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### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1-BROMOPROPANE IN THE UNITED STATES

1-Bromopropane is a brominated hydrocarbon that was originally used as an intermediate in the production of pesticides, flavors and fragrances, pharmaceuticals, and other chemicals. It is currently used as a solvent in the adhesives, dry cleaning, vapor degreasing, and electronic and metal cleaning industries. There has been an increased use of 1-bromopropane in the last decade due to its application as a substitute for ozone-depleting substances and suspected carcinogens in various industrial and commercial applications. Due to the increased use of 1-bromopropane, exposure to workers has been increasing, and this has caused some human health concern, such as neurological alterations and reproductive toxicity. Therefore, its use in certain industries is being reevaluated.

The dominant process affecting the overall environmental fate and transport of 1-bromopropane is volatilization. In water, estimated volatilization half-lives for a model river and a model lake were reported as 1.2 hours and 4.4 days, respectively. 1-Bromopropane in air will be degraded by photochemically produced hydroxyl radicals, with 1-bromopropane having a half-life of 14 days. Hydrolysis and biodegradation by microorganisms have also been shown to break down 1-bromopropane in aquatic and terrestrial environments. 1-Bromopropane is not expected to bioaccumulate in aquatic organisms.

Exposure to 1-bromopropane occurs mainly in occupational settings. Use of 1-bromopropane in aerosol applications can lead to dermal and inhalation exposure of workers. Workers using 1-bromopropane as a spray adhesive have the highest dermal and inhalation exposures. Workers involved in the production of 1-bromopropane, as well as those using it in commercial applications, such as adhesive sprays, degreasing operations for cleaning metals, plastics, and electronic components, dry cleaning, asphalt production, aircraft maintenance, and synthetic fiber manufacturing, also have potential for high exposure. The general population may be exposed to 1-bromopropane in air when it is used during aerosol applications due to potential vapor migration, particularly at locations in close proximity to the emissive use of 1-bromopropane.

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**2.2 SUMMARY OF HEALTH EFFECTS**

The preponderance of health effects information on 1-bromopropane is from studies of laboratory animals and human studies in which the main exposure route is inhalation, but dermal exposure may have also occurred in the human studies. As summarized below and detailed in Chapter 3 (Health Effects), the main target organ of concern following 1-bromopropane exposure in humans is the nervous system.

Reported health effects in workers exposed to 1-bromopropane for months or years range from subtle neurological deficits (e.g., decreased vibration sense and paresthesias) at workplace air concentrations as low as 1.28 ppm to frank neurotoxic effects (e.g., ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy) in workers exposed to concentrations  $\geq 100$  ppm. Although the principal route of exposure was likely inhalation, dermal exposure could have been significant since often no gloves were used when handling 1-bromopropane, or the use of gloves, as noted in some reports, may have enhanced dermal uptake of 1-bromopropane by occlusion effect. Evidence of alterations of the autonomic nervous system has also been presented. A study that followed workers as outpatients for 2 years post-exposure reported persistent symptoms including headache, decreased memory, decreased mood, lower extremities numbness, cramping, paresthesias, weakness, and difficulty walking/poor balance. Clinical signs noted in these individuals included decreased cognition, lower extremities spasticity and weakness, gait ataxia, hyperreflexia, and decreased lower extremities sensation. It was suggested that the pathogenesis of 1-bromopropane neurotoxicity in humans may reflect a central distal axonopathy syndrome.

Results from animal studies support the conclusion that exposure to 1-bromopropane can result in neurotoxicity. Reported effects in acute- and intermediate-duration inhalation studies at concentrations  $\geq 50$  ppm 1-bromopropane included changes in neurobehavior, electrophysiological parameters, and in morphology and biochemistry of the central and peripheral nervous systems. Impaired learning and memory, sedation, and biochemical changes were also reported in rats after 12 days of ingestion of doses of 200 mg 1-bromopropane/kg/day in oral studies that assessed neurological end points in laboratory animals.

Various *in vivo* and *in vitro* mechanistic studies have been conducted to investigate the mechanism(s) involved in the neurotoxic action of 1-bromopropane in animals (see Section 3.5.2, Mechanisms of Toxicity). Proposed mechanisms include changes in neurotransmitter systems, electrophysiological

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alterations, decreased neurogenesis, glial activation, inhibition of anti-apoptotic processes, and oxidative stress; however, no definitive mechanism of action has yet been determined.

