAEL of 15 mg/kg-day for reduced body weight in female rats (Sherman, 1974) and a composite UF of 100 (10 for sensitive individuals and 10 for species extrapolation). It should be noted that a database uncertainty factor was not considered at the time that the chronic RfD was derived, which accounts for why the proposed subchronic p-RfD presented above is lower than the chronic RfD.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RFC VALUES FOR DICHLORODIFLUOROMETHANE

Table 3 summarizes the data available to derive subchronic and chronic p-RfCs for dichlorodifluoromethane. To provide a common basis of comparison among studies, animal effect levels have been adjusted to human equivalent concentrations ($NOAEL_{HEC}$ and $LOAEL_{HEC}$) using the appropriate dosimetric adjustment (U.S. EPA, 1994b). Because extrarespiratory effects (i.e., liver effects and reduction in body-weight gain) are the only reliable phenotypes associated with dichlorodifluoromethane exposure, the chemical has been treated as a Category 3 gas.

Under Category 3, the equation used to calculate a $NOAEL_{HEC}$ is as follows:

$$NOAEL_{HEC} = (NOAEL_{ADJ}) \times [(H_{b/g})_A \div (H_{b/g})_H]$$

where:

$NOAEL_{ADJ}$ = duration-adjusted NOAEL for discontinuous exposures; for continuous exposure studies no such adjustment is made.

and,

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

Blood:air partition coefficients have been considered to make dosimetric adjustments for all studies. Blood:air partition coefficients for dichlorodifluoromethane have been located for humans and rats (i.e., Ng et al., 2007), but no coefficients have been located for any of the other species of animals reported in the inhalation literature; therefore, for all experimental animals other than rat, the default ratio of 1.0 has been used. Furthermore, although dichlorodifluoromethane blood:air partition coefficients reported in rats and humans result in a $(H_{b/g})_A/(H_{b/g})_H$ ratio greater than 1, a value of 1 is used in the calculation of human equivalent concentrations per U.S. EPA guidance (1994b). Table 3 shows the calculated $NOAEL_{HEC}$ and $LOAEL_{HEC}$ values for each study.

SUBCHRONIC p-RFC

The human data from Stewart et al. (1978) were considered for the derivation of a subchronic p-RfC, but were deemed inappropriate due to the small number of subjects examined and the short-term exposure duration. Comprehensive indices of potential toxicity were examined in subchronic duration inhalation studies in rats (Leuschner et al., 1983; Prendergast et al., 1967), guinea pigs (Prendergast et al., 1967; Sayers et al., 1930), rabbits (Prendergast et al., 1967), dogs (Leuschner et al., 1983; Prendergast et al., 1967; Sayers et al., 1930), and monkeys (Prendergast et al., 1967; Sayers et al., 1930). As shown in Table 3, LOAEL values of 985 mg/m^3 are available for guinea pigs, rabbits, dogs, and monkeys following intermittent inhalation exposure. All four species of animal exhibit significantly reduced body-weight gains at this exposure concentration.

In addition, at this inhalation concentration, Prendergast et al. (1967) observed focal necrosis and fatty infiltration in the livers of guinea pigs. However, liver effects were not observed in any of the other animal species tested. Furthermore, the study by Leuschner et al. (1983), which included comprehensive investigation of hepatotoxicity in rats and dogs, showed no effects of dichlorodifluoromethane at exposure levels up to 12,375 mg/m^3. Therefore, due to the apparent differences in species sensitivity to dichlorodifluoromethane-induced liver effects, this endpoint is not considered a critical effect via the inhalation route. $LOAEL_{HEC}$ values for reduced body-weight gains in guinea pigs, rabbits, dogs, and monkeys are 985 mg/m^3 from the intermittent (6-week) exposure studies (see Table 3). Corresponding NOAEL values are not identified for these effects following intermittent exposure because these studies each included only a single exposure level, at which toxicity was observed. Reduced body-weight gain is selected as the critical effect, and the duration-adjusted (for intermittent exposure) $LOAEL_{HEC}$ of 985 mg/m^3 identified in guinea pigs, rabbits, dogs, and monkeys from the Prendergast et al. (1967) study is selected as the most appropriate POD for derivation of the subchronic p-RfC. BMD modeling was not possible because only one exposure level was used.

