United States
Environmental Protection
Agency

EPA/690/R-04/004F
Final
11-24-2004

Provisional Peer Reviewed Toxicity Values for

Chloroacetic Acid

(CASRN 79-11-8)

Superfund Health Risk Technical Support Center
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Acronyms

bw - body weight
cc - cubic centimeters
CD - Caesarean Delivered
CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act of 1980
CNS - central nervous system
cu.m - cubic meter
DWEL - Drinking Water Equivalent Level
FEL - frank-effect level
FIFRA - Federal Insecticide, Fungicide, and Rodenticide Act
g - grams
GI - gastrointestinal
HEC - human equivalent concentration
Hgb - hemoglobin
i.m. - intramuscular
i.p. - intraperitoneal
i.v. - intravenous
IRIS - Integrated Risk Information System
IUR - Inhalation Unit Risk
kg - kilogram
L - liter
LEL - lowest-effect level
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
m - meter
MCL - maximum contaminant level
MCLG - maximum contaminant level goal
MF - modifying factor
mg - milligram
mg/kg - milligrams per kilogram
mg/L - milligrams per liter
MRL - minimal risk level
MTD - maximum tolerated dose

MTL - median threshold limit
NAAQS - National Ambient Air Quality Standards
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-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
PBPK - physiologically based pharmacokinetic
ppb - parts per billion
ppm - parts per million
PPRTV - Provisional Peer Reviewed Toxicity Value
RBC - red blood cell(s)
RCRA - Resource Conservation and Recovery Act
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

11-24-2004

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR CHLOROACETIC ACID (CASRN 79-11-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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 (PPRTV) 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 Integrated Risk Information System (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 two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program 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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript 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

In this update of the Provisional Peer Reviewed Toxicity Value, no p-RfD, p-RfC or cancer assessment are provided because of a lack of sufficient data. Further, the provisional subchronic RfD and the provisional chronic RfD described below are being retracted for the following reasons:

- The NTP (1992) conducted a 2-year gavage study with rats and identified the lowest dose (15 mg/kg-day) as a Frank-Effect-Level (FEL) because of reduced survival at that dose.

- A NOAEL was not identified for the most sensitive species (rats), at any dose or exposure duration, in a variety of studies.

- The LOAEL (30 mg/kg-day) used as the basis for the existing provisional subchronic and chronic RfDs (IRDC, 1982a,b) was determined to be too close to the FEL and inappropriate for deriving a Provisional Reference Dose.

The HEAST (U.S. EPA, 1997) lists subchronic and chronic oral RfD values of 2E-2 and 2E-3 mg/kg-day, respectively, for chloroacetic acid. The RfDs are based on a LOAEL (increased incidences of myocarditis) of 21.4 mg/kg-day (30 mg/kg-day adjusted for a 5 day/week dosing schedule) in rats administered chloroacetic acid for 90 days (IRDC, 1982a,b). Uncertainty factors of 1000 (10 each for use of a LOAEL, rat to human extrapolation, and protection of sensitive individuals) for the subchronic RfD and 10,000 (1000 as for the subchronic RfD and another factor of 10 for use of a subchronic study) for the chronic RfD were applied to the LOAEL to derive the critical values. The source document for the derivation was a Health and Environmental Effects Document (HEED) for chloroacetic acid (U.S. EPA, 1988a). The HEAST and source HEED do not include RfC derivations due to lack of data. Chloroacetic acid was classified in Group D (not classifiable as to human carcinogenicity) in the HEED because the evidence regarding the carcinogenicity of chloroacetic acid was inconclusive.

No RfD, RfC, or carcinogenicity assessment for chloroacetic acid is available on IRIS (U.S. EPA, 2003a). The Drinking Water Standards and Health Advisories list (U.S. EPA, 2002b) does not report an RfD or MCL for chloroacetic acid, although an MCL of 0.06 mg/L is reported for five haloacetic acids combined (including chloroacetic acid). No relevant documents other than the previously mentioned HEED were located in the CARA list (U.S. EPA, 1991, 1994). ATSDR (2002) has not produced a Toxicological Profile for chloroacetic acid. WHO (2002) does not have an Environmental Health Criteria Document for chloroacetic acid, but does have a Poison Information Monograph for the chemical (WHO, 1998). The carcinogenicity of chloroacetic acid has not been assessed by IARC (2002). The NTP (2002) management status report was checked for recent studies. Exposure limits have not been recommended by OSHA (2002) or NIOSH (2002), but ACGIH (2002) recommends a ceiling TWA of 1 ppm for 15 minutes. Literature searches were conducted from 1987 thru 2002 for studies relevant to the derivation of provisional toxicity values for chloroacetic acid. Databases searched included: TOXLINE, MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/ EMICBACK, HSDB, and GENETOX. Another search of the literature was conducted in May of 2004. No studies relevant to this document were located.

REVIEW OF PERTINENT DATA

Human Studies

A 5-year-old girl died from consumption of 5-6 mL of an 80% chloroacetic acid solution (Feldhaus et al., 1993; Rogers, 1995). The girl developed signs of toxicity at approximately 1.5

hours post-ingestion that included refractory ventricular tachycardia, pulmonary edema, and acidemia, and she died 8 hours after ingestion. Autopsy revealed diffuse gastric erosion, fatty liver, and pulmonary and cerebral edema. Post mortem serum chloroacetic acid level was 100 mg/L. Chloroacetic acid and its sodium salt also cause eye and mucous membrane corrosion, and death has resulted from dermal exposure to approximately 6-10% body surface (WHO, 1998). Reported clinical symptoms resulting from dermal exposure include vomiting, diarrhea, CNS stimulation followed by CNS depression, coma, myocardial depression, shock, renal failure, metabolic acidosis, and damage to the skeletal muscle, heart, and brain. Dose-response data in humans are not available (Kulling et al., 1992).