Limited data are available regarding non-neoplastic health effects in humans exposed to 1-bromopropane other than neurological effects. Preliminary health surveys and occupational case studies suggest that 1-bromopropane may be a respiratory tract irritant. These data are supported by findings of respiratory tract lesions in rats and mice exposed to  $\geq 125$  or  $\geq 62.5$  ppm 1-bromopropane, respectively, for intermediate-duration periods. Limited human clinical chemistry data do not indicate that the liver or kidney are sensitive targets of 1-bromopropane, although animal studies suggest that liver and/or kidney damage may occur with repeated exposure to concentrations  $\geq 50$  ppm. Limited reproductive data available in two NIOSH Health Hazard Evaluation reports and two preliminary health surveys are inadequate to assess the reproductive toxicity of 1-bromopropane in humans. The available animal data, however, show that 1-bromopropane exposure can adversely affect the male and female reproductive systems (sperm damage, altered hormone concentrations, altered estrous cycles, altered reproductive development) at exposure concentrations  $\geq 50$  ppm.

There are no developmental studies in humans exposed to 1-bromopropane. Studies in rats suggest that maternal exposure to  $\geq 500$  ppm 1-bromopropane can result in reduced body weight in the offspring. 1-Bromopropane was not teratogenic in animal studies. No human data are available regarding immune system effects, but one inhalation and one oral study in animals suggest that 1-bromopropane exposure can suppress immune responses. Available data do not provide consistent evidence for exposure-related effects in other organ systems (cardiovascular, dermal, endocrine, gastrointestinal, hematological, or ocular); therefore, non-neoplastic effects in these systems following exposure to 1-bromopropane are unlikely to occur.

There are no cancer studies in humans exposed to 1-bromopropane. The potential carcinogenicity of 1-bromopropane has been examined in 2-year inhalation bioassays with F-344 rats and B6C3F1 mice. 1-Bromopropane was a multi-site carcinogen in rats, significantly increasing the incidence of large intestine adenomas in females (500 ppm), skin keratoacanthoma in males ( $\geq 250$  ppm), skin keratoacanthoma, basal cell adenoma, or squamous cell carcinoma in males ( $\geq 125$  ppm), malignant mesothelioma in males (500 ppm), and pancreatic islet adenoma in males ( $\geq 125$  ppm). In mice, exposure to 1-bromopropane significantly increased the incidence of combined alveolar/bronchiolar adenoma or carcinoma in females ( $\geq 62.5$  ppm). Based on the findings from the NTP bioassay, ACGIH has assigned 1-bromopropane a classification of “A3 – *Confirmed animal carcinogen with unknown relevance to*

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*humans,*” and the Department of Health and Human Services has classified 1-bromopropane as “*reasonably anticipated to be a human carcinogen*”. IARC and the EPA have not evaluated the carcinogenicity of 1-bromopropane.

### 2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for 1-bromopropane. 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*

- An MRL of 1 ppm (5 mg/m<sup>3</sup>) has been derived for acute-duration inhalation exposure (14 days or less) to 1-bromopropane.

The MRL is based on a BMCL<sub>1SD</sub> of 97.40 ppm for neurological effects in rats exposed intermittently to 1-bromopropane for 14 days (Honma et al. 2003). No adequate data in humans are available. The only acute-duration inhalation studies in humans were a few case studies reporting subjective symptoms in workers within 2 weeks of 1-bromopropane introduction into the workplace. Symptoms included respiratory irritation, headache, nausea, and lower extremity numbness, pain, and weakness; the geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm) (Raymond and Ford 2007). Acute animal inhalation studies included two single-exposure studies evaluating lethality (Elf AtoChem S.A. 1997; Kim et al. 1999), a single-exposure study evaluating sperm motility (Garner et