Table 3. Summary of Inhalation Noncancer Dose-Response Information for Dichlorodifluoromethane

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	$NOAEL_{HEC}$ (mg/m^3)	$LOAEL_{HEC}$ (mg/m^3)	Responses at the LOAEL	Comments	Reference
Subchronic toxicity								
Human Volunteers 8 males	4,950 mg/m^3 (1,000 ppm) for 8 hours/day, 5 days/week for up to 4 weeks	1,179[a]	NA	NA	NA	NA	Subjects served as their own controls.	Stewart et al., 1978
Animal Sprague-Dawley rat 20/sex/group	0 or 49,500 mg/m^3 (0 or 10,000 ppm) for 6 hours/day, 7 days/week for 90 days	12,375[a]	NA	12,375[b]	NA	NA	Results presented qualitatively (data not shown).	Leuschner et al., 1983
Sprague-Dawley or Long-Evans rat 15/unspecified sex	0 or 4,136 mg/m^3 (836 ppm) for 8 hours/day, 5 days/week for 6 weeks	985[a]	NA	985[b]	NA	NA	Compared to pooled control group. Most results presented qualitatively (data not shown).	Prendergast et al., 1967
Sprague-Dawley or Long-Evans rat 15/unspecified sex	0 or 3,997 mg/m^3 (808 ppm) continuously for 90 days	3,997	NA	3,997[b]	NA	NA	Compared to pooled control group. Most results presented qualitatively (data not shown).	Prendergast et al., 1967
Hartley guinea pig 15/unspecified sex	0 or 4,136 mg/m^3 (836 ppm) for 8 hours/day, 5 days/week for 6 weeks	NA	985[a]	NA	985[b]	Focal necrosis and fatty infiltration of the liver; reduction in body-weight gain.	Compared to pooled control group. Most results presented qualitatively (data not shown).	Prendergast et al., 1967

Table 3. Summary of Inhalation Noncancer Dose-Response Information for Dichlorodifluoromethane

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	$NOAEL_{HEC}$ (mg/m^3)	$LOAEL_{HEC}$ (mg/m^3)	Responses at the LOAEL	Comments	Reference
Hartley guinea pig 15/unspecified sex	0 or 3,997 mg/m^3 (808 ppm) continuously for 90 days	NA	3,997	NA	3,997[b]	Focal necrosis and fatty infiltration of the liver, reduction in percentage of body-weight gain.	Compared to pooled control group. Most results presented qualitatively (data not shown). Liver effects more severe than with repeated exposure.	Prendergast et al., 1967
New Zealand white rabbit 3/unspecified sex	0 or 4,136 mg/m^3 (836 ppm) for 8 hours/day, 5 days/week for 6 weeks	NA	985[a]	NA	985[b]	Reduction in body-weight gain.	Very small sample size used. Compared to pooled control group. Most results presented qualitatively (data not shown).	Prendergast et al., 1967
New Zealand white rabbit 3/unspecified sex	0 or 3,997 mg/m^3 (808 ppm) continuously for 90 days	NA	3,997	NA	3,997[b]	Reduction in body-weight gain.	Very small sample size used. Compared to pooled control group. Most results presented qualitatively (data not shown).	Prendergast et al., 1967
Beagle dog 3/sex/dose	0 or 25,000 mg/m^3 (0 or 5,000 ppm) for 6 hours/day, 7 days/week for 90 days	6,250[a]	NA	6,250[b]	NA	NA	Results presented qualitatively (data not shown).	Leuschner et al., 1983
Beagle dog 2/unspecified sex	0 or 4,136 mg/m^3 (836 ppm) for 8 hours/day, 5 days/week for 6 weeks	NA	985[a]	NA	985[b]	Reduction in body-weight gain	Very small sample size used. Compared to pooled control group. Most results presented qualitatively (final body-weight data not shown).	Prendergast et al., 1967

Table 3. Summary of Inhalation Noncancer Dose-Response Information for Dichlorodifluoromethane