Animal Studies

The subchronic and chronic toxicity of chloroacetic acid in rats and mice was studied by the National Toxicology Program (NTP, 1992; Bryant et al., 1992; IRDC, 1982a,b). In the subchronic study, which was designed to provide data for selecting dose levels for the chronic bioassay, F344 rats and B6C3F_1 mice (10/sex/dose) were administered chloroacetic acid (99% pure) by gavage in deionized water 5 days/week for 13 weeks. Satellite groups of 5 rats and 5 mice per sex and dose were sacrificed after 4 and 8 weeks of treatment (a total of 20 rats and mice per sex and dose were used in the studies). Rats and mice were administered chloroacetic acid in deionized water at 0, 30, 60, 90, 120, or 150 mg/kg-day, and 0, 25, 50, 100, 150, or 200 mg/kg-day, respectively. The following parameters were evaluated: clinical signs of toxicity (twice daily), mortality, body weight, organ weight (brain, heart, kidney, liver, lung, right testis, and thymus [rats and mice], adrenal gland [rats only], and gall bladder [mice only]), gross pathology, clinical chemistry (sodium, potassium, calcium, chloride [rats], phosphorus [rats], blood urea nitrogen [BUN], creatinine [rats], total bilirubin [rats], aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase, total protein, albumin, albumin-globulin ratio, cholinesterase, ornithine carbamyl transferase [rats], sorbitol dehydrogenase, triiodothyronine, and thyroxin [T4] at Weeks 4, 8, and 13), hematology (erythrocyte count, leukocyte count [and differential], hematocrit, hemoglobin, mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, and methemoglobin at Weeks 4, 8, and 13), urinalysis (color, appearance, specific gravity, pH, protein, glucose, occult blood, nitrites, urobilinogen, ketones, and bilirubin), and histopathology examination of 36 tissues in all animals that died early, in rats dosed at 0, 30 (heart, lung with bronchi, and liver only), 60, 90, 120, or 150 mg/kg-day, and mice dosed at 0 or 200 mg/kg.

In rats, mortality rates at 0, 30, 60, 90, 120, and 150 mg/kg-day were 0/10, 0/10, 2/10, 9/10, 13/13, and 15/15 in males and 0/10, 1/10, 1/10, 10/10, 15/15, and 17/17 in females, respectively (NTP, 1992). Only deaths at $\geq$90 mg/kg-day were considered related to treatment (IRDC, 1982a). Clinical signs of toxicity included unspecified incidences of rattled breathing or respiratory congestion in all treated groups (IRDC, 1982a). There were no biologically significant changes in mean body weight throughout the study. Hematology and clinical

chemistry evaluations were performed at 4, 8 and 13 weeks. Clinical pathology data, however, were not evaluated at 150 mg/kg-day in males or at 120 or 150 mg/kg-day in females at the 8-week evaluations or at 90, 120, or 150 mg/kg-day in males or females at the 13-week evaluations due to excessive mortality. All dose groups were evaluated at the 4-week evaluations. Changes in hematology parameters consistent with dehydration (increased hematocrit values, hemoglobin concentrations, and erythrocyte counts) were observed in males at 150 mg/kg-day (4-week evaluation) (NTP, 1992). Similarly, increased red blood cell counts in females dosed at 90 mg/kg-day (8-week evaluation) were also attributed to mild dehydration. Water consumption values were not reported. Significant increases in segmented neutrophils observed in males at $\geq$90 mg/kg-day (4-week evaluation) and significant decreases in lymphocyte counts at $\geq$30 mg/kg-day (8-week evaluation) were attributed to stress.

A significant dose-related increase in BUN was observed in both males and females at 4 and 8 weeks. When compared with controls, BUN was significantly elevated in males at $\geq$90 mg/kg-day and in females at $\geq$60 mg/kg-day at the 4- and 8-week evaluations (NTP, 1992). Increased BUN was considered a secondary effect caused by decreased renal perfusion from cardiovascular failure, dehydration, or protein catabolism. Significant dose-related increases in ALT activity were observed in males and females at 4 and 8 weeks. When compared with controls, serum ALT activity was significantly elevated in males at 150 mg/kg-day (4-week evaluation) and females at 60 (4- and 8-week), 120, and 150 mg/kg-day at the 4-week evaluation. Significant dose-related trends in AST activity were observed at 4 and 8 weeks in males and at 4 weeks in females. When compared with controls, serum AST levels were significantly increased in males and females at 150 mg/kg-day (4-week evaluation). Elevated AST activity was considered indicative of either hepatocellular or cardiac muscle damage. Significant dose-related decreases in cholinesterase activity were observed at 8 and 13 weeks in males and at 4, 8, and 13 weeks in females. When compared with controls, serum cholinesterase activity in females was significantly decreased at $\geq$30 mg/kg-day (4- and 8-week evaluations) and at 60 mg/kg-day after 13 weeks, and in males at $\geq$30 mg/kg-day at the 13-week evaluation. T4 was significantly greater than controls in males at $\geq$90 mg/kg-day at 4 and 8 weeks. The researchers speculated that the effect on T4 may have been caused by a disruption in the tricarboxylic acid cycle, causing caloric deprivation. Significant dose-related trends were observed at 4 and 8 weeks in males and at 8 weeks in females. No effects were observed on urinalysis indices.

Statistically significant alterations in absolute or relative organ weights occurred in several dose groups; these included decreased relative heart weight in females at 30 and 60 mg/kg-day and males at 60 mg/kg-day, decreased absolute heart weight at 60 mg/kg-day in males and females, and significantly decreased absolute adrenal weight at 60 mg/kg-day in males (NTP, 1992). Decreased absolute and relative heart weights observed in this study may indicate treatment-related effects, because the heart has been shown to be a target organ for chloroacetic acid. Relative liver and kidney weights were significantly greater than controls at 30 and 60

mg/kg-day in males, relative liver weights were significantly greater than controls at 60 mg/kg-day in females, and absolute liver weights were significantly increased in males at 60 mg/kg-day. These effects were considered to be related to chronic congestion (IRDC, 1982a). Gross pathologic alterations in rats, which were considered secondary to myocarditis, included lung congestion and presence of clear/red fluid or blood in the thoracic cavity in rats that died early (IRDC, 1982a; NTP, 1992). Microscopic examinations revealed increased incidences of cardiomyopathy in males and females at ≥60 mg/kg-day. The incidence at 0, 30, 60, 90, 120, or 150 mg/kg-day was 0/10, 0/10, 5/10, 9/9, 13/13, and 15/15, respectively, in males and 0/10, 0/10, 6/9, 10/10, 15/15, and 17/17, respectively, in females. The incidence at ≥60 mg/kg-day was statistically significantly greater than control in both males and females. There appears to be a discrepancy between the incidences reported in the IRDC report and the NTP report. IRDC reported observing myocarditis in one low-dose male and female. Mild to severe multifocal or diffuse acute passive congestion in the lungs was observed in rats that died early, but not in rats that survived until terminal sacrifice. The lung congestion was considered to be secondary to myocardial failure.

