2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BROMOMETHANE IN THE UNITED STATES

Bromomethane is a gas; at below 38°F, it can exist as a liquid. Bromomethane is primarily used in the form of a gas, compressed liquid, or in solution as a fumigant for the control of insects, fungi, and rodents. Under EPA’s Clean Air Act, production and use of bromomethane in the United States was phased out in 2005, except for two critical use exemptions—to eliminate quarantine pests and for agricultural use where there are no technically or financially feasible alternatives. Oceans are natural sources of bromomethane production and its release into the atmosphere. Bromomethane in the atmosphere breaks down slowly, with a half-life of 11 months. Bromomethane in water and soil is likely to volatilize at a faster rate than it would break down. Bromomethane levels in ambient air are relatively low; U.S. monitoring surveys conducted by EPA reported a mean concentration of 0.014 ppb in 2013 and a maximum mean concentration of 0.46 ppb in other surveys conducted in 2015. The primary route of exposure to bromomethane for the general population is inhalation.

2.2 SUMMARY OF HEALTH EFFECTS

The available data in humans and animals provide strong evidence that the respiratory tract and the nervous system are the most sensitive targets of bromomethane toxicity following inhalation exposure. In humans, the lungs appear to be the primary target of toxicity in the respiratory tract; cough, edema, hemorrhagic lesions, and dyspnea have been reported following acute exposure. In laboratory animals, most of the observed damage to the respiratory tract is confined to the nasal cavity, although some studies have reported thrombi or hemorrhagic lesions, congestion, or pneumonia in the lungs. Within the nasal cavity, the bromomethane-induced damage is limited to the olfactory epithelium; the observed effects include degeneration, hyperplasia, metaplasia, and loss of sensory cells. Comparison of LOAEL values from intermediate- and chronic-duration studies suggests that the nasal effects are duration-related.

Neurological effects have been observed in fumigators, other workers exposed post-fumigation, and non-workers accidentally exposed to bromomethane. The initial neurological effects observed in humans exposed to high levels of bromomethane occur within a few hours of exposure and include headache, weakness, and nausea/vomiting. Depending on the exposure level, these symptoms may progress into ataxia, tremors, paralysis, and clonic seizures. The neurological effects typically begin to wane after several days, but recovery may not be complete even after many months. Only limited information is
available on the effects of long-term inhalation exposure of humans to low levels of bromomethane.

Headache, weakness, and increased prevalence of neurological signs such as muscle ache, fatigue, and dizziness have been noted in workers exposed repeatedly or for extended periods in the workplace. A variety of concentration-related neurological effects ranging from alterations in neurotransmitter levels to cerebral and cerebellar degeneration have been observed in laboratory animals. Mild neurobehavioral signs (decreased locomotor activity in mice) are the most sensitive effects of inhaled bromomethane; it is noted that impaired performance on neurobehavioral tests have not been consistently found at all testing times. As exposure levels increase, overt signs of neurotoxicity such as abnormal gait, tremors, ataxia, hind-limb paralysis, and convulsions have been reported in rats, mice, rabbits, and monkeys. At higher concentrations, histological damage, particularly necrosis and degeneration, was observed in the cerebrum and cerebellum of rats and mice exposed to bromomethane for \( \geq 2 \) weeks; increases in mortality were also observed at these concentrations.

Other targets of bromomethane toxicity that have been observed in laboratory animal inhalation studies include the heart (myocardial fibrosis and degeneration and cardiomyopathy) and kidneys (nephrosis) (Eustis et al. 1988); these effects are typically observed at higher, lethal concentrations.

Limited data are available on the toxicity of bromomethane following oral or dermal exposure. In general, the primary target of toxicity for these routes appears to be the site of contact. For oral exposure, damage to the epithelium of the forestomach has been observed in rats administered \( \geq 2 \) mg/kg/day bromomethane in oil via gavage. However, no adverse effects were associated with oral exposure of dogs exposed to dietary bromomethane at doses up to 0.28 mg/kg/day for 52 weeks or 11.0 mg/kg/day (microencapsulated) in dogs for 2 years. Erythema, edema, and blisters have been observed in humans dermally exposed to liquefied bromomethane or bromomethane vapor. A study in animals found histological damage to the epidermis and dermis following a very brief exposure (\( \leq 5 \) minutes) to liquefied bromomethane. Thermal effects resulting from the rapid evaporation of bromomethane were not addressed.

