APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: Neurological and respiratory systems are the primary targets of acute inhalation of bromomethane in humans. Studies in laboratory animals identify several organ systems (respiratory tract, cardiovascular system, liver, kidneys, immunological system, reproductive system, neurological system, and the developing fetus) as targets of acute exposure to inhaled bromomethane, with neurotoxicity identified as the most sensitive effect. A 2-week study in mice identified neurological effects at an exposure level of 12 ppm (NTP 1992). 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). At this time, the database is not considered 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.

Agency Contacts (Chemical Managers): Sam Keith

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.02 ppm
Critical Effect: Decreased locomotor activity
Reference: NTP 1992
Point of Departure: $LOAEL_{[HEC]}$ of 1.8 ppm
Uncertainty Factor: 90
LSE Graph Key: 41
Species: Mouse

MRL Summary: The intermediate-duration inhalation MRL for bromomethane was derived based on neurobehavioral effects (temporary decreased locomotor activity in male mice) observed at the 6-month (but not at the 0-, 3-, 9-, 12-, 15-, 18-, 21-, or 24-month) evaluation period of a 2-year cancer bioassay (NTP 1992). In this study, various neurological effects were sporadically observed in male and female mice, but effects did not exhibit temporal- or exposure-related dependence. The 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).

Selection of the Principal Study: The NTP (1992) study in rats and mice was selected as the principal study for deriving the intermediate-duration inhalation MRL because this study identified the lowest LOAEL value for neurological effects. The study conducted extensive evaluations of neurobehavioral and neurological endpoints using functional observational battery (FOB) testing at numerous intermittent exposure durations and exposure levels. In addition, the study evaluated comprehensive toxicological endpoints.

Selection of the Critical Effect: The MRL was based on a minimal LOAEL of 10 ppm for decreased locomotor activity in male mice. The 10 ppm concentration was considered a minimal LOAEL because of the small magnitude of change (16%) in locomotor activity.

Alterations in performance on neurobehavioral tests were observed in rats and mice throughout the exposure period. However, statistically significant alterations in neurobehavioral effects were not observed at all time points (see Table A-1 for an overview of the statistically significant alterations). The earliest effect was an increased startle response latency in male rats exposed to 120 ppm for 3 weeks and the lowest LOAEL was 10 ppm for decreased locomotor activity in male mice and altered exploratory behavior (decreased novel side crossings and decreased novel side duration) in female mice exposed for 6 months. It is noted that the decreases in locomotor activity were not statistically significant at 9 months, but were significant at ≥10 ppm in female mice exposed for 12 months. There is extensive evidence in humans and laboratory animals that the nervous system in general and motor function specifically is a sensitive target of bromomethane toxicity. Ataxia has been reported in some severe cases of bromomethane poisoning in humans (Balagopal et al. 2011; Behrens and Dukes 1986). Ataxia, gait disturbances, paralysis, and limb crossing and twitching have been observed in laboratory animals exposed to lethal concentrations (Alexeeff et al. 1985; EPA 1988a; Eustis et al. 1988; Hurtt et al. 1987;

NTP 1992). Cerebellar and cerebral degeneration or necrosis have also been observed in rats and mice exposed to ≥100 ppm (Eustis et al. 1988; Kato et al. 1986; NTP 1992).

Although the alterations were not observed at all time points, the decrease in locomotor activity observed in male and female mice exposed for 6 months was selected as the critical effect for the MRL.