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	$NOAEL_{HEC}$ (mg/m^3)	$LOAEL_{HEC}$ (mg/m^3)	Responses at the LOAEL	Comments	Reference
Beagle dog 2/unspecified sex	0 or 3,997 mg/m^3 (808 ppm) continuously for 90 days	3,997	NA	3,997[b]	NA	NA	Very small sample size used. Compared to pooled control group. Most results presented qualitatively (data not shown).	Prendergast et al., 1967
Squirrel monkey 3/unspecified sex	0 or 4,136 mg/m^3 (836 ppm) for 8 hours/day, 5 days/week for 6 weeks	NA	985[a]	NA	985[b]	Reduction in body-weight gain	Very small sample size used. Compared to pooled control group. Most results presented qualitatively (final body-weight data not shown).	Prendergast et al., 1967
Squirrel monkey 3/unspecified sex	0 or 3,997 mg/m^3 (808 ppm) continuously for 90 days	3,997	NA	3,997[b]	NA	NA	Very small sample size used. Compared to pooled control group. Most results presented qualitatively (data not shown).	Prendergast et al., 1967
Chronic toxicity								
Sprague-Dawley rat 90/sex/group	0, 4,900, or 25,000 mg/m^3 (0, 1,000, or 5,000 ppm) for 4 hours/day, 5 days/week for 104 weeks	2,976[a]	NA	2,976[b]	NA	NA	Limited noncancer endpoints reported and no nonneoplastic pathology findings.	Maltoni et al., 1988

Table 3. Summary of Inhalation Noncancer Dose-Response Information for Dichlorodifluoromethane

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	$NOAEL_{HEC}$ (mg/m^3)	$LOAEL_{HEC}$ (mg/m^3)	Responses at the LOAEL	Comments	Reference
Swiss mouse 60/sex/group	0, 4,900, or 25,000 mg/m^3 (0, 1,000, or 5,000 ppm) for 4 hours/day, 5 days/week for 78 weeks	2,976[a]	NA	2,976[b]	NA	NA	Unexplained deaths in the control group; limited noncancer endpoints reported and no nonneoplastic pathology findings.	Maltoni et al., 1988
Reproductive and developmental toxicity								
Wistar rat 10 females/group	0 or 989,000 mg/m^3 (200,000 ppm) of a 9:1 mixture of CF_2Cl_2:$CFCl_3$ for 2 hours/day on Days 4–16 of gestation	82,417[a]	NA	82,417[b]	NA	NA	No indication of maternal or developmental toxicity. 90% CF_2Cl_2 mixture tested.	Paulet et al., 1973
Rabbit 10 females/group	0 or 989,000 mg/m^3 (0 or 200,000 ppm) of a 9:1 mixture of CF_2Cl_2:$CFCl_3$ for 2 hours/day on Days 5–20 of gestation	82,417[a]	NA	82,417[b]	NA	NA	No indication of maternal or developmental toxicity. 90% CF_2Cl_2 mixture tested.	Paulet et al., 1973

[a]Adjusted to equivalent continuous exposure duration (hours/day × days/week × intermittent exposure concentration).
[b]HEC calculated as follows: $N(L)OAEL_{HEC}$ = duration-adjusted N(L)OAEL × dosimetric adjustment factor; for systemic effects, the dosimetric adjustment factor is the ratio of the animal:human blood:gas partition coefficients for dichlorodifluoromethane (a default value of 1 was used for the dosimetric adjustment factor).

Using the $LOAEL_{HEC}$ of 985 mg/m^3 from the intermittent exposure study in guinea pigs, rabbits, dogs, and monkeys (Prendergast et al., 1967) as the POD, a **subchronic p-RfC** is derived for dichlorodifluoromethane as follows:

$$\textbf{Subchronic p-RfC} = LOAEL_{HEC} \div UF$$
$$= 985 \text{ mg/m}^3 \div 1000$$
$$\mathbf{= 1 \times 10^0 \text{ mg/m}^3}$$

The composite UF of 1000 is composed of the following UFs:

