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Provisional Peer-Reviewed Toxicity Values for

Bromochloromethane
(CASRN 74-97-5)

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

COMMONLY USED ABBREVIATIONS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR BROMOCHLOROMETHANE (CASRN 74-97-5)

Background

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

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

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

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

Disclaimers

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

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

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

INTRODUCTION

IRIS (U.S. EPA, 2008) does not report an RfD or RfC for bromochloromethane. The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) includes a Health and Environmental Effects Profile (HEEP) (U.S. EPA, 1985), a Health and Environmental Effects Document (HEED) (U.S. EPA, 1990), and a Drinking Water Health Advisory (DWHA; U.S. EPA, 1989) for bromochloromethane. Although the HEEP (U.S. EPA, 1985) concluded that data were inadequate to support quantitative risk assessment, the HEED (U.S. EPA, 1990) subchronic and chronic oral RfD values (1 and 0.1 mg/kg-day, respectively) were derived by route-to-route extrapolation from inhalation data using a model no longer recommended for long-term steady-state exposures. The DWHA derived a chronic oral RfD of 0.01 mg/kg-day from the same inhalation data used by the HEED—but with a UF of 10,000 rather than 1000. The DWHA RfD of 0.01 mg/kg-day is included on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Agency for Toxic Substances and Disease Registry (ATSDR, 2008) has not produced a Toxicological Profile for bromochloromethane, and no Environmental Health Criteria Document is available from the World Health Organization (WHO, 2008). The American Conference of Governmental Industrial Hygienists (ACGIH, 2007) recommends a Threshold Limit Value (TLV) of 200 ppm for bromochloromethane based on CNS effects. The National Institute of Occupational Safety and Health (NIOSH) recommended exposure limit (REL) and the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) are also 200 ppm (1050 mg/m^3) (NIOSH, 2005; OSHA, 2008). On IRIS (U.S. EPA, 2008), bromochloromethane is assigned to cancer Weight-of-Evidence Group D (not classifiable as to human carcinogenicity) based on inadequate human and animal data. The source document for this assessment, which was verified 01/10/1991, is the HEED (U.S. EPA, 1990). The carcinogenicity of bromochloromethane has not been assessed by the International Agency for Research on Cancer (IARC, 2008) or the National Toxicology Program (NTP, 2005, 2008).

Literature searches were conducted from the 1960s through December 2007 for studies relevant to the derivation of provisional toxicity values for bromochloromethane. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS, TSCATS/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. An updated literature search was conducted using PubMed through November 2008.

REVIEW OF PERTINENT DATA

Human Studies

Three male firefighters who used bromochloromethane as a fire-extinguishing agent reported gastrointestinal disturbances (e.g., vomiting, stomach pains) and manifestations of CNS involvement (e.g., headache, loss of consciousness) (Rutstein, 1963).

Animal Studies

Oral Exposure

No information was located regarding effects of subchronic or chronic oral exposure to bromochloromethane in laboratory animals.

Inhalation Exposure

Torkelson et al. (1960) exposed groups of 20 male and 20 female rats (strain not reported) to nominal bromochloromethane concentrations of 0, 500, or 1000 ppm for 7 hours/day, 5 days/week, for 79−82 exposures in 114 days. The actual average concentrations were 490 ppm (2593 mg/m^3) and 1010 ppm (5345 mg/m^3). Appearance, activity, body-weight gain, and survival were evaluated throughout treatment. Gross pathology, relative organ weights (lungs, heart, liver, kidneys, spleen, and testes), and histopathology (organs that were weighed, pancreas and adrenals) were evaluated at termination. Hematological evaluations of 10 females exposed to 0 or 1010 ppm and blood bromide and blood nitrogen (urea nitrogen and nonprotein nitrogen) determinations of 3 rats/sex from all groups were also conducted at termination. Although not reported as statistically significant, mean body weight was reduced 10−12% in both groups of treated male rats relative to controls. At 490 and 1010 ppm, relative liver weight was increased in males (12.6 and 30.1% higher than controls) and females (14.2 and 36.7% higher than controls). Other effects attributed to treatment include liver histopathology in females at 490 ppm (slight bile duct epithelial proliferation, slight portal fibrosis, occasional vacuolization) and both sexes at 1010 ppm (effects similar to those at 490 ppm, as well as cloudy swelling and frequent vacuolization), and increased relative kidney weights in both sexes at 1010 ppm. Incidences of liver lesions were not reported. Blood bromide levels were elevated in both sexes at both exposure concentrations, but the effects typical of bromism (apathy, obesity, inactivity) were not observed. Based on increased liver weight and liver histopathology, this study identifies a LOAEL of 490 ppm (2593 mg/m^3) and no NOAEL in rats.

