

TOXICITY SUMMARY FOR  
BROMOFORM

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## EXECUTIVE SUMMARY

Bromoform (CAS No. 75-25-2), also referred to as tribromomethane, is a halogenated aliphatic hydrocarbon with a molecular formula of  $\text{CHBr}_3$  (Budavari et al., 1989). Bromoform is formed as a byproduct during water chlorination when chlorine reacts with endogenous organic materials such as humic and fulvic acid and bromide ions. The principal route of human exposure is from the ingestion of contaminated drinking water (ATSDR, 1990).

Bromoform is readily absorbed from the gastrointestinal tract (Mink et al., 1986) and, by analogy to related compounds, is expected to be absorbed from the respiratory tract. It is distributed to various tissues, with highest levels in adipose tissue and blood (Parra et al., 1986). Bromoform is metabolized in the liver by cytochrome P-450 oxidases; carbon monoxide and carbon dioxide are the primary metabolites (Stevens and Anders, 1979, 1981; Ahmed et al., 1977). Bromoform and its metabolites are primarily excreted through the lungs and to some extent in the urine (Mink et al., 1986).

In humans, accidental ingestion of bromoform has led to listlessness, headache, and vertigo and at higher doses to central nervous system (CNS) depression, coma, and death. The estimated lethal dose for a 10- to 20-kg child is 250 to 500 mg/kg. Exposure to bromoform vapor has caused irritation of the respiratory tract, pharynx, and larynx, as well as lacrimation and salivation (von Oettingen, 1955).

In animals, the liver, kidneys, and central nervous system are the primary target organs for bromoform toxicity. The principal cause of death following acute oral exposure is CNS depression (Chu et al., 1980). An oral dose of 1 g/kg has produced ataxia, sedation, and anesthesia within 30 minutes in mice (Bowman et al., 1978) and oral  $\text{LD}_{50}$  values for rodents range from 1.14 to 1.55 g/kg (Chu et al., 1980; Bowman et al. 1978). Subchronic and chronic oral exposure (100 mg/kg by gavage for 13 weeks or 2 years) have caused lethargy in rats (NTP, 1989). Hepatic effects observed in rats and/or mice following subchronic (14-90 days) or chronic (2-year) exposure to bromoform at oral doses ranging from 50 to 200 mg/kg/day include vacuolization of hepatocytes, fat accumulation, liver enzyme changes, and increased liver weight (NTP, 1989; Chu et al., 1982; Munson et al., 1982). Kidney effects, characterized by histopathologic changes in the epithelial tubules and glomeruli and altered enzyme levels, were seen in mice exposed to bromoform by gavage at doses of \$145 mg/kg/day for 14 days (Condie et al., 1983). Additional effects following oral administration of bromoform include immune depression in mice treated with 250 mg/kg/day for 14 days (Munson et al., 1982) and fetotoxic effects (minor skeletal abnormalities) in rats treated with 100 mg/kg/day during gestation (Ruddick et al., 1983).

Acute inhalation exposure may produce severe CNS depression in animals. Inhalation of \$7000 ppm bromoform has caused deep anesthesia in dogs after 8 minutes and death after 1 hour (ACGIH, 1991). CNS effects were also observed in rabbits exposed to 240 ppm for 10 days (Dykan, 1964) and impaired liver and kidney function has been reported in rats following exposure to 24 ppm for 2 months (Dykan, 1962). Bromoform is moderately irritating to rabbit skin and eyes (Torkelson, 1994).

Based on liver lesions seen in rats in a 13-week gavage study, an oral Reference Dose (RfD) of  $2.00\text{E-}02$  mg/kg/day was derived for chronic exposure (U.S. EPA, 1995a) and  $2.00\text{E-}01$  mg/kg/day for subchronic exposure to bromoform (U.S. EPA, 1995b). An inhalation Reference Concentration (RfC) has not been calculated for bromoform.