Table A-1. Alterations in Performance on Neurobehavioral Tests in Rats and Mice Exposed to Inhaled Bromomethane for Intermediate Durations[a]

Test and exposure duration	Male rats	Female rats	Male mice	Female mice
Startle response latency				
3 weeks	—	120 ppm ↑	No assessment	No assessment
6 weeks	—	—		
9 weeks	—	—	No assessment	No assessment
12 weeks		120 ppm ↑		
3 months	Not evaluated	Not evaluated	100 ppm ↓	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—
Startle response amplitude				
3 weeks	—	—	No assessment	No assessment
6 weeks	60 ppm ↓ 120 ppm ↓	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	120 ppm ↓	—	—
3 months	Not evaluated	Not evaluated	100 ppm ↑	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—
Activity latency				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	80 ppm ↑	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	—	—	80 ppm ↓
3 months	Not evaluated	Not evaluated	100 ppm ↑	—
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—
Novel side time				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment

Table A-1. Alterations in Performance on Neurobehavioral Tests in Rats and Mice Exposed to Inhaled Bromomethane for Intermediate Durations[a]

Test and exposure duration	Male rats	Female rats	Male mice	Female mice
12 weeks	—	—	—	—
3 months	Not evaluated	Not evaluated	100 ppm ↓	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	10 ppm ↓ 33 ppm ↓ 100 ppm ↑
9 months	Not evaluated	Not evaluated	—	—
Novel side crossings				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	120 ppm ↑		—	—
3 months	Not evaluated	Not evaluated	100 ppm ↓	
6 months	Not evaluated	Not evaluated	—	10 ppm ↓ 33 ppm ↓ 100 ppm ↑
9 months	Not evaluated	Not evaluated	—	—
Locomotor activity				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	—	—	—
3 months	Not evaluated	Not evaluated	100 ppm ↓	—
6 months	Not evaluated	Not evaluated	10 ppm ↓ 33 ppm ↓	33 ppm ↓ 100 ppm ↓
9 months	Not evaluated	Not evaluated	—	—
Hindlimb foot splay				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	120 ppm ↓	—	—
3 months	Not evaluated	Not evaluated	—	—
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—

Table A-1. Alterations in Performance on Neurobehavioral Tests in Rats and Mice Exposed to Inhaled Bromomethane for Intermediate Durations[a]

Test and exposure duration	Male rats	Female rats	Male mice	Female mice
Hindlimb grip strength				
3 weeks	—	—	No assessment	No assessment
6 weeks	120 ppm ↓	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	—	—	—
3 months	Not evaluated	Not evaluated	100 ppm ↑	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	33 ppm ↓	—
Forelimb grip strength				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	—	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	120 ppm ↓	—	—
3 months	Not evaluated	Not evaluated	—	—
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—
Hot plate latency				
3 weeks	—	—	No assessment	No assessment
6 weeks	—	—	80 ppm ↑	—
9 weeks	—	—	No assessment	No assessment
12 weeks	—	—	—	—
3 months	Not evaluated	Not evaluated	—	100 ppm ↑
6 months	Not evaluated	Not evaluated	—	—
9 months	Not evaluated	Not evaluated	—	—

— = no significant alterations; ↓ = decreased response; ↑ = increased response

[a]See Table A-2 for magnitude of the alteration.

Source: NTP 1992

Selection of the Principal Study: The NTP (1992) study was selected as the principal study for deriving an intermediate-duration inhalation MRL for bromomethane because it identified the lowest reliable LOAEL for acute effects.

Summary of the Principal Study:

NTP. 1992. Toxicology and carcinogenesis studies of methyl bromide (CAS No. 74-83-9) in B6C3F1 mice (inhalation studies). National Toxicology Program. Technical report series No. 385. http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr385.pdf. May 27, 2015

