2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BROMOFORM AND DIBROMOCHLOROMETHANE IN THE UNITED STATES

Bromoform ($CHBr_3$; CAS Number 75-25-2), also known as tribromomethane, and dibromochloromethane ($CHClBr_2$; CAS Number 124-48-1) belong to a group of chemicals referred to as trihalomethanes; the other two chemicals in this group are chloroform (also known as trichloromethane) and dichlorobromomethane. Trihalomethanes are formed when raw source water is disinfected by chlorination. In the United States, over 280 million people are served by public water systems that apply chlorine or some of its compounds as disinfectants to water in order to provide protection against microbial contaminants that otherwise might cause serious water-borne diseases. While these chlorine-containing disinfectants are effective in controlling many microorganisms, they react with natural organic or carbon-containing matter in the water to form disinfection byproducts. Therefore, the principal source of human exposure to bromoform and dibromochloromethane is chlorinated water supplied to homes, work, and public places. Bromoform and dibromochloromethane concentrations in public supply or tap water are in the low microgram/L range. Dibromochloromethane is often found more frequently than bromoform in samples from chlorinated water systems.

In the past, it was thought that most of the human exposure to bromoform and dibromochloromethane occurred through consumption of chlorinated drinking water. However, because of their physical properties (see Henry's law constants in Chapter 4), some bromoform and dibromochloromethane volatilize into the air from normal household use of water containing these chemicals. Recent models for residential exposure predict that exposure by the inhalation and dermal routes may be significant. Dermal exposure is expected from showering or bathing. Total administered doses of bromoform or dibromochloromethane for residential tap water having low microgram/L concentrations are predicted to be on the order of 10^{-4} mg/kg/day.

2.2 SUMMARY OF HEALTH EFFECTS

The general population is primarily exposed to bromoform and dibromochloromethane via tap water. The primary routes of exposure are ingestion and inhalation (from volatized compounds) and dermal exposure during showering and bathing. Bromoform and dibromochloromethane are readily absorbed from the

gastrointestinal tract and may be absorbed through the respiratory tract and skin. They are rapidly distributed throughout the body. In the liver, bromoform and dibromochloromethane are metabolized by the cytochrome P-450 mixed function oxidase system to a highly reactive metabolite, which is ultimately metabolized to carbon dioxide or carbon monoxide.

Studies in animals, combined with limited observations in humans, indicate that the principal adverse health effects associated with inhalation or oral exposure to bromoform or dibromochloromethane are central nervous system depression and liver and kidney damage. Although limited dermal data were located, it is likely that similar adverse health effects would occur from dermal exposure. Based on the no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values identified in animal studies, the liver appears to be the most sensitive target organ. Two types of liver effects have been observed in laboratory animals: lipidosis and hepatocellular necrosis. Lipidosis is an accumulation of lipids in the hepatocytes resulting in cellular vacuolization and swelling. Hepatocellular necrosis is observed at higher doses. It is not known if these effects represent a continuum of liver damage or are due to separate modes of action. Kidney effects are typically observed at higher doses than the hepatic effects; tubular cell degeneration and nephrosis are the most commonly reported effects in laboratory animals. Central nervous system depression, as evidenced by lethargy, ataxia, and shallow breathing, is typically observed at very high, often lethal, doses. High-dose exposure is also associated with decreases in body weight gain. There are limited data on the immunotoxicity of bromoform and dibromochloromethane. Impaired humoral and cell-mediated (only observed with dibromochloro-methane) immunity were observed in a study of mice administered bromoform or dibromochloromethane via gavage for 14 days. For bromoform, the immune and liver effects occurred at the same dose level; for dibromochloromethane, the immune effects occurred at a lower dose than liver effects.

The available data on the potential of bromoform and dibromochloromethane to induce reproductive and/or developmental effects are inconclusive. Human data primarily come from epidemiological studies of pregnancy outcomes in women exposed to trihalomethanes in drinking water. These studies involved mixed exposures to the trihalomethane compounds (chloroform, dichlorobromomethane, bromoform, and dibromochloromethane), and many did not analyze for possible risks associated with bromoform or dibromochloromethane water concentrations. These data are inadequate for establishing a causal relationship between trihalomethane exposure and reproductive and/or developmental toxicity. The animal data suggest that exposure to bromoform or dibromochloromethane does not cause histological damage to reproductive organs or impair reproductive function; although high-dose exposure may result in reduced fertility. The available developmental toxicity data suggest that bromoform and

dibromochloromethane may be toxic to the developing fetus, but these data are inadequate to establish firm conclusions.

