Bromodichloromethane; CASRN 75-27-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Bromodichloromethane

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	02/01/1993

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Bromodichloromethane
CASRN — 75-27-4
Last Revised — 09/30/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Renal cytomegaly **Chronic Mouse Gavage Bioassay** **NTP, 1986**	NOAEL: None LOAEL: 17.9 mg/kg/day	1000	1	2E-2 mg/kg/day

*Conversion Factors -- Dose adjusted for treatment schedule (5\days/week).

I.A.2. Principal and Supporting Studies (Oral RfD)

NTP (National Toxicology Program). 1986. Toxicology and Carcinogenesis Studies of Bromodichloromethane in F344/N Rats and B6C3F1 Mice (gavage studies). NTP Technical Report, Ser. No. 321, NIH Publ. No. 87-2537.

Bromodichloromethane (BDCM) was administered in corn oil by gavage, 5 days/week for 102 weeks, to groups of 50 male and 50 female F344/N rats at doses of 0, 50, or 100 mg/kg/day; to groups of 50 male B6C3F1 mice at doses of 0, 25, or 50 mg/kg/day; and to groups of 50 B6C3F1 female mice at doses of 0, 75, or 150 mg/kg/day. Final survival of dosed female mice was reduced compared with controls. Final mean body weights of dosed female mice and high-dose male and female rats were 75 to 91% that of vehicle controls. Compound-related nonneoplastic lesions included cytomegaly and tubular cell hyperplasia of the kidney and fatty metamorphosis of the liver in male rats; eosinophilic cytoplasmic change, clear cell change, focal cellular change, and fatty metamorphosis of the liver and tubular cell hyperplasia of the kidney in female rats; fatty metamorphosis of the liver, renal cytomegaly, and follicular cell hyperplasia of the thyroid gland in male mice; and follicular cell hyperplasia of the thyroid gland in female mice. A LOAEL of 17.9 mg/kg/day (25 mg/kg/day x 5 days/7 days) based on renal cytomegaly in male mice, an effect considered minimal in the absence of data demonstrating renal functional impairment, is indicated by these results.

In a subchronic bioassay conducted by NTP (1986), male and female rats received doses of 19 to 300 mg/kg/day, male mice received doses of 6.25 to 100 mg/kg/day, and female mice received doses of 25 to 400 mg/kg/day for 5 days/week. Five of 10 male rats and 2/10 female rats at 300 mg/kg/day died. Final body weights of male and female rats in the 150 or 300 mg/kg/day treatment groups, male mice receiving 100 mg/kg/day and female mice receiving 200 or 400 mg/kg/day, were lower than those of controls. Centrilobular degeneration of the liver and degeneration and necrosis of the kidney were seen in high-dose male rats; liver lesions were observed in high-dose female rats and in female mice at 200 or 400 mg/kg/day, and kidney lesions were seen in male mice at 100 mg/kg/day. These data define a NOAEL of 35.7 mg/kg/day (50 mg/kg/day x 5 days/7 days), a dose above which produced kidney lesions and depressed body weight in male mice. Because the chronic study used more animals/dose, was of longer duration, and presented more complete data, more confidence is placed in the chronic LOAEL than in the subchronic NOAEL.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — A factor of 100 was employed for extrapolation from animal data and for protection of sensitive human subpopulations. An additional factor of 10 was used because the RfD was based on a LOAEL (although minimally adverse), and to account for database deficiencies (no reproductive studies).

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

A study by Chu et al. (1982) who administered bromodichloromethane in the drinking water to rats for 90 days reported a no-effect level of 0.45 mg/kg/day. This study, however, is not considered suitable for derivation of the RfD because of difficulties in interpretation of study design and statistical methodology.

There are no published data on teratogenicity or reproductive effects of trihalomethanes.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

Confidence in the study is rated medium because although NTP (1986) incorporated both chronic and subchronic exposures in two species using sufficient numbers of animals and

measured multiple endpoints, including histopathology of most organ systems, a NOEL was not determined. Although there are some discrepancies in the dose levels producing adverse effects, there are several published subchronic studies of bromodichloromethane permitting confidence in the database to be rated medium to low. Thus, overall confidence in the RfD is rated medium to low.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 12/02/1985, 02/05/1986, 05/14/1986, 07/16/1987

Verification Date — 07/16/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Bromodichloromethane conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Bromodichloromethane
CASRN — 75-27-4

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Bromodichloromethane
CASRN — 75-27-4
Last Revised — 02/01/1993

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Based on inadequate human data and sufficient evidence of carcinogenicity in two animal species (mice and rats) as shown by increased incidence of kidney tumors and tumors of the large intestine in male and female rats, kidney tumors in male mice, and liver tumors in female mice.