There is some evidence that bromomethane is a developmental toxicant. Increased incidences of gallbladder agenesis and fused vertebrae (a minor variation) and decreases in fetal weight have been observed in the offspring of rabbits exposed to a maternally toxic concentration (80 ppm). Other studies in rats and rabbits using similar exposure levels and an oral exposure study in rats and rabbits have not reported developmental effects.
2. RELEVANCE TO PUBLIC HEALTH

There are limited data on the carcinogenic potential of bromomethane. EPA determined that bromomethane is not a likely human carcinogen. IARC has placed bromomethane in Group 3, not classifiable as to carcinogenic potential. Several studies of agricultural workers and a study of workers exposed to a variety of brominated chemicals have found increases in specific types of cancer; however, the workers were exposed to numerous chemicals and none of the studies established that bromomethane was the causative agent. No evidence of carcinogenic effects was observed in rats or mice exposed via inhalation to bromomethane for at least 2 years or in rats administered bromomethane via gavage.

Health effects of bromomethane following inhalation and oral exposure in humans and laboratory animals and the concentration ranges at which these effects occur are shown in Figures 2-1 and 2-2, respectively. Estimates of inhalation concentrations posing minimal risk to humans (MRL) are also presented in this figure. These health effects occur at much higher concentrations than those found in ambient air in the United States (see Section 2.1).
### Figure 2-1. Health Effects in Animals Following Inhalation Exposure to Bromomethane

<table>
<thead>
<tr>
<th>Concentration in Air (ppm)</th>
<th>Effects in Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-100</td>
<td><strong>Acute:</strong> Histological alterations in liver</td>
</tr>
<tr>
<td>80-90</td>
<td><strong>Acute:</strong> Gall bladder agenesis in offspring</td>
</tr>
<tr>
<td>40-50</td>
<td><strong>Acute:</strong> Histological alterations in kidney</td>
</tr>
</tbody>
</table>
| 20-30                      | **Acute:** Minimal histological alterations in testes, nasal cavity, heart, thymus, and spleen  
**Intermediate:** Decreased sperm density, minimal histological alterations in liver and thymus  
**Chronic:** Histological alterations in sternum |
| 5-20                       | **Intermediate:** Decreased pup weight, histological alterations in lungs, heart  
**Chronic:** Histological alterations in heart, esophagus |
| 0.5-5                      | **Acute:** Neurobehavioral signs (trembling, jumpiness, paralysis)  
**Intermediate:** Decreased locomotor activity  
**Chronic:** Slight histological alterations in nasal cavity, decreased locomotor activity |
| 0.02 ppm                   | Provisional Intermediate MRL |
| 0.001 ppm                  | Provisional Chronic MRL |

*Concentrations were duration adjusted*
Figure 2-2. Health Effects in Animals Following Oral Exposure to Bromomethane

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Effects in Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td><strong>Acute:</strong> Histological alterations in nonglandular stomach</td>
</tr>
<tr>
<td>10-15</td>
<td><strong>Chronic:</strong> Decreased bodyweight gain and decreased food consumption</td>
</tr>
<tr>
<td>1-5</td>
<td><strong>Intermediate:</strong> Histological alterations in forestomach</td>
</tr>
</tbody>
</table>
2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for bromomethane. 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.

Inhalation MRLs

Bromomethane exists as a gas at room temperature, so the most likely route of human exposure is by inhalation. The hazard of this compound is increased by the fact that it has very little odor at potentially toxic levels and effects are generally delayed more than 1 hour (Alexeeff and Kilgore 1983). Thus, people may be exposed to hazardous levels without being aware that the exposure is occurring.

There are a number of studies that provide good quantitative dose-response data by the inhalation route, and ATSDR has derived provisional inhalation MRLs for intermediate and chronic inhalation exposure; the database was not considered adequate for derivation of an acute-duration inhalation MRL.

A number of studies have evaluated the acute toxicity of bromomethane. In animals acutely exposed to inhaled bromomethane, toxicity has been observed to the respiratory system, liver, kidney, heart, neurological system, immunological/lymphoreticular system, reproductive system, and the developing fetus. Neurotoxicity appears to be the most sensitive effect of acute exposure of animals. The
neurological effects observed in laboratory animals included overt signs of neurotoxicity such as trembling, ataxia, lethargy, paralysis, and hyperactivity; decreases in brain neurotransmitter levels; impaired olfactory function; and histopathological damage in the cerebrum, cerebellum, and olfactory bulb. NTP (1992) identified the lowest duration-adjusted LOAEL of 2.14 ppm; however, there is considerable uncertainty associated with classifying this concentration as a LOAEL. NTP (1992) reported that “neurological signs including trembling, jumpiness, and paralysis were observed in all groups but were most pronounced in the three highest dose groups (50, 100, 200 ppm).” However, the NTP report did not include incidence data for these effects and it is unclear whether any or all of the effects were observed at the lowest concentration tested (12 ppm). In the absence of additional information, ATSDR considered 12 ppm a LOAEL for neurological effects. At this time, ATSDR does not consider the database suitable for identifying a point of departure (POD) for derivation of an acute-duration inhalation MRL because of the uncertainty in establishing the NOAEL and/or LOAEL values in the NTP (1992) study based on the information provided in the study report. If a conservative approach of assuming that all neurological effects occurred at all bromomethane test concentrations is used, then the lowest concentration would be considered a serious LOAEL for paralysis and would not be suitable as a POD for derivation of an MRL.

