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Provisional Peer Reviewed Toxicity Values for

Bromomethane
(CASRN 74-83-9)

Superfund Health Risk Technical Support Center
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Acronyms and Abbreviations

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
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
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-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
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
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR BROMOMETHANE (CASRN 74-83-9)

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 new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-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 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.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

INTRODUCTION

IRIS (U.S. EPA, 2007) lists an RfD and an RfC for bromomethane (also known as methyl bromide). The RfD of 0.0014 mg/kg-day is based on a NOAEL of 1.4 mg/kg-day for forestomach lesions in a subchronic gavage study in rats (Danse et al., 1984). The RfC of 5E-3 mg/m^3 is based on a LOAEL of 11.7 mg/m^3 for lesions to the olfactory epithelium in a chronic study in rats (Reuzel et al., 1987, 1991). The HEAST (U.S. EPA, 1997) contains a reference to the IRIS values. The Drinking Water Standards and Health Advisories list (U.S. EPA, 2004) reports an RfD of 0.001 mg/kg-day based on the same critical study and effect that served as the basis for the RfD on IRIS. The CARA list (U.S. EPA, 1991, 1994a) includes a HEEP (U.S. EPA, 1986) and HEA (U.S. EPA, 1987) for methyl bromide. The HEEP derived a chronic ADI of 0.0014 mg/kg-day and the HEA derived a subchronic RfD of 0.014 mg/kg-day and chronic RfD of 0.0014 mg/kg-day based on forestomach lesions from the Danse et al. (1984) study. The HEEP (U.S. EPA, 1986) did not derive an inhalation RfD for bromomethane. The HEA (U.S. EPA, 1987) derived a subchronic inhalation RfD of 0.076 mg/kg-day and a chronic inhalation RfD of 0.0076 mg/kg-day based on a NOAEL of 130 mg/m^3 for paralysis in rabbits identified by Irish et al. (1940). ATSDR (1992) has published a Toxicological Profile for bromomethane in which intermediate-duration oral and intermediate- and chronic-duration inhalation MRLs were derived. The intermediate-duration oral MRL of 0.003 mg/kg-day is based on the Danse et al. (1984) data. The intermediate-duration inhalation MRL of 0.05 ppm (0.19 mg/m^3) is based on a

NOAEL of 5 ppm (19 mg/m^3) for altered brain neurochemistry in a 3-week study in rats (Honma et al., 1982). The chronic-duration inhalation MRL of 0.005 ppm (0.019 mg/m^3) is based on a LOAEL of 2.3 ppm (8.9 mg/m^3) for muscle ache, fatigue, and ataxia in occupationally-exposed humans (Anger et al., 1986). OSHA (2006a, b) has promulgated a PEL of 20 ppm (ceiling) (78 mg/m^3), with a skin designation, and the ACGIH (2006) has recommended a TLV of 1 ppm (3.9 mg/m^3) for protection against upper respiratory tract and skin irritation.

IRIS (U.S. EPA, 2007) lists bromomethane as Group D (not classifiable as to human carcinogenicity) based on inadequate human and animal data, and does not list an oral slope factor or inhalation unit risk. The Drinking Water Standards and Health Advisories list (U.S. EPA, 2004) also lists bromomethane as Group D, and does not report a quantitative estimate of cancer risk. The HEAST (U.S. EPA, 1997) does not report a cancer classification or risk values for bromomethane. Neither the HEEP (U.S. EPA, 1986) nor the HEA (U.S. EPA, 1987) for bromomethane derived quantitative carcinogenicity risk values. An IARC monograph (IARC, 1999) reported that bromomethane was not classifiable as to its carcinogenicity in humans (Group 3), based on inadequate evidence in humans and limited evidence in animals. ACGIH (2006) has classified bromomethane in category A4 - not classifiable as a human carcinogen. A WHO Environmental Criteria Document (WHO, 1995) found data on carcinogenic effects of bromomethane to be inadequate.

Literature searches were performed from 1989 to August, 2001 for studies relevant to the derivation of provisional subchronic RfD and RfC values and a provisional carcinogenicity assessment for bromomethane. Databases searched included: TOXLINE, MEDLINE, TSCATS, RTECS, CCRIS, DART, Emic, HSDB, Genetox, and CANCERLIT. A WHO Environmental Criteria Document (WHO, 1995), an IARC monograph (IARC, 1999), the ATSDR Toxicological Profile for bromomethane (ATSDR, 1992), and the NTP Status Reports (NTP, 2002) were also searched for relevant information. Additional literature searches from 2001 to October 10, 2006 were conducted by NCEA-Cincinnati using TOXLINE, MEDLINE, Chemical and Biological Abstract data bases.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure. Reports of bromomethane-induced toxicity in orally exposed humans were not located. As bromomethane is a gas at room temperatures, ingestion exposure is likely to be rare. Michalodimitrakis et al. (1997) reported a case of suicide in which a 43-year-old male had attempted to ingest and finally inhaled an unknown quantity of bromomethane.

No data were located regarding the oral carcinogenicity of bromomethane in humans.

Inhalation Exposure. Bromomethane is highly acutely toxic to humans. There are numerous reports of humans who have died or suffered permanent disability following acute exposure (ATSDR, 1992). Most cases were associated with accidental exposure during manufacturing and packaging operations, use of fire extinguishers containing bromomethane, or fumigation

activities. Death was not immediate, but usually occurred within 1-2 days. The cause of death is not certain, but may be related to neurological and/or lung injury.

Few epidemiological studies of humans occupationally exposed to bromomethane have been conducted. IRIS (U.S. EPA, 2007) describes one study of individuals working in the fumigation industry (Anger et al., 1986). Although the study suggested mild neurological effects of exposure to bromomethane, it is difficult to draw any conclusions because of several confounding factors. The exposed and reference groups were not well matched for age, use of prescription medication, alcohol, use of illegal drugs, education or ethnic group. In addition, participation in the study was voluntary and no information on use of personal protective equipment was provided.

Intact bromomethane was measured in the tissues of a man who committed suicide by ingesting and inhaling bromomethane (Michalodimitrakis et al., 1997). Previous attempts to demonstrate intact bromomethane in the blood of humans had been unsuccessful. Head space gas chromatography analysis showed bromomethane concentrations of 3.3 μg/ml in peripheral blood and 3.8 μg/ml in subclavian blood. Concentrations in lung, brain, adrenal gland, kidney, liver, and testis were 2.9, 3.5, 3.4, 2.6, 1.9, and 2.8 μg/g, respectively.

Recent investigations on enzymes that conjugate bromomethane with glutathione (GSH) in human erythrocytes suggest that, at least for acute exposures, potentially sensitive human subpopulations may exist. Schröder et al. (1992) reported the isolation of a new glutathione-S-transferase (GST) enzyme from human erythrocytes that conjugates bromomethane with GSH. The isoenzyme has been shown to be suitable for differentiation between individuals who are conjugators of small molecular weight halogenated hydrocarbons, like bromomethane, and non-conjugators. In one study, investigation of 45 human individuals showed that 27 possessed activity for conjugation of methyl chloride with GSH ("conjugators"), while 18 did not ("non-conjugators") (Peter et al., 1989). Another study (Hallier et al., 1993) examined 36 volunteers, and reported that 8 were negative ("non-conjugators") for rapid bromomethane disappearance while 32 were positive; their results suggested a 1:2:1 distribution of non-conjugators, intermediate conjugators, and conjugators with high activity. The isoenzyme that is responsible for bromomethane conjugation in humans is not found in rodents. Instead, rodents rapidly metabolize bromomethane by an apparently different enzyme. Thus, it is possible that the human subpopulation of non-conjugators may be at a greater risk for systemic effects from bromomethane than indicated by the results of rodent bioassays. However, the possible importance of this mechanism to chronic exposure to bromomethane in humans has not yet been established.