The epidemiological evidence for an association between ingestion of chlorinated drinking water containing bromoform and increased cancer risk is inadequate (U.S. EPA, 1989). One long-term oral study and a lung tumor assay provide evidence of carcinogenicity for bromoform in animals. An increased incidence of intestinal tumors (adenomatous polyps and adenocarcinomas) was seen in female rats receiving 200 mg/kg/day for 2 years (NTP, 1989) and an increased incidence of lung tumors was seen in male mice administered intraperitoneal injections of 4-100 mg/kg (3 times weekly for a total of 18-24 injections) of bromoform (Theiss et al., 1977).

Based on U.S. EPA guidelines, bromoform was assigned to weight-of-evidence group B2, probable human carcinogen (U.S. EPA, 1995a). For oral exposure, the slope factor and unit risk are  $7.90\text{E-}03$   $(\text{mg/kg/day})^{-1}$  and  $2.3\text{E-}07$   $(\mu\text{g/L})^{-1}$ , respectively (U.S. EPA, 1995a) and for inhalation exposure, the slope factor and unit risk are  $3.90\text{E-}03$   $(\text{mg/kg/day})^{-1}$  (U.S. EPA, 1995b) and  $1.10\text{E-}06$   $(\mu\text{g/m}^3)^{-1}$ , respectively (U.S. EPA, 1995a).

## 1. INTRODUCTION

Bromoform (CAS No. 75-25-2), also referred to as tribromomethane, is a halogenated aliphatic hydrocarbon with a molecular formula of  $\text{CHBr}_3$  and a molecular weight of 252.77. It has a boiling point of 149-150°C, a melting point of 7.5°C, and a density of 1.6005 g/mL at 15°C (Budavari et al., 1989). Bromoform, a colorless, heavy liquid, with an odor and taste similar to chloroform, is sparingly soluble in water, but soluble in ethanol, ethyl ether, benzene, solvent naphtha, and fixed and volatile oils. It is produced commercially from chloroform by replacement of chloride by reaction with anhydrous aluminum bromide, treatment with bromine and aluminum, or reaction with hydrogen bromide in the presence of an aluminum halide catalyst (U.S. EPA, 1989). Bromoform is used as an intermediate in organic synthesis; in gauge fluids; as a solvent for waxes, greases, and oils; as an ingredient in fire-resistant chemicals; as a heavy-dense liquid in separating mixtures of chemicals (U.S. EPA, 1989), and has been formerly used in pharmaceuticals as a sedative and antitussive (NTP, 1989).

Bromoform is formed as a byproduct during water chlorination when chlorine reacts with endogenous organic materials such as humic and fulvic acid and bromide ions and the principal route of human exposure is from the ingestion of contaminated drinking water. Bromoform volatilizes from water to air, and in the atmosphere, it is expected to be relatively stable, with a half-life of about 1 to 2 months (ATSDR, 1990). In soil, bromoform is moderately to highly mobile and is expected to leach into ground water (U.S. EPA, 1989). Bromoform is not easily biodegradable under aerobic conditions. It has been found at 13 hazardous waste sites on the National Priority List (NPL) in the United States (ATSDR, 1990).

## 2. METABOLISM AND DISPOSITION

### 2.1. ABSORPTION

Gastrointestinal absorption of bromoform was determined in rats and mice by Mink et al. (1986) following gavage administration of a single dose (100 mg/kg for rats and 150 mg/kg for mice). Excretion data indicate that absorption occurred rapidly, and that total gastrointestinal absorption was at least 76% for rats and 62% for mice.

No studies were found regarding the absorption of bromoform in humans or animals following inhalation exposure. By analogy to related halomethanes such as chloroform, it is expected that bromoform would be readily absorbed by the lungs. Systemic effects seen in experimental animals following inhalation exposure also indicate that absorption occurs from the respiratory tract. According to von Oettingen (1955), bromoform is absorbed to some extent through the skin.

### 2.2. DISTRIBUTION

Bromoform was identified in the liver, kidney, brain, lungs, and stomach/intestines of a child who died following accidental ingestion of bromoform (von Oettingen, 1955).

