

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Bromomethane is a gas at room temperatures, but can be liquified under sufficient pressure, and is a liquid below 38°F (Piccirillo and Piccirillo 2010). 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 the U.S. Environmental Protection Agency (EPA) Clean Air Act, production and most uses of bromomethane in the United States were phased out in 2005; however, bromomethane is still allowed to be used under two critical use exemptions—to eliminate quarantine pests and for agricultural use where there are no technically or financially feasible alternatives.

Bromomethane naturally occurs in oceans, from which it is released 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. The maximum annual mean 24-hour bromomethane concentration at 104 sites across the United States was 0.15 ppbv in 2018 (EPA 2019a).

The most likely route of human exposure is by inhalation because bromomethane exists as a gas at room temperature. Bromomethane has very little odor at concentrations that may produce toxicity; therefore, exposure to hazardous levels may occur without awareness of exposure. However, tracer amounts of acrolein have been added to help facilitate odor recognition. Exposure to inhaled bromomethane is more likely to occur in workers than in the general population. 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.

1.2 SUMMARY OF HEALTH EFFECTS

As noted in Section 1.1, because bromomethane exists as a gas at room temperature, inhalation is the most likely exposure route. However, it is possible that humans could be exposed to very small amounts in food or water. Given the predominance of the inhalation exposure route, most animal toxicity studies have examined effects of inhaled bromomethane, with few studies evaluating effects of oral exposure. In addition to animal studies, some information is available from studies of exposed workers to bromomethane vapor, although reliable quantitative estimates of exposure have not been reported in these

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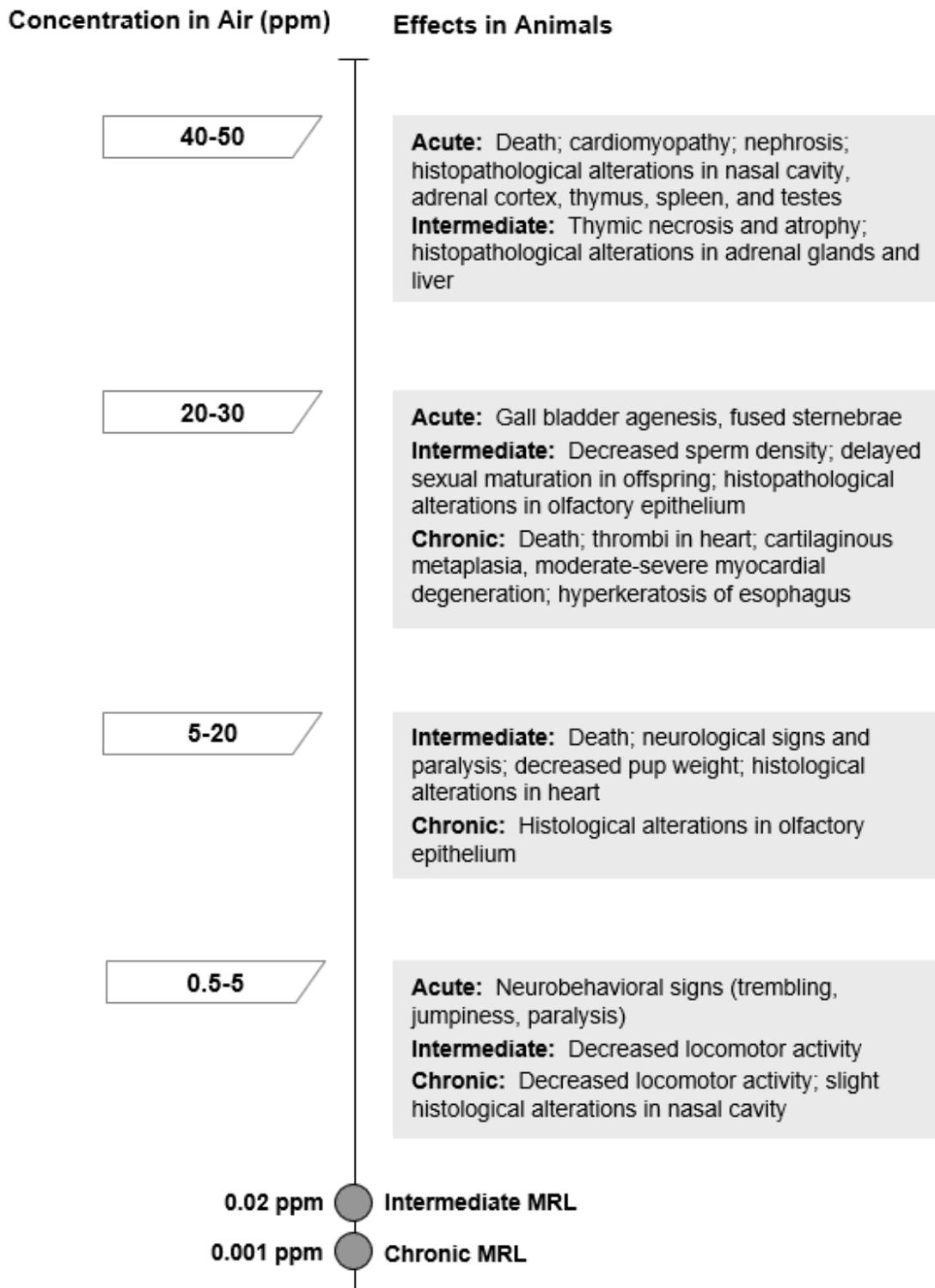
studies. The available data in humans and animals provide strong evidence that the respiratory tract and the nervous system are the most sensitive targets of bromomethane toxicity following inhalation exposure (Figure 1-1). There is some evidence of developmental effects following inhalation exposure of rats, although this has not been substantiated in other studies. Other effects observed in inhalation studies include cardiovascular, reproductive, hepatic, and renal effects; however, these effects occur at higher exposures. Based on the small number of oral studies in animals, the primary target of gavage exposure to bromomethane is damage to the stomach (Figure 1-2). However, chronic-duration oral studies did not identify target organ systems for bromomethane. Dermal and ocular exposure to bromomethane vapor or liquid produces damage at the site of contact.