Torkelson et al. (1960) also exposed groups of 10 female rats (strain not reported) to nominal bromochloromethane concentrations of 0 or 400 ppm for 7 hours/day, 5 days/week, for 135 exposures in 195 days. The actual average concentration was 370 ppm (1958 mg/m^3). Air-exposed and unexposed control groups were used. Evaluations of appearance, activity, body weight, survival, pathology, blood bromide and blood nitrogen were conducted as in the 114-day rat study. Hematological examinations were not performed. The only reported effect was an increase in relative liver weight (10.4% higher than unexposed controls). This study establishes a LOAEL of 370 ppm (1958 mg/m^3) based on increased relative liver weight and no NOAEL in rats.

Torkelson et al. (1960) also exposed groups of 10 female mice (strain not reported) to bromochloromethane at 0, 490, or 1010 ppm (2593 or 5345 mg/m^3) for 7 hours/day, 5 days/week, for 79−82 exposures in 114 days. Evaluations of appearance, activity, body

weight, survival and pathology were conducted as in the 114-day rat study. Blood bromide and blood nitrogen determinations and hematological examinations were not performed. Decreased body weight and increased relative liver and kidney weights occurred at exposures ≥490 ppm. Final average body weight in the 490- and 1010-ppm female mice was 26.7 and 10.0% less than controls, respectively. Relative liver weight in the 490- and 1010-ppm female mice was 20.8 and 37.8% higher than controls, respectively. Relative kidney weight was increased 25% relative to controls in both the 490- and 1010-ppm female mice. No microscopic lesions were observed in either liver or kidneys. Based on decreased body weight, and increased relative liver and kidney weights, this study identifies a LOAEL of 490 ppm (2593 mg/m^3) and no NOAEL in mice.

Torkelson et al. (1960) also exposed groups of 10 male and 10 female guinea pigs (strain not reported) to bromochloromethane at 0, 490, or 1010 ppm (2593 or 5345 mg/m^3) for 7 hours/day, 5 days/week, for 79−82 exposures in 114 days. Evaluations of appearance, activity, body weight, survival, and pathology were conducted as in the 114-day rat study. Hematological examinations were conducted on 3 females from each group. Final body weight was decreased at 490 and 1010 ppm in males (16.8 and 18.8% less than controls) and females (8.4 and 12.8% less than controls). Other effects attributed to treatment included increased relative liver weight in both sexes at ≥490 ppm, increased relative kidney weight in males at ≥490 ppm, increased number of circulating leukocytes (primarily neutrophils; additional details not reported) in females at ≥490 ppm, and testicular effects in males at 1010 ppm. The testicular effects include reduced relative testes weight and histopathological changes consisting of decreased spermatogenesis in the tubules and fibrosis in numerous tubules with only germinal epithelium remaining in the other tubules. No microscopic lesions were observed in either liver or kidneys. Blood bromide levels were elevated in both sexes at both exposure concentrations. Based on reduced body weight, increased relative liver and kidney weights and neutrophilia, this study identifies a LOAEL of 490 ppm (2593 mg/m^3) and no NOAEL in guinea pigs.

Torkelson et al. (1960) also exposed groups of 2 male and 2 female rabbits (strain not reported) to bromochloromethane at 0, 490, or 1010 ppm (2593 or 5345 mg/m^3) for 7 hours/day, 5 days/week, for 79−82 exposures in 114 days. Evaluations of appearance, activity, body weight, survival and pathology were conducted as in the 114-day rat study. Blood bromide and blood nitrogen were determined in all rabbits except one 490-ppm female. Hematological examinations were not performed. Liver weights appeared to be elevated in both sexes at both exposure concentrations, but the small number of rabbits precluded definitive analysis. Results of the blood-nitrogen determinations were not reported. The histological examinations showed testicular changes (decreased spermatogenesis with replacement fibrosis in the tubules) in one of the males at 1010 ppm. Blood-bromide levels were elevated in both sexes at both exposure levels. The small number of animals precludes identification of a NOAEL or LOAEL.