Garnier et al. (1996) reported an accidental exposure of two workers to bromomethane (~17,000 mg/m^3 for up to 45 minutes) while fumigating a building. A few minutes after exposure, both workers experienced nausea, vomiting, headache, and dizziness. Two hours later, one of the workers had severe myoclonic seizures, and both workers were admitted to the local hospital. One patient developed very severe poisoning, whereas the other only developed mild neurotoxic symptoms. The severely affected patient was identified as a conjugator, with normal GST activity, whereas this activity was undetectable in the second patient. The study authors suggested that for a similar exposure, non-conjugators receive a higher internal dose of the

parent compound, and conjugators are exposed to higher internal doses of metabolites of bromomethane such as methanethiol and formaldehyde. They further suggested that the difference in the severity of the neurological damage experienced by these two workers was due to difference in GST activity; however, this conclusion is based only on the reactions of two people. Although the authors assume that the exposures of the two individuals working together were similar, no quantitative data on actual exposure were available.

Hustinx et al. (1993) also reported marked differences in the severity of reaction of humans exposed to similar concentrations of bromomethane. Nine greenhouse workers were accidentally exposed to bromomethane concentrations probably in excess of 200 ppm (777 mg/m^3) for six hours. Two of the patients needed intensive care for several weeks due to severe myoclonus and tonic-clonic generalized convulsions. The other seven patients were discharged after overnight observation, and there were few residual symptoms. No information on the GSH conjugator status of these patients was reported.

A prospective mortality study was reported for a population of 3579 white male chemical workers. The men, employed between 1935 and 1976, were potentially exposed to 1,2-dibromo-3-chloropropane, 2,3-dibromopropyl phosphate, polybrominated biphenyls, DDT, and several brominated organic and inorganic compounds (Wong et al., 1984). Overall mortality for the cohort, as well as for several subgroups, was less than expected. Of the 665 men exposed to bromomethane, two died from testicular cancer, as compared with 0.11 expected. This finding may be noteworthy, as testicular cancer is usually associated with a low mortality rate. Therefore, there could be more cancer cases than there appear to be based on mortality. However, the authors noted that it was difficult to draw definitive conclusions as to causality because of the lack of exposure information and the likelihood that exposure was to many brominated compounds. No additional studies of the potential carcinogenic effects of bromomethane in humans were located.

Animal Studies

Oral Exposure. Danse et al. (1984) administered bromomethane by gavage in arachis oil at doses of 0, 0.4, 2, 10 or 50 mg/kg to male and female Wistar rats (10/sex/group) 5 days/week (adjusted doses of 0, 0.3, 1.4, 7.1 or 35.7 mg/kg-day) for 13 weeks. The following parameters were used to assess toxicity: body weights (determined weekly), food consumption (measured three times per week), hematology (erythrocyte count, hemoglobin, packed cell volume, mean corpuscular volume, mean corpuscular hemoglobin concentration and white blood cell count, measured one week prior to termination), and gross and histopathological examination of the stomach (all groups), liver, spleen, esophagus (0 and 50 mg/kg groups), and lungs (0, 10 and 50 mg/kg groups).

No changes in appearance or general behavior were observed during the study. One female in the 2 mg/kg group died due to gavage error, and one male rat in the 50 mg/kg exposure group died during week 10. Extensive ulceration and inflammation in the esophagus were observed in the high-dose male that died. A statistically significant decrease in body weight gain was observed in the high-dose males, but no significant differences in body weight of females was observed at any dose level. At termination, the high-dose males weighed approximately

25% less than the controls. A slight, but statistically significant, decrease in food intake was observed in the male rats dosed with 2 mg/kg or greater and in the females dosed with 50 mg/kg. In the high-dose males, significant decreases in erythrocyte level and increases in mean corpuscular volume and neutrophil levels were observed. Significantly increased total white blood cell count and lymphocyte levels were observed in the high-dose females. No hematological alterations were observed at the lower dose levels. Adhesive peritonitis was observed in the all of the high-dose rats of both sexes. Focal hyperemia of the forestomach was observed at a low frequency in the lowest-dose group (0/10 females and 1/10 males), and was observed in most animals in the 10 mg/kg-group (8/10 females and 10/10 males). A statistically significant increase was observed (Fisher's exact test performed for NCEA) in the incidence of diffuse hyperplasia of the forestomach squamous epithelium in the 10 mg/kg-group (9/10 females and 6/10 males). The hyperplasia was characterized by an increase and rearrangement of atypical basal cells, increased mitosis, and a marked downward out-growth of the basal layer. Microscopic examination of the lungs revealed a slightly increased incidence of focal interstitial pneumonia and slight atelectasis in the two highest dose groups. The investigators noted that the decreased body weight gain and food consumption and mild anemia may have been secondary to the forestomach lesions, and the lung effects may have been due to aspirated bromomethane. The increased incidence of forestomach hyperplasia in the 10 mg/kg-group establishes this dose as a LOAEL and the 2 mg/kg-group as a NOAEL.

Danse et al. (1984) diagnosed the forestomach lesions induced in 13/20 of the rats administered 50 mg/kg of bromomethane as squamous cell carcinomas. These results were subsequently questioned (U.S. EPA, 1985; Schatzow, 1984). NTP re-evaluated the histology slides from this study and determined that the lesions were hyperplasia and inflammation rather than neoplasia (Anonymous, 1984). Subsequent experiments, with a period for recovery, have demonstrated that the forestomach lesions regress following cessation of bromomethane exposures (Boorman et al., 1986; Hubbs, 1986). Regression of the lesions after cessation of bromomethane administration argues against the forestomach lesions being of a malignant nature.

Boorman et al. (1986) administered 0 or 50 mg/kg of bromomethane in peanut oil to male Wistar rats (15/group) for 5 day/week (adjusted doses of 0 or 36 mg/kg-day) for 13-25 weeks. At 13 weeks, bromomethane administration was stopped for half of the rats, to investigate whether the hyperplastic forestomach lesions observed by Danse et al. (1984) would continue to develop without further irritation or whether these lesions would regress. Groups of continuously treated and bromomethane-stopped treatment animals were killed after 13, 17, 21 and 25 weeks of treatment. Weekly body weight determinations and histopathological examinations of the lung, liver, esophagus, stomach, and all gross lesions were used to assess toxicity. The Student's *t* test was employed to assess the significance of treatment effects within two groups; for comparison of more than two groups data were analyzed by one-way ANOVA or one-way Kruskal-Walis multiple-comparison test, after testing for normality.

A significant decrease in body weight gain (approximately 20%) was observed in the rats receiving 50 mg/kg bromomethane for 13 weeks. Animals in the bromomethane-stopped treatment group resumed weight gain after cessation of bromomethane administration, and by week 25 the average body weight in the stopped group was significantly greater than

continuously treated animals. At 13 weeks the forestomachs of rats receiving bromomethane were contracted and adherent to the liver and spleen. Inflammation (38.5%), acanthosis (23.1%) fibrosis (38.5%) and hyperplasia (84.6%) were common after 13 weeks of treatment. At 25 weeks, fibrosis (44.4%) was still frequently observed in the stomachs of animals in the bromomethane-stopped treatment group, but the incidences of inflammation, acanthosis, and hyperplasia were reduced to control levels. Peritoneal adhesions, however, were still present. In continuously treated animals, the incidence of hyperplasia was 100%, and the pseudoepitheliomatous hyperplasia was characterized by epithelial peg formation and accompanied by hyperkeratosis and acanthosis. One continuously-exposed animal had a severe dysplastic lesion with a relatively high mitotic activity that was considered to represent an early carcinoma.