Respiratory Effects. 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 (Akca et al. 2009; Greenberg 1971; O'Neal 1987; Prain and Smith 1952). 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 (Eustis et al. 1988; Irish et al. 1940; Kato et al. 1986). 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 (Eustis et al. 1988; Gotoh et al. 1994; Hastings et al. 1991; Hurtt et al. 1987, 1988; NTP 1992; Reuzel et al. 1987, 1991; Youngentob and Schwob 2006). Comparison of LOAEL values from intermediate- and chronic-duration studies suggests that the nasal effects are exposure duration-related (NTP 1992).

Neurological Effects. 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 and vomiting (Akca et al. 2009; Deschamps and Turpin 1996; Marraccini et al. 1983; Wyers 1945). Depending on the exposure level, these symptoms may progress into ataxia, tremors, paralysis, and clonic seizures (Balagopal et al. 2011; Deschamps and Turpin 1996; Hine 1969; Hustinx et al. 1993; Prain and Smith 1952; Prockop and Smith 1986). The neurological effects typically begin to wane after several days, but recovery may not be complete even after many months (Bishop 1992; Deschamps and Turpin 1996; Longley and Jones 1965; O'Neal 1987; Rathus and Landy 1961). 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

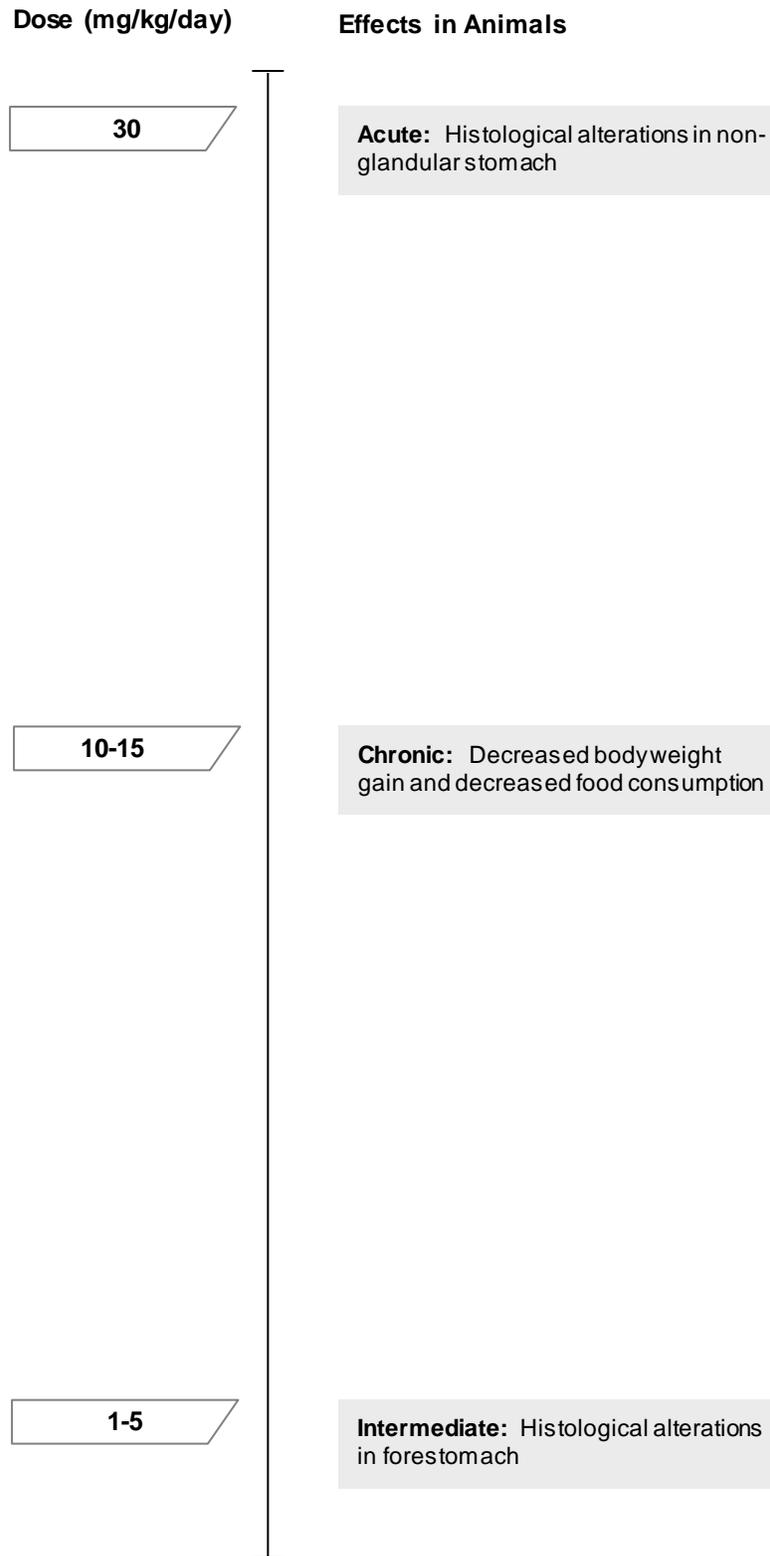
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Figure 1-1. Health Effects in Animals Following Inhalation Exposure to Bromomethane^a



^aConcentrations were duration adjusted

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Figure 1-2. Health Effects in Animals Following Oral Exposure to Bromomethane