- UF_A: A factor of 3 is applied for interspecies extrapolation. This factor comprises two areas of uncertainty: pharmacokinetics and pharmacodynamics. In this assessment, the pharmacokinetic component is addressed by the dosimetric adjustment (i.e., calculation of the HEC according to the procedures in the RfC methodology [U.S. EPA, 1994b]). No toxicity was observed in human volunteers at an inhalation concentration of 1,179 mg/m^3 following 4 weeks of exposure. In contrast, following a relatively similar duration of exposure (e.g., 6 weeks) in several animal species including monkeys, significantly reduced (>10%) body-weight gains were observed at a $LOAEL_{HEC}$ of 985 mg/m^3, which suggests that animal species may be modestly more sensitive to inhaled dichlorodifluoromethane than humans. However, there is insufficient evidence available to draw conclusions on the relative sensitivities between humans and experimental animal species following dichlorodifluromethane exposure via any route. Consequently, the pharmacodynamic component of this UF is a 3.
- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating a susceptible human response are insufficient.
- UF_L: A factor of 10 is applied for extrapolation from a LOAEL to a NOAEL because the only exposure concentration utilized in the principal study is associated with reduced body-weight gain; a NOAEL is not established.
- UF_D: The database for inhalation exposure to dichlorodifluoromethane includes studies in humans, subchronic toxicity studies in several species of animals, a chronic study that presented only limited data on noncancer endpoints, and a limited developmental toxicity study in two species that tested a mixture containing 90% dichlorodifluoromethane in which no effects were seen at high doses. A factor of 3 ($10^{0.5}$) is applied for database inadequacies because data for evaluating reproductive and developmental toxicity via the inhalation route are inadequate.

Confidence in the principal study (i.e., Prendergast et al., 1967) is low. The study assessed comprehensive toxicological endpoints in several species of animals, including guinea pigs, following intermittent or continuous exposure for up to 90 days. However, the study in guinea pigs employed only one inhalation exposure concentration and was poorly documented. Confidence in the database is low-to-medium. Although subchronic studies are available in several species, the studies are limited by use of a single exposure concentration, incomplete (mostly qualitative) reporting of results, and small group sizes for some species (Leuschner et al., 1983; Prendergast et al., 1967). A multigeneration reproduction study is available for dichlorodifluoromethane, but it was performed by the oral exposure route (Sherman, 1974). The

developmental toxicity study (in rats and rabbits) is limited by incomplete reporting and use of a fluorocarbon mixture (Paulet et al., 1973). Low confidence in the subchronic p-RfC follows.

CHRONIC p-RFC

For dichlorodifluoromethane it is inappropriate to derive a provisional chronic p-RfC. No chronic duration human inhalation studies exists, and the few subchronic human inhalation studies identified are either of poor design, short-term exposure duration (e.g., 3−4 weeks), or involve exposure to mixtures of compounds containing dichlorodifluoromethane. In animals, there are no dose-response data available for nonneoplastic effects following chronic inhalation exposure. Indeed, the only chronic inhalation toxicity studies available are two experiments in rats and mice that were designed primarily as cancer bioassays (see Maltoni et al., 1988). There are a number of subchronic duration inhalation studies in various experimental animal species (e.g., rats, guinea pigs, rabbits, dogs, and monkeys; Prendergast et al., 1967), however, the exposure duration for the most sensitive animal species (guinea pigs, rabbits, dogs, and monkeys) was only 6 weeks. Due to a high level of overall uncertainty associated with using the 6-week data from the Prendergast et al. (1967) study, a provisional chronic RfC cannot be confidently derived here. However a "screening level" value for chronic inhalation exposure is provided in Appendix A.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR DICHLORODIFLUOROMETHANE

WEIGHT-OF-EVIDENCE DESCRIPTOR

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "***Inadequate Information to Assess [the] Carcinogenic Potential***" of dichlorodifluoromethane. No information has been located regarding carcinogenicity in humans following oral or inhalation exposure to dichlorodifluoromethane. The only available animal study conducted by the oral route of exposure found no evidence for increased tumors in rats or dogs following chronic exposure to dichlorodifluoromethane for 2 years (Sherman, 1974). Although the rat study is considered adequate, the findings in dogs are inconclusive because the group sizes are very small, the study may not have been of sufficient duration to detect tumors with long latency periods, and it appears that the MTD was not reached. In the only available inhalation study (Maltoni et al., 1988), there were no significant increases over control levels in the incidence of any tumor type in rats or mice. However, these findings are also limited in that only two doses were tested, and, again, it appears that the MTD was not reached. Genotoxicity data for dichlorodifluoromethane are primarily negative.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

A provisional oral slope factor and inhalation unit risk for dichlorodifluoromethane cannot be derived; human cancer data are lacking, and the available animal data are inadequate to assess potential carcinogenicity.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2001) Dichlorodifluoromethane. Documentation of the threshold limit values for chemical substances. 7th Edition. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). (2007) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

Antti-Poika, M; Heikkila, J; Saarinen, L. (1990) Cardiac arrhythmias during occupational exposure to fluorinated hydrocarbons. Br J Ind Med 47:138–140.