- A provisional MRL of 0.02 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to bromomethane.

The provisional intermediate-duration inhalation MRL is based neurobehavioral effects (decreased locomotor activity in male mice) observed at the 6-month evaluation period of a 2-year cancer bioassay (NTP 1992). The provisional MRL of 0.02 ppm was derived from a minimal LOAEL of 10 ppm, adjusted for intermittent exposure, converted to a human equivalent concentration [HEC] of 1.8 ppm, and divided by a total uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

- A provisional MRL of 0.001 ppm has been derived for chronic-duration inhalation exposure (>365 days) to bromomethane.

The provisional chronic inhalation MRL is based on nasal lesions (very slight basal cell hyperplasia of the olfactory epithelium) in female rats exposed to bromomethane for 2 years (Reuzel et al. 1991). The provisional chronic-duration inhalation MRL was derived from a minimal LOAEL value of 3.1 ppm (adjusted for intermittent exposure and converted to a HEC; LOAEL_{HEC} of 0.108 ppm) and a total
uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

**Oral MRLs**

Because bromomethane tends to volatilize and exists mainly as a gas at room temperature, the oral toxicity of this compound has not been thoroughly studied. The general population is not likely to be exposed to bromomethane via the oral route; however, exposure to a small amount of bromomethane could occur via contaminated water or food. A gestational exposure gavage study provides data on the acute toxicity of bromomethane (Kaneda et al. 1998); two intermediate-duration gavage studies have been conducted in rats (Boorman et al. 1986; Danse et al. 1984) and two chronic-duration dietary studies in dogs (Wilson et al. 2000) and rats (EPA 1999c) have been conducted. Results of the acute- and intermediate-duration gavage studies show that damage to the stomach is the primary effect. However, no gastrointestinal effects were observed in the two chronic dietary studies.

Acute- and intermediate-duration gavage studies have identified the forestomach as the most sensitive target of toxicity. In the acute study, stomach lesions (erosion and thickening of the wall of the non-glandular stomach and adhesion of the stomach to the spleen, liver, or diaphragm) were observed in rats administered by gavage 30 mg/kg/day bromomethane in corn oil during days 6–15 of gestation (Kaneda et al. 1998). The intermediate-duration studies reported mild focal hyperemia in the forestomach at 2 mg/kg/day (Danse et al. 1984) and forestomach ulceration at 50 mg/kg/day (Boorman et al. 1986; Danse et al. 1984). In contrast to these findings, no gastrointestinal effects were found in dogs fed a diet fumigated with bromomethane (Wilson et al. 2000) or in rats fed a diet containing microencapsulated bromomethane (EPA 1999c). The highest dose tested in the dog study was 0.27 mg/kg/day, which is lower than the NOAEL of 0.4 mg/kg in the Danse et al. (1984) study. However, the highest doses tested in the rat study (EPA 1999c) were 11.10 and 15.12 mg/kg/day in males and females, respectively, which are higher than the LOAEL and slightly higher than the gavage dose of 10 mg/kg associated with forestomach ulceration and necrosis (Danse et al. 1984). There is some question as to whether the forestomach effects are due to the bolus administration of a very reactive chemical and whether gavage administration would be an appropriate model for human exposure to bromomethane. Given the uncertainty of whether the observed forestomach lesions are unique to gavage administration of bromomethane, derivation of an intermediate-duration oral MRL is not recommended at this time.
The chronic-duration oral studies were not considered suitable for MRL derivation. In a study of dogs exposed to a diet fumigated with bromomethane, no adverse effects were observed after 52 weeks of exposure to doses as high as 0.28 mg/kg/day in males and 0.27 mg/kg/day in females (Wilson et al. 2000). In a 12–24-month study in rats exposed to a diet containing microencapsulated bromomethane, decreases in body weight gain were observed in the first 12–18 months at the highest dose levels (11.10 and 15.12 mg/kg/day in males and females, respectively); decreases in food consumption were also observed at these doses (EPA 1999c). No other compound-related effects were observed. This database was not considered adequate for derivation of an MRL because the targets of toxicity have not been established.