Overall, the study appeared sufficient to evaluate the subchronic toxicity of chloroacetic acid in rats, although microscopic evaluations of most tissues were not conducted on low-dose rats (NTP, 1992). The results suggest that the heart and liver, and possibly the kidneys are target organs. The heart was the most obvious target for chloroacetic acid. The incidence of cardiomyopathy was significantly increased at ≥60 mg/kg-day in both males and females. Increased serum AST at high doses is also consistent with cardiac toxicity. Decreases in heart weight were probably treatment-related and were the most sensitive measure of cardiac toxicity, occurring even at the low dose of 30 mg/kg-day. Liver lesions were not observed, but hepatotoxicity is suggested by serum chemistry changes (increased ALT and T4, decreased cholinesterase) and increased liver weight. The most sensitive of these effects were seen at the low dose of 30 mg/kg-day. Renal effects are suggested by increased kidney weight (as low as 30 mg/kg-day) and increased BUN, which occurred only at higher doses and may have been secondary to cardiac toxicity. The low dose of 30 mg/kg-day was, therefore, a LOAEL in this study for effects on the heart, liver and kidney. A NOAEL was not established.

An additional pilot study also was conducted that evaluated effects of chloroacetic acid treatment on mitochondrial aconitase activity in female rats (3 rats/dose) administered a single dose of chloroacetic acid at 24, 48, or 96 mg/kg-day (NTP, 1992). Heart (but not liver) mitochondrial aconitase activity was inhibited in the pilot study at ≥24 mg/kg-day. These data provide a potential mechanism of heart-induced toxicity of chloroacetic acid. It is not clear if aconitase activity provides a sensitive endpoint for chloroacetic acid toxicity, because the doses evaluated for the pilot study are not substantially different than those studied in the main study.

In mice, treatment-related mortality occurred at 200 mg/kg-day in both sexes (NTP, 1992). Mortality at study termination at 0, 25, 50, 100, 150, and 200 mg/kg-day was 2/10, 0/10,

0/10, 0/10, 0/10, and 10/10 in males, and 0/10, 0/10, 0/10, 1/10, 0/10, and 2/10 in females, respectively. Most of the deaths occurred before the fourth week; the death of the female mouse at 100 mg/kg-day was attributed to gavage injury. Body weights of female mice dosed at 200 mg/kg-day were 10% lower than controls after 13 weeks of treatment; the difference was statistically significant ($p<0.05$). A significant dose-related decrease in cholinesterase activity was observed at 8 and 13 weeks in females. Mean values at ≥150 mg/kg-day were significantly less than controls. There were no other compound-related effects on other mean clinical chemistry indices or on any hematology or urinalysis indices evaluated. Absolute and relative liver weights were significantly greater than controls in females at 200 mg/kg-day. No effects on macroscopic appearance of tissues were observed. No treatment-related microscopic lesions were observed that were considered to be a direct toxicological effect. The cardiac lesions observed in rats were not observed in mice. Overall, the study appeared sufficient to evaluate the subchronic toxicity of chloroacetic acid in mice, although microscopic evaluations were only performed on control and high-dose survivors and all mice that died early. The results suggest that the liver is a target organ in mice, based on the observed decrease in serum cholinesterase and increase in liver weight. The LOAEL was 150 mg/kg-day for decreased cholinesterase activity in females. The NOAEL was 100 mg/kg-day.

Studies also were conducted by NTP as described above, except that chloroacetic acid was administered in corn oil. Results of these studies were not included in the Technical Report published by NTP (NTP, 1992); those data were obtained from IRDC (1982a,b). The results of those studies were similar to the water vehicle studies in both rats and mice. In rats, treatment-related increased mortality was observed at ≥90 mg/kg-day (IRDC, 1982a). Mortality rates were 0/10, 1/10, 1/10, 8/10, 10/10, and 10/10 in males and 0/10, 0/10, 1/10, 8/10, 10/10, and 10/10 in females, respectively. There were no clinical signs of toxicity, and no biologically significant changes in mean body weight throughout the study. IRDC reported that all significant changes in hematology and clinical chemistry indices observed were random and not treatment-related. Statistically significantly increased adrenal weights in males and females at 30, 60, and 90 mg/kg-day were observed. The toxicological significance of the adrenal weight changes is not clear. Increased incidences of microscopic lesions of the adrenals were not observed; however, in the absence of an effect on body weight, the effect on adrenal weight may indicate toxicity. Gross pathologic alterations, which were considered secondary to myocarditis, included lung congestion and presence of clear/red fluid or blood in the thoracic cavity in rats that died early. Microscopic examinations revealed increased incidences of cardiomyopathy in males and females at ≥30 mg/kg-day. Mild to severe multifocal or diffuse acute passive congestion in the lungs was observed in rats that died early, but not in rats that survived until terminal sacrifice. The lung congestion was considered to be secondary to myocardial failure. This study established a LOAEL of 30 mg/kg-day for cardiac toxicity in rats. A NOAEL was not identified.

In mice, mortality rates were similar to those observed when chloroacetic acid was administered in water (IRDC, 1982b). Mortality rates were 0/10, 0/10, 0/10, 0/10, 3/10, and

10/10 in males and 0/10, 0/10, 0/10, 1/10, 0/10, and 7/10 in females, respectively. Most of the deaths occurred before the fourth week; the death of the female mouse at 100 mg/kg-day was attributed to gavage injury. Infrequent signs of toxicity, including piloerection, body tremors, hypoactivity, ataxia, hypothermia, bradycardia, low carriage, prostration, and hypopnea were observed at 200 mg/kg-day. No effects on body weight were observed. There did not appear to be any treatment-related effects on hematology, clinical chemistry, or urinalysis indices. All statistically significant organ weight changes were considered to be within the range of normal biological variability. No effects on macroscopic appearance of tissues were observed, and there were no treatment-related microscopic lesions that were considered to be a direct toxicological effect. The study did not identify any target organs in mice. The 150 mg/kg-day dose was a FEL for treatment-related mortality. No effects were observed at 100 mg/kg-day or lower.

Another oral subchronic study was conducted by Daniel et al. (1991). Male and female Sprague-Dawley rats (10/sex/dose) were administered daily doses (7 days/week) of chloroacetic acid sodium salt in distilled water via oral gavage at 15, 30, 60, or 120 mg/kg-day at a dosing volume of 2 mL/kg for 90 days. The doses correspond to approximately 12, 24, 48, and 96 mg/kg-day of chloroacetic acid. The following parameters were evaluated for treatment-related effects: clinical signs of toxicity, body weights (twice weekly and at study initiation and termination), water and food consumption (three times per week), hematology (red and white blood cell counts, hemoglobin, hematocrit, reticulocyte counts, mean corpuscular volume, and differential leukocyte count), clinical chemistry (BUN, serum calcium and phosphorous, creatinine, total cholesterol, glucose, lactate dehydrogenase, ALT, and AST), complete gross necropsy, organ weights (brain, liver, spleen, lung with lower half of trachea, thymus, kidneys, adrenal gland, heart, and gonads), and microscopic examination of 38 tissues and all gross lesions. Only tissues from control and high-dose animals were microscopically examined, except that target organs (identified in high-dose animals) in animals of all dose groups were microscopically examined (due to high mortality at 120 mg/kg-day, however, 60 mg/kg-day was the highest male dose group evaluated for microscopic pathology). Tissues from 5 control animals per sex (and all surviving high-dose animals) were also subjected to microscopic evaluations.