Hubbs (1986) administered gavage doses of 0, 25 or 50 mg/kg of bromomethane dissolved in peanut oil 5 days/week (duration-adjusted doses of 0, 18 or 36 mg/kg-day) to groups of 10 male Wistar rats for 30, 60, 90 or 120 days. Another group of animals received 50 mg/kg bromomethane 5 days/week for 90 days and then were allowed to recover for 30 or 60 days before sacrifice. Weekly body weight determinations, hematological parameters (erythrocyte, hemoglobin, hematocrit, mean corpuscular volume and white blood cell levels) and histopathological examination of the stomach were used to assess toxicity. Lethargy, distended abdomens, and soft feces were observed in the high-dose group. A significant decrease in food consumption was observed in both groups of bromomethane treated rats and was inversely related to dose. Significant decreases in body weight gain were observed in the low- (10%) and high- (20%) dose groups. Erythrocyte mean corpuscular volume was significantly lower in the high-dose rats killed after 30 and 120 days of exposure as compared with controls. No other effects on hematological parameters were observed. Gross and histological alterations of the stomach were observed, with the effects being most pronounced in the non-glandular stomach. Histological changes in the squamous epithelial portion included ulceration and pseudoepitheliomatous hyperplasia characterized by hyperkeratosis, acanthosis, and epithelial peg formation. Following a 60-day recovery period, marked but incomplete regression of lesions was observed. No evidence of malignancy was observed in the stomachs of treated rats.

Peters et al. (1981) administered daily gavage doses of 0, 0.5, 5, 25 or 50 mg/kg of bromomethane (purity not reported) to groups of 23-25 pregnant rats in peanut oil during days 5-20 of gestation. A control group of 48 pregnant rats was used. The dams were killed on gestational day 20. Four dams in the high-dose group were killed in a moribund state; inflammation and perforation of the peritoneum were observed in these animals. Diarrhea, lethargy, pilo-erection, and weight loss were observed in the surviving high-dose dams. Clinical signs of toxicity were not observed in the other groups. Histopathological examination revealed plastic peritonitis in the 25 mg/kg-day dose level dams and adhesions of the stomach with the liver, spleen, diaphragm, adrenal and kidney, and hyperplasia and hyperkeratosis with extensive necrotic ulceration and chronic inflammation of the stomach in the 50 mg/kg-day dose level dams. Maternal body weight gain was not affected in the 0.5 or 5.0 mg/kg-day dose levels, but a significant decrease in body weight gain was observed in the 25 mg/kg-day dose level. A highly significant reduction was observed at the 50 mg/kg-day dose level. In the 50 mg/kg-day group, no live fetuses were observed. No compound-related effects on post-implantation loss, number of resorptions, fetal weight, placental weight, or percentage of female fetuses were observed in

the dams receiving 25 mg/kg-day bromomethane or lower. No treatment related alterations were observed in the fetuses. This study identifies a NOAEL of 5 mg/kg-day and LOAEL of 25 mg/kg-day for maternal toxicity. The authors concluded that bromomethane had no embryotoxic effects since maternal toxicity, evidenced by a reduction in maternal body weight gain, was evident at the 25 mg/kg-day dose level, but no effects on number of live fetuses or fetus weight gain were observed.

Kaneda et al. (1993) performed a 2-generation reproduction study in rats exposed to diets which were fumigated with bromomethane to achieve concentrations of 200 or 500 ppm total bromine. Levels of bromomethane in the feed were not reported. This is of considerable concern, as the vast majority of the bromine found in fumigated food is not present as bromomethane (Shrader et al., 1942). Food consumption was significantly reduced in high-dose F1 parental males during the second half of the dosing period, and high-dose F2 females showed lower body weights throughout the lactation period. No other significant changes in any evaluated endpoint were reported. The lack of reported concentrations of bromomethane in the diet limits the interpretability of this study.

In a later study, Kaneda et al. (1998) exposed groups (n=24) of pregnant rats by gavage to 0, 3, 10 or 30 mg/kg-day of bromomethane in corn oil from gestational days 6-15. Rats were sacrificed on gestational day 20 and evaluated for maternal toxicity and effects on the offspring. No changes in clinical signs were reported at any dose level. Rats exposed to 30 mg/kg-day showed a significant decrease in body weight gain and food consumption throughout the dosing period, and necropsy on day 20 revealed pathologic changes in the forestomach, or adhesion of the stomach with the liver, spleen or diaphragm. No changes in the number of corpora lutea, implants and live fetuses, fetal sex ratio, percent resorptions, or fetal and placental weights were reported at any exposure level. Teratological examination of the live fetuses found no differences in the incidence of malformations and variations, with the exception of a small but significant increase in the incidence of fetuses with 25 presacral vertebrae in the high-dose group; the study authors considered this effect unrelated to bromomethane treatment since it occurred in only a small fraction of litters (2/24).

In the second part of the study, the authors exposed groups (n=18) of pregnant rabbits to 0, 1, 3 or 10 mg/kg-day of bromomethane in corn oil from gestational days 6-18. As with rats, high-dose animals had significantly decreased body weight gain and food consumption during the dosing period. No treatment-related changes in clinical signs were noted at any dose level, nor were any changes noted upon necropsy. In examination of the ovaries and uterus, no differences were noted between the control and exposed groups except for a significantly low value of the sex ratio in the low dose group, which was considered to be incidental. Teratological examination revealed no significant increase in the incidence of malformations between control and treated groups.

The database of chronic oral animal studies consists of two studies in which dogs were fed a diet that had been fumigated with bromomethane (Rosenblum et al., 1960; Wilson et al., 1998) and one such study in rats (Mitsumori et al., 1990). In the Rosenblum et al. (1960) and Mitsumori et al. (1990) studies, levels of bromomethane in the dogs' fumigated diet were not

measured; rather, exposure was based on concentration of bromine in the feed. However, it has been demonstrated that little of the bromide residue following bromomethane fumigation is in the form of bromomethane (Shrader et al., 1942). Because it is likely that the bulk of the bromine residues in the diet were not in the form of bromomethane, these studies were not considered for risk assessment purposes.

Wilson et al. (1998) exposed groups of dogs for one year to a diet which had been fumigated with bromomethane. The study authors reported TWA doses of bromomethane, calculated based on analysis of feed consumption and bromomethane concentration in the food, of 0, 0.006, 0.13 and 0.28 mg/kg-day. No changes in clinical signs, body weights, feed consumption, ophthalmology, clinical pathology, urinalysis, or organ weights were reported. Macroscopic and microscopic pathology of a comprehensive list of organs and tissues (including the stomach) revealed no treatment-related effects.

Inhalation Exposure. Hastings (1990) exposed 15 rats per group (sex and strain not reported) to 0 or 200 ppm (777 mg/m^3) of bromomethane 4 hours/day 4 days/week for 2 weeks, and followed recovery for 30 days after exposures were stopped. Prior to exposure, rats were food-deprived and trained to find a buried food pellet as a test of olfactory function. During the exposure period, the rats were tested the morning following exposure. After a single 4-hour exposure, the latency time required to find the buried feed pellet was increased from 25 seconds to almost 200 seconds. Recovery as determined by the buried-feed retrieval task was rapid, and after the fourth day of continuous exposures, there was no statistically significant difference in latency time. Examination of the olfactory epithelium by standard histological techniques revealed extensive damage that was maximal four days after start of the exposure. Regeneration of the olfactory epithelium was not complete until 30 days from the start of exposure. The authors interpreted the recovery in performance in the buried pellet retrieval task to indicate recovery of olfactory function, despite the observed histological damage to the olfactory epithelium. They did not consider the possibility that the rats may have learned to use other stimuli to detect the buried feed pellet, such as detecting a lump under the bedding.

An acute study performed by Hurtt et al. (1987) also revealed evidence of olfactory epithelial degeneration following inhalation of bromomethane. Groups of male Fischer 344 rats (n=10) were exposed to 0, 90, 175, 250 or 325 ppm (0, 350, 680, 971 or 1262 mg/m^3) of bromomethane (99.9% pure) 6 hour/day for 5 days. The brain, nasal cavity, liver, kidney, adrenal glands, testes, and epididymides were examined histopathologically, but not the lungs. Three animals exposed to 1262 mg/m^3 died after the fourth exposure. Diarrhea, hemoglobinuria, gait disturbances, convulsions, and acute hepatocellular degeneration were observed in animals exposed to 971 mg/m^3 or greater. Minor alterations in testicular histology (delayed spermiation in 6 of 7 males) and cerebrocortical degeneration were observed in the 1262 mg/m^3 exposure group. Vacuolar degeneration of the zona fasciculata of the adrenal gland and cerebellar granule cell degeneration were observed in rats exposed at 680 mg/m^3 and greater. A dose-dependent degeneration of the nasal olfactory sensory cells was also observed in rats exposed to 680 mg/m^3 or greater. This degeneration affected 50-80% of the olfactory mucosa, and was characterized by complete or partial destruction of the olfactory epithelium at the concentrations of 680 mg/m^3 and greater.