The carcinogenicity of bromoform and dibromochloromethane has been studied in both humans and laboratory animals. The human data consist of studies of trihalomethane exposure via tap water. As with the reproductive and developmental toxicity studies, these data are inconclusive and do not establish causal relationships. Carcinogenic effects have been observed in animals exposed to bromoform and dibromochloromethane. Chronic oral exposure to bromoform resulted in increases in the occurrence of intestinal tumors in female rats. Dibromochloromethane induced liver tumors in male and female mice. The Department of Health and Human Services (DHHS) has not categorized the human carcinogenic potential of bromoform or dibromochloromethane. The International Agency for Research on Cancer (IARC) concluded that there were inadequate human data and limited animal data and assigned bromoform and dibromochloromethane to weight of evidence category 3, not classifiable as to carcinogenicity in humans. EPA classified bromoform as a probable human carcinogen, group B2 and dibromochloromethane as a possible human carcinogen, group C.

The primary targets of bromoform and dibromochloromethane toxicity—liver, kidney, and central nervous system—are discussed in greater detail below. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Liver Effects. Acute, intermediate-, and chronic-duration studies in laboratory animals provide strong evidence that the liver is the critical target of bromoform and dibromochloromethane toxicity. There are very limited human data on the toxicity of these two compounds; data for other trihalomethanes, particularly chloroform, suggest that the liver would also be a target of toxicity in humans.

There is strong evidence that the hepatotoxicity of bromoform and dibromochloromethane is due to their metabolism to reactive intermediates and highly reactive trihalomethyl free radicals. At lower doses, the hepatotoxicity of bromoform and dibromochloromethane is characterized by fatty infiltration, cellular vacuolization and swelling, and increases in liver weight. Consistent with the accumulation of lipids is the observed decrease in serum triglyceride levels and alterations in serum cholesterol levels. At higher doses, focal centrolobular necrosis and increases in SGOT and SGPT levels have been observed. For bromoform, the LOAEL is 50 mg/kg (5 days/week; 36 mg/kg/day) for fatty changes observed in rats administered bromoform in corn oil via gavage for 13 weeks. Necrosis was observed in rats receiving gavage doses of 200 mg/kg (143 mg/kg/day), 5 days/week for 2 years, but not after 13 weeks of dosing.

For dibromochloromethane, the LOAEL is 40 mg/kg (5 days/week; 28 mg/kg/day) for fatty liver changes in rats receiving gavage doses of dibromochloromethane in corn oil for 2 years. Necrosis was observed at 173 mg/kg/day in rats exposed via the diet for 1 month.

Species and possible gender differences in the hepatotoxicity of bromoform and dibromochloromethane have been identified. Rats appear to be more sensitive than mice to the liver effects. Under similar exposures scenarios, respective NOAEL and LOAEL values of 25 and 50 mg/kg (5 days/week) for fatty changes were identified in rats exposed to bromoform for 13 weeks; the NOAEL and LOAEL values in mice were 100 and 200 mg/kg (5 days/week), respectively. For dibromochloromethane, the NOAEL and LOAEL values for fatty changes following a 13-week gavage exposure (5 days/week) were 30 and 60 mg/kg for rats and 125 and 250 mg/kg for mice.

Kidney Effects. Renal effects have not been consistently found in studies of laboratory animals, particularly in the case of bromoform exposure. One study reported mesangial nephrosis in mice exposed to 145 mg/kg/day bromoform via gavage for 14 days and identified a NOAEL of 37 mg/kg/day. Comprehensive intermediate- and chronic-duration studies in rats and mice did not find significant renal effects at doses as high as 400 mg/kg (5 days/week; 286 mg/kg/day). In contrast, exposure to dibromochloromethane resulted in mesangial hyperplasia in mice exposed to ≥37 mg/kg/day via gavage for 14 days. Toxic nephropathy was observed in rats and mice exposed to 250 mg/kg (179 mg/kg/day) for 13 weeks and in mice receiving gavage doses of 100 mg/kg (71 mg/kg/day) for 2 years.