At 120 mg/kg-day, 8/10 males and 3/10 females died (Daniel et al., 1991). Also, one male each at 15 and 60 mg/kg-day died. Increased early mortality at 120 mg/kg-day was attributed to chemical-induced toxicity. It also appears that mortality at 15 (1/10) and 60 (1/10) mg/kg-day was attributed to chloroacetic acid treatment because the study authors used early mortality at 15 mg/kg-day as supporting evidence of a LOAEL at that dose. No effects on clinical signs of toxicity or body weight were reported. Water consumption at 120 mg/kg-day was greater than controls in males and females, and food consumption was lower than controls in males at 120 mg/kg-day. Statistical analyses were not performed on those data, however, because of low survival. At lower doses, no statistically significant effects on food or water consumption were observed. Hematology analyses indicated that white blood cell counts at ≥ 30

mg/kg-day and segmented neutrophils at ≥60 mg/kg-day were significantly increased (statistical significance was not determined for high-dose males due to decreased survival). Also, monocyte counts were significantly increased in males at 15, 30, and 60 mg/kg-day and were significantly decreased at 15 mg/kg-day in females. Clinical chemistry results suggest effects on the liver and kidney. Indications of liver effects included significantly increased ALT activity at 15 and 30 mg/kg-day in males (ALT was also elevated at 120 mg/kg-day in males, but the data were not statistically evaluated) and at 120 mg/kg-day in females. AST activity in high-dose females also was statistically greater than controls (AST also was elevated at 120 mg/kg-day in males, but the data were not statistically evaluated). Increased AST activity also could represent toxicity to the heart. Evidence of kidney toxicity included statistically significant increases in BUN levels at 15 and 30 mg/kg-day in males and at 120 mg/kg-day in females, increased creatinine levels at ≥15 mg/kg-day in males and at 30 and 60 mg/kg-day in females, increased phosphate levels at 120 mg/kg-day in females, and increased calcium levels in males at 15 and 30 mg/kg-day.

Gross pathology examinations revealed increased incidences of pale-yellow livers at ≥15 mg/kg-day in males and at 60 and 120 mg/kg-day in females (Daniel et al., 1991). Reddened lungs also were observed in male and female animals that died early (Days 1-3) at 120 mg/kg-day. A statistically significant (P=0.035) trend in the incidence of heart inflammation was observed (pooled male and female data), although the incidence did not achieve statistical significance at any dose group in pair-wise comparison with controls. The incidence at 0, 15, 30, 60, and 120 mg/kg-day was 1/10, 1/10, 3/10, 3/10, and 4/7, respectively, in males and 4/10, 5/9, 6/10, 7/9, and 2/2, respectively, in females. A significant (P≤0.001) dose-related increase in the incidence of chronic nephropathy in the 90-day study also was observed in males that achieved statistical significance at ≥60 mg/kg-day (high-dose males were excluded from analysis due to high early mortality). The incidence at 0, 15, 30, and 60 mg/kg-day was 3/10, 4/9, 5/10, and 9/9, respectively. A significant dose-related trend (P=0.013) also was observed in the incidence of hepatocytic vacuolated foci in males, although the incidence was not significant at any dose in pair-wise comparison with controls. The incidence at 0, 15, 30, and 60 mg/kg-day was 0/10, 0/10, 1/10, and 3/9. A significant dose-related trend (P<0.001) also was observed in the incidence of splenic pigments in males that achieved statistical significance at 60 mg/kg-day when compared with controls. Incidence of this lesion at 0, 15, 30, and 60 mg/kg-day was 2/10, 1/9, 6/10, and 9/9, respectively. Congestion and hemorrhage of the lungs was observed in treated animals that died early (particularly at the two highest male and the highest female dose groups), but was not observed in surviving animals.

Overall, there were no serious deficiencies in the study design or conduct that are expected to substantially affect the sensitivity of the study but a high incidence of heart inflammation (4/10) in untreated females and chronic nephropathy (3/10), in untreated males, limits the confidence which can be placed in the results. Although the hematology and clinical chemistry evaluations were somewhat limited and urinalysis and ophthalmic examinations were not conducted, an independent 90-day gavage study [NTP, 1992] did not report treatment-related

effects on urinalysis or ophthalmic parameters. In the Daniel et al. (1991) study, a LOAEL of 15 mg/kg-day of chloroacetic acid sodium salt (approximately 12 mg/kg-day of chloroacetic acid) was achieved based on the observation of one early death, discolored livers in males, changes in serum enzymes (BUN, ALT, serum calcium, and creatinine), and significant dose-related trends in incidences of microscopic lesions (cardiac inflammation, chronic nephropathy, hepatocytic vacuolated foci, splenic pigmentation) in males (although statistical significance was not achieved at the low dose for any lesion). A NOAEL was not achieved.

In a subchronic drinking water study (Bhat et al., 1991), five male Sprague-Dawley rats were exposed to chloroacetic acid (>99% pure) at a concentration (1.9 mM) intended to provide a daily dose of 19 mg/kg-day (1/4 the LD50) for 90 days (other chloroacetic acids also were evaluated; those results are not reported in this evaluation). The following parameters were evaluated: body weights, organ weights (unspecified organs, but included the liver and testes), gross pathology (unspecified details), and microscopic pathology on selected tissues (including liver, lung, heart, spleen, thymus, kidneys, testes, pancreas, and brain). Mortality data were not reported, and there were no effects on body weight. A statistically significant (10%) decrease in absolute, but not relative, liver weights compared with controls was observed. The biological significance of the liver weight changes is not clear because results of subchronic gavage studies revealed treatment-related *increases* in liver weights and because relative liver weights were not affected by treatment. No gross lesions were reported. Microscopic examinations revealed minimal to mild collagen deposition, portal vein dilation/extention, fibrosis, edema, and occasional foci of inflammation in the liver (incidence not reported). These observations were generally not observed in controls (except that one control rat was observed with mild collagen deposition). Perivascular inflammation of the lungs also was observed. This lesion was "extremely rare" in controls; incidences were not reported. The study design was limited by the use of only one dose group that contained only 5 males, the lack of clinical chemistry and hematology evaluations, limited histopathology examinations, and lack of dose confirmation. A LOAEL of approximately 19 mg/kg-day was achieved for this study (the only dose evaluated).