Araki, A; Noguchi, T; Kato, F; et al. (1994) Improved method for mutagenicity testing of gaseous compounds by using a gas sampling bag. Mutat Res 307:335–344.

ATSDR (Agency for Toxic Substances and Disease Registry). (2009) Toxicological Profile Information Sheet. U.S. Department of Health and Human Services, Public Health Service. Online. http://www.atsdr.cdc.gov/toxpro2.html.

Azar, A; Reinhardt, CF; Maxfield, ME; et al. (1972) Experimental human exposures to fluorocarbon 12 (dichlorodifluoromethane). Am Ind Hyg Assoc J 33:207–216.

CalEPA (California Environmental Protection Agency). (2009a) OEHHA/ARB Approved chronic reference exposure levels and target organs. Online. http://www.arb.ca.gov/toxics/healthval/chronic.pdf.

CalEPA (California Environmental Protection Agency). (2009b) Air chronic reference exposure levels adopted by OEHHA as of February 2005. Online. http://www.oehha.ca.gov/air/chronic_rels/AllChrels.html.

CalEPA (California Environmental Protection Agency). (2009c) Hot spots unit risk and cancer potency values. Online. http://www.oehha.ca.gov/air/hot_spots/pdf/TSDlookup2002.pdf.

Clayton, WJ. (1967) Fluorocarbon toxicity and biological action. Fluorine Chemistry Reviews 1(2):197–252.

Culik, R; Sherman, H. (1973) Teratogenic study in rats with dichlorodifluoromethane (Freon 12). Haskell Laboratory Report No. 206–273, DuPont de Nemours, Inc. (Cited in U.S. EPA 1987a,b)

Emmen, HH; Hoogendijk, EM; Klopping-Ketelaars, WA; et al. (2000) Human safety and pharmacokinetics of the CFC alternative propellants HFC 134a (1,1,1,2-tetrafluoroethane) and HFC 227 (1,1,1,2,3,3,3-heptafluoropropane) following whole-body exposure. Regul Toxicol Pharmacol 32:22–35.

Harrison, LI; Donnell, D; Simmons, JL; et al. (1996) Twenty-eight-day double-blind safety study of an HFA-134a inhalation aerosol system in healthy subjects. J Pharm Pharmacol 48:596–600.

IARC (International Agency for Research on Cancer). (2009) Search IARC monographs. Online. http://monographs.iarc.fr/ENG/Monographs/allmonos90.php.

Kehoe, RA. (1943) Report on human exposure to dichlorodifluoromethane in air (unpublished report). Kettering Laboratory, Cincinnati, OH. (Cited in Azar et al., 1972).

Krahn, DF; Barsky, FC; McCooey, KT. (1982) CHO/HGPRT mutation assay: evaluation of gases and volatile liquids. Environ Sci Res 25:91–103.

Leuschner, F; Neumann, RW; Hubscher, F. (1983) Report on subacute toxicological studies with several fluorocarbons in rats and dogs by inhalation. Arzneim Forsch 33:1475–1476.

Longstaff, E. (1988) Carcinogenic and mutagenic potential of several fluorocarbons. Ann NY Acad Sci 534:283–298.

Longstaff, E; Robinson, M; Bradbrook, C; et al. (1984) Genotoxicity and carcinogenicity of fluorocarbons: assessment by short term in vitro tests and chronic exposure in rats. Toxicol Appl Pharmacol 72:15–31.

Maltoni, C; Lefemine, G; Tovoli, D; et al. (1988) Long-term carcinogenicity bioassays on three chlorofluorocarbons (trichlorofluoromethane, FC11; dichlorodifluoromethane, FC12; chlorodifluoromethane, FC22) administered by inhalation to Sprague-Dawley rats and Swiss mice. Ann NY Acad Sci 534:261–282.

