MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY
WATER BUREAU

TOXICOLOGICAL ASSESSMENT FOR BROMODICHLOROMETHANE (CASRN: 75-27-4) HUMAN NONCANCER VALUE

Literature Review Date: June 30, 2008
D. Bush

Several subchronic/chronic studies have been conducted using bromodichloromethane (BDCM). Chu et al. (1982) exposed rats (20 animals/sex/group) to drinking water containing 0, 5, 50, 500, or 2,500 ppm BDCM for 90 days. Ten animals per sex were killed at 90 days while the remaining ten were given uncontaminated tap water for an additional 90 days. The lowest dose group was the only group that did not exhibit reversible liver lesions. The authors considered 5 ppm (0.45 mg/kg/d) as the NOAEL for this study. EPA (1996) considered this study to be unsuitable for the derivation of an RfD because of difficulties in interpretation of the study design and statistical methodology.

Aida et al. (1992) conducted a chronic rat feeding study using microencapsulated BDCM. The test material was administered in the diet to Wistar rats (40 animals/sex/treatment group) at doses of 0, 0.014, 0.055, and 0.22% for 24 months. Rats were sacrificed after 6, 12, 18, and 24 months of continuous dosing. Fatty degeneration of the liver was found in all male treatment groups, whereas, fatty degeneration and granuloma of the liver occurred in females in the higher two dose groups. Bile duct proliferation, cholangiofibrosis, and body weight depression occurred in males and females in the 0.22% treatment group. The dose of 0.014% (6.1 mg/kg/d) was considered the LOAEL for this study based on histopathological lesions in the livers of male rats.

In a study conducted by NTP (1986), B6C3F1 mice (50 animals/sex/group) were exposed via gavage to BDCM at doses of 0, 25, or 50 mg/kg (males) and 0, 75, or 150 mg/kg (females), 5 days/week for 102 weeks. Survival and body weight were decreased in the female mice and body weight was decreased in male mice exposed to the highest dose. Fatty metamorphosis of the liver, renal cytomegaly, and follicular cell hyperplasia of the thyroid gland occurred in male mice. Follicular cell hyperplasia of the thyroid gland occurred in female mice. A LOAEL of 25 mg/kg (17.9 mg/kg/d) was determined based on renal cytomegaly in male mice.

The NTP (1986) study also exposed F344/N rats (50 animals/sex/group) to 0, 50, or 100 mg/kg, 5 days /week, for 102 weeks. Cytomegaly and tubular cell hyperplasia of the liver occurred in male rats, whereas, cellular changes and fatty metamorphosis of the liver and tubular cell hyperplasia of the kidneys occurred in female rats. The LOAEL for this study is 50 mg/kg (36 mg/kg/d).

EPA (1996) used the LOAEL of 17.9 mg/kg/d identified for male mice in the NTP (1986) study to derive an RfD for BDCM. This study was not used to derive an HNV because the LOAEL of 6.1 mg/kg/d identified by Aida et al. (1992) was lower than the LOAEL found in the NTP (1986) study. The Chu et al. (1982) study was not used to derive the HNV even though it identified a NOAEL below the LOAEL found in the NTP and Aida et al. studies due to study weaknesses. The HNV was derived using the LOAEL of 6.1 mg/kg/d with an uncertainty factor of 1,000 to account for intraspecies, interspecies, and LOAEL-to-NOAEL extrapolations.

References:

Aida, Y., K. Yasuhara, K. Takada et al. 1992. Chronic toxicity of microencapsulated bromodichloromethane administered in the diet to Wister rats. J. Toxicol. Sci. 17:51-68.

Chu, I., D.C. Villeneuve, V.E. Secours et al. 1982. Toxicity of trihalomethanes: I. The acute and subacute toxicity of chloroform, bromodichloromethane, chlorodibromomethane and bromoform in rats. J. Environ. Sci. Health. B17:205-224.

National Toxicology Program (NTP). 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.

U.S. EPA. 2008. Integrated Risk Information System (IRIS database). Chemical file for bromodichloromethane (75-27-4). Oral RfD verification date 7/16/87.

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WORKSHEET

Chemical Name: Bromodichloromethane CAS No.: 75-27-4
Developed By: D. Bush
Reviewed By: _____ Verification Date: _____

Key Study: The HNV is based on a 24 month study in rats which found a LOAEL (fatty degeneration) in male rats of 6.1 mg/kg/d (Aida et al., 1992).

$$ADE = \frac{6.1 \text{ mg/kg/d}}{1000}$$

Where UF = 1000 (10x for each LOAEL-to-NOAEL, interspecies, and intraspecies extrapolation)

ADE = 0.0061 mg/kg/d

$$HNV_{dw} = \frac{(0.0061 \text{ mg/kg/d})\ (70 \text{ kg})\ (0.8)}{2.0 \text{ L/d} + [(.0036 \text{ kg/d} \times 3.3 \text{ L/kg}) + (.0114 \text{ kg/d} \times 4.8 \text{ L/kg})]} = 170 \text{ ug/L}$$

HNV drinking water = 170 ug/L

$$HNV_{non\text{-}dw} = \frac{(0.0061 \text{ mg/kg/d})\ (70 \text{ kg})\ (0.8)}{0.01 \text{ L/d} + [(.0036 \text{ kg/d} \times 3.3 \text{ L/kg}) + (.0114 \text{ kg/d} \times 4.8 \text{ L/kg})]} = 4{,}500 \text{ ug/L}$$

HNV non-drinking water = 4,500 ug/L

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Literature Review Date: June 30, 2008
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NTP (1987) exposed F344/N rats and B6C3F1 mice to bromodichloromethane (BDCM) via gavage for 102 weeks. Based on the results of this study, NTP concluded that there was "clear evidence of carcinogenicity" of BDCM in rats and mice. EPA now classifies BDCM as a possible human carcinogen based on these study findings (ATSDR, 2003).