Torkelson et al. (1960) also exposed one male and one female dog (strain not reported) to bromochloromethane at 0 or 370 ppm (1958 mg/m^3) for 7 hours/day, 5 days/week, for 135 exposures in 195 days. Evaluations of appearance, activity, body weight, survival, blood bromide, blood nitrogen, and hematology were conducted as in the 114-day rat study. Pathological examinations were not performed. The only reported effect was elevated blood bromide levels. The small number of animals and lack of histopathology data preclude identification of a NOAEL or LOAEL.

MacEwen et al. (1966) exposed groups of 50 male and 50 female albino rats (descendants of germ-free Wistar rats) to nominal bromochloromethane concentrations of 500 or 1000 ppm for 6 hours/day, 5 days/week, for a total of 124 exposures conducted over 6 months. Actual measured concentrations averaged 515 and 1010 ppm (2725 and 5345 mg/m^3). There were 50 chamber-air-exposed male rats that served as controls; no female controls were used. Body weight, survival, and serum bromide levels were evaluated throughout the treatment period. After 2 and 4 months of exposure, groups of 10 rats in each treatment group and 5 control rats were subjected to white blood cell count and clinical chemistry determinations and sacrificed for organ weight and histological examinations. These endpoints were evaluated in the remaining rats at termination of treatment. The clinical chemistry tests consisted of serum aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT), total protein, albumin, and albumin/globulin (A/G) ratio. It is not specified whether organs other than liver, kidneys, and spleen were weighed and histologically examined. The only effect observed was significantly decreased body-weight gain in male rats exposed to concentrations ≥515 ppm, the magnitude of which increased with dose and duration of exposure. Final average body weight in the male rats was 9.5 and 12.8% lower than controls at 515 and 1010 ppm, respectively. Blood bromide levels were increased at both exposure concentrations throughout the treatment period. The investigators indicated that similar levels of blood bromide in humans may produce mild sedation. The investigators also suggested that lethargy (observed during the first few weeks of the study), altered eating habits, and altered metabolic activity may have been responsible for the reduction in body-weight gain. Based on reduced body-weight gain, this study identifies a LOAEL of 515 ppm (2725 mg/m^3) and no NOAEL in rats. However, chronic murine pneumonia was a prominent finding in both treated and control rats and may have had an effect on the reported findings.

MacEwen et al. (1966) also exposed groups of 4 male and 4 female beagle dogs to 0, 515, or 1010 ppm (2725 and 5345 mg/m^3) for 6 hours/day, 5 days/week, for a total of 124 exposures conducted over 6 months. Toxicity was evaluated, as in the rat study, with the addition of other clinical chemistry tests (serum LDH, sodium, potassium, and calcium). Evaluations were performed on two treated and one control dog (sex not specified), after 2 and 4 months, and on the remaining dogs at termination of treatment. The only effect attributable to treatment was increased serum bromide levels at both concentrations. This study identifies a NOAEL of 1010 ppm (5345 mg/m^3) and no LOAEL in dogs.

Svirbely et al. (1947) exposed groups of 20 male rats (strain not reported) to a nominal bromochloromethane concentration of 1000 ppm for 7 hours/day, 5 days/week, for a total of 67 exposures conducted over 14 weeks. The measured concentration was reported to be generally 11% lower than the calculated value (i.e., approximately 890 ppm or 4710 mg/m^3). An equal number of unexposed animals served as controls. Body-weight gain and survival were evaluated throughout the exposure period, and histology and bromide levels in blood and brain were evaluated at termination of treatment. The investigators do not indicate whether the histological examinations were performed on tissues other than liver, kidney, and spleen. Effects consisted of a "slight" increase in hemosiderin in the spleen (additional details not reported) and increased concentrations of bromide in the blood and brain. Based on hemosiderosis in the spleen, this study identifies a LOAEL of 890 ppm (4710 mg/m^3) in rats. However, confidence in this LOAEL is low due to poor reporting of results.