Central Nervous System Depression. In children, oral doses of around 60 mg/kg/day of bromoform typically produced only mild sleepiness, while doses of 150 mg/kg sometimes produced stupor or deep narcosis, usually accompanied by depressed respiration and erratic heartbeat. The onset of sedation after ingestion is rapid, reportedly minutes in children and about an hour in mice. In intermediate and chronic oral studies in animals, doses of bromoform ≥100 mg/kg (5 days/week; 71 mg/kg/day) caused lethargy. Airborne concentrations of bromoform leading to central nervous system depression in humans are not known, but brief exposures of laboratory animals to high concentrations (7,000 ppm) leads to deep sedation within minutes. Central nervous system effects were also observed in laboratory animals at a concentration of 240 ppm in a short-term, repeated dose study. These depressant effects on the nervous system appear to be fully reversible both in animals and humans, but it is difficult to rule out the possibility of subtle, but enduring, neurological changes following narcotizing doses.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for bromoform and dibromochloromethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

The details regarding calculations of the MRLs for bromoform and dibromochloromethane are described in Appendix A.

Inhalation MRLs

MRLs for acute- (≤14 days), intermediate- (15–364 days), and chronic-duration (≥364 days) inhalation exposure to bromoform or dibromochloromethane have not been derived because quantitative data were not available to determine NOAELs or LOAELs.

Information on the toxicity of bromoform or dibromochloromethane in humans following inhalation exposure was not available. Brief summaries of adverse effects in laboratory animals following inhalation exposure to bromoform, reported in abstract form, do not provide sufficient basis for MRL derivation. No studies were located regarding effects of dibromochloromethane in animals exposed via inhalation. Therefore, inhalation MRLs were not derived for either bromoform or dibromochloro-methane.

Oral MRLs

Bromoform

- An MRL of 0.7 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to bromoform.

The acute toxicity of bromoform has been investigated in a number of animal studies. These studies have identified several targets of toxicity. The available data suggest that the liver is the most sensitive target. The threshold for liver effects appears to be between 50 and 125 mg/kg/day. Increases in absolute and relative liver weights were observed in mice exposed to 125 mg/kg/day bromoform in emulphor in water for 14 days (Munson et al. 1982). Centrilobular pallor, considered to be indicative of hepatocellular degeneration, was observed at 145 mg/kg/day in mice receiving gavage doses of bromoform in corn oil for 14 days (Condie et al. 1983). Hepatocellular vacuolization and/or swelling was observed at 200 mg/kg (9 days/11 days) and higher (Coffin et al. 2000). Other effects observed in acute-duration animal studies include mesangial nephrosis in mice exposed to 145 mg/kg/day via gavage for 14 days (Condie et al. 1983), central nervous system depression, as evidenced by lethargy, labored and shallow breathing, and ataxia in rats and mice at ≥600 mg/kg/day for 1–14 days (Balster and Borzelleca 1982; Bowman et al. 1978; NTP 1989a), and developmental effects (increases in the occurrence of skeletal anomalies) in the offspring of rats exposed to 200 mg/kg/day on gestational days 6–15 (Ruddick et al. 1983).

The Condie et al. (1983) and Munson et al. (1982) studies identify the lowest LOAELs for liver effects. The Condie et al. (1983) study identified a NOAEL of 72 mg/kg/day and LOAEL of 145 mg/kg/day for centrilobular pallor in mice receiving daily gavage doses of bromoform in corn oil for 14 days. Focal inflammation and increase in SGPT levels were observed at 280 mg/kg/day. The Munson et al. (1982) study identified a NOAEL of 50 mg/kg/day and LOAEL of 125 mg/kg/day for increases in absolute and relative liver weights in mice receiving daily gavage doses of bromoform in a 10% emulphor/de-ionized water solution for 14 days. At 250 mg/kg/day, increases in SGOT and SGPT levels were also observed. The Condie et al. (1983) study was selected as the basis of the MRL because it identified a higher NOAEL for liver effects than the Munson et al. (1982) study and included histopathological examination of the liver which was not included in the Munson et al. (1982) study. The NOAEL of 72 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to yield an acute-duration oral MRL of 0.7 mg/kg/day.

- An MRL of 0.2 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to bromoform.

The oral toxicity database in animals provides strong evidence that the liver is the most sensitive target of bromoform toxicity. Several intermediate-duration studies have reported liver effects, typically at the lowest dose level. At lower doses, fatty changes, characterized as hepatocellular vacuolization and swelling, were observed in rats and mice. Focal necrosis was observed at higher oral doses. The lowest LOAEL for liver effects identified in an intermediate-duration study is 50 mg/kg in rats receiving gavage doses of bromoform in corn oil 5 days/week for 13 weeks (NTP 1989a); this study identified a NOAEL of 25 mg/kg. The intermediate-duration oral MRL of 0.2 mg/kg/day for bromoform was derived by applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to the duration-adjusted NOAEL of 18 mg/kg/day.