Neurobehavioral effects of bromomethane inhalation were studied in rats and rabbits by Anger et al. (1981). In one set of experiments, Sprague-Dawley rats and New Zealand white rabbits were exposed to 0 (2 rabbits or 4 rats, sex not specified) or 65 ppm (252 mg/m^3, 6 rabbits or 16 rats) of bromomethane (99.9% purity) 7.5 hours/day, 4 days/week for 4 weeks. Neurobehavioral testing, consisting of conduction velocity in the sciatic and ulnar nerves (rats and rabbits), eye-blink reflex (rabbits), open field activity (rats), and grip/coordination (rats) were conducted weekly. Exposed rabbits exhibited depressed body weight gain as compared with the controls, and signs of hind limb paralysis were evident during the last week of exposure. Statistically significant decreases in the eye blink reflex magnitude and in nerve conduction velocity were also observed in the exposed rabbits. In contrast, no effects on weight gain, grip/coordination, or nerve conduction velocity were observed in the rats exposed to 252 mg/m^3 for four weeks. In a separate experiment, Sprague-Dawley rats (8 controls and 32 treated) were exposed to 0 or 55 ppm (0 or 214 mg/m^3) of bromomethane 6 hour/day, 5 day/week for 36 weeks. Neurobehavioral tests (conduction velocity in the sciatic and ulnar nerves, open-field activity, and grip/coordination) conducted at 25- to 30-day intervals did not reveal any exposure-related effects.

The brain and heart appeared to be the target organs following inhalation exposure to bromomethane in a study conducted by Kato et al. (1986). Male Sprague-Dawley rats (10-12/group) were exposed to 0 or 150 ppm (0 or 582 mg/m^3) of bromomethane (purity unspecified) 4 hours/day, 5 days/week for 11 weeks. Focal necrosis and fibrosis of coronary ventricles and papillary muscle disorders were observed in the exposed animals. In the same study, male Sprague-Dawley rats (10-12/ group) were exposed to 0, 200, 300 or 400 ppm (0, 777, 1165, or 1553 mg/m^3) of bromomethane, 4 hours/day, 5 days/week for 6 weeks. Neurological dysfunction (ataxia, paralysis) was reported at levels greater than or equal to 1165 mg/m^3; necrosis in the bilateral regions of the dorso-external cortex of the cerebral hemisphere was observed in animals exposed to 1553 mg/m^3. Testicular atrophy with suppression of spermatogenesis was apparent in 6 of the 8 animals exposed to 1553 mg/m^3. Focal necrosis and fibrosis of coronary ventricles and papillary muscle were also observed in all exposed animals.

A six-week inhalation toxicity study was conducted using near lethal concentrations, because the 14-day and 13-week inhalation studies had not established target organs for bromomethane toxicity (NTP, 1992; Eustis et al., 1988). Male and female F344 rats and B6C3F1 mice were exposed to 0 or 160 ppm (0 or 621 mg/m^3) of bromomethane (99.5% pure) for 6 hours/day, 5 days/week for up to 30 exposure days (6 weeks total). Each exposure group consisted initially of 20 animals/sex/species, with sacrifices planned after 3, 10 or 30 exposure days. Exposures were discontinued if mortality exceeded 50% in any group, and the remaining animals were sacrificed and necropsied at that time. Toxicological endpoints assessed included clinical observations, mortality, body and organ weights, hematology, clinical chemistry, urinalysis and gross histopathology. Tissues examined microscopically included adrenal glands, brain, testes, thymus, spleen, heart, liver, kidneys, lung and nasal cavity. All variables were compared by ANOVA, and *t* tests were performed to compare individual treatments.

Only female rats survived the entire six weeks with less than 50% mortality. Mice were more sensitive than rats, and mortality exceeded 50% after six or eight exposure days for female or male mice, and after 14 exposure days for male rats. Clinical observations of toxicity in mice

included red urine, lethargy, and neurological signs (curling and crossing of the hind limbs, forelimb twitching, and tremors). Similar neurological signs were observed in rats, although to a lesser degree. Significant differences in body weight gain were seen in mice after five exposure days and in rats after 14 exposure days. Significant reductions in weights of several organs were observed in both mice and rats, but the affected organs differed between species. In mice, lung, heart, thymus, brain and liver weights were reduced; and in rats, lung, kidney, spleen, liver, brain and testes weights were reduced. In female mice, the most sensitive species and sex, significant reductions in red blood cell numbers and elevated white blood cell numbers were observed, but hematological parameters in male mice or female or male rats showed little change. Target organs affected by exposure to 621 mg/m^3 of bromomethane were the brain, kidney, nasal cavity, heart, adrenal gland, liver and testis. Species differences were noted in the responses of these organs. For example, neuronal necrosis in the cerebral cortex, hippocampus and thalamus of the brain were seen in the rats, whereas neuronal necrosis was seen predominantly in the internal granular layer of the cerebellum of the mice. Nephrosis, characterized by degeneration, necrosis and sloughing of the epithelium of the cortical convoluted tubules was seen in all of the exposed mice and was considered by the authors to be partially responsible for the increase in mortality; these lesions were not observed in the rats. Degeneration and atrophy of the seminiferous tubules was observed in several of the exposed rats and mice, but was less severe in the mice. Olfactory epithelium degeneration was observed in the rats of both sexes, and this was seen to a lesser degree in the male mice, with only one female mouse exhibiting this lesion. Myocardial degeneration was seen in rats of both sexes, and to a lesser degree in the male mice. Atrophy of the inner zone of the adrenal cortex was observed in the female mice, and cytoplasmic vacuolation of the adrenal cortex was seen in rats.

A 13-week subchronic inhalation range-finding study was conducted in F344 rats (18/sex/group) exposed to target concentrations of 0, 30, 60 or 120 ppm (0, 116, 233 or 466 mg/m^3) of bromomethane 6 hours/day, 5 days/week (NTP, 1992). Additional groups of eight rats of each sex were exposed for neurobehavioral studies. The test compound used was 99.8% pure. Animals were observed twice daily, and body weights were recorded weekly. Necropsies were performed on all animals and organ weights were determined for the lungs, heart, liver, right kidney, spleen, adrenal gland, brain, and left testis. Neurobehavioral testing was conducted at weeks 0, 6 and 12, and neuromorphological studies were conducted on four rats/sex from the control and high-concentration groups. Histological examination of 40 tissues and all gross lesions was conducted on all control and high-dose animals. Statistical tests for dose-related effects on survival used the method of Cox and Tarone's life table test for dose-related trends. Incidence data were examined using Fisher's exact test and the Cochran-Armitage test for trend. Statistical analyses of continuous variables were performed using the nonparametric multiple comparison test of Dunn or Shirley. Jonckheere's test was used to assess the significance of dose-response trends.