Svirbely et al. (1947) also exposed three male rabbits (strain not reported) to approximately 890-ppm (4710 mg/m^3) bromochloromethane for 7 hours/day, 5 days/week, for a total of 67 exposures conducted over 14 weeks (Svirbely et al., 1947). An equal number of unexposed animals served as controls. Toxicity was evaluated as in the rat study with the addition of hematological examinations at "regular" intervals. Hematological endpoints consisted of RBC count, hemoglobin concentration, hematocrit value, reticulocyte count, and total and differential WBC counts. The only effects attributed to treatment were increased blood and brain bromide levels. The small number of animals and poor reporting of results precludes identification of a NOAEL or LOAEL.

Svirbely et al. (1947) also exposed two female dogs (strain not reported) to approximately 890-ppm (4710 mg/m^3) bromochloromethane for 7 hours/day, 5 days/week, for a total of 67 exposures (Svirbely et al., 1947) conducted over 14 weeks. An equal number of unexposed animals served as controls. Toxicity was evaluated as in the rats and rabbits with the addition of liver function evaluation (bromsulfalein excretion) and urinalysis (pH, specific gravity, sugar, albumin, urobilin, and urobilinogen) at "regular" intervals and blood inorganic bromide determinations throughout the treatment period. Effects consisted of a "slight" increase in hemosiderin in the spleen and kidneys, increased fat in the kidneys, and increased bromide levels in the blood and brain. The small number of animals and poor reporting of results precludes identification of a NOAEL or LOAEL.

Highman et al. (1948) exposed 100 strain-A mice (sex not reported, age 2 months) and 45 C3H mice (sex not reported, age 3−7 months) to bromochloromethane at 1000 ppm (5292 mg/m^3). Use of a control group is not indicated. Exposures were administered 5 times/week with occasional long rest periods of unspecified frequency and duration when necessary—as indicated by mortality and abnormal general condition. Surviving strain-A mice each received a total of 64 exposures of 3−7 hours in a period of approximately 5 months, and surviving C3H mice each received a total of 49 exposures of 3−7 hours in a period of 4 months. Most of the mice (numbers not reported) died at unspecified, irregular intervals during treatment, and some died—or were sacrificed—at unspecified intervals following treatment. A total of 21 mice (one Strain A and 20 C3H) survived until terminal sacrifice at 13−16 months of age. Histological examinations were conducted on mice that were sacrificed and some (number unspecified) that died. The mice that died during exposure generally showed slight fatty changes in the liver and kidneys. Extensive tubular necrosis of the inner zone of the renal cortex was observed in two strain-A mice that died during the fourth daily exposure. Several other mice that died during exposure showed coagulation or karyorrhectic necrosis of a few isolated liver cells. No treatment-related effects were observed in the mice that survived until terminal sacrifice. Confidence in this study is low due to the lack of control data, unclear exposure schedule, and poor reporting of results.

Other Studies

Acute and Short-term Oral Toxicity

Groups of five rats were fed (apparently by gavage) an unspecified range of single doses of bromochloromethane in corn oil (Torkelson et al., 1960). Observation for 14 days showed that all rats survived a dose of 5000 mg/kg and all rats died within 24 hours after a dose of 7000 mg/kg. Pathological examinations were not conducted.

Groups of 10 mice were fed (apparently by gavage) single doses of 500−4400 mg/kg bromochloromethane in olive oil (Svirbely et al., 1947). The LD_{50} (6-day observation) was approximately 4300 mg/kg. Clinical signs showing dose-related CNS depression were observed at ≥500 mg/kg, but the lowest dose producing death was not reported. Pathological examinations were not conducted.

Unspecified numbers of Swiss mice were administered single gavage doses of 0-, 500-, 3000-, or 4000-mg/kg bromochloromethane in olive oil (Highman et al., 1948). Histological examinations conducted ≤96 hours after treatment showed no significant changes at 500-mg/kg exposures. Effects occurred at exposures ≥3000 mg/kg that included death, fatty degeneration of the liver and kidneys, and focal subcapsular necrosis and hydropic degeneration of the liver.

A group of 32 Swiss mice was administered 3000-mg/kg-day bromochloromethane in olive oil by gavage for 1−10 consecutive days (Highman et al., 1948). Several mice were sacrificed after each of the 10 doses. Histological examination of mice that died or were sacrificed showed fatty degeneration of the liver, kidneys and sometimes heart. Other hepatic effects include subcapsular necrosis, hydropic degeneration and an increased number of mononuclear periportal cells.