Ng, LJ; Stuhmiller, LM; Stuhmiller, JH. (2007) Incorporation of acute dynamic ventilation changes into a standardized physiologically based pharmacokinetic model. Inhal Toxicol 19:247–263.

NIOSH (National Institute for Occupational Safety and Health). (2005) NIOSH pocket guide to chemical hazards. Online. http://www.cdc.gov/niosh/npg/.

NTP (National Toxicology Program). (2005) 11th report on carcinogens. Online. http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932.

NTP (National Toxicology Program). (2009) Management status report. Online. http://ntp.niehs.nih.gov/index.cfm?objectid=78CC7E4C-F1F6-975E-72940974DE301C3F.

OSHA (Occupational Safety and Health Administration). (2009) OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Paulet, GS; Desbrousser, S; Vidal, E. (1973) Absence d'effetteratogogene des fluorocarbones chez le rat et le lapin. [Absence of teratogenic effects of fluorocarbons in the rat and the rabbit]. Arch Mal Prof Med Trav Secur Soc 34:658–662.

Prendergast, JA; Jones, RA; Jenkins, LJ; et al. (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(2):270–289.

Russell, JF; Sippel, ME; Krahn, DF. (1980) Methods for the detection of mutagenic gases and volatile liquids in the *Salmonella* microsome assay. Environ Mutagen 2:307.

Sayers, RR; Yant, WP; Chomyak, J; et al. (1930) Toxicity of dichloro-difluoromethane: a new refrigerant. Bureau of Mines Report Investigation 3013:1–15.

Sherman, H. (1974) Long-term feeding studies in rats and dogs with dichlorodifluoromethane (FREON 12 food freezant). Haskell Laboratory for Toxicology and Industrial Medicine. Medical Research Project No. 1388. Haskell Laboratory Report No. 24–74. Unpublished study conducted for DuPont de Nemours Co.

Stephens, S; De Sha, C; Fuerst, R. (1971) Phenotypic and genetic effects in *Neurospora crassa* produced by selected gases and gases mixed with oxygen. Dev Ind Microbiol 12:346–353.

Stewart, RD; Newton, PE; Baretta, ED; et al. (1978) Physiological response to aerosol propellants. Environ Health Perspect 26:275–285.

Taylor, GJ; Drew, RT. (1975) Cardiovascular effects of acute and chronic inhalation of fluorocarbon twelve in rabbits. J Pharmacol Exp Ther 192:129–135.

U.S. EPA (U.S. Environmental Protection Agency). (1982) Errata: Halomethanes ambient water quality criterion for the protection of human health. 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 (U.S. Environmental Protection Agency). (1987a) Drinking water health advisory for dichlorodifluoromethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (1987b) Health effects assessment for fully halogenated methanes. 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 (U.S. Environmental Protection Agency). (1991) Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (1994a) Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC.

U.S. EPA (U.S. Environmental Protection Agency). (1994b) Methods of derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. October 1994. EPA/600/8-90/066F.

U.S. EPA (U.S. Environmental Protection Agency). (1997) Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA (U.S. Environmental Protection Agency). (2002) A Review of the Reference Dose and Reference Concentration Processes. Risk Assessment Forum, Washington, DC. EPA/630/P-02/002F. Online. http://www.epa.gov/ncea/iris/RFD_FINAL[1].pdf.

U.S. EPA (U.S. Environmental Protection Agency). (2005) Guidelines for carcinogen risk assessment, Final Report. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001F. Online. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.

U.S. EPA (U.S. Environmental Protection Agency). (2006) 2006 Edition of the drinking water standards and health advisories. Office of Water, Washington, DC. EPA 822-R-02-038. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf.

U.S. EPA (U.S. Environmental Protection Agency). (2009) Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/.

Van't Hof, J; Schairer, LA. (1982) *Tradescantia* assay system for gaseous mutagens. A report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat Res 99:303–315.

Waritz, RS. (1971) The toxicology of some commercial fluorocarbons. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio. AMRL Report No. AMRL-TR-71-120. NTIS Report No. AD-751-429.

WHO (World Health Organization). (1975) Dichlorodifluoromethane. In: Toxicological evaluation of some food colours, thickening agents and certain other substances. WHO Food Additives Series No. 8. Online. http://www.inchem.org/documents/jecfa/jecmono/v08je10.htm.