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extended periods in the workplace (Anger et al. 1986; Hine 1969; Kantarjian and Shaheen 1963; Kishi et al. 1988). 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 and transient 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 durations. 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 (Breslin et al. 1990; Eustis et al. 1988; Irish et al. 1940; NTP 1992). At higher concentrations, histological damage, particularly necrosis and degeneration, was observed in the cerebrum and cerebellum of rats and mice exposed to bromomethane for ≥ 2 weeks (Eustis et al. 1988; Kato et al. 1986; NTP 1992); increases in mortality were also observed at these concentrations.

Developmental Effects. There is some evidence that inhaled bromomethane is a developmental toxicant. Increased incidences of gallbladder agenesis and fused sternbrae (a minor variation) and decreases in fetal weight have been observed in the offspring of rabbits exposed to a maternally toxic concentration (80 ppm) (Breslin et al. 1990). However, other inhalation studies in rats and rabbits respectively using similar or lower exposure levels (Hardin et al. 1981; NIOSH 1980) and an oral exposure study in rats and rabbits (Kaneda et al. 1998) have not reported developmental effects.

Gastrointestinal Effects. For oral exposure, damage to the epithelium of the forestomach has been observed in rats administered bromomethane in oil via gavage. However, no adverse gastrointestinal effects were associated with oral exposure of dogs exposed to dietary bromomethane in microencapsulated form at higher doses for up to 2 years. There is some question as to whether the forestomach effects in rats are due to the bolus administration of a very reactive chemical and whether gavage administration is an appropriate model for human exposure to bromomethane. Thus, there is uncertainty regarding the relevance of this effect to humans.