There was no increase in mortality, but the males and females exposed to 466 mg/m^3 and the females exposed to 233 mg/m^3 of bromomethane exhibited significant decreases in body weight and body weight gain; final body weights were 88% of controls in high-dose males and 94 and 87% of control in mid- and high-dose females. Mild neurobehavioral effects were noted in the high-concentration animals of both sexes. Females exposed to 466 mg/m^3 were found to have significantly lower hematocrit, hemoglobin, and erythrocytes counts, but males did not

exhibit these changes. The only exposure-related effect noted at histopathological examination was an increase in the incidence of olfactory epithelial dysplasia (2/10, 3/10, 2/9 and 7/10 in control, low-, mid- and high-dose males, and 1/10, 1/10, 4/10 and 8/10 in control, low-, mid- and high-dose females, respectively) and cysts (0/10, 0/10, 0/9 and 7/10 in control, low-, mid- and high-dose males, and 0/10, 0/10, 0/10 and 9/10 in control, low-, mid- and high-dose females, respectively) in the rats of both sexes; statistically significant changes were only seen in animals exposed to 466 mg/m^3. The results of trend tests were not reported for any endpoint in the 13-week study. Based on these results, a subchronic NOAEL of 233 mg/m^3 [NOAEL(HEC)=4 mg/m^3] and a LOAEL of 466 mg/m^3 [LOAEL(HEC)=8 mg/m^3] for nasal olfactory epithelial changes (epithelial cysts and dysplasia) in rats can be identified.

A 13-week subchronic inhalation range-finding study also was conducted using B6C3F1 mice (NTP, 1992). Groups of 18–27 mice/sex were exposed to target concentrations of 0, 10, 20, 40, 80 or 120 ppm (0, 39, 78, 155, 311 or 466 mg/m^3) of bromomethane 6 hours/day, 5 days/week. The experimental protocol was otherwise the same as used for the rat 13-week study.

Exposure-related changes in the mice included a significant (58%) body weight gain reduction and a 17% increase in mortality in male mice exposed to 466 mg/m^3 bromomethane; 466 mg/m^3 is, therefore, considered to be the frank effect level (FEL). Mice exposed to this level exhibited severe curling and crossing of the hind limbs and twitching of the forelimbs, both more severe in the males. Hematological parameters that were found to be statistically significantly different from control values included decreased mean cell hemoglobin and mean cell volume, and increased erythrocyte count, in males exposed to 155, 311 or 466 mg/m^3, and increased hemoglobin in males exposed to 466 mg/m^3. No exposure-related effects were seen at histopathological examinations. Based on these results, the NOAEL can be estimated as 311 mg/m^3 [NOAEL(HEC)=56 mg/m^3].

Male and female rats (n=135), rabbits (n=104), guinea pigs (n=98) and female rhesus monkeys (n=13) were exposed to 0, 17, 33, 66, 100 or 220 ppm (0, 66, 128, 256, 388 and 854 mg/m^3) of 99% pure bromomethane 7.5-8 hours/day, 5 days/week for 6 months or until the majority exhibited severe reactions or died (Irish et al., 1940). The FELs were 388 mg/m^3 for rats, guinea pigs and monkeys and 128 mg/m^3 for rabbits. Marked pulmonary damage consisting of congestion, edema, and leukocytic infiltration with frequent hemorrhage into the alveoli was observed in most of the guinea pigs that died, but the rats did not exhibit these changes. Rabbits and monkeys exhibited paralysis after exposure to 256 mg/m^3, whereas rats and guinea pigs exhibited no adverse effects. Rats (8/sex), guinea pigs (5 male and 6 female) and monkeys (3 females) survived repeated exposures to 128 mg/m^3 for six months with no gross evidence of toxic effects. Histopathological examination of the rats and guinea pigs showed no exposure related lesions at this concentration, and hematological analysis for the monkeys was normal. At the same concentration, 128 mg/m^3, pulmonary damage was seen in all rabbits (15 died on account of severe lung infection) and the surviving 34 rabbits exhibited the characteristic paralysis observed at higher concentrations. None of the species exhibited adverse effects following repeated exposure to 66 mg/m^3. From these results a LOAEL of 128 mg/m^3 [LOAEL(HEC) of 30 mg/m^3] and a NOAEL of 66 mg/m^3 [NOAEL(HEC) of 15 mg/m^3], based on the neurological effects, can be derived.

Male New Zealand White rabbits were exposed to 0 (n=2) or 26.6 ppm (103 mg/m^3, n=6) of 99% pure bromomethane for 7.5 hours/day, 4 days/week for 8 months (Russo et al., 1984). Neurobehavioral tests examined the latency rates of the sciatic and ulnar nerves and the amplitude of the eye blink reflex of the orbicularis oculi muscle. No other parameters, including respiratory effects, were monitored. No exposure-related neurological effects were observed.

Pregnant New Zealand White rabbits and Wistar or Sprague-Dawley rats were exposed to 0, 20 or 70 ppm (0, 78 or 272 mg/m^3) of bromomethane 6-7 hours/day during gestational days 1-24 or 1-19, respectively (Sikov et al., 1981). The target number of litters per group was 20 for rats and 30 for rabbits. No adverse effects were noted in either the dams or the fetuses in the rat study (NOAEL for maternal and fetal toxicity is 272 mg/m^3). The rabbits exposed to 272 mg/m^3 of bromomethane exhibited body weight loss at approximately one week of exposure which was followed by convulsions, hind limb paresis, and deaths on day 9 of exposure. Exposure was terminated in the rabbits on day 15 in all groups, but the rabbits continued to die through day 27 of gestation. There was no evidence of toxicity in the offspring of these rabbits. Therefore, the FEL for maternal toxicity in rabbits is 272 mg/m^3, with a NOAEL of 78 mg/m^3.

American Biogenics Corporation (1986) conducted a 2-generation reproduction study for bromomethane. Sprague-Dawley rats (25/sex/group) were exposed to 0, 3, 30 or 90 ppm (0, 12, 116 or 350 mg/m^3) for 6 hours /day, 5 days/week. Exposure of the F_0 generation was initiated at 62 days of age and was continuous until sacrifice at 247-248 days of age (133-134 exposures) for males or at 258-259 days of age (132-137 exposures) for females (a 4-day pause in exposure was made from parturition until lactation day 4). Two breeding trials were conducted with both the F_0 and F_1 generations. Weanlings from the second breeding trial were used as the F_1 parental generation. Exposure of the F_1 parental animals was initiated at 29-33 days of age and continued until sacrifice at 224-228 days of age for males (139-140 exposures) or 244-248 days of age (143-145 exposures) for females. Organ weights were measured for the brain, heart, kidneys, liver and gonads. Reproductive organs were examined histopathologically. Continuous data were statistically evaluated by ANOVA followed by Tukey's multiple comparison test, and organ weights were evaluated by Kruskal-Wallis tests.

Significant reductions in body weight gain were observed in the 350 mg/m^3 exposure group males during the 8-week premating period, and also in final body weight. No treatment-related effects on reproduction were found in either generation. A significant dose-related reduction in body weight gain, however, was observed in the neonates in the 116 and 350 mg/m^3 exposure groups in both generations. The decrease was first apparent in 14-day-old neonates, and the difference was highly significant in both sexes by 28 days. No histopathological lesions were observed in the reproductive organs in either generation. Statistical analysis of parental organ weights showed decreases in brain weight for 350 mg/m^3 exposure group males in the F_0 generation and males and females in the F_1 generation. Significant decreases in the heart, kidney, and liver weights in the 350 mg/m^3 F_1 females, and in liver weight in the 177 mg/m^3 F_1 females were also observed. Due to decreases in body weight, however, relative organ weights were not significantly reduced, and the toxicological significance of the organ weight decreases is not clear. No significant teratological effects were observed in either generation. This study establishes a LOAEL of 116 mg/m^3 [LOAEL(HEC)=32 mg/m^3] and a NOAEL of 12 mg/m^3 [NOAEL(HEC)=2.1 mg/m^3].

No effect on testes weight, testicular or epididymal pathology, daily sperm production, sperm concentration, or motility were observed in 75 male Fischer 344 rats exposed to 200 ppm of bromomethane 6 hours/day for 5 days (Hurtt and Working, 1988). A decrease in body weight gain and a significant decrease in nonprotein sulfhydryl levels in the testes and plasma testosterone concentration were observed.