NTP (1992) conducted the following series of studies: (1) groups of 10 male and 10 female B6C3F1 mice exposed to 0, 10, 20, 40, 80, or 120 ppm, 6 hours/day, 5 days/week for 13 weeks; (2) groups of 10 male and 10 female F344/N rats exposed to 0, 30, 60, or 120 ppm, 6 hours/day, 5 days/week for 13 weeks; (3) groups of 8 male and 8 female F344/N rats exposed to 0, 30, 60, or 120 ppm, 6 hours/day, 5 days/week for 13 weeks; (4) groups of 8 male and 8 female B6C3F1 mice exposed to 0, 20, 40, or 80 ppm, 5 days/week for 13 weeks; (5) interim neurobehavioral and histopathological assessments (conducted at 3, 6, and 9 months) in groups of 6–13 male and 6–16 female B6C3F1 mice exposed to 0, 10, 33, and 100 ppm bromomethane for 6 hours/day, 5 days/week as part of a 2-year cancer bioassay, and (6) groups of 15 male and female B6C3F1 mice exposed to 0 or 160 ppm, 6 hours/day, 5 days/week for up to 6 weeks (the data for this study are reported in detail in Eustis et al. 1988). In the 13-week studies involving eight animals/sex/species, neurobehavioral assessment were conducted at weeks 3 (rats only), 6, 9, 12 (rats only), and 13 (mice only). Other evaluations at the end of the 13-week treatment period (10 animals/sex/species) included body weight, hematology, clinical chemistry, organ weights, and histopathology of comprehensive tissues. In the 6-week study, histopathology of selected tissues, including brain, was assessed at the end of the treatment period, which was the duration in which mortality was >50% (14 exposures for male rats, 30 exposures female rats, 8 exposures in male mice, and 14 exposures in female mice). In the 2-year cancer bioassay, neurobehavioral effects were evaluated at 3, 6, and 9 months, and histopathology of comprehensive tissues was conducted at 6 months.

Adverse neurological effects of inhaled bromomethane and LOAEL values, with associated NOAELs, for each exposure level and assessment time-point are summarized in Table A-2. Neurobehavioral effects were observed in mice throughout the 6-week to 6-month assessment period. The study authors classified the severity of neurobehavioral effects as mild. In rats, neurobehavioral effects were observed at 3, 6, and 12 weeks, but not at 9 weeks. The study authors classified the severity of neurobehavioral effects as minor. Microscopic evaluation of brain tissues showed neuronal necrosis of the cerebral cortex (mice and rats), cerebellum (mice), and thalamus (rats) following 6 weeks of exposure to 160 ppm. However, no histopathological changes to the brain were observed in mice and rats exposed to ≤120 ppm for 13 weeks. Comparison of LOAEL values for rats and mice in the 6-week exposure study with exposure concentrations up to 120 ppm suggests that mice are more sensitive than rats; the NOAEL and LOAEL values for neurological effects were 80 and 120 ppm in rats, respectively, and 40 and 60 ppm in mice, respectively.

In addition to neurological effects, decreased body weight and histopathological alterations in several tissue types were observed. In rats and mice exposed to 160 ppm for up to 6 weeks (exposures levels that produced substantial mortality), histopathological changes were observed in the nasal cavity, heart, spleen, liver, adrenal glands, and testes. Decreased body weight gain was observed in male and female mice and rats exposed to 160 ppm for up to 6 weeks and to 120 ppm for 13 weeks. In female rats exposed for 13 weeks, decreased erythrocyte count was observed at 60 and 120 ppm, and decreased hematocrit and hemoglobin were observed at 120 ppm (NTP 1992). Additional details on non-neurological adverse effects reported in NTP (1992) are provided in Table 2-1 in Chapter 2.

Table A-2. Neurological Effects Observed in Mice and Rats Exposed to Inhaled Bromomethane for Intermediate-Duration Exposures