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al. 2007), a 1-week study evaluating neurogenesis and endocrine end points (Zhang et al. 2013), a 1-week study evaluating morphological and biochemical changes in the brain (Wang et al. 2002), and a 3-week study that also provided results of neurobehavioral tests conducted in rats during the first 2 weeks of exposure (Honma et al. 2003). Garner et al. (2007) reported significantly reduced sperm motility in mice following a single 6-hour exposure to 800 ppm 1-bromopropane for 6 hours. It should be noted, however, that because the initial concentration of 800 ppm 1-bromopropane decreased steadily during the 6-hour exposure period, the true LOAEL may have been somewhat lower. Wang et al. (2002) reported morphological changes in the medulla oblongata and posterior tibial nerve in rats exposed to 800 ppm 1-bromopropane, but not  $\leq 400$  ppm, for 1 week (Wang et al. 2002). However, only one rat/group was assessed for morphological alterations. Wang et al. (2002) also reported several biochemical changes in the central nervous system of rats following exposure to  $\geq 200$  ppm 1-bromopropane. The toxicological significance of these changes is unknown because there were no clear associations between biochemical and morphological changes. Other reported neurological effects included decreased activity and ataxia after single exposures to  $\geq 1,800$  ppm, but not 300 ppm; however, only qualitative data were provided in that study (Kim et al. 1999). In the Zhang et al. (2013) study, there were no exposure-related changes in hippocampal neurogenesis, adrenal weight, or plasma corticosterone levels in male rats intermittently exposed to 1,000 ppm 1-bromopropane (the highest exposure concentration tested) for 1 week. Honma et al. (2003) conducted several neurobehavioral tests in male F-344 rats following exposure to  $\leq 1,000$  ppm 1-bromopropane 8 hours/day, 7 days/week for 3 weeks. All tests were conducted at various times after the 3-week exposure period except a traction test that was also conducted on exposure days 1, 7, and 14. The traction test was used to measure forelimb grip strength. No statistically significant differences in grip strength were observed between exposed rats (10, 50, 200, 1,000 ppm 1-bromopropane) and controls on days 1 or 7. On day 14, however, rats exposed to 1,000 ppm 1-bromopropane showed a statistically significant decrease in grip strength compared to lower exposure groups and controls, thus defining a no-observed-adverse-effect level (NOAEL) and LOAEL of 200 and 1,000 ppm, respectively, for neurological effects in an acute-duration inhalation study. Because all data were presented graphically, the means and standard errors (standard deviations [SDs] were subsequently calculated) for traction time (assessed on day 14) were extracted digitally using GrabIt! software (version XP2) for benchmark dose (BMD) analysis. The  $BMCL_{1SD}$  of 97.40 ppm from the selected model (Exponential model 4) was duration-adjusted (8/24 hours) to calculate a  $BMCL_{[HEC]}$  of 32.3 ppm. Applying an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability) to the  $BMCL_{[HEC]}$  of 32.3 ppm yields an acute-duration inhalation MRL of 1 ppm for 1-bromopropane. A duration adjustment (8/24 hours) seemed appropriate in the absence of information regarding whether

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Haber's Law is applicable under the experimental conditions of the study. Further details of the MRL derivation are presented in Appendix A.

- An MRL of 0.1 ppm (0.5 mg/m<sup>3</sup>) has been derived for intermediate-duration inhalation exposure (15–364 days) to 1-bromopropane.

Adequate human data are not available. There are three publications of human cases exposed for intermediate durations (from weeks to months) that provide exposure levels. A case discussed by Ichihara et al. (2002) (case 3) was a woman who showed signs of staggering and numbness and paresthesias in the feet, thighs, lower back, and hips, and complained of headaches after 2 months of using 1-bromopropane as a solvent with a spray gun. Estimates of the exposure levels using a passive sampler indicated that the daily time-weighted average (TWA) concentration ranged from 60 to 261 ppm with an average of 133±67 ppm (SD). An MRL cannot be based on a single case. Raymond and Ford (2007) reported that four workers developed severe ataxia, sensory motor, and cognitive impairments soon after the introduction of 1-bromopropane into their workplace as a furniture adhesive. A survey conducted by the National Institute of Occupational Safety and Health (NIOSH) 9 months after the four workers became ill showed that the workers could have been exposed to a mean concentration of 1-bromopropane of 107 ppm (range 58–254 ppm). This study is not suitable for MRL derivation because of the small size of the cohort, the fact that the workers studied had elevated urinary arsenic concentrations from unknown sources, a major confounder, and lack of exposure data at the time of the illnesses. In a brief communication, Wang et al. (2015) reported that 6 out of 20–25 workers in a golf-club cleaning business in Taiwan developed neurological symptoms, including tingling pain, soreness in the lower extremities, and paresthesia after exposure to 1-bromopropane for 3–10 months. Workers were assigned to wash and dry golf clubs with the solvent. The mean of three measurements of 1-bromopropane in air over the platform of the washing tank was 128.8 ppm (range 97.3–188.6 ppm). Because only qualitative data were presented, no personal air sampling was available, and dermal contact with 1-bromopropane may have been considerable (no data on the use of gloves were provided), this study is inadequate for MRL derivation.