Bromoform was distributed rapidly to tissues and organs of rats following a single gavage dose (2-16 mg/kg), with highest levels detected in adipose tissue and blood (Parra et al., 1986). Lower levels were found in several other organs including kidneys, brain, and liver. Fifteen minutes after treatment, the levels in fat were about one order of magnitude lower than those in blood. The levels in the liver were below the detection limit after 1 hour, presumably because metabolism of bromoform occurred rapidly in this organ. Mink et al. (1986) determined that only 1-2% of a single gavage dose was retained in soft tissues of rats 8 hours after dosing. Measurable levels of radiolabel were found in brain, kidney, liver, lungs, muscle, pancreas, stomach, thymus, and urinary bladder. A similar tissue distribution was observed in mice except that blood contained approximately 10% of the administered dose. The half-life of bromoform was 0.8 hours in rats and 8 hours in mice.

### 2.3. METABOLISM

Bromoform can be metabolized via tribromomethanol to carbon monoxide by a cytochrome 450 oxidase system in rat liver microsomal fraction (Stevens and Anders, 1979), and sulfhydryl compounds such as glutathione increase the rate of formation of carbon monoxide from bromoform (Ahmed et al., 1977). The glutathione-dependent production of carbon monoxide is part of the detoxification pathway for bromoform and as well as halomethanes in general (Stevens and Anders 1981). The overall metabolic

pathway includes formation of dibromocarbonyl, a highly reactive intermediate, that may undergo a number of reactions including hydrolysis to yield carbon dioxide, reaction with glutathione to form carbon monoxide, and formation of covalent adducts with cellular nucleophiles (ATSDR, 1990).

Dibromocarbonyl has been suggested as an intermediate responsible for bromoform induced hepatotoxicity (NTP, 1989). Bromoform can also be metabolized through a reductive pathway that produces free radical intermediates (U.S. EPA, 1989).

## **2.4. EXCRETION**

No studies were located regarding the excretion of bromoform by humans. In rats and mice treated orally with a single dose of radiolabeled bromoform, elimination occurred primarily through the lungs in expired air within 8 hours of dosing (Mink et al., 1986). Rats excreted approximately 4% of the total dose as CO<sub>2</sub> and 70% as unmetabolized compound, while mice eliminated 40% as CO<sub>2</sub> and 6% as unmetabolized parent compound, indicating that mice metabolize bromoform more extensively than rats. The urine of rats and mice contained <5% of the radiolabel after 8 hours, and <10% after 36-48 hours. Lucas (1928) reported that rabbits injected rectally with a bromoform/olive oil mixture excreted 0.3% to 1.2% of the administered dose (as bromine) in the urine.

## **3. NONCARCINOGENIC HEALTH EFFECTS**

### **3.1. ORAL EXPOSURES**

#### **3.1.1. Acute Toxicity**

##### **3.1.1.1. Human**

In the early 1900s, bromoform was administered as a sedative to children suffering from whooping cough, and several deaths resulted from accidental overdoses (von Oettingen, 1955). The principal clinical signs in the fatal cases were central nervous system (CNS) depression with coma and loss of reflexes. Death was usually due to respiratory failure. Although the doses were not quantified, it was estimated that 250 to 500 mg/kg would be fatal for a 10- to 20-kg child. Smaller doses have led to listlessness, headache, and vertigo.

##### **3.1.1.2. Animal**

Oral LD<sub>50</sub> values for bromoform are 1388 and 1147 mg/kg for male and female rats, respectively (Chu et al., 1980) and 1400 and 1550 mg/kg for male and female mice, respectively (Bowman et al., 1978). The principal cause of death in laboratory animals following acute oral exposure is CNS depression. Clinical signs recorded in rats included piloerection, sedation, flaccid muscle tone, ataxia, prostration, and hypothermia. Also seen were enlarged livers and kidneys (Chu et al., 1980). At doses of 1000 mg/kg, ataxia, sedation, and anesthesia occurred in mice within 60 minutes, with sedation persisting for about 4 hours (Bowman et al., 1978). In rats, a single gavage dose of 1000 mg/kg produced reductions in liver cytochrome P-450 content and aminolevulinic acid-dehydratase activity and increases in porphyrin content, suggesting disturbances in hepatic heme metabolism (Moody and Smuckler, 1986). In a screening test of motor performance with mice, Balster and Borcelleca (1982) determined an ED<sub>50</sub> of 500 mg/kg for acute effects.