In a chronic inhalation study sponsored by the National Institute of Public Health and Environmental Hygiene of the Netherlands, male and female Wistar rats were exposed to 0, 3, 30 or 90 ppm (0, 12, 116 or 350 mg/m^3) of 98.8% pure bromomethane 6 hours/day, 5 days/week for 29 months (Reuzel et al., 1991). Bromomethane concentrations were measured by gas chromatography every 30 minutes. Each exposure level consisted of 50 animals/sex with four satellite groups of 10 animals/sex/exposure level. The animals in the satellite groups were sacrificed at 14, 53 and 105 weeks of exposure. Animals were observed daily; body weight was recorded weekly for the first 12 weeks and monthly thereafter. Hematology, clinical chemistry and urinalyses were conducted at 12-14 weeks and 52-53 weeks in the satellite groups. Eleven organs were weighed at necropsy, and approximately 36 tissues, including the lungs with trachea and larynx, and six cross-sections of the nose, were examined histopathologically.

The only significant treatment-related effects observed at 14 and 53 weeks were decreased body weight gains in males and females exposed to 350 mg/m^3. Body weight gain decreases were statistically significant for most time points from day 28 to study completion. An increase in mortality was observed in the 350 mg/m^3 males that was statistically significant only at the 114-week sacrifice. No treatment-related changes in hematological, biochemical or urine parameters were noted throughout the study. A significant concentration-related decrease in relative kidney weights was reported in the 116 and 350 mg/m^3 males, and a decrease in mean absolute brain weight was reported to occur in the 350 mg/m^3 females at weeks 53 and 105, but there was no change in relative brain weight. Microscopic evaluation revealed that the nose, the heart, and the esophagus and forestomach were the principle targets of bromomethane toxicity in this study. Very slight to moderate hyperplastic changes in the basal cells accompanied by degeneration in the olfactory epithelium in the dorso-medial part of the nasal cavity were observed in all exposed groups of both sexes by 29 months of exposure. Lesions in the heart included increased incidence of thrombi and cartilaginous metaplasia, as well as myocardial metaplasia. These effects were statistically significant in the males exposed to 350 mg/m^3 of bromomethane, and the females exposed to 12 mg/m^3 (cartilaginous metaplasia only). The authors attributed part of the increased mortality in the high-concentration animals to the cardiac lesions. A statistically significant increase in hyperkeratosis of the esophagus was observed in the 350 mg/m^3 males after 29 months of exposure. No other exposure-related effects were noted. Based on these results, a chronic LOAEL of 12 mg/m^3 [LOAEL(HEC)=0.43 mg/m^3] for nasal effects was identified; no NOAEL was identified by this study.

No differences between control and treated animals in sites or types of incidences of tumors were observed at either the 14-week or 53-week sacrifices (Reuzel et al., 1991). In the groups of 50 animals exposed for 29 months, the incidence of females bearing fibroadenomas of the mammary glands was statistically significantly decreased in the 350 mg/m^3 exposure group. Also, the incidence of pheochromocytomas in the adrenals of males was significantly decreased. The incidences of other neoplastic lesions either showed no significant differences between the

groups, or the tumors occurred only in one or a few animals. The authors concluded that the data did not indicate carcinogenic activity of bromomethane.

In a chronic inhalation study in mice (NTP, 1992), a total of 86 B6C3F1 mice/sex/dose were exposed to 0, 10, 33 or 100 ppm (0, 39, 128 or 388 mg/m^3) of bromomethane 6 hours/day 5 days/week for either 6 months, 15 months, or 103 weeks (39 or 128 mg/m^3). Exposure to 388 mg/m^3 produced greater than 31% mortality in males and greater than 8% mortality in females by 20 weeks; exposure was, therefore, discontinued in this group, and the surviving animals were observed for an additional 84 weeks, except for the females scheduled for the 15-month sacrifice. The endpoints studied included clinical observations, mortality, body and organ weights, hematology, clinical chemistry, urinalysis, gross pathology and histopathology of a standard set of tissues, including the lungs and nasal turbinates. In addition, neurobehavior was assessed in 16 mice/sex/group and neuropathological examination on 3-8 animals/sex/group at 20 weeks, 6, 15, and 24 months.

Body weights were significantly depressed in the animals exposed to 388 mg/m^3 (33% in the males and 31% in the females) beginning at week 11 and persisting until study termination. Significant body weight changes were not observed in the lower exposure groups. Because of the reduced body weight in the 388 mg/m^3 animals, organ weight changes were difficult to interpret, but reduced absolute and relative thymus weights were observed in both the males and females exposed to 388 mg/m^3 of bromomethane. Clinical signs of toxicity, observed almost exclusively in the 388 mg/m^3 animals, that persisted throughout the 103 weeks included tremors, abnormal posture, and limb paralysis. Functional neurobehavioral changes consisting of hypoactivity, a heightened startle response, and higher hind limb grip scores and hot plate latency were observed in both sexes exposed to 388 mg/m^3, but were more pronounced in the males. The target organs of toxicity identified in this study were the brain, bone (sternum), heart and nose, with lesions in these organs occurring more frequently in the males. In the brain, there was a statistically significant increase in the incidence of cerebellar degeneration in the animals exposed to 388 mg/m^3. Cerebral degeneration was also observed in these animals, but the incidence of this lesion was statistically significant in the males only. Because these lesions were observed more frequently in the animals that died prior to study termination, the authors concluded that they may have contributed to the early mortality in this group. Dysplasia of the sternal bone marrow was observed at a statistically significant increased rate in both the males and the females exposed to 388 mg/m^3, but because it was observed more frequently in the animals that survived to study termination than in those that died early, it was not considered to be a contributing factor to the death of these animals. Myocardial degeneration and chronic cardiomyopathy were also observed at a statistically higher incidence in both males and females exposed to 388 mg/m^3, and occurred at a higher incidence in those animals dying early. Finally, a statistically significant increase in the incidence of olfactory epithelial necrosis and metaplasia was seen in the nasal cavities of both the male and female mice exposed to 388 mg/m^3. Necrosis was seen only in the animals dying early, whereas metaplasia was exhibited mainly in those animals surviving until study termination. Histopathological changes in other organs were observed and considered to be secondary to stress and weight loss rather than a direct toxic effect of bromomethane. Animals exposed to lower concentrations did not exhibit significant increases in any of the lesions described above. Based on the results of this study, a NOAEL of 128

mg/m^3 [NOAEL(HEC)=5 mg/m^3] and a LOAEL of 388 mg/m^3 [LOAEL(HEC)= 14 mg/m^3] for extrathoracic effects is estimated for chronic exposure to bromomethane.

No tumors were observed at the time of the 6-month interim evaluation (NTP, 1992). Tumors observed at the 15-month interim sacrifice included four hepatocellular adenomas (control: 1/9, 39 mg/m^3: 3/9), one alveolar/bronchiolar adenoma in a 39 mg/m^3 male, one alveolar/bronchiolar carcinoma in a 128 mg/m^3 male, one pheochromocytoma of the adrenal gland in a 128 mg/m^3 female, and one hemangiosarcoma in a control female. No treatment-related increases in tumor incidence were observed at any time during the study. The authors concluded that under the conditions of this 2-year study there was no evidence of carcinogenic activity of bromomethane in male or female B6C3F1 mice.

Toxicity and carcinogenicity studies were conducted by inhalation exposure of groups of 50 male and 50 female Crj:BDF1 mice (6 h/day, 5 days/week) to bromomethane (99.9% pure) for 104 weeks (Japanese Ministry of Labour, 1992; Gotoh et al., 1994). Bromomethane concentrations of 0, 16, 62 and 250 mg/m^3 were used. Body weight gains in male and female mice exposed to 250 mg/m^3 were lower than those in chamber controls. No significant differences in survival were observed between exposed and control groups of either sex. Increased incidences of atrophy (slight) of the granular layer of the cerebellum were observed in male and female mice exposed to 250 mg/m^3. There were no treatment-related neoplasms in male or female mice.