A summary of the subchronic effect levels is presented in Table 1. A NOAEL has not been established in rats in any of the available studies. Target organs identified by the subchronic studies include the heart, liver, kidneys, and lungs. The lowest LOAEL observed was 15 mg/kg-day for chloroacetic acid sodium salt, which corresponds to approximately 12 mg/kg-day of chloroacetic acid.

In a 2-year bioassay conducted by the National Toxicology Program (NTP, 1992), 53 F344/N rats and 60 B6C3F_1 mice per sex and dose were administered chloroacetic acid in deionized water via oral gavage 5 days/week for 2 years at 15 or 30 mg/kg-day (rats) or 50 or 100 mg/kg-day (mice). The following toxicological parameters were evaluated in animals treated for 2 years: body weights (recorded once pretest, weekly for 13 weeks, monthly between Week 13 and 21 months, and biweekly thereafter), mortality, clinical signs of toxicity (animals were

observed twice daily for morbidity and mortality, and detailed observations of clinical signs were conducted every 4 weeks), gross pathology, and microscopic pathology of 33 tissues (in addition to all gross lesions and associated lymph nodes). An additional 10 rats per sex and dose were sacrificed after 6 months of treatment (NTP, 1992). A complete necropsy was conducted on those animals, the brain, heart, and right kidney were weighed, and sections of the heart were microscopically examined (the heart was identified as a target organ in the 13-week range-finding study). No other toxicological parameters were evaluated on 6-month interim sacrifice animals. Also, an additional 7 rats per sex and dose were sacrificed after 15 months of treatment. A complete necropsy was conducted on those animals, the brain, heart, right kidney, and liver were weighed, and a microscopic examination of 33 tissues (and all gross lesions with associated lymph nodes) was performed in control and high-dose animals (gross lesions also were microscopically examined at lower doses). In addition, clinical chemistry (alkaline phosphatase, alanine aminotransferase, lactate dehydrogenase, creatine phosphokinase, hydroxybutyrate dehydrogenase, total protein, and albumin) and hematology (leukocyte count [absolute and differential], erythrocyte count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration) parameters were evaluated.

In rats, survival rates at control, low-, and high-dose groups were 53%, 40%, and 32%, respectively, in males and 70%, 38%, and 51%, respectively, in females (NTP, 1992). Increased mortality followed a statistically significant trend in treated males (P=0.011) and females (P=0.043). Pairwise comparisons revealed significantly increased mortality in the high-dose male group (P=0.015) and low- (P=0.001) and high-dose (P=0.046) female groups compared with controls. Increased mortality at all dose groups was attributed by the researchers to chemical toxicity. NTP concluded that survival was adequate for detection of chemical-related neoplasms because over 50% of the animals in all dose groups survived until at least Week 93. Also, appropriate survival-adjusted analyses were used to statistically evaluate tumor incidences. No treatment-related clinical signs of toxicity were observed. The average mean body weight of high-dose males was 5% less than controls for the second year of the study. Final mean body weights of low- and high-dose animals were 5% and 8% less than controls, respectively, in males and were 2% and 3% less than controls, respectively, in females. Statistical significance was not indicated. No treatment-related changes in clinical chemistry or hematology parameters were observed. Statistically significant changes in absolute and relative organ weights were observed at the 6-month interim sacrifice (NTP, 1992). Relative kidney weights of low- and high-dose females and absolute kidney weights of high-dose females were significantly less than controls, and relative kidney weights of high-dose males were significantly greater than controls. Absolute brain weights of low- and high-dose females were significantly less than controls, and relative brain weights of low-dose animals were significantly less than controls. Relative heart weights of high-dose females were significantly greater than controls. No effects on organ weights were observed at the 15-month sacrifice; therefore, it is not clear whether effects seen at 6 months are

Table 1. A Summary of the Effect Levels from the Available Oral Subchronic Studies

Study Citation	Exposure Route	Species Tested	Dose Range (mg/kg-day)	LOAEL (mg/kg-day)	NOAEL (mg/kg-day)	Basis for LOAEL
NTP, 1992; IRDC, 1982a,b	Oral, gavage in water	Rats	30 - 150	30	None	Decreased cholinesterase activity, increased liver and kidney weight, decreased heart weight
		Mice	25 - 200	150	100	Decreased cholinesterase activity
IRDC, 1982a,b	Oral, gavage in corn oil	Rats	30 - 150	30	None	Cardiomyopathy
		Mice	25 - 200	150	100	Mortality
Daniel et al., 1991	Oral, gavage in water	Rats	15 - 120 (salt) 12 - 96 (CA)	15 (salt) 12 (CA)	None	Discolored livers, increased serum enzymes (ALT, BUN, creatinine), possible early mortality
Bhat et al, 1991	Oral, drinking water	Rats	19	19	None	Microscopic lesions in liver and lung
CA = chloroacetic acid						

indicative of chloroacetic acid-induced toxicity. These results also are not consistent with organ weight changes observed in the subchronic study, which observed decreases in absolute and relative heart weights and increases in relative kidney weights.

No treatment-related gross lesions were reported (NTP, 1992). A statistically significant positive trend in incidences of uterine endometrial stromal polyps was observed in females that achieved statistical significance at both dose groups compared with controls (incidence in the control, low, and high-dose group was 1/53, 7/53, and 9/53). NTP concluded that the increased incidences of stromal polyps were not likely treatment-related because the control incidence was unusually low and the incidences in the dose groups were within historical control values (range of 10% to 38%). Small decreases in several common neoplasms (e.g., adrenal medulla, neoplasms of the thyroid C-cells, and mononuclear cell leukemia in males and adenoma of the pituitary pars distalis in males and females) were observed. NTP considered these decreases to be related to decreased survival. Microscopic lesions of the heart had been observed in the subchronic range-finding study in rats, but were not observed in the 2-year bioassay. The lack of

effects on the heart may have been caused by the lower doses employed in the long-term study. Although target organ effects were not found, the low dose of 15 mg/kg-day is a FEL for reduced survival in the female rats. The decrease in survival indicates that the maximum tolerated dose (MTD) was achieved, but also may have limited the sensitivity of the study to detect tumor development. Although NTP concluded that survival was adequate for detection of chemical-related neoplasms (because at least 50% of animals in each group survived to week 93), NTP also conceded that small decreases in incidences of several tumor types in treated animals were probably secondary to reduced survival. The study found no evidence of tumor production by chloroacetic acid in rats.

