CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Bromodichloromethane (CHBrCl₂; CAS Number 75-27-4) belongs to a group of chemicals referred to as trihalomethanes; the other chemicals in this group are chloroform, bromoform, and dibromochloromethane. The major source of bromodichloromethane in the environment is its formation as a byproduct during the chlorination of water containing organic matter and bromide. Approximately 86% of the population in the United States are served by public water systems that use chlorine or chlorine-containing compounds to disinfectant water supplies; the disinfection helps protect against microbial contaminants that might otherwise cause serious water-borne diseases when exposure occurs (EPA 2016, 2015d; USGS 2010a).

The most likely source of exposure to bromodichloromethane is from chlorinated waters supplied to homes, work, and public places. Exposure can occur through ingestion, inhalation of vapors during showering or bathing, and dermal absorption during water-related activities. Bromodichloromethane levels in drinking water in the United States have been reported to range from below the detection limit to 183 μg/L (EPA 2005b). Another survey reported mean concentrations ranging from 1.0 to 20.3 μg/L (Savitz et al. 2006). Ingestion of food sources contaminated with bromodichloromethane is not an important exposure pathway because it is not frequently detected in foodstuff and levels are typically very low. Very low levels of bromodichloromethane have been detected in ambient air, and this is not likely an exposure route of concern for the general population; the median concentration detected in ambient air, in the United States was 0.0090 ppbv (EPA 2015c).

Blood bromodichloromethane level is the most commonly used biomarker of exposure; alveolar air and urine levels of bromodichloromethane are also reliable biomarkers. In the 2005–2006 National Health and Nutrition Examination Survey (NHANES) survey, the geometric mean blood bromodichloromethane concentration was 1.52 pg/mL (CDC 2017). Studies comparing the relative contribution of different activities to blood bromodichloromethane levels found that showering was the largest contributor, followed by bathing, and then consumption of drinking water (Backer et al. 2000; Nuckols et al. 2005).

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of bromodichloromethane comes primarily from oral studies in laboratory animals. Although a large number of epidemiology studies have examined the toxicity of
trihalomethanes, only a small percentage have analyzed the risks associated with exposure to 
bromodichloromethane. These studies evaluated hepatic, reproductive, developmental, and cancer 
endpoints. Over 60 laboratory animal toxicity studies have been identified. More than 90% of them 
involve oral exposure, and no dermal studies were identified.

As illustrated in Figure 1-1, the most sensitive effects appear to be liver damage, kidney damage, 
decreases in sperm velocity, impaired immune response, and increases in resorptions. A systematic 
review of these endpoints resulted in the following hazard identification conclusions:

- Hepatic effects are a presumed health effect for humans
- Renal effects are a suspected health effect for humans
- Immunological effects are a suspected health effect for humans
- The data are inadequate to conclude whether reproductive effects will occur in humans
- Developmental effects are a presumed health effect for humans

**Hepatic Effects.** Results from numerous inhalation and oral animal studies support the identification of 
the liver as a presumed target in humans. Oral studies in rats and mice have found marked increases in 
serum enzymes (e.g., alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase) 
and centrilobular hepatocellular vacuolar degeneration in rats following acute exposure (Condie et al. 
chronic-duration exposures have resulted in hepatocellular fatty degeneration or metamorphosis (Aida et 
al. 1992; NTP 1987). Hepatocellular degeneration was also observed in an acute-duration mouse 
inhalation study (Torti et al. 2001). Bile duct damage (proliferation, cholangiofibrosis, hyperplasia) has 
also been observed in rats following intermediate and chronic exposure (Aida et al. 1992; NTP 1987); 
these effects occur at higher doses than the hepatocellular effects. Animal studies found oral route-
specific differences in toxicity. The available data suggest a higher toxicity when bromodichloromethane 
was administered via gavage in an oil vehicle compared to an aqueous vehicle (Lilly et al. 1994) and was 
greater when administered via gavage compared to dietary exposure (bromodichloromethane was 
microencapsulated and added to the diet) (Aida et al. 1992). Only one epidemiology study examined 
hepatic outcomes and did not find a significant association between blood bromodichloromethane levels 
and alterations in serum alanine aminotransferase levels (Burch et al. 2015).
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#### Figure 1-1. Health Effects Found in Animals Following Oral Exposure to Bromodichloromethane