Examination of the intermediate-duration inhalation database in animals suggests that the liver and the nervous system might be targets for 1-bromopropane toxicity. Four studies identified the lowest LOAEL of 50 ppm 1-bromopropane. At this exposure concentration, Kim et al. (1999) reported hepatocyte vacuolization in Sprague-Dawley rats exposed intermittently for 8 weeks; Liu et al. (2009) reported hepatocellular degeneration and focal necrosis and alterations in sperm parameters in BALB/cA mice exposed intermittently for 4 weeks, Zong et al. (2016) reported mild hepatocyte degeneration in rats

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exposed intermittently for 4 weeks, and Honma et al. (2003) reported increased spontaneous locomotor activity in Fischer-344 rats exposed intermittently for 3 weeks. The 50 ppm exposure concentration was the lowest concentration tested in the Kim et al. (1999), Liu et al. (2009), and Zong et al. (2016) studies, whereas Honma et al. (2003) identified a NOAEL of 10 ppm for neurological effects. Of these three studies, the Honma et al. (2003) study appears to be the most appropriate for MRL derivation for the following reasons: (1) the nervous system is the most sensitive target for 1-bromopropane in humans as evidenced in studies in workers and case reports (no adverse hepatic effects have been reported in individuals showing clear signs of neurotoxicity) and (2) it identified a NOAEL for neurological effects. In the Honma et al. (2003) study, spontaneous locomotor activity was monitored in groups of male F-344 rats (4/group) following 3 weeks of daily 8-hour whole-body exposures to 0, 10, 50, or 200 ppm 1-bromopropane vapors. After the 3-week exposure period, rats were tested once per day for 6 consecutive days. Significant increases in spontaneous locomotor activity relative to controls occurred in the groups exposed to 50 ppm 1-bromopropane on post-exposure days 1, 2, and 3 and in the group exposed to 200 ppm on post-exposure days 1, 2, 3, and 4. No significant difference from controls was observed in rats exposed to 10 ppm 1-bromopropane. The spontaneous locomotor activity results were presented graphically; however, the data were not amenable for extraction using GrabIt! Software (version XP2). Thus, the NOAEL/LOAEL approach was used to identify the point of departure (POD) for the MRL. The data (Figure 3 in the study) are presented as changes in spontaneous locomotor activity relative to pre-exposure levels (assigned as 100% activity) for each day post-exposure that the test was performed (up to 6 days post-exposure). The selection of which post-exposure day (1 to 6) to model to compare treated and controls would have been entirely arbitrary. The NOAEL of 10 ppm was duration-adjusted ( $8/24$ ) to calculate the  $\text{NOAEL}_{[\text{HEC}]}$  of 3.33 ppm. Applying an uncertainty factor of 30 (3 for dosimetric adjustment and 10 for human variability) resulted in an intermediate-duration inhalation MRL of 0.1 ppm for 1-bromopropane. A duration adjustment ( $8/24$  hours) seemed appropriate in the absence of information regarding whether Haber's Law is applicable under the experimental conditions of the study. Further details of the MRL derivation are presented in Appendix A.

- An MRL of 0.02 ppm ( $0.1 \text{ mg/m}^3$ ) has been derived for chronic-duration inhalation exposure (365 days or more) to 1-bromopropane.

This MRL was based on a minimal LOAEL of 1.28 ppm for mild neurological impairment (increased vibration sense threshold in toes, indicating decreased vibration sense) in female workers from three 1-bromopropane production facilities in China employed for an average duration of ~40 months (Li et al. 2010). The study examined a number of neurological parameters in a population of workers and age-, sex-, and region-matched controls in three 1-bromopropane production plants in China. The final analysis