In mice, a significant ($P<0.001$) positive dose-related trend in mortality was observed in males (NTP, 1992). Survival rates for the control, low-, and high-dose males were 79%, 65%, and 38%, respectively. The decrease in the high-dose group was statistically significant and appeared to be due, at least in part, to chemical-related toxicity. NTP concluded that survival was adequate for detection of chemical-related neoplasms because over 50% of male mice survived until Week 85, even though only 38% of high-dose male mice survived to study termination. Survival of female mice was similar to controls. Appropriate survival-adjusted analyses were used to statistically evaluate tumor incidences. No treatment-related clinical signs of toxicity were observed. Body weights of female mice were consistently 8% to 11% less than controls throughout the second year of the study. Final mean body weights of low- and high-dose animals were 2% and 0% less than controls, respectively, in males and were 2% and 6% less than controls, respectively, in females. Statistical significance was not indicated. NTP concluded that the consistent decrease in body weight of high-dose females represented a treatment-related toxic effect. No treatment-related effects on clinical chemistry or hematology were observed. No treatment-related gross lesions were reported (NTP, 1992). Microscopic pathology revealed a significant increase in the incidence of squamous cell hyperplasia of the forestomach in high-dose males and females that was attributed to the irritant properties of chloroacetic acid. The incidence of this lesion in control, low-, and high-dose groups, respectively, was 5/60, 2/60, and 13/60 in males and 5/60, 8/59, and 15/60 in females. Squamous cell papillomas of the forestomach occurred in two high-dose females (no control or low-dose females were observed with this lesion); however, NTP concluded that the incidence was within historical-control range reported for this type of lesion. Acute nasal inflammation was significantly greater than controls in high-dose males and low- and high-dose females. The incidence of this lesion in control, low-, and high-dose groups, respectively, was 3/60, 7/59, and 24/60 in males and 5/60, 15/60, and 31/60 in females. Increased incidences of metaplasia of the olfactory epithelium also was significantly increased in high-dose females. The incidence of this lesion in control, low-, and high-dose female groups, respectively, was 2/60, 5/60, and 17/60. NTP concluded that the nasal lesions may have resulted from reflux of the gavage solution rather than systemic chloroacetic acid toxicity (NTP, 1992). However, because nasal inflammation was also observed in a 2-year drinking water-exposure study, the nasal lesions observed in this study may be relevant to human exposure (DeAngelo et al., 1997).

No increases in tumor incidences were found (NTP, 1992). A significant dose-related decreasing trend in the incidence of malignant lymphomas was observed in female mice that achieved statistical significance at the high-dose group (incidence of 29/60, 18/60, and 13/60 in the control, low-, and high-dose groups, respectively). A reason for the decrease is not clear. A LOAEL of 50 mg/kg-day in mice (the lowest dose evaluated) appeared to be established for this study based on increased incidences of microscopic lesions of the nasal mucosa in low-dose females. Effects at the higher dose included metaplasia of the olfactory epithelium in females, squamous cell hyperplasia of the forestomach in males and females, reduced body weight in females, and reduced survival in males. Therefore, the maximum tolerated dose appears to have been achieved in mice. Increased early mortality of high-dose male mice could have limited the sensitivity of the study to detect tumor development, but NTP considered survival in all groups to be adequate because 50% or more survived to week 85. The study found no evidence of tumor production by chloroacetic acid in mice.

In a drinking water study, groups of 50 male F344/N rats were exposed to chloroacetic acid (≥99% pure) in drinking water at concentrations of 0.05, 0.5, or 2 g/L (the high concentration was lowered to 1.5 g/L at 8 weeks and 1 g/L at 24 weeks due to excessive toxicity [substantially decreased body weight gains]) for up to 104 weeks (DeAngelo et al., 1997). Between 18 and 21 rats from each group were removed for interim sacrifice at 15, 30, 45, or 60 weeks (unspecified number of animals per sacrifice period). Time-weighted average doses calculated by the researchers were 3.5, 26.1, or 59.9 mg/kg-day. The following parameters were evaluated: mortality, body weights, water consumption, clinical signs of toxicity, clinical pathology (serum AST, ALT, cyanide-insensitive palmitoyl coenzyme A oxidase activity, and hepatocyte proliferation), organ weights (liver, kidneys, spleen, and testes), gross pathology (comprehensive in all animals at terminal sacrifice, but limited to body, liver, kidneys, spleen, urinary bladder, and testes in animals at interim sacrifices), and histopathology (comprehensive in high-dose animals [and apparently controls, although that was not specified] at terminal sacrifice, but limited to the liver, kidneys, spleen, and testes in lower dose animals at terminal sacrifice and interim sacrifice animals at all dose groups).

Survival in treated groups was reported in the text not to be significantly different from controls (DeAngelo et al., 1997). Table 1 of the report shows an apparent increase in unscheduled deaths in the high-dose group (6, 7, 9, and 14 in the control, low-, mid- and high-dose groups, respectively), but contains an error, as the numbers of animals killed at interim sacrifice (21), dying early (14), and killed at terminal sacrifice (25) in the high-dose group add up to 60, rather than group size of 50 listed in the table and reported in the methods section. Group sizes reported for organ weight and histopathology results in Tables 2 and 3 of the report correspond to the numbers given for terminal sacrifice in Table 1. Therefore, it appears that the text is correct in stating that there was no effect of treatment on survival and that the number of animals surviving to terminal sacrifice was 23-25 in all groups, including the high-dose group, as reported in Table 1. Water consumption of mid- and high-dose animals was significantly less

than controls throughout the study. Final mean body weights of mid- and high-dose animals were statistically and biologically significantly less than controls (final mean body weights of mid- and high-dose animals were 13% and 38% lower than controls, respectively). No effects were observed on the limited clinical pathology parameters evaluated. Analysis of organ weight data is complicated by the substantially decreased body weights in the mid- and high-dose groups. In these groups, absolute and relative liver weights were significantly less than controls, relative testes weights were significantly greater than controls, and absolute kidney weights were significantly less than controls. Also, absolute and relative spleen weights were significantly increased at the low dose (absolute spleen weights at the mid- and high-doses were less than controls, possibly due to decreased body weights). These effects may have been caused by decreased body weights.

Increased incidences of myocardial degeneration and inflammation of the nasal cavities of high-dose rats were observed at 104 weeks compared with controls (incidence not reported) that exceeded historical-control values for Fischer rats (although values in the historical-control database were not obtained from the testing laboratory) (DeAngelo et al., 1997). It did not appear that the heart or nasal cavity was microscopically examined at lower doses. Increased incidences of chronic liver inflammation were observed that were not considered treatment related. Incidence data were not reported, and the study authors did not specify why the lesions were not considered treatment related. No treatment-related increase in neoplasms was observed. Although no effects were observed at the low dose, study design limitations (particularly the absence of a microscopic examination of tissues other than liver, kidneys, spleen, and testes from low- and mid-dose animals, regardless of the presence of lesions in the high-dose group) preclude derivation of reliable chronic NOAEL or LOAEL values. The body weight data indicate that the MTD was achieved at the mid dose and exceeded at the high dose. Sufficient numbers of animals survived to terminal sacrifice in all groups for evaluation of tumor data. No increase in tumor incidence was seen in any group.