II.A.2. Human Carcinogenicity Data

Inadequate. There are no epidemiologic studies of bromodichloromethane alone. Bromodichloromethane is one of several trihalomethanes (including chloroform, bromoform and dibromochloromethane) that are formed from the interaction of chlorine with organic materials found in water. A large number of other byproducts are present in chlorinated water as well. Several ecologic studies (Cantor et al., 1978; Aldrich and Peoples, 1982; Isacson et al., 1983) and case-control studies (Young and Kanarek, 1983; Cantor et al., 1987) suggest a positive

correlation between drinking chlorinated water and the incidence of several human cancers, particularly bladder, rectal and colon cancer. These studies have design limitations such as lack of individual exposure information, misclassification of exposure, and lack of data to control for diet, smoking or alcohol consumption. The agreement of findings in several independent studies strengthens the association between drinking chlorinated water and cancer (Cantor, 1983; Crump, 1983). However, in all studies exposure to chlorinated water resulted in intake of a mixture of compounds, including chloroform, which is considered to be a probable human carcinogen. Thus, these data are inadequate for assessing the carcinogenic potential of bromodichloromethane in humans.

II.A.3. Animal Carcinogenicity Data

Sufficient. In a 2-year carcinogenicity study (NTP, 1987), bromodichloromethane was administered in corn oil by gavage, 5 days/week for 102 weeks, to F344/N rats (50/sex/dose) at 0, 50 or 100 mg/kg/day. Similarly, groups of 50 male B6C3F1 mice were given oral doses of 0, 25 or 50 mg/kg/day and groups of 50 female B6C3F1 mice were administered doses of 0, 75 or 150 mg/kg/day. The study using the male rats was restarted 10.5 months into the original study because a temperature elevation killed 45/50 of the vehicle control male rats. Survival was reduced 52%, 26% and 30% in the control, low- dose and high-dose females, respectively, after week 84; the mortality was associated with ovarian abscesses.

Bromodichloromethane caused compound-related statistically significant increases in tumors of the kidney in male mice, the liver in female mice, and the kidney and large intestine in male and female rats. In male mice, the incidence of tubular cell adenomas (vehicle control, 1/46; low dose, 2/49; high dose, 6/50) and the combined incidence of tubular cell adenomas and adenocarcinomas of the kidneys were significantly increased in the high-dose (50 mg/kg/day) group (1/46, 2/49 and 9/50 in the control, low-dose and high- dose groups, respectively). In female mice, significant increases of hepatocellular adenomas occurred at 75 mg/kg/day and 150 mg/kg/day while hepatocellular carcinomas were significantly increased at 150 mg/kg/day. The combined incidence of hepatocellular adenomas or carcinomas in vehicle control, low-dose and high-dose groups were 3/50, 18/48 and 29/50, respectively.

In male and female rats, the incidences of tubular cellular adenomas, adenocarcinomas, and the combined incidence of adenomas and adenocarcinomas of the kidneys were statistically significantly increased only in the high-dose (100 mg/kg/day) groups. The combined incidence of tubular cell adenomas or adenocarcinomas in vehicle control, low-dose and high-dose groups were 0/50, 1/49 and 13/50 for males, and 0/50, 1/50 and 15/50 for females, respectively. Tumors of large intestines, namely adenocarcinomas (vehicle control, 0/50; low dose, 11/49; high dose, 38/50) and adenomatous polyps (0/50, 3/49 and 33/50 in the vechicle control, low-dose and high-dose groups, respectively) were significantly increased in male rats in a dose-dependent manner.

These large intestinal tumors, however, were only observed in high-dose (100 mg/kg/day) female rats (adenocarcinomas 0/46, 0/50, 6/47; adenomatous polyps 0/46, 0/50, 7/47 in the vehicle control, low-dose and high-dose groups, respectively). The combined incidence of large intestine adenocarcinomas and/or adenomatous polyps in vehicle control, low-dose and high-dose groups were 0/50, 13/49 and 45/50 for males and 0/46, 0/50 and 12/47 for females. The combined tumor incidence of large intestine and kidney in male and female rats at control, low dose and high dose were 0/50, 13/49, 46/50 and 0/46, 1/50, 24/48, respectively. Under the conditions of this bioassay, NTP concluded there was clear evidence of carcinogenicity of bromodichloromethane in male and female F344/N rats and B6C3F1 mice.

Hepatic tumor data reported in female mice should be interpreted with caution, however, because of the possible role of the corn oil vehicle in induction of these tumors. Chloroform, a closely related structural analogue, induced hepatocellular carcinoma in mice (NCI, 1979) when administered in corn oil (NCI, 1976; Roe et al., 1976), but not in drinking water (Jorgenson et al., 1985). Based primarily on the fact that the drinking water study did not replicate hepatic tumors in female mice and on the potential role of corn oil in enhancing toxicity, the NAS Subcommittee on the Health Effects of Disinfectants and Disinfection By-Products recommended that kidney tumor data obtained from Jorgenson's study be used for estimating carcinogenic risk of chloroform (NAS, 1987; U.S. EPA, 1992a,b,c, 1993).