Other Targets. Other targets of bromomethane toxicity that have been observed in laboratory animal inhalation studies include the heart (myocardial fibrosis and degeneration and cardiomyopathy) (Eustis et al. 1988; Kato et al. 1986; NTP 1992), liver (necrosis) (Hurr et al. 1987), kidneys (nephrosis) (Eustis et al. 1988), and the male reproductive system (decreased sperm density and testicular degeneration) (EPA 1988a; Eustis et al. 1988; Kato et al. 1986); these effects are typically observed at higher concentrations that are near-lethal or lethal.

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Dermal Effects. 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 (≤ 5 minutes) direct dermal contact to liquefied bromomethane. In addition, the temperature of liquidized bromomethane can be below -93°C ; therefore, exposed tissue can freeze and develop erythema, edema, and blisters (Vivas et al. 2015). This could be a possible contributor to dermal effects of bromomethane.

Ocular Effects. In humans exposed to bromomethane vapor, conjunctivitis, erythema, and edema of the eyelids have been reported (Langard et al. 1996; O'Neal 1987; Prain and Smith 1952; Wyers 1945).

Cancer Effects. There are limited data on the carcinogenic potential of bromomethane in humans. Several studies of agricultural workers (Alavanja et al. 2003; Barry et al. 2012) and a study of workers exposed to a variety of brominated chemicals (Wong et al. 1984) 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 (NTP 1992; Reuzel et al. 1987, 1991) or in rats administered bromomethane via gavage (Danse et al. 1984; IRIS 2002).

The U.S. Department of Health and Human Services (NTP 2016) has not categorized the carcinogenicity of bromomethane. The International Agency for Research on Cancer (IARC 2016) classified bromomethane as a Group 3 carcinogen (not classifiable as to its carcinogenicity to humans). EPA (IRIS 2002) has determined that bromomethane is classified as a Group D carcinogen (not classifiable as to human carcinogenicity).

1.3 MINIMAL RISK LEVELS (MRLs)

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Appendix A for detailed information on the MRLs for bromomethane.

MRLs for bromomethane are summarized Table 1-1. As noted in Section 1.1, the most likely route of human exposure is by inhalation because bromomethane exists as a gas at room temperature. Numerous studies have been conducted in laboratory animals for acute, intermediate, and chronic exposure

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durations, with sufficient data to derive intermediate- and chronic-duration inhalation MRLs. Neurotoxicity and lesions of the upper respiratory tract are the most sensitive effects of inhalation exposure to bromomethane (Figure 1-3). The general population is not likely to be exposed to bromomethane via the oral route; thus, very few animal studies on the oral toxicity of bromomethane have been conducted. One acute- and one intermediate-duration gavage studies show that the most sensitive effect of oral exposure to bromomethane is stomach lesions; however, these studies administered bromomethane by gavage. As discussed in Section 1.2, there is uncertainty as to whether the observed forestomach lesions in animals are unique to gavage administration of bromomethane, and how these effects are related to humans who have no forestomach. Chronic-duration oral studies did not identify target organs for bromomethane; the only effect observed in chronic-duration oral studies is decreased body weight.

Table 1-1. Minimal Risk Levels (MRLs) for Bromomethane^a

| Exposure duration | MRL | Critical effect | Point of departure | Uncertainty factor | Reference |
|----------------------------------|--------------------------------------|-------------------------|---------------------------------|--------------------|--------------------|
| Inhalation exposure (ppm) | | | | | |
| Acute | Insufficient data for MRL derivation | | | | |
| Intermediate | 0.02 | Neurobehavioral effects | 1.8 ppm (LOAEL _{HEC}) | 90 | NTP 1992 |
| Chronic | 0.001 | Nasal lesions | 0.11 (LOAEL _{HEC}) | 90 | Reuzel et al. 1991 |
| Oral exposure (mg/kg/day) | | | | | |
| Acute | Insufficient data for MRL derivation | | | | |
| Intermediate | Insufficient data for MRL derivation | | | | |
| Chronic | Insufficient data for MRL derivation | | | | |

^aSee Appendix A for additional information.

LOAEL_{HEC} = lowest-observed-adverse-effect level, human equivalent concentration

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Figure 1-3. Summary of Sensitive Targets of Bromomethane – Inhalation

The respiratory tract and neurological system are the most sensitive target of bromomethane inhalation exposure.