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comprised 120 women (60 exposed and 60 referents) and 52 men (26 exposed and 26 referents). Median individual TWA exposure to 1-bromopropane ranged from 0.07 to 106.4 ppm for females and from 0.06 to 114.8 ppm for males. After conducting multiple analyses, the vibration sense threshold showed the clearest dose-related effect, with significant increases (indicative of decreased vibration sense) in all exposed female groups. No significant differences between controls and individual male groups were seen regarding neurological parameters in this analysis. The minimal LOAEL of 1.28 ppm for increased vibration sense threshold (decreased vibration sense) in females was adjusted for continuous exposure ( $1.28 \text{ ppm} \times 5 \text{ days}/7 \text{ days} \times 12 \text{ hours}/24 \text{ hours} = 0.46 \text{ ppm}$ ) and was divided by an uncertainty factor of 30 (3 for use of minimal LOAEL and 10 to account for human variability) to derive the MRL of 0.02 ppm ( $0.1 \text{ mg}/\text{m}^3$ ). However, the confidence in the MRL is low due to a number of limitations of the principal study, most notably potential underestimation of 1-bromopropane exposure levels and concerns regarding the sensitivity of the vibration sense measurement method utilized in the study. However, after careful review of limitations and criticisms, as well as the available human and animal data, this study was considered to be the best available study on which to base the chronic MRL. In support, basing an MRL on the most sensitive animal study identifying a LOAEL for respiratory lesions (Morgan et al. 2011; NTP 2011) would yield an MRL of 0.03 ppm ( $0.15 \text{ mg}/\text{m}^3$ ), which is essentially equivalent to the MRL based on the selected human study. The rationale for selecting the Li et al. (2010) study as the principal study for the derivation of the chronic inhalation MRL, despite acknowledged limitations, is discussed in detail in Appendix A.

ACGIH (2014, 2016) has recommended a Threshold Limit Value (TLV) of 0.1 ppm 1-bromopropane based on the same end point from the Li et al. (2010) study. This value is designed to be protective for healthy adult workers exposed daily over a working lifetime.

***Oral MRLs***

- An MRL of 0.2 mg 1-bromopropane/kg/day has been derived for acute-duration (14 days or less) oral exposure to 1-bromopropane

This MRL was based on a  $\text{BMDL}_{1SD}$  of 19.75 mg 1-bromopropane/kg/day for impaired memory in the Morris water maze test in Wistar rats exposed to 0, 200, 400, or 800 mg 1-bromopropane/kg/day via gavage for 12 days (Zhong et al. 2013). On days 8–12, cognitive function (spatial learning and memory) was assessed with the Morris water maze test and dose-related impairments were observed in learning and memory measures. On day 5, when the escape platform was removed to assess memory, all exposure groups showed a significant decrease in the number of times they crossed the former location of the



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escape platform. A LOAEL of 200 mg/kg/day was identified for this study based on impaired spatial learning and memory (increased swimming distance, altered search pattern, decreased number of crossings of the escape platform); no NOAEL was identified. All data were presented graphically. The SDs could not be extracted from day 1–4 figures, either because they overlapped between dose groups (total swimming distance) or they were not reported (distribution of search patterns); therefore, these data could not be used for BMD analysis. However, the means and standard deviations for the number of crossings of the escape platform (assessed on day 5) were extracted digitally using GrabIt! software (version XP2) for BMD analysis. Alternate data extraction of the means and SDs using DigitizeIt software resulted in BMDLs that differed by <17% on average, which would yield the same MRL. The BMDL<sub>1SD</sub> of 19.75 mg 1-bromopropane/kg/day from the selected model (Hill) was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 to account for human variability) to derive an MRL of 0.2 mg 1-bromopropane/kg/day. Further details regarding the Zhong et al. (2013) study can be found in Appendix A. A more recent study by the same groups of investigators confirmed the previous results and reported that treatment of male Wistar rats with  $\geq 200$  mg 1-bromopropane/kg/day for 12 days impaired spatial memory and spatial learning ability (Guo et al. 2015). In this study, rats exposed to  $\geq 200$  mg 1-bromopropane/kg/day in the Morris Water Maze showed a significantly dose-related decreased percent of time at the target platform; the NOAEL was 100 mg 1-bromopropane/kg/day. Modeling of these data yielded a BMDL<sub>1SD</sub> (POD) of 77.94 mg 1-bromopropane/kg/day, which is higher than the BMDL<sub>1SD</sub> of 19.75 mg 1-bromopropane /kg/day used to derive the current MRL. Therefore, it is still more appropriate (more protective) to use data from Zhong et al. (2013) to derive an acute-duration oral MRL for 1-bromopropane.

No intermediate-duration oral MRL was derived for 1-bromopropane due to a lack of adequate studies. No chronic-duration oral MRL was derived for 1-bromopropane due to a lack of oral studies for chronic durations.