In the NTP (1987) study, BDCM was administered in corn oil via gavage, 5 days/week for 102 weeks, to male and female B6C3F1 mice (50/sex/group) at doses of 0, 25, or 50 mg/kg/d and 0, 75, or 150 mg/kg/d, respectively. Five, 6 and 13 female mice in the vehicle control, low dose and high dose groups, respectively, died prior to the end of the study as a result of ovarian abscesses. BDCM also induced the formation of tumors in the large intestine, kidney and liver. The occurrence of tubular cell adenomas of the kidneys was statistically significant in the males administered the high dose. Females exhibited a dose-related increase in the incidence of hepatocellular adenomas and carcinomas which were significantly higher than controls for both the low and high dose groups.

In the same study, male and female F344/N rats (50/sex/group) were administered 0, 50 or 100 mg/kg/d BDCM using the same dosing schedule as was used for the mice. The incidence of tubular cell adenomas/adenocarcinomas was significantly increased in male and female rats in only the high dose group. Tumors of the large intestine were significantly increased in males in a dose-dependent manner, whereas these tumors were observed only in the high dose females.

In another study, NTP (2006) exposed male F344/N rats and female B6C3F1 mice to BDCM in drinking water for two years. The estimated doses received by the male rats were 0, 6, 12, and 25 mg/kg/d, whereas, the estimated doses received by the female mice were 0, 9, 18, and 36 mg/kg/d. No significant increase in the incidence of tumors was found in this study. The NTP therefore concluded that under the conditions of this study, there was no evidence of carcinogenic activity in rats or mice. They attributed the differences in response between the drinking water and gavage studies to "differences in organ dosimetry by these routes of exposure and possible influences of dietary factors and differences in body weight on neoplasm development".

The results of the NTP (1987) study were used to derive an HCV for BDCM. The occurrence of hepatocellular adenomas/carcinomas in female B6C3F1 mice resulted in the highest potency as determined by the Global 82 Linear Multistage Model. However, this slope factor could not be used to derive an HCV since corn oil has been shown to enhance the formation of liver tumors when administered with trihalomethanes. Therefore, the next higher slope factor was used for criteria development. This slope factor was based on the incidence of male mouse kidney tumors. EPA (2008) also used the data from the male B6C3F1 mice to derive a slope factor in the IRIS database.

References:

ATSDR. 2003. Toxicological Profile for Bromoform/Dibromochloromethane.

National Toxicology Program (NTP). 1987. Toxicological and Carcinogenesis Studies of Bromodichloromethane (Cas No. 75-27-4) in F344/N Rats and B6C3F1 Mice (Gavage studies). Technical Report Series No. 321.

National Toxicology Program (NTP). 2006. Toxicology and Carcinogenesis Studies of Bromodichloromethane (Cas No. 75-27-4) in Male F344/N Rats and Female B6C3F1 Mice (Drinking Water Studies). NTP TR 532.

U.S. Environmental Protection Agency (EPA). 2008. Integrated Risk Information System (IRIS database). Chemical file for bromodichloromethane (75-27-4). Last revised 3/1/93.

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Chemical Name: Bromodichloromethane CAS No. 75-27-4
Developed By: D. Bush
Reviewed By: _____ Verification Date: _____

Key Study: The HCV is based on an increase in tubular cell adenomas and carcinomas in the kidneys of male B6C3F1 mice (NTP, 1987).

SAD (mg/kg/d)	Tumors / animals at risk	Animal Weight
0	1/34	0.0425 kg
17.86	2/32	
35.71		

GLOBAL 82 Results:

$$q = \frac{\text{95\% Upper Confidence Limit}}{\text{MLE}}$$

$$q = \frac{0.00193812}{0.248765794}$$ **q = 0.007790942(mg/kg/d)-1**

q* = (q) (species scaling factor)

$q^* = 0.007790942(mg/kg/d)\text{-}1 * (70\ kg/0.0425\ kg)^{1/4}$

q* = 0.04963 (mg/kg/d)-1

$$RAD = \frac{0.00001}{0.04963\ (mg/kg/d)\text{-}1}$$ **RAD = 0.0002015 mg/kg/d**

$$HCV_{dw} = \frac{0.0002015\ mg/kg/d * 70\ kg}{2.0\ L/d + [(0.0036\ kg/d * 3.3\ L/kg) + (0.0114\ kg/d * 4.8\ L/kg)]}$$

HCV_{dw} = 6.8 µg/L

$$HCV_{non\text{-}dw} = \frac{0.0002015\ mg/kg/d * 70\ kg}{0.01\ L/d + [(0.0036\ kg/d \times 3.3\ L/kg) + (0.0114\ kg/d \times 4.8\ L/kg)]}$$

$HCV_{non\text{-}dw}$ = 180 µg/L