WHO (World Health Organization). (1990) International Programme on Chemical Safety: Fully halogenated chlorofluorocarbons. Environmental Health Criteria 113:1–164. Online. http://www.inchem.org/documents/ehc/ehc/ehc113.htm.

APPENDIX A. PROVISIONAL SCREENING VALUE

DERIVATION OF A SCREENING CHRONIC p-RFC VALUE

For reasons noted in the main portion of this PPRTV document, it is inappropriate to derive a provisional inhalation reference concentration (p-RfC) for chronic dichlorodifluoromethane exposure. However, information is available for this chemical which, although insufficient to support derivation of a p-RfC, under current guidelines, may be of use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. In the OSRTI hierarchy, screening values are considered to be *below* Tier 3, "Other (Peer-Reviewed) Toxicity Values."

Screening Values are intended for use in limited circumstances when no Tier 1, 2, or 3 values are available. Screening values may be used, for example, to rank relative risks of individual chemicals present at a site to determine if the risk developed from the associated exposure at the specific site is likely to be a significant concern in the overall cleanup decision. Screening values are not defensible as the primary drivers in making cleanup decisions because they are based on limited information. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

The 6-week intermittent inhalation study in guinea pigs, rabbits, dogs, and monkeys from Prendergast et al. (1967) is selected as the principal study for derivation of a screening chronic p-RfC. Reduced body-weight gain is selected as the critical effect, and the duration-adjusted (for intermittent exposure) $LOAEL_{HEC}$ of 985 mg/m^3 is selected as the most appropriate POD. This value, which also serves as the POD for derivation of the subchronic p-RfC, is used as the POD for deriving the Screening Chronic p-RfC for dichlorodifluoromethane.

Using the $LOAEL_{HEC}$ of 985 mg/m^3 from Prendergast et al. (1967) as the POD, a **screening chronic p-RfC** is derived for dichlorodifluoromethane as follows:

Screening Chronic p-RfC $= LOAEL_{HEC} \div UF$
$= 985 \text{ mg/m}^3 \div 10{,}000$
$\mathbf{= 1 \times 10^{-1} \text{ mg/m}^3}$

The composite UF of 10,000 is composed of the following UFs:

- UF_A: A factor of 3 is applied for interspecies extrapolation. This factor comprises two areas of uncertainty: pharmacokinetics and pharmacodynamics. In this assessment, the pharmacokinetic component is addressed by the dosimetric adjustment (i.e., calculation of the HEC according to the procedures in the RfC methodology [U.S. EPA, 1994b]). No toxicity was observed in human volunteers at an inhalation concentration of 1,179 mg/m^3 following 4 weeks of exposure. In contrast, following a relatively similar duration of exposure (i.e., 6 weeks) in several animal species including monkeys, significantly reduced (>10%) body-weight gains were observed at a $LOAEL_{HEC}$ of 985 mg/m^3, which suggests that animal species may

be modestly more sensitive to inhaled dichlorodifluoromethane than humans. However, there is insufficient evidence available to draw conclusions on the relative sensitivities between humans and experimental animal species following dichlorodifluromethane exposure via any route. Consequently, the pharmacodynamic component of this UF is a 3.

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
- UF_L: A factor of 10 is applied for extrapolation from a LOAEL to a NOAEL because the only exposure concentration utilized in the principal study is associated with reduced body weight gain; a NOAEL is not established.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure because data for evaluating response after chronic exposure are insufficient.
- UF_D: The database for inhalation exposure to dichlorodifluoromethane includes studies in humans, subchronic toxicity studies in several species of animals, a chronic study that presents only limited data on noncancer endpoints, and a limited developmental toxicity study in two species that tested a mixture containing 90% dichlorodifluoromethane. A factor of 3 ($10^{0.5}$) is applied for database inadequacies because data for evaluating reproductive and developmental toxicity via the inhalation route are inadequate.

As discussed in the subchronic p-RfC section, confidence in the principal study (Prendergast et al., 1967) is low. Confidence in the database is reduced to low due to the lack of adequate chronic studies for evaluation of noncancer effects. Low confidence in the screening chronic p-RfC follows.