#### **3.1.2. Subchronic Toxicity**

##### **3.1.2.1. Human**

Information on the subchronic oral toxicity of bromoform in humans was not available.

##### **3.1.2.2. Animal**

In a gavage study, F344/N rats and B6C3F<sub>1</sub> mice were treated 5 times weekly for 13 weeks with bromoform at doses of 0, 12, 25, 50, 100, or 200 mg/kg (rats) or 0, 25, 50, 100, 200, or 400 mg/kg (mice) (NTP, 1989). All male rats treated with 100 or 200 mg/kg and all female rats treated with 200 mg/kg were lethargic. Dose-related increases of cytoplasmic vacuolization of hepatocytes were observed in males of both species, but not in females. Chu et al. (1982) reported that administration of 5, 50, 500, or 2500 ppm bromoform in drinking water for 90 days caused no adverse effects in male and female Sprague-Dawley rats at 5 or 50 ppm. Exposure to 500 or 2500 ppm produced mild histological changes in the liver and thyroid that were not evident 90 days after cessation of exposure.

Munson et al. (1982) administered bromoform to male and female mice by gavage at daily doses of 50, 125, or 250 mg/kg/day for 14 days. Several indices of humoral and cellular immunity were depressed in male but not in female mice exposed to the highest dose. In addition, liver weights and serum glutamate oxaloacetate transaminase (SGOT) levels were increased and serum glucose and blood urea nitrogen (BUN) levels were decreased in the high-dose animals. In a similar study, Condie et al. (1983) administered 72, 145, or 289 mg/kg/day of bromoform by gavage to CD-1 mice for 14 days. BUN levels and serum creatinine values were not altered, but serum glutamate-pyruvate transaminase (SGPT) levels were elevated in high-dose animals. Histological changes were seen in the kidneys and liver in the mid- and high-dose groups and included hyperplasia of tubular epithelial cells, and hypertrophy and degenerative changes of the glomeruli in the kidney, and centrilobular cytoplasmic pallor and slight focal inflammation of the liver.

Balster and Borcelleca (1982) reported effects on operant behavior in mice treated by gavage with 100 or 400 mg/kg bromoform for 60 days.

### **3.1.3. Chronic Toxicity**

#### **3.1.3.1. Human**

Information on the chronic toxicity of bromoform in humans following oral exposure was not available.

#### **3.1.3.2. Animal**

Groups of F344/N rats and B6C3F<sub>1</sub> mice were administered bromoform in corn oil by gavage at doses of 0, 100, or 200 mg/kg (male and female rats and female mice) or at doses of 0, 50, or 100 mg/kg (male mice), 5 days/week for 2 years (NTP, 1989). Decreased survival was seen in high-dose male rats compared with controls. The body weights of low- and high-dose males and high-dose females were lower than those of controls by the end of the study. Clinical signs of toxicity included lethargy in both sexes and aggressiveness in males. Histopathologic examination revealed fatty liver changes in both sexes of treated rats, increased mixed cell foci and decreased basophilic foci in females, and necrosis of the liver in high-dose males. Also seen in male rats were forestomach ulcers, chronic inflammation of the lungs, and squamous metaplasia of the prostate gland. The inflammatory changes in the lungs may have been secondary as a result of a SDA virus infection, and forestomach ulcers may have been due to a direct irritating effect of the chemical.