On October 25-26, 1990, the Science Advisory Board's Drinking Water Committee held a meeting in Washington, DC to review the Office of Water's draft Drinking Water Criteria Document for Trihalomethanes (including bromodichloromethane) (1990 version). Based on the concern of the corn oil vehicle effect cited for chloroform, the Committee concluded that hepatic tumor induction by a trihalomethane administered in an oil vehicle should be utilized only in making the weight-of-evidence judgement for carcinogenicity, and these hepatic tumor data should be disregarded in making a quantitative estimation of the carcinogenic risk of a trihalomethane. Commenting on bromodichloromethane specifically, the Committee considered the use of renal or intestinal tumor incidence for carcinogenic risk calculation to be appropriate. The Committee regarded the resulting kidney tumors to be independent from the vehicle effects (U.S. EPA, 1992d). The Committee also commented that large intestinal tumors are not commonly seen in the rat, the tumor incidence was high in males, and was observed in both sexes (U.S. EPA, 1992d).

Theiss et al. (1977) tested bromodichloromethane in a short-term lung adenoma test in strain A/St male mice. Twenty mice/group were injected intraperitoneally with 0, 20, 40 or 100 mg/kg of bromodichloromethane in tricaprylin, 3 times/week for a total of 18-24 injections (total doses were 0, 360, 960 or 2400 mg/kg, respectively). There was no effect of treatment on survival. Twenty-four weeks after the first injection, the mice were sacrificed and the lungs examined for surface adenomas. The number of pulmonary tumors per mouse appeared elevated in the high-

dose animals, although the increase was not statistically significant (p=0.062).

In a unpublished but documented 2-year study, SPF Wistar rats (40/sex/group) were fed a diet supplemented with 0.014, 0.055 or 0.22% microencapsulated bromodichloromethane (Tobe et al., 1982). Based on reported body weights (150-475 g) and food consumption (15-20 g/day), these levels correspond to doses of about 6, 24 or 130 mg/kg/day for males and 11, 41 or 220 mg/kg/day for females. Controls (70/sex) received empty microcapsules. At 6, 12 and 18 months, 9-12/sex of the controls and 5-7/sex/group of the treated rats were sacrificed. The remainder of the animals were sacrificed at 24 months. Body weight was decreased in the high-dose animals by 25% relative to controls. Mortality was not correlated with dose in either males or females. Survival at 24 months was 77, 81, 75 and 77% in females and 58, 60, 62 and 79% in males for the control, low-, mid- and high-dose groups, respectively. No gross tumors were observed at 18 or 24 months; histopathology was not reported.

Tumasonis et al. (1985) administered 1.2 mL bromodichloromethane per liter of drinking (tap) water to male and female Wistar rats for 72 weeks, after which concentrations were halved for the remainder of the lifetime of the animals (140-180 weeks). Controls were untreated. Body weight decreased in treated animals relative to controls by approximately 35-40%. The authors estimated the treated animals consumed 150 mg/kg/day (females) or 200 mg/kg/day (males). Hepatic neoplastic nodules were significantly elevated in female rats (17/53) when compared with controls (0/18). Neoplastic nodules in males and lymphosarcomas and pituitary tumors in both sexes were reported, but did not have an significantly increased incidence relative to the controls. Of the treated animals, two males and one female were noted to have renal adenoma or adenocarcinoma, while none were reported in the control group.

Voronin et al. (1987) examined the carcinogenicity of bromodichloromethane in CBA x C57Bl/6 mice. Groups of 50-55 mice/sex were treated with bromodichloromethane in drinking water at concentrations of 0.04, 4.0 or 400 mg/L (0.0076, 0.76 or 76 mg/kg/day) for 104 weeks. An untreated control group with 75 male and 50 female mice was also maintained. Total tumor incidences, based on the number of mice surviving until detection of the first tumor, were 4/63 (6%), 3/35 (8%), 1/16 (6%) and 1/18 (9%) for males, and 3/34 (9%), 1/45 (2%), 1/18 (6%) and 1/13 (8%) for females in the control, low-, mid- and high- dose groups, respectively. The authors concluded that the results were not statistically significant by chi square analysis, and that under the conditions of this bioassay, bromodichloromethane was not carcinogenic.