Toxicity and carcinogenicity studies were also conducted by inhalation exposure to bromomethane (99.9% pure) of groups of 50 male and 50 female F344/DuCrj rats (6 h/day, 5 days/week) for 104 weeks (Japanese Ministry of Labour, 1992; Gotoh et al., 1994). Bromomethane concentrations of 0, 16, 78, and 389 mg/m^3 were used. Body weight gains in males and female rats exposed to 389 mg bromomethane/m^3 were lower than those in chamber controls. No significant differences in survival were observed between exposed and control groups of either sex. Increased incidences of necrosis and respiratory metaplasia of the olfactory epithelium of the nasal cavity were observed in male rats exposed to 389 mg bromomethane/m^3, and increased incidence and severity of inflammation of the nasal cavity were observed in male rats exposed at all concentrations used. Necrosis of the olfactory epithelium and inflammation of the nasal cavity were marginally increased in female rats exposed to 389 mg bromomethane/m^3. There were no exposure-related increased incidences of neoplasms in male and female rats.

Rosenblum et al. (1960) reported a 1-year study in which beagle dogs of either sex (4/treatment group, 6/control) were fed bromomethane fumigated food *ad libitum*. Diets were fumigated to residue levels of 0, 35, 75 or 150 ppm of bromide. High-dose animals gained more weight than the controls or the two lower treatment groups; they also became lethargic and displayed excessive salivation and occasional diarrhea. Other than mild hepatic focal inflammation, which did not demonstrate a clear dose-response relationship, no other effects of exposure were seen. No tumors were reported at any dose level; however, there was no indication that the dogs were examined for tumors. Additionally, the authors noted that Shrader et al. (1942) demonstrated that little of the bromide residue following bromomethane fumigation is in the form of bromomethane. Because it is likely that the bromine residues in the diet were not in the form of bromomethane, this study was not considered adequate for risk assessment

purposes. Similar studies by Wilson et al. (1998) in dogs and Mitsumori et al. (1990) in rats also found no evidence of tumor formation in animals fed diets fumigated with bromomethane for 1 (dogs) or 2 (rats) years, but were of limited utility for bromomethane assessment due to very low doses of unchanged chemical remaining in the diet (0.28 mg/kg-day in the high-dose group in the Wilson et al. 1998 study).

Other Studies

Data summarized in NTP (1992) and by Bolt and Gansewendt (1993) clearly indicate that bromomethane can cause genotoxic and/or mutagenic changes. Bromomethane was positive for reverse mutation, either with or without S9 activation, in *Salmonella typhimurium* strains TA 100 and TA 1535, but negative in strains TA 1537, TA 1538, and TA 98. It was positive for mutation induction in *Escherichia coli* WP2 hcr and Sd4 and in the *Klebsiella pneumoniae* fluctuation test. It was positive in *Drosophila melanogaster* sex-linked recessive lethal test and for somatic recombination. Bromomethane has also been shown to induce SCE in human lymphocytes *in vitro* and in rats and mice *in vivo*. It tested positive for induction of 6-thioguanine and bromodeoxyuridine resistance in L5178Y mouse lymphoma cells, but negative in an assay in primary rat hepatocytes and for transformation by SA7 adenovirus in Syrian hamster embryo cells.

Bromomethane is a very reactive methylating agent and readily methylates thiols, thioether sulfurs, nitrogen in amino groups and rings, and oxygen atoms in carboxylate ions and hydroxy groups (Vogel and Nivard, 1994). Gansewendt et al. (1991) exposed male and female F344 rats to [^{14}C]bromomethane by inhalation (4 hours) or oral administration. DNA adducts were detected in the liver, lung, stomach, and forestomach, with the highest activity in the stomach and forestomach regardless of the route of administration. They isolated [^{14}C]3-methyl adenine, [^{14}C]7-methylguanine, and [^{14}C]O^{6}-methylguanine from hydrolyzed DNA. These results clearly indicate that bromomethane is distributed throughout the body and is capable of methylating DNA *in vivo*.

DERIVATION OF A PROVISIONAL SUBCHRONIC RfD FOR BROMOMETHANE

The most sensitive toxicological response to oral bromomethane exposure was the development of forestomach hyperplasia in rats in the 13-week study of Danse et al. (1984); the study identified the 2 mg/kg exposure level as a NOAEL and the 10 mg/kg exposure level as a LOAEL for this effect. Hubbs (1986) also observed hyperplasia in the forestomachs of rats orally administered doses of either 25 or 50 mg/kg bromomethane for 90 days; however, a NOAEL was not established in this study. The study of Peters et al. (1981) reported a NOAEL of 5 mg/kg-day and a LOAEL of 25 mg/kg-day for maternal toxicity in a developmental study, with forestomach lesions the most prevalent toxic effect. Wilson et al. (1998) exposed dogs to up to 0.28 mg/kg-day for 1 year, and reported no effects on any endpoint examined. Therefore, the study of Danse et al. (1984), which identified the lowest reliable subchronic LOAEL, was selected as the principal study and the NOAEL of 2 mg/kg was selected as the point-of-departure for calculation of a provisional RfD. The NOAEL of 5 mg/kg-day for the same endpoint in

maternal rats identified by Peters et al. (1981) was not selected as the point of departure because the exposure duration was only 16 days. Calculation of the provisional subchronic RfD is as follows:

The NOAEL of 2 mg/kg was first adjusted for the 5 days/week exposure schedule:

$$\text{NOAEL(ADJ)} = 2 \text{ mg/kg} \times 5 \text{ days/7days}$$
$$= 1.4 \text{ mg/kg-day}$$

Using this value, the subchronic p-RfD was calculated as follows:

$$\text{Subchronic p-RfD} = \text{NOAEL(ADJ)} \div \text{UF}$$
$$= 1.4 \text{ mg/kg-day} \div 300$$
$$\mathbf{= 5E\text{-}3 \text{ mg/kg-day}}$$

The uncertainty factor of 300 was calculated as follows: 10 for extrapolation of the results of animal study to humans; 10 for intrahuman variability, in acknowledgement of the possible presence of individuals or subpopulations who may be more sensitive to the effects of bromomethane; and 3 to account for deficiencies in the database, including a lack of an adequate 2-generation reproduction study. While it has been suggested that the rat forestomach may be more sensitive than the human stomach with regards to the development of irritation-like lesions (for review, see Wester and Kroes, 1988), the relevance of the differences in physiology between rats and humans to the toxicity of bromomethane are not sufficiently clear to warrant a departure from the default uncertainty factor for extrapolation from animal data to humans; a full factor of 10 for extrapolation from an animal study to humans was used. A full factor of ten was not deemed necessary for database deficiencies because while an adequate 2-generation study of reproductive effects is not available, studies of the developmental effects of bromomethane in rats and rabbits exist, and both a 1-generation oral study of reproduction in rats and a 2-generation rat reproduction study by the inhalation route (American Biogenics Corporation, 1986) have shown no effects on reproductive or developmental endpoints. The NOAEL(ADJ) was then divided by the uncertainty factor (UF) of 300 to derive a subchronic p-RfD of 5E-3 mg/kg-day. This value is 3-fold lower than the subchronic RfD in the HEA (U.S. EPA, 1987) because the uncertainty factor of 3 to account for database deficiencies was not applied in the earlier assessment.

Confidence in the principal study is medium. The study by Danse et al. (1984) used an adequate number of animals (10/sex/treatment), and the study design included an adequate range of dose levels to establish LOAEL and NOAEL values. The study was well conducted and characterized; however, only a limited range of organs was examined histologically. The finding of forestomach hyperplasia was supported by similar observations in two other subchronic studies (Hubbs, 1986; Boorman et al., 1986) and in a developmental study (Peters et al., 1981). Confidence in the database is medium. The database contains several adequate evaluations of the subchronic toxicity of bromomethane in rats, as well as analysis of the developmental effects of bromomethane. However, adequate subchronic studies that identify LOAELs in species other than the rat are lacking, and a 2-generation study of reproductive effects was not located. Medium confidence in the provisional subchronic RfD results.