In the study with mice, decreased survival was seen in low- and high-dose female mice compared with controls (NTP, 1989). The body weights of males were comparable to controls, whereas the body weights of dosed females were lower than those of controls. No clinical signs of toxicity were observed. Histopathologic examination revealed increased incidences of hyperplasia of the glandular stomach in low- and high-dose males, cytoplasmic vacuolization of hepatocytes in low- and high-dose females, and thyroid follicular cell hyperplasia in high-dose females.

### **3.1.4. Developmental and Reproductive Toxicity**

#### **3.1.4.1. Human**

Information on the developmental and reproductive toxicity of bromoform in humans following oral exposure was not available.

#### **3.1.4.2. Animal**

Ruddick et al. (1983) administered 0, 50, 100, or 200 mg/kg of bromoform by gavage to rats on days 6 to 15 of gestation. An increased incidence of minor skeletal abnormalities, including appearance of a 14th rib, intraparietal deviations, and delayed ossification of sternbrae, was seen in developing fetuses at 100 and 200 mg/kg.

### **3.1.5. Reference Dose**

#### **3.1.5.1. Subchronic**

ORAL RfD: 2.00E-01 (mg/kg/day) (U.S. EPA, 1995b)

NOEL: 17.9 mg/kg/day

UNCERTAINTY FACTOR: 100

PRINCIPAL STUDY: NTP, 1989

COMMENTS: The subchronic RfC is based on the same study as the chronic RfD. An uncertainty factor of 10 each was applied for interspecies variation and for protection of sensitive populations (U.S. EPA, 1995b).

### **3.1.5.2. Chronic**

ORAL RfD: 2.00E-02 (mg/kg/day) (U.S. EPA, 1995a)

NOEL: 17.9 mg/kg/day

LOAEL: 35.7 mg/kg/day

UNCERTAINTY FACTOR: 1000

CONFIDENCE:

Study: Medium

Data Base: Medium

RfD: Medium

VERIFICATION DATE: 8/13/87

PRINCIPAL STUDY: NTP, 1989

COMMENTS: The RfD is based on hepatic lesions seen in male rats treated by gavage with bromoform for 13 weeks. An uncertainty factor of 10 each was applied for use of a subchronic assay, for interspecies variation, and for protection of sensitive populations (U.S. EPA, 1995a).

## **3.2. INHALATION EXPOSURES**

### **3.2.1. Acute Toxicity**

#### **3.2.1.1. Human**

Exposure to bromoform vapor has caused irritation of the respiratory tract, pharynx, and larynx, as well as lacrimation and salivation (von Oettingen, 1955).

#### **3.2.1.2. Animal**

An inhalation LC<sub>10</sub> of 4500 mg/m<sup>3</sup> was reported for rats exposed to bromoform for 4 hours (ACGIH, 1991). Dogs exposed to 7000 ppm became deeply anesthetized after 8 minutes and died after a 1-hour exposure (ACGIH, 1991). A single inhalation exposure (duration not reported) to 1070-1260 ppm bromoform produced CNS effects in rabbits and exposure to 240 ppm for 10 days produced CNS effects as well as dystrophic and vascular changes in the liver and kidneys in rats (Dykan, 1964). Severe CNS depression was observed in dogs and guinea pigs following acute exposure to "very high" concentrations of bromoform (Graham, 1915). Clinical signs included sleep, deep sedation, and narcosis. Onset of CNS depression was rapid and transient, disappearing within a day following cessation of exposure.

### **3.2.2. Subchronic Toxicity**

#### **3.2.2.1. Human**

Information on the subchronic toxicity of bromoform in humans following inhalation exposure was not available.

#### **3.2.1.2. Animal**

Hepatic changes (decreased blood clotting and impaired glycogenesis) and renal injury (proteinuria and decreased creatinine clearance) were reported in rats exposed to 24 ppm bromoform for 2 months. A concentration of 4.8 ppm elicited no adverse effects after 2 months of exposure (Dykan, 1962).

### **3.2.3. Chronic Toxicity**

#### **3.2.3.1. Human**

According to an abstract of a study by Dykan (1964), workers involved with bromoform production exhibited CNS and liver alterations. Further details were not provided.