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Effects in Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>145-150</td>
<td><strong>Acute:</strong> Histological alterations in kidneys, death</td>
</tr>
<tr>
<td>95-100</td>
<td><strong>Intermediate:</strong> Altered response on neurobehavioral tests</td>
</tr>
<tr>
<td>80-85</td>
<td><strong>Intermediate:</strong> Delayed skeletal ossification in offspring</td>
</tr>
</tbody>
</table>
| 70-75            | **Acute:** Histological alterations in liver; impaired immune response  
|                  | **Intermediate:** Histological alterations in kidneys |
| 45-50            | **Acute:** Full litter resorption  
|                  | **Intermediate:** Impaired immune response |
| 35-40            | **Chronic:** Histological alterations in kidneys; decreased sperm velocity |
| 5-10             | **Intermediate:** Histological alterations in liver  
|                  | **Chronic:** Histological alterations in liver |
| 0.1 mg/kg/day    | **Provisional Acute MRL** |
| 0.008 mg/kg/day  | **Provisional Chronic MRL** |

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**Renal Effects.** Identification of the kidney as a suspected target in humans comes from the results of inhalation and oral studies in rats and mice. Renal tubular degeneration has been observed in mice following acute- and intermediate-duration inhalation exposure (Torti et al. 2001) and following acute-, intermediate-, and chronic-duration oral exposure (George et al. 2002; Lilly et al. 1994, 1996; NTP 1987). Acute oral studies at relatively high doses also reported increases in blood urea nitrogen, urinary glucose, and urinary protein levels (Lilly et al. 1996). No human studies examined this endpoint.

**Immune Effects.** Several studies have reported impaired immune responses in rats orally administered bromodichloromethane for acute or intermediate durations. Decreased immune responses to humoral and cell-mediated immune stimulants were observed in animals receiving gavage doses of bromodichloromethane (French et al. 1999; Munson et al. 1982). A comparison of lowest-observed-adverse-effect level (LOAEL) values identified in rats and mice suggest that rats may be more sensitive than mice to the immunotoxicity of bromodichloromethane. No human studies examining the immune system were identified.

**Reproductive Effects.** Three epidemiology studies evaluated potential reproductive targets. A decrease in menstrual cycle length, specifically the follicular phase length, was significantly associated with bromodichloromethane drinking water levels (Windham et al. 2003). Another epidemiology study found a significant association between a shorter time-to-pregnancy and an estimate of bromodichloromethane levels intake from tap water (MacLehose et al. 2008). The third study did not find an association between alterations in sperm parameters and blood bromodichloromethane levels (Zeng et al. 2013).

Although several laboratory animal studies have examined potential reproductive endpoints, additional data are needed to evaluate the adversity of the observed effects. A diminished response to luteinizing hormone levels in pregnant rats (Bielmeier et al. 2001, 2004, 2007) and decreased sperm velocity (with no change in the percentage of motile or progressive motile sperm) (Klinefelter et al. 1995) were observed in rats. It is unclear if these effects would result in a decrease in reproductive function. A 2-generation study did not find alterations in fertility in rats (Christian et al. 2001b).

**Developmental Effects.** Epidemiology and laboratory animal studies have reported developmental effects associated with bromodichloromethane exposure. Inconsistent results have been observed in epidemiology studies with some studies finding decreases in birth weight and increased risk of small for gestational age (Summerhayes et al. 2012; Rivera-Nuñez and Wright 2013; Wright et al. 2004) and other studies not finding these effects (Cao et al. 2016; Danileviciute et al. 2012; Hoffman et al. 2008).
Epidemiology studies have also found increases in the risk of stillbirth (King et al. 2000) and spontaneous abortions (Waller et al. 1998).