DERIVATION OF A PROVISIONAL SUBCHRONIC RfC FOR BROMOMETHANE

The dose response curve for bromomethane in animal studies is steep, and in many studies the transition from a NOAEL to a FEL occurred in a single step in experimental exposure concentration (NTP, 1992; Irish et al., 1940). Dramatic increases in toxicity can also be observed with relatively small increases in the exposure time. For example, in the NTP study (NTP, 1992), exposure of B6C3F1 mice to 388 mg/m^3 for 14 days did not cause mortality or any obvious signs of toxicity, whereas exposure to 388 mg/m^3 for 20 weeks, as part of the chronic study, produced mortality exceeding 31% in males and 8% in females. However, the next lower exposure level (128 mg/m^3) was a NOAEL for all effects in the chronic study in mice. In the 13-week exposure study, there was a lack of any marked toxicological findings in mice exposed to 466 mg/m^3 (NTP, 1992). The 6-month study by Irish et al. (1940) reported that in exposed rabbits, 128 mg/m^3 was a FEL (based on paralysis and severe pulmonary damage), while 66 mg/m^3 was a NOAEL. The same study (Irish et al., 1940) reported a NOAEL of 128 mg/m^3 and FEL of 388 mg/m^3 in both rats and monkeys. Thus, animals may appear normal when exposed to a given concentration of bromomethane, only to suffer mortality or other serious toxic responses with a relatively small increase in concentration or exposure time.

The pharmacokinetics of inhaled bromomethane are reviewed in Yang et al. (1995). Bromomethane is rapidly absorbed from respiratory tissues, and widely distributed throughout the body. Metabolism is rapid and extensive, with virtually none of the parent compound present in the expired air, urine, or feces. The major clearance pathway for bromomethane is the expired air, primarily as CO_2; elimination follows first-order kinetics. In humans, a glutathione-based metabolic pathway exists that is not believed to be present in rodents; the potential role of this pathway in the effects of bromomethane in man is not known.

To select the most appropriate indicator of potential adverse effects in humans, human equivalent concentrations (HEC) were calculated for the most sensitive toxic effect in the most sensitive species in the summarized studies. For this purpose it was first necessary to evaluate the properties of bromomethane to select the most appropriate model for calculation of the HEC values.

At low concentrations bromomethane behaves mostly like a Category 1 gas, as its absorption is not concentration limited, and metabolism is rapid. Although Bond et al. (1985) apparently detected intact bromomethane in the organs of rats, no bromomethane was detected in the blood of rats in the first four hours after exposure. Exhalation of intact [^{14}C]bromomethane was observed to be minimal, both in humans (Raabe, 1988) and in rats (Medinsky et al., 1985). Thus, bromomethane appears to be metabolized rapidly and irreversibly. This is commensurate with the lack of extrarespiratory effects observed at low concentrations. Several experiments demonstrated that the most sensitive indicator of bromomethane toxicity in rats was degeneration of the nasal olfactory epithelium (NTP, 1992; Reuzel et al., 1991). Thus, for the extrathoracic effects on nasal olfactory epithelium, HECs were calculated using the equations for a Category 1 gas (U.S. EPA, 1994b).

At higher concentrations, however, sufficient bromomethane apparently enters the blood and is distributed throughout the body to induce extrarespiratory toxicity. Thus, at high concentrations bromomethane behaves as a Category 3 gas. Therefore, HECs for extrarespiratory effects were calculated by the equation for Category 3 gases (U.S. EPA, 1994b).

After calculation of the NOAEL(HEC) values, presented in Table 1, the 13-week rat inhalation study by NTP (1992) was selected as the critical study, with degeneration of the olfactory epithelium of the nasal cavity as the critical effect. This choice of NOAEL is supported by the interim sacrifice data from Reuzel et al. (1991) which similarly identified a NOAEL of 4 mg/m^3, though for body weight changes rather than histological evaluations. Neurological effects, while of toxicological relevance, appear to occur at somewhat higher concentrations than the nasal effects; an RfC based on irritation of the nasal epithelium should, therefore, also be protective of neurological effects. Available studies of the reproductive and developmental effects of bromomethane have not demonstrated these endpoints to be sensitive effects of bromomethane.

Table 1. Subchronic NOAEL and LOAELs, and Corresponding HEC Values

Study	Species	Critical Endpoint	NOAEL	LOAEL	$NOAEL_{(HEC)}$	$LOAEL_{(HEC)}$
NTP (1992)	Rat	Respiratory	233 mg/m^3	466 mg/m^3	4 mg/m^3	8 mg/m^3
NTP (1992)	Mouse	Respiratory	310 mg/m^3	466 mg/m^3	56 mg/m^3	84 mg/m^3
Irish et al. (1940)	Rabbit	Neurological	128 mg/m^3	256 mg/m^3	13 mg/m^3	27 mg/m^3
Irish et al. (1940)	Monkey	Neurological	128 mg/m^3	256 mg/m^3	13 mg/m^3	27 mg/m^3
Russo et al. (1984)	Rabbit	Neurological	103 mg/m^3	None	16 mg/m^3	None
Reuzel et al. (1991)	Rat	Body Weight	116 mg/m^3	350 mg/m^3	4 mg/m^3	12.5 mg/m^3

The NOAEL (HEC) value of 4 mg/m^3 from the subchronic NTP (1992) study was divided by an uncertainty factor of 30 (10 to protect unusually sensitive individuals and 3 for interspecies extrapolation using dosimetric adjustments) to derive a subchronic p-RfC for bromomethane. An additional database uncertainty factor was not applied because the database includes adequate supporting subchronic, chronic, reproductive, and developmental studies.

Subchronic p-RfC = 4 mg/m^3 ÷ 30 = 1E-1 mg/m^3

Confidence in the critical study is high. The critical study (NTP, 1992) was well-conducted, used an appropriate number of animals and exposure levels, and histopathological examination of the respiratory tract was thorough and complete. The NOAEL identified in this study is supported by the effects seen in rats in the five-day rat study of Hurtt et al. (1987), the subacute two-week rat study of Hastings (1990), and the chronic study of Reuzel et al. (1991). Additionally, the database is given a high confidence rating because there is a chronic inhalation study in two species supported by subchronic inhalation studies in several species, and because data are available on the developmental and reproductive effects, including a two-generation reproductive study. The database is further strengthened by studies on the pharmacokinetics following inhalation exposure. Therefore, confidence in the subchronic p-RfC is high.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR BROMOMETHANE

Weight-of-evidence Classification

Data on the carcinogenicity of bromomethane following oral exposure are lacking. As bromomethane is a highly volatile gas at room temperature, this is not unexpected. A 1-year study in dogs consuming bromomethane-exposed food (Rosenblum et al., 1960) found no evidence of carcinogenicity; however, it is likely that the bromide reported in the food was not in the form of bromomethane (Shrader et al., 1942). Data on the carcinogenicity of bromomethane following inhalation exposure in humans are not available. Adequate inhalation studies in F344 and Wistar rats (Reuzel et al., 1991; Japanese Ministry of Labour, 1992; Gotoh et al., 1994), and in B6C3F1 and Crj:BDF1 mice (NTP, 1992; Japanese Ministry of Labour, 1992; Gotoh et al., 1994) have not demonstrated evidence of bromomethane-induced carcinogenic changes. Adequate oral studies of bromomethane carcinogenicity have not been reported. A 3-month oral study in rats (Danse et al., 1984) reported neoplastic changes in the forestomach of exposed animals. However, questions regarding these results (U.S. EPA, 1985; Schatzow, 1984) resulted in a re-evaluation of the histological results of the study that concluded that the lesions were hyperplasia and inflammation rather than neoplasia. *In vitro* studies in both bacteria and mammalian cells have demonstrated a mixed genotoxic response to bromomethane. Female mice exposed to bromomethane for 2 weeks showed increased incidence of micronucleus formation (NTP, 1992), and rats of either sex exposed to radiolabeled bromomethane by inhalation for 4 hours showed increases in labeled DNA adducts. Under EPA cancer guidelines (U.S. EPA, 2005), there is inadequate information to assess the carcinogenic potential of bromomethane in humans.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for bromomethane is precluded by the absence of data demonstrating carcinogenicity associated with bromomethane exposure.

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