An older study included groups of 18 $B6C3F_1$ and 18 $B6AKF_1$ mice/sex that were administered chloroacetic acid in distilled water by stomach tube daily at 46.4 mg/kg from days 7-28 of age (BRL, 1968). The mice were subsequently treated in the diet at a concentration of 149 ppm for 78 weeks. Dose selection was based on prechronic studies; the dose was not adjusted to changing body weight during the 3 weeks of gavage treatment, but a single adjustment was made at the time of conversion from stomach tube to incorporation in the feed. Based on U.S. EPA (1988b) reference values, the daily dose during the feeding part of the study was approximately 25.6 mg/kg-day. Four untreated groups and 1 gelatin treated group containing 18 mice/strain/sex each served as controls. Following the treatment period, all surviving mice were dissected and examined grossly, and tissue samples from the chest contents, liver, spleen, kidneys, adrenals, stomach, intestines, and genitals were examined microscopically. Mice that were sacrificed when moribund were subjected to gross pathologic examinations, but histological examinations were performed only when deemed appropriate (criteria not specified).

At least 15 treated mice per strain survived to the end of the study. No statistically significant ($p<0.05$) increases in tumor incidences were found when any group or combination of treated groups was compared with individual or pooled control groups.

A summary of effect levels from the chronic oral studies is reported in Table 2. Effect levels suitable for use in risk assessment cannot be derived based on the available studies. In the study conducted by NTP, increased incidences of early mortality was observed at all dose levels in the most sensitive species tested, thus precluding the use of chronic RfD derivation. The study conducted by BRL was not adequate based on the limited histopathology evaluation and the lack of clinical pathology examinations.

Ten sexually mature female Hsd:Sprague Dawley SD rats were exposed to chloroacetic acid in the drinking water throughout pregnancy (Days 1 - 22 of pregnancy) at 1570 ppm (193 mg/kg-day) (Johnson et al., 1998). Controls (N=55) were given distilled water. On Day 22 of gestation, all rats were sacrificed and examined for external and internal abnormalities, and the gravid uterus was removed and opened. The number of implantation sites and resorption sites were tabulated, and fetuses and placentas were examined *in situ*, removed, and individually examined, and the ovaries were removed. The following parameters were evaluated: fetal placements, weights, placental weights, crown rump lengths, and gross fetal abnormalities. Congenital abnormalities were examined in abdominal organs, and the heart was examined *in situ*, removed and microscopically examined for abnormalities (the great arterial and venous connections also were inspected). There were no treatment-related effects on any parameter evaluated, although the scope of parameters evaluated was somewhat limited compared with standard guidelines for developmental toxicity studies.

Data on the developmental toxicity of chloroacetic acid were reported in a study abstract (Smith et al., 1990). A full report does not appear to be available in the publically available literature. Chloroacetic acid in distilled water was administered to pregnant Long-Evans rats on gestation days 6-15 via oral gavage at 17, 35, 70, or 140 mg/kg-day. The following maternal toxicity endpoints were evaluated: clinical signs of toxicity, body weight change, gross pathology of unspecified tissues, and uterine contents at necropsy. Toxicity to live fetuses was determined by external, skeletal, and soft-tissue malformations (additional details were not provided). Maternal body weight gains were significantly less than controls at the high dose. The mean soft tissue malformation frequency was elevated at 140 mg/kg-day compared with controls (incidence was 6.37% at the high dose, but was not reported for lower doses); however, a clear, consistent dose-related trend was not observed. Incidences of cardiovascular malformations were significantly greater than controls at 140 mg/kg-day (including levocardia). The maternal and developmental LOAEL was 140 mg/kg-day, and the maternal and developmental NOAEL was 70 mg/kg-day.

Table 2. A Summary of the Effect Levels from the Available Chronic Oral Studies

Study Citation	Exposure Route	Species Tested	Doses (mg/kg-day)	LOAEL (mg/kg-day)	NOAEL (mg/kg-day)	Basis for LOAEL	Neoplasms
NTP, 1992	Oral, gavage	Rats	15 or 30	15	None	Increased mortality	None
		Mice	50 or 100	50	None	Microscopic lesions of the nasal mucosa	None
DeAngelo et al., 1997	Oral, drinking water	Rats	3.5, 26.1, or 59.9	N/A	N/A	N/A	None
BRL, 1968	Oral, gavage and diet	Mice	46.4 from age 7-28, then 25.6	N/A	N/A	N/A	None
N/A = precluded by study design							

An English summary of a Russian study (Maksimov and Dubinina, 1974) reported that chronic inhalation of chloroacetic acid caused weight reduction, decreased oxygen uptake and rectal temperature, hemoglobinemia and inflammatory changes in the respiratory organs of rats and guinea pigs at $\geq$ 5.8 mg/m^3. Additional information regarding the design and results of this study was not reported in the summary (U.S. EPA, 1988a).

Dermal chloroacetic acid exposure (2 mg, 3 times/week for life) to 50 female IcR/Ha mice did not result in significant increases in tumor incidences (Van Duuren et al., 1974), although study adequacy could not be evaluated based on lack of experimental design details. Also, Van Duuren et al. (1974) reported observing sarcomas at the application site in 3 out of 50 IcR/Ha mice administered 0.5 mg s.c. injections of chloroacetic acid weekly for life, versus 0/50 in controls. Four of 18 treated B6C3F1 mice administered a single s.c. injection of chloroacetic acid and monitored for 78 weeks were observed with hepatomas; however, control incidences were not reported (BRL, 1968). Identically treated B6AKF1 mice did not develop hepatomas. The increase was not statistically significant and was not clearly associated with chloroacetic acid treatment.