### **3.2.3.2. Animal**

Information on the chronic toxicity of bromoform in animals following inhalation exposure was not available.

### **3.2.4. Developmental and Reproductive Toxicity**

Information on the developmental and reproductive toxicity of bromoform in humans or animals following inhalation exposure was not available.

### **3.2.5. Reference Concentration**

An inhalation Reference Concentration (RfC) has not been derived for bromoform.

## **3.3. OTHER ROUTES OF EXPOSURE**

### **3.3.1. Acute Toxicity**

#### **3.3.1.1. Humans**

Information on the acute toxicity of bromoform in humans by other routes of exposure was not available.

#### **3.3.1.2. Animals**

The intraperitoneal (i.p.) LD<sub>50</sub> for bromoform is 414 µL/kg (1196 mg/kg) in male rats (Agarwal and Mehendale, 1983) and the subcutaneous (s.c.) LD<sub>50</sub> is 7.2 mmol/kg (1820 mg/kg) in male mice (Kutob and Plaa, 1962). Prolongation of pentobarbital sleeping time and liver lesions were reported in male mice administered a s.c. injection of 4.4 mmol/kg bromoform (Kutob and Plaa, 1962). Agarwal and Mehendale (1983) tested the potentiation of chlordecone on bromoform toxicity and concluded that bromoform is not a potent hepatotoxin and that chlordecone does not potentiate its effects.

Undiluted bromoform was moderately irritating to rabbit eyes, but healing was complete in 1 to 2 days. Repeated skin contact caused moderate irritation to rabbit skin. Rabbits survived a single dose of 2000 mg/kg administered under a cuff of intact skin. Lethargy and slight weight loss were noted (Torkelson, 1994).

### **3.3.2. Subchronic Toxicity**

Information on the subchronic toxicity of bromoform by other routes of exposure in humans or animals was not available.

### **3.3.3. Chronic Toxicity**

Information on the chronic toxicity of bromoform by other routes of exposure in humans or animals was not available.

### **3.3.4. Developmental and Reproductive Toxicity**

Information on the developmental or reproductive toxicity of bromoform by other routes of exposure in humans or animals was not available.

## **3.4. TARGET ORGANS/CRITICAL EFFECTS**

### **3.4.1. Oral Exposures**

#### **3.4.1.1. Primary Target Organs**

1. Liver. Subchronic and/or chronic oral exposure produced generally mild hepatic effects in rodents that included fatty liver changes, increased vacuolization, increased liver weights, and altered serum enzyme levels.

2. Kidneys. Subchronic oral exposure produced histopathologic renal changes affecting the tubular epithelial cells and glomeruli, and altered serum enzyme levels.

#### **3.4.1.2. Other Target Organs**

1. Central nervous system. Subchronic and/or chronic oral exposure has caused lethargy in both sexes of rats, aggressiveness in male rats, and effects on operant behavior in mice.
2. Development. Minor skeletal abnormalities were observed in fetuses of dams administered bromoform during gestation.
3. Immune system. Subchronic oral exposure depressed humoral and cellular immunity in male mice.

#### **3.4.2. Inhalation Exposures**

##### **3.4.2.1. Primary target organs**

1. Liver. Subchronic exposure produced impaired liver function in rats. Unspecified liver changes were reported in workers exposed to bromoform.
2. Kidneys. Subchronic exposure produced impaired kidney function in rats.

##### **3.4.2.2. Other Target Organs**

Central nervous system: Unspecified CNS effects were reported in workers exposed to bromoform.

#### **3.4.3. Other Routes of Exposure**

Target organs for other routes of exposure to bromoform were not identified.