II.A.4. Supporting Data for Carcinogenicity

Bromodichloromethane was mutagenic in Salmonella typhimurium strain TA100 in the absence of liver homogenate in a vapor phase test performed in a desiccator. When tested in a standard Salmonella/microsomal assay, however, the compound was not mutagenic (Simmon et al.,

1977). Varma et al. (1988) reported that bromodichloromethane was mutagenic in Salmonella typhimurium strain TA1537 without rat liver homogenate activation. Similar results were also reported by Ishidate et al. (1982) using Salmonella typhimurium strain TA100. Mortelmans et al. (1986) reported bromodichloromethane was not mutagenic in S. typhimurium strains TA98, TA100, TA1535 or TA1538 both with and without rat or hamster liver homogenate. Bromodichloromethane did not induce mitotic recombination in the presence or absence of liver homogenate in studies with Saccharomyces cerevisiae strain D3 (Simmon and Kauhanen, 1978). However, Nestmann and Lee (1985) observed weak mutagenic effects in S. cerevisiae strains D7 and XV185-14C following exposure to bromodichloromethane in the absence of liver homogenate.

Bromodichloromethane was not mutagenic in the mouse lymphoma L5178/TK+/- assay in the absence of rat liver homogenate, but did induce forward mutations in this system in the presence of rat liver homogenate (NTP, 1987). Morimoto and Koizumi (1983) reported that bromodichloromethane produced a significant increase in the frequency of SCEs in both cultured human peripheral blood lymphocytes treated in vitro and mouse bone marrow cells treated in vivo. Similarly, Sobti (1984) reported statistically significant increases in the frequency of SCEs in human lymphocytes and rat liver cells exposed in vitro. A statistically significant increase in the frequency of chromosomal aberrations in Chinese hamster fibroblast was observed by Ishidate et al. (1982), but only in the presence of rat liver homogenate. NTP (1987) reported no induction of chromosomal aberrations or SCEs in CHO cells following treatment with bromodichloromethane in either the presence or absence of liver homogenate. Bromodichloromethane is structurally similar to other known animal carcinogens such as dibromochloromethane and chloroform.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 6.2E-2 per (mg/kg)/day

Drinking Water Unit Risk — 1.8E-6 per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	6E+1 ug/L
E-5 (1 in 100,000)	6E+0 ug/L
E-6 (1 in 1,000,000)	6E-1 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: Kidney (tubular cell adenoma and tubular cell adenocarcinoma)
Test animals: B6C3F1 mice, male
Route: gavage, corn oil
Reference: NTP, 1987

----------Dose----------		
Administered (mg/kg/day)	**Human Equivalent (mg/kg/day)**	**Combined Tumor Incidence**
0	0	1/46
25	1.5	2/49
50	3.0	9/50

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Using the linearized multistage procedure, a range of oral slope factors were calculated for bromodichloromethane, based on the observed incidence of various types of tumors (large intestine, kidney, or combined) in mice or rats reported in the NTP bioassay. The resulting cancer slope factors fall between 4.9E-3 and 6.2E-2 per (mg/kg)/day (U.S. EPA, 1992a,b,c). An oral slope factor of 1.3E-1 per (mg/kg)/day was derived from the incidence of hepatic tumors in

female mice (U.S. EPA, 1993). However, because of the possible role of corn oil used as gavage vehicle (in the NTP study) in induction of hepatic tumors, carcinogenic risk estimates based on the tumor incidence in the liver is considered inappropriate.

In accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), the slope factor of the greatest sensitivity (6.2E-2 per (mg/kg)/day) is selected as the oral quantitative cancer risk estimate for bromodichloromethane (U.S. EPA, 1992b). Survival adjustments were made for the animal counts in the control and low-dose groups by subtracting 3 and 1 early death, respectively. Additional animal count adjustment was also made in the control group due to the escape of one mouse.

The unit risk should not be used if the water concentration exceeds 6E+3 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Adequate numbers of animals were used for a lifetime bioassay with two animal species. Bromodichloromethane was administered at two dose levels. Tumors of multiple tissue types were observed in a dose-related manner. Slope factors derived from tumor incidences of kidney and large intestine are similar and within one order of magnitude in differences.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not Available

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1992c

The Drinking Water Criteria Document for Trihalomethanes received Science Advisory Board (SAB) review in 1992.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 09/07/1989, 01/11/1990, 04/01/1992, 04/02/1992

Verification Date — 04/02/1992

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Bromodichloromethane conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Bromodichloromethane
CASRN — 75-27-4

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Bromodichloromethane
CASRN — 75-27-4

Date	Section	Description
10/01/1990	II.	Carcinogen assessment on-line
02/01/1993	II.	Carcinogen assessment replaced; oral slope factor changed
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Bromodichloromethane
CASRN — 75-27-4
Last Revised — 09/30/1987

- 75-27-4
- Bromodichloromethane
- Dichlorobromomethane
- Dichloromonobromomethane
- Methane, bromodichloro-
- Monobromodichloromethane