Other Studies

Chloroacetic acid was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98, with or without exogenous metabolic activation, but was mutagenic in

cultured mammalian (L5178Y) cells *in vitro* (NTP, 1992). Chloroacetic acid induced sister chromatid exchanges in Chinese hamster ovary cells and produced positive results in an *in vivo* chromosome aberrations assay (NTP, 1992; Bhunya and Das, 1987). However, chloroacetic acid did not produce chromosome aberrations in Chinese hamster ovary cells *in vitro*, with or without metabolic activation (NTP, 1992). Chloroacetic acid was positive in an *in vivo* sperm abnormality assay in mice (Bhunya and Das, 1987). Chloroacetic acid administered in feed was negative for the induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster*; however, equivocal results were obtained when the test substance was administered by injection (NTP, 1992). These data suggest that chloroacetic acid has some genotoxic potential.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR CHLOROACETIC ACID

Critical effect levels from subchronic and chronic oral studies of chloroacetic acid are shown in Tables 1 and 2, respectively. The subchronic studies identified the heart, liver, and kidneys as targets of chloroacetic acid in laboratory animals (NTP, 1992; IRDC, 1982a,b; Daniel et al., 1991; Bhat et al., 1991). These organs are also among the targets that have been identified in humans following acute exposure to high doses of chloroacetic acid (Feldhaus et al., 1993; Rogers, 1995; Kulling et al., 1992). No human data are available for repeated exposure to lower doses of the chemical. In the animal studies, rats were considerably more sensitive to chloroacetic acid than mice. Gavage studies in mice (corn oil or water vehicle) found no effects at doses up to 100 mg/kg-day, with the first indication of toxicity being decreased serum cholinesterase activity at 150 mg/kg-day when tested with water vehicle (NTP, 1992) or increased mortality at 150 mg/kg-day when tested with corn oil vehicle (IRDC, 1982b). NOAEL values were not identified in any of the rat studies. The lowest dose tested produced effects in each of the studies (cardiomyopathy at 30 mg/kg-day in the corn oil gavage study [IRDC, 1982a], decreased serum cholinesterase activity and heart weight and increased liver and kidney weights at 30 mg/kg-day in the water gavage study by NTP [1992], liver pathology and serum enzyme markers of liver and kidney toxicity at 12 mg/kg-day in the water gavage study by Daniel et al. [1991], and liver and lung histopathology at 19 mg/kg-day in the drinking water study [Bhat et al., 1991]). The lowest LOAEL was 12 mg/kg-day in the study by Daniel et al. (1991).

Developmental toxicity was studied in two strains of rat. No fetal effects were observed in a limited study of Sprague-Dawley rats at 193 mg/kg-day (Johnson et al., 1998). The other study, available only as an abstract (Smith et al., 1990), reported an increased incidence of cardiovascular malformations, but only at a high dose that also produced maternal toxicity (140 mg/kg-day, with a NOAEL of 70 mg/kg-day). These results suggest that the developing fetus is not a sensitive target for chloroacetic acid. Studies of reproductive toxicity were not located in the available literature.

The data do not support derivation of a provisional subchronic RfD for chloroacetic acid. Confidence in the overall database is low-to-medium because, although several subchronic studies on chloroacetic acid are available, there are no available reproductive toxicity studies, and developmental studies, available for only one species, were limited by deficiencies in study design or reporting. Although the LOAEL of 12 mg/kg-day in the Daniel et al. (1991) study is the most sensitive effect level identified, the high incidence of heart inflammation (4/10) in untreated females and chronic nephropathy (3/10) in untreated male control rats limits the confidence which can be placed in the results. Furthermore, the unexplained death of a male rat at the LOAEL suggests that 12 mg/kg-day could be considered to be an adverse effect. That concern is supported by the NTP (1992) 2-year study with rats which reported reduced survival at an exposure level of 15 mg/kg-day. The subchronic LOAEL (30 mg/kg-day) identified in the NTP (1992) study was considered too close to the chronic FEL of 15 mg/kg-day which cause reduced survival in male rats. Because none of the subchronic studies cited here has identified a NOAEL or an unequivocal LOAEL that was not associated with mortality, an RfD for subchronic exposure cannot be derived for chloroacetic acid.

The data do not support derivation of a provisional chronic RfD for chloroacetic acid. The lowest dose tested in the NTP (1992) study, 15 mg/kg-day, was a FEL that produced decreased survival in treated rats. DeAngelo et al. (1997) included a lower dose level in their study, and found no effect on survival, but the study could not be used to derive a NOAEL or LOAEL because there was no histopathological examination of the heart and nasal cavity in the two lower dose groups, even though both of these tissues were identified as targets in the histopathological examination of the high-dose group. Nasal lesions were the most sensitive target in mice in the NTP (1992) study and occurred at the lowest dose tested (50 mg/kg-day), but the doses used in this species were considerably higher than in rats. The only other chronic study available (BRL, 1968) was conducted at a high dose and did not provide any information regarding nonneoplastic endpoints. The subchronic data in the NTP (1992) study could not be used to derive a chronic RfD due to the proximity of the subchronic LOAEL (30 mg/kg-day) to the chronic FEL (15 mg/kg-day; 10.7 mg/kg-day adjusted for intermittent dosing).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR CHLOROACETIC ACID

No adequate human or animal data are available regarding the toxicity of chloroacetic acid following subchronic or chronic inhalation exposure, precluding derivation of p-RfC values for this substance.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR CHLOROACETIC ACID

There are no data on the carcinogenicity of chloroacetic acid in humans. Cancer bioassays in rats and mice exposed via gavage or drinking water have provided no evidence that chloroacetic acid produces tumors (NTP, 1992; DeAngelo et al., 1997; BRL, 1968). There is some question as to interpretation of these studies, however. Increased early mortality of high-dose male rats, low- and high-dose female rats, and high-dose male mice in the NTP study appears to have limited the sensitivity of the study to detect tumor development, which is supported by the observation of marginal decreases in incidences of several tumor types in treated animals. Furthermore, the study by DeAngelo et al. (1997) was not adequately designed to characterize the carcinogenicity of chloroacetic acid because all tissues from animals at the low- and mid-dose groups were not subjected to a microscopic examination even when lesions were observed at higher doses. Because tumor development may have been affected by the severe decreases in body weight (38%) at the high dose compared with controls, microscopic evaluation at lower doses (where the decrease in body weight was less severe) may have provided useful data regarding the tumorigenic capability of chloroacetic acid. The study by BRL (1968) included small group sizes, considerably less than lifetime exposure, and only limited histopathological examination. Dermal and subcutaneous injection cancer studies found no evidence for tumorigenicity of chloroacetic acid (Van Duuren et al., 1974; BRL, 1968), but were not adequate bioassays. There is some evidence from genotoxicity studies that chloroacetic acid has potential to produce genetic effects. Chloroacetic acid has been shown to induce forward mutations in L5178Y cells *in vitro* and sister chromatid exchanges in Chinese hamster ovary cells (NTP, 1992). Chloroacetic acid also was positive in an *in vivo* sperm abnormality assay in mice and produced positive results in an *in vivo* chromosome aberrations assay (NTP, 1992; Bhunya and Das, 1987). Due to questions regarding interpretation of the negative cancer bioassays available for chloroacetic acid, and data indicating that the chemical has some genotoxic potential, the negative bioassays are not considered to represent sufficient evidence of noncarcinogenicity. Therefore, under the proposed U.S. EPA (1999) cancer guidelines, *the available data are inadequate for an assessment of human carcinogenic potential*.

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