### **4. CARCINOGENICITY**

#### **4.1. ORAL EXPOSURES**

##### **4.1.1. Human**

Some epidemiologic studies suggest that there may be an association between exposure to trihalomethanes in drinking water and increased frequencies of cancers of the stomach, colon, rectum, or pancreas. However, these studies do not provide information whether the observed effects are due to bromoform or to one or more of the hundreds of other byproducts also present in chlorinated water (ATSDR, 1990). The evidence for carcinogenicity of bromoform in humans is considered inadequate (U.S. EPA, 1989).

##### **4.1.2. Animal**

Groups of F344/N rats and B6C3F<sub>1</sub> mice were administered bromoform in corn oil by gavage, 5 days/week for 2 years, at doses of 0, 100, or 200 mg/kg (male and female rats and female mice) or at doses of 0, 50, or 100 mg/kg (male mice) (NTP, 1989). There was no evidence of carcinogenic activity in mice. Neoplastic lesions (adenomatous polyps or adenocarcinomas) were observed in the colon or rectum of 3/50 male rats treated with 200 mg/kg and in 1/50 or 8/50 female rats treated with 100 or 200 mg/kg, respectively. Based on the occurrence of these uncommon neoplasms of the large intestine, NTP (1989) concluded that there is some evidence of carcinogenic activity for male rats and clear evidence of carcinogenic activity for female rats. However, in a 24-month dietary study, Kurokawa (1987) observed no carcinogenic activity in male or female Wistar rats administered microencapsulated bromoform at concentrations of 400, 1600, or 6500 ppm (20, 80, or 325 mg/kg).

#### **4.2. INHALATION EXPOSURES**

Information on the carcinogenicity of bromoform in humans or animals following inhalation exposure was not available.

### 4.3. OTHER ROUTES OF EXPOSURE

#### 4.3.1. Human

Information on the carcinogenicity of bromoform in humans by other routes of exposure was not available.

#### 4.3.2. Animal

In a lung tumor assay, Theiss et al. (1977) administered bromoform by i.p. injection to male strain A mice at doses of 4, 48, or 100 mg/kg, three times weekly for a total of 24, 23, or 18 injections, respectively. Controls received the vehicle, tricaprilyn. Animals were sacrificed 24 weeks after the first injection. There was no effect on survival in any of the treated groups. The number of lung tumors/mouse for the control, low-, mid-, and high-dose groups were 0.27, 0.53, 1.13, and 0.67, respectively (statistically significant only for the mid-dose group).

### 4. EPA WEIGHT-OF-EVIDENCE

Classification -- B2, probable human carcinogen (U.S. EPA, 1995a)

Basis -- Based on inadequate human data and sufficient evidence of carcinogenicity in animals (increased tumor incidence after oral and i.p. administration in rats and mice, respectively).

Bromoform is genotoxic in several assay systems and is structurally related to other trihalomethanes which have been verified as either probable or possible carcinogens.

### 4.5. CARCINOGENICITY SLOPE FACTORS

#### 4.5.1. Oral

SLOPE FACTOR:  $7.9E-3$  (mg/kg/day)<sup>-1</sup> (U.S. EPA, 1995a)

UNIT RISK:  $2.3E-7$  (µg/L)<sup>-1</sup> (U.S. EPA, 1995a)

PRINCIPAL STUDY: NTP, 1989

COMMENT: The slope factor and unit risk are based on neoplastic lesions in the large intestines in female rats exposed to bromoform by gavage for 2 years.

#### 4.5.2. Inhalation

SLOPE FACTOR:  $3.9E-3$  (mg/kg/day)<sup>-1</sup> (U.S. EPA, 1995b)

UNIT RISK:  $1.1E-6$  (µg/m<sup>3</sup>)<sup>-1</sup> (U.S. EPA, 1995a)

COMMENT: The inhalation slope factor and unit risk are based on route-to-route extrapolation from a 2-year gavage study with rats showing an increased incidence of neoplastic lesions in the large intestines. The tumorigenic response is considered a systemic rather than portal-of-entry effect. Pharmacokinetic data suggest that gastrointestinal absorption is rapid and biotransformation is an activating mechanism. A default value of 50% absorption was used because no data are available to quantify the extent of respiratory absorption.

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