Acute and Short-term Inhalation Toxicity

LC_{50} values ranged from 2268−2995 ppm (12,000−15,850 mg/m^3) for mice exposed to bromochloromethane for 7 hours (Highman et al., 1948; Svirbely et al., 1947). No deaths occurred in rats exposed to bromochloromethane at 5000 ppm (26,460 mg/m^3) for 7 hours, although exposure to 10,000 ppm (52,920 mg/m^3) for 4 hours resulted in 50−60% mortality (Torkelson et al., 1960). Clinical signs indicative of CNS toxicity were observed in both species; in mice, these include restlessness, muscular twitching, uncoordinated movements, labored respiration, and narcosis (Svirbely et al., 1947). In rats, these included drowsiness and unconsciousness (Torkelson et al., 1960).

Histopathologic changes occurred in the liver of rats exposed to 1500 ppm (7938 mg/m^3) for 7 hours, 5000 ppm (26,460 mg/m^3) for 7 hours, 10,000 ppm (52,920 mg/m^3) for 0.7 hours or 40,000 ppm (211,681 mg/m^3) for 0.1 hours (Torkelson et al., 1960). The changes were characterized as small vacuoles in the parenchyma not typical of fatty degeneration that are often accompanied by increased liver weight. Mice that were exposed to bromochloromethane at 7−17 mg/L (7000−17,000 mg/m^3 or 1323−3212 ppm) for 7 hours/day for 1−5 days had histological changes that mainly included fatty degeneration in the liver and kidneys (Highman et al., 1948).

Mutagenicity

A limited amount of information is available on the mutagenicity of bromochloromethane. Bromochloromethane induced reverse mutations in *Salmonella typhimurium* strains TA100 without metabolic activation (Simmon et al., 1977), strains TA100 and TA1535 (but not TA1950) without metabolic activation (Osterman-Golkar et al., 1983), and strains TA97, TA98, TA100, and TA104 with and without metabolic activation (Strobel and Grummt, 1987). Bromochloromethane also produced reverse mutations in *Escherichia coli* strain WU361089 without metabolic activation, forward mutations in *E. coli* Sd-4 without metabolic activation, and lambda prophage induction in *E. coli* K39 without metabolic activation

(Osterman-Golkar et al., 1983). In mammalian cells, bromochloromethane induced sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster embryonic lung fibroblasts (Strobel and Grummt, 1987). In vivo genotoxicity studies of bromochloromethane were not located.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL p-RfD VALUES FOR BROMOCHLOROMETHANE

No relevant subchronic or chronic oral studies of bromochloromethane were located. No PBPK models suitable for route-to-route extrapolation from the inhalation exposure data were found. Derivation of oral p-RfD values is not feasible.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR BROMOCHLOROMETHANE

Subchronic inhalation studies of bromochloromethane have been conducted with rats, mice, guinea pigs, rabbits, and dogs (Highman et al., 1948; MacEwen et al., 1966; Svirbely et al., 1947; Torkelson et al., 1960). The studies are old and reported incompletely. Table 1 presents a summary of the available literature. Exposure concentrations ranged from 370−1010 ppm, and exposure durations were 6−7 hours/day, on a 5-days/week regimen, and ranged from 14 weeks to approximately 6 months. The table includes the human equivalent concentrations (HECs) calculated for the various studies. As only systemic effects were reported in the existing studies, the U.S. EPA (1994b) default procedure for calculating a HEC for an extrarespiratory effect from a vapor is used for all endpoints and studies (see Table 1).

The Torkelson et al. (1960) study establishes a $LOAEL_{HEC}$ of 540 mg/m^3 in rats, female mice and guinea pigs based primarily on liver histopathology in rats, and a decrease in body-weight and increase in kidney weight in the other species. Other studies establish $LOAEL_{HEC}$ values of 487 and 981 mg/m^3 in rats based on decreased body weight (MacEwen et al., 1966) and splenic hemosiderosis (Svirbely et al., 1947), respectively. The $LOAEL_{HEC}$ of 487 mg/m^3 in rats (MacEwen et al., 1966) is discounted because of the chronic pneumonia, unrelated to bromochloromethane exposure, seen in control and treated animals alike. In addition to the aforementioned studies, Torkelson et al. (1960) also performed a longer experiment that identified a $LOAEL_{HEC}$ of 395 mg/m^3 for increased relative liver weight in rats, which was selected as the POD for the subchronic p-RfD. The data are insufficiently reported for benchmark concentration analysis.