- An MRL of 0.02 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to bromoform.

Three studies have examined the chronic toxicity of bromoform in animals. Rat and mouse studies conducted by NTP (1989a) are comprehensive studies that found fatty liver changes (hepatocellular vacuolization) at the lowest dose tested, 100 mg/kg (5 days/week; 71 mg/kg/day). The third study (Tobe et al. 1982) identified a similar LOAEL (140 mg/kg/day) in rats exposed to bromoform in the diet for 2 years; this study also identified a NOAEL of 35 mg/kg/day. At 140 mg/kg/day, yellowing of the liver and increased absolute and relative liver weights were observed. The NTP (1989a) rat study was selected as the basis of the chronic-duration oral MRL for bromoform. Even though the Tobe et al. (1982) study identified a NOAEL for liver effects, this study was not selected as the critical study because no histological examination of the liver was conducted and the results were poorly reported. The duration-adjusted LOAEL of 71 mg/kg/day was divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and a modifying factor of 10 to account for the identification of a lower LOAEL in a 13-week study (NTP 1989a) resulting in an MRL of 0.02 mg/kg/day.

Dibromochloromethane

- An MRL of 0.1 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to dibromochloromethane.

The available data on the oral toxicity of dibromochloromethane in animals strongly suggest that the liver is the most sensitive target of toxicity. In most studies, liver effects are observed at lower doses than kidney effects (the next most sensitive end point). The study of Condie et al. (1983) was selected as the basis for the acute-duration oral MRL for dibromochloromethane because it showed dose-related incidences of liver and kidney lesions and identified the lowest LOAEL for liver effects among the available studies. A LOAEL of 37 mg/kg/day, the lowest dose tested, was identified for liver damage (hepatocellular vacuolization) in mice administered dibromochloromethane in corn oil for 14 consecutive days. A reliable NOAEL for liver or kidney effects could not be determined from the available acute data. Applying an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) to the LOAEL of 37 mg/kg/day yields an acute-duration oral MRL of 0.1 mg/kg/day for dibromochloromethane.

No data were located regarding the toxicity of dibromochloromethane following intermediate-duration oral exposure in humans. A number of intermediate-duration studies of rats and mice were located. The liver was identified as the most sensitive target. Hepatocellular vacuolization was observed at 43 mg/kg/day (60 mg/kg, 5 days/week) and higher (Aida et al. 1992; Daniel et al. 1990; NTP 1985); the highest NOAEL for liver effects is 21 mg/kg/day (30 mg/kg, 5 days/week) (NTP 1985). At higher doses (≥100 mg/kg/day), proximal tubular degeneration and nephropathy were observed (Daniel et al. 1990; NTP 1985). Impaired humoral immune function was observed in mice administered 125 mg/kg/day via gavage for 14 days (Munson et al. 1982). Several animal studies also reported neurological effects: decreases in brain weight and decreases in operant behavior at ≥100 mg/kg/day (Balster and Borzelleca 1982; Daniel et al. 1990). Borzelleca and Carchman (1982) found decreases in fertility at high dibromomochloromethane doses (685 mg/kg/day).

Derivation of an intermediate-duration oral MRL for dibromochloromethane based on the NTP (1985) rat study, which identified NOAEL and LOAEL values of 21 and 43 mg/kg/day, was considered. However, the resultant MRL would be higher than the acute-duration oral MRL.

- An MRL of 0.09 mg/kg/day has been derived for chronic-duration oral exposure (365 days or less) to dibromochloromethane.

Studies of dibromochloromethane consistently indicate that the liver is a target organ. The NTP (1985) study, in which rats received gavage doses of 0, 40, or 80 mg/kg of dibromochloromethane in corn oil, 5 days/week, for 104 weeks, was selected as the basis for the chronic-duration oral MRL. This study (NTP 1985) was selected because it showed dose-related incidences of microscopic hepatic lesions and

also identified the lowest LOAEL of 40 mg/kg (duration-adjusted LOAEL of 28 mg/kg/day) for hepatic effects in chronic studies (NTP 1985; Tobe et al. 1982) of dibromochloromethane toxicity. A chronic-duration oral MRL of 0.09 mg/kg/day was derived by applying an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) to the LOAEL of 28 mg/kg/day.