In rats, increases in the occurrence of full-litter resorptions have been found following early gestational gavage administration of bromodichloromethane (Bielmeier et al. 2001; Narotsky et al. 1997). A delay in skeletal ossification was observed in rats exposed to bromodichloromethane in drinking water (Christian et al. 2001a; Ruddick et al. 1983).

**Cancer Effects.** The carcinogenic potential of bromodichloromethane has been evaluated in one epidemiology study and several chronic-duration oral studies in rats and mice. An epidemiology study did not find an increased risk of colorectal cancer associated with bromodichloromethane levels in public water supplies (Bove et al. 2007). Gavage administration of relatively high doses has resulted in increases in neoplastic lesions in the large intestine and kidneys of rats (NTP 1987) and livers of mice (NTP 1987). No increases in tumor incidences were observed in drinking water studies testing lower doses (George et al. 2002; NTP 2006) or at slightly higher doses in a dietary exposure study (Aida et al. 1992).

The U.S. Department of Health and Human Services categorized bromodichloromethane as reasonably anticipated to be a human carcinogen (NTP 2016), EPA categorized it as a probable human carcinogen (Group B2) (IRIS 2002), and the International Agency for Research on Cancer categorized it as possibly carcinogenic to humans (IARC 2016).

**1.3 MINIMAL RISK LEVELS (MRLs)**

The inhalation database was not considered adequate for deriving inhalation MRLs. As presented in Figure 1-2, the limited available inhalation data for bromodichloromethane suggest that the liver and kidney are sensitive targets of toxicity. However, other potentially sensitive endpoints, particularly developmental toxicity, have not been examined for this exposure route and the inhalation.

The oral database was considered adequate for derivation of provisional acute- and chronic-duration oral MRLs for bromodichloromethane. As with inhalation exposure, the liver and kidney are sensitive targets following oral exposure to bromodichloromethane. Developmental, immunological, and reproductive endpoints also have relatively low LOAEL values, as illustrated in Figure 1-3. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.
Figure 1-2. Summary of Sensitive Targets of Bromodichloromethane—Inhalation

The kidney is the most sensitive target of bromodichloromethane inhalation exposure. Numbers in circles are the lowest LOAEIs for all health effects in animals; no human data were identified.

### Acute (ppm)

- Renal: 10
- Ocular: 10
- Hepatic: 30

### Intermediate (ppm)

- Renal: 10
Figure 1-3. Summary of Sensitive Targets of Bromodichloromethane—Oral

The liver is the most sensitive target of bromodichloromethane oral exposure. Numbers in circles are the lowest LOAELs for all health effects in animals. No reliable dose response data were available for humans.

### Acute (mg/kg/day)
- Developmental: 50
- Hepatic: 74
- Immunological: 75
- Renal: 148

### Intermediate (mg/kg/day)
- Hepatic: 6.1
- Immunological: 49
- Renal: 71
- Developmental: 82

### Chronic (mg/kg/day)
- Hepatic: 6.1
- Renal: 36
- Reproductive: 36
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### Table 1-1. Minimal Risk Levels (MRLs) for Bromodichloromethane\(^{a}\)

<table>
<thead>
<tr>
<th>Exposure duration</th>
<th>MRL</th>
<th>Critical effect</th>
<th>Point of departure</th>
<th>Uncertainty factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalation exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td></td>
<td>Insufficient data for MRL derivation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>Insufficient data for MRL derivation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
<td>Insufficient data for MRL derivation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral exposure (mg/kg/day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>0.1(^{b})</td>
<td>Full-litter resorption in rats</td>
<td>10 (BMDL(_{05}))</td>
<td>100</td>
<td>Narotsky et al. 1997</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>Insufficient data for MRL derivation; chronic MRL considered protective for intermediate duration exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>0.008(^{b})</td>
<td>Hepatocellular fatty degeneration in rats</td>
<td>0.78 (BMDL(_{10}))</td>
<td>100</td>
<td>Aida et al. 1992</td>
</tr>
</tbody>
</table>

\(^{a}\)See Appendix A for additional information

\(^{b}\)Provisional MRL values