Table 1. Summary of Inhalation Noncancer Dose-Response Information

Species	Sex	Exposure Concentration (ppm)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	$NOAEL_{HEC}$[a] (mg/m^3)	$LOAEL_{HEC}$[a] (mg/m^3)	Responses	Reference
Subchronic Exposure									
Rat	M,F	0, 500, or 1000 (0, 490, 1010 measured; 0, 2593, or 5345 mg/m^3)	7hr/d, 5 d/wk, for 79−82 exposures in 114 days	None	2593	None	540	Increased relative liver wt.; Liver pathology (slight bile duct epithelial proliferation, slight portal fibrosis, occasional vacuolization)	Torkelson et al., 1960
Rat	F	0, 370 (0, 1958 mg/m^3)	7 hr/d, 5 d/wk, for 135 exposures in 195 days	None	1958	None	395	Increased relative liver wt	Torkelson et al., 1960
Rat	M,F	0, 515, and 1010 (0, 2725, and 5345 mg/m^3)	6 hr/d, 5 d/wk, for 6 months	None	2725	None	487	Reduced body-weight gain; Chronic murine pneumonia was a prominent finding in both treated and control rats	MacEwen et al., 1966
Rat	M	0 or 890 (0 or 4710 mg/m^3)	7 hr/d, 5 d/wk, for 14 weeks for a total of 67 exposures	None	4710	None	981	Hemosiderosis in the spleen	Svirbely et al., 1947
Mouse	F	0, 490, or 1010 (0, 2593, or 5345 mg/m^3)	7 h/d, 5 d/wk, for 79−82 exposures in 114 days	None	2593	None	540	Decreased body weight and increased kidney weights	Torkelson et al., 1960
Mouse	NR[b]	1000 (5292 mg/m^3)	Unclear and poorly reported	Cannot determine effect levels due to poorly reported experimental design, including use of controls, exposure regiment and results					Highman et al., 1948
Guinea pig	M,F	0, 490, or 1010 (0, 2593. or 5345 mg/m^3)	7 h/d, 5 d/wk, for 79−82 exposures in 114 days	None	2593	None	540	Reduced body weight, increased kidney weights and neutrophilia	Torkelson et al., 1960
Rabbit	M,F	0, 490, or 1010 (0, 2593, or 5345 mg/m^3)	7 h/d, 5 d/wk, for 79−82 exposures in 114 days	Small numbers of animals preclude reliable determination of effect levels					Torkelson et al., 1960

Table 1. Summary of Inhalation Noncancer Dose-Response Information

Species	Sex	Exposure Concentration (ppm)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	$NOAEL_{HEC}$[a] (mg/m^3)	$LOAEL_{HEC}$[a] (mg/m^3)	Responses	Reference
Rabbit	M	0 or 890 (0 or 4710 mg/m^3)	7 hours/day, 5 days/week for 14 weeks for a total of 67 exposures	Small numbers of animals and poor reporting preclude reliable determination of effect levels					Svirbely et al., 1947
Dog	M,F	0, 370 (0, 1958 mg/m^3)	7 hr/d, 5 d/wk for 135 exposures in 195 days	Small numbers of animals and lack of histopathology preclude reliable determination of effect levels					Torkelson et al., 1960
Dog	M,F	0, 515, and 1010 (0, 2725, and 5345 mg/m^3)	6 hours/day, 5 days/week for 6 months	5345	None	954	None	None	MacEwen et al., 1966
Dog	F	0 or 890 (0 or 4710 mg/m^3)	7 hours/day, 5 days/week for 14 weeks for a total of 67 exposures	Small numbers of animals and poor reporting preclude reliable determination of effect levels					Svirbely et al., 1947

[a]Exposure concentration adjusted to human equivalent concentration (HEC) based on exposure regimen (number of hours/day and days/week) and U.S. EPA (1994b) methodology for extrarespiratory effects of a vapor:

$NOAEL_{ADJ}$ = NOAEL × (hours exposure per day/24)(days exposure per week/7)

$NOAEL_{HEC}$ = $NOAEL_{ADJ} \times (H_{b/g})_A/(H_{b/g})_H$
where $(H_{b/g})_A/(H_{b/g})_H$ = rat-to-human blood:air partition coefficient ratio. A default ratio of 1 is used because a $H_{b/g}$ value for bromochloromethane was located for rats (41.5 [Gargas et al., 1986]), but not for humans

[b]NR = Not Reported

Subchronic p-RfC

The $LOAEL_{HEC}$ of 395 mg/m^3 for increased relative liver weight in rats (Torkelson et al., 1960) was used to derive the subchronic p-RfC.

$$\begin{aligned} \textbf{Subchronic p-RfC} &= LOAEL_{HEC} \div UF \\ &= 395\ mg/m^3 \div 3000 \\ &= \mathbf{0.1\ or\ 1 \times 10^{-1}\ mg/m^3} \end{aligned}$$

The composite Uncertainty Factor (UF) is derived as follows:

- A partial UF_A of 3 was applied for interspecies extrapolation; this includes a factor of 1 for species differences in pharmacokinetic considerations (because a dosimetric adjustment was used) and a factor of 3 for pharmacodynamic considerations.
- A full UF_H of 10 for extrapolation to sensitive humans was used to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A full UF_D of 10 was used to account for database uncertainty; the database consists of several old, poorly reported subchronic studies. The database lacks developmental and reproductive toxicity studies.
- A full UF_L of 10 was applied to account for the use of a LOAEL as the point of departure.

Confidence in the principal study is low. The study is old and incompletely reported. A NOAEL is not identified. Confidence in the database is low because all of the subchronic studies are very old and there are no developmental or reproductive toxicity data. Low confidence in the subchronic p-RfC results.

Chronic p-RfC

Chronic toxicity testing of bromochloromethane has not been conducted and large composite UF (3000) used in the derivation of the subchronic p-RfC precludes its use as the basis for derivation of a chronic p-RfC. Therefore, derivation of a provisional chronic RfC is not feasible. However, Appendix A presents a screening chronic p-RfC.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR BROMOCHLOROMETHANE

Weight-of-Evidence Descriptor

There are no human or animal carcinogenicity data for bromochloromethane. A limited amount of in vitro genotoxicity data are available indicating that bromochloromethane is mutagenic. Bromochloromethane induced mutations in *S. typhimurium* and *E. coli* (Osterman-Golkar et al., 1983; Simmon et al., 1977; Strobel and Grummt, 1987), as well as sister chromatid exchanges and chromosomal aberrations in Chinese hamster embryonic lung fibroblasts (Strobel and Grummt, 1987). In accordance with current U.S. EPA cancer guidelines, there is "*Inadequate Information to Assess Carcinogenic Potential*" in humans (U.S. EPA, 2005).

Quantitative Estimates of Carcinogenic Risk

Due to the lack of adequate data, it is neither possible nor appropriate to derive quantitative estimates of carcinogenic risk for bromochloromethane for either oral (p-OSF) or inhalation (p-IUR) exposures.

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APPENDIX A. DERIVATION OF A SCREENING VALUE FOR BROMOCHLOROMETHANE

For reasons noted in the main PPRTV document, it is inappropriate to derive a provisional chronic inhalation toxicity values for bromochloromethane. However, information is available for this chemical, which, although insufficient to support derivation of a provisional chronic inhalation toxicity value, under current guidelines, may be of limited 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. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a PPRTV presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

A **screening chronic p-RfC value of 0.04 mg/m^3** can be derived from the subchronic $LOAEL_{HEC}$ of 395 mg/m^3 for increased relative liver weights in rats (Torkelson et al., 1960) by dividing by a composite UF of 10,000. The composite UF consists of four full areas of uncertainty (UF_H, UF_L, UF_D, UF_S) and a factor of 3 for UF_A, reduced by convention for use of a dosimetric inhalation exposure adjustment. The composite UF is 30,000 using standard risk assessment methodologies ($10 \times 3 \times 10 \times 10 \times 10 = 30{,}000$); however, the composite UF has been limited to 10,000 due to significant uncertainty.