Time of observation	Effects in rats	Effects in mice
13-Week exposure study (6 hours/day, 5 days/week)		
3 Weeks 0, 30, 60, or 120 ppm	No death at any exposure 60 ppm: decreased startle response amplitude (males; 15%; p≤0.05) 120 ppm: decreased startle response amplitude (males; 28%; p≤0.01); increased startle response latency (females; 12%; p≤0.05) **NOAEL/LOAEL: 30 ppm/60 ppm**	No assessment in mice
6 Weeks Mice: 0, 20, 40, 80, or 120 ppm Rats: 0, 30, 60, or 120 ppm	No death at any exposure 120 ppm: decreased hindlimb strength (males: 32%; p≤0.05) **NOAEL/LOAEL: 80 ppm/120 ppm**	No death at any exposure 80 ppm: increased activity latency (males: 156%, p≤0.01); increased hot plate latency (males: 80%, p≤0.05) 120 ppm: severe curling and crossing of the hindlimbs and twitching of the forelimbs **NOAEL/LOAEL: 40 ppm/80 ppm**
9 Weeks 0, 30, 60, or 120 ppm	No death at any exposure No neurobehavioral effects observed (increased hot plate latency in females at 120 ppm was <0.5% and was not considered toxicologically relevant) **NOAEL/LOAEL: 120 ppm/X**	No assessment in mice
12 Weeks (rats), 13 weeks (mice) Mice: 0, 10, 20, 40, 80, or 120 ppm Rats: 0, 30, 60, or 120 ppm	No death at any exposure 120 ppm: increased novel side crossing frequency (males: 480%; p≤0.05); decreased hindlimb foot splay (females: 20%; p≤0.05); decreased forelimb grip strength (females: 25%; p≤0.05); increased startle response latency (females: 17%; p≤0.05); decreased startle response amplitude (females: 22%, p≤0.05) **NOAEL/LOAEL: 80 ppm/120 ppm**	No death at any exposure 80 ppm: decreased activity latency (females 76%, p<0.05) 120 ppm: severe curling and crossing of hindlimbs and twitching of forelimbs **NOAEL/LOAEL: 80 ppm/120 ppm**

Table A-2. Neurological Effects Observed in Mice and Rats Exposed to Inhaled Bromomethane for Intermediate-Duration Exposures

Time of observation	Effects in rats	Effects in mice
6-Week exposure study (6 hours/day, 5 days/week) (detailed report of this study is presented in Eustis et al. 1988)		
Rats and mice: 0 or 160 ppm Male rats and male mice were sacrificed after 14 exposures due to high mortality; female mice were sacrificed after 8 exposures	Substantial mortality was observed in both sexes[a]. Lethargy and neurological signs (curling and crossing of the hindlimbs, forelimb twitching and tremors); the study authors noted that severity was less than in mice Neuronal necrosis of cerebral cortex (males and females) and thalamus (females) **NOAEL/LOAEL: not applicable (serious LOAEL at 160 ppm)**	Substantial mortality was observed in both sexes[a] Lethargy and neurological signs (curling and crossing of the hindlimbs, forelimb twitching and tremors) Neuronal necrosis of cerebral cortex (males) and cerebellum (males and females) **NOAEL/LOAEL: not applicable (serious LOAEL at 160 ppm)**
24-Month exposure study (6 hours/day, 5 days/week)		
3 Months 0, 10, 33, or 100 ppm	–	10 ppm: no mortality 33 ppm: no mortality 100 ppm: 10/86 deaths in males; 1/86 deaths in females; decreased startle response latency (males: 32%, p≤0.01; females; 38%, p≤0.01); increases startle response amplitude (males: 62%, p≤0.01; females: 66%, p≤0.01); increased activity latency (males: 370%; p≤0.01); decreased novel side time (males: 44%, p≤0.05); increased novel side time (females: 19%, p≤0.05), decreased novel side crossing (males: 67%, p≤0.01); decreased locomotor activity (males: 39%; p≤0.01); increased hind limb grip strength (males: 30%, p≤0.05; females: 32%, p≤0.01); increased hot plate latency (females: 39%; p≤0.01) **NOAEL/LOAEL: 33 ppm/100 ppm**
6 Months 0, 10, 33, or 100 ppm	–	10 ppm: 1/86 deaths in males; no deaths in females; decreased novel side crossings (females: 37%, p≤0.05); decreased locomotor activity (males: 16%, p≤0.01; females: 10%, p≤0.05) 33 ppm: no mortality; decreased novel side crossings (females: 28%, p≤0.05);

Table A-2. Neurological Effects Observed in Mice and Rats Exposed to Inhaled Bromomethane for Intermediate-Duration Exposures

Time of observation	Effects in rats	Effects in mice
		deceased locomotor activity (males: 14%, p≤0.01; females: 11%, p≤0.05) 100 ppm: 45/86 deaths in males; 14/86 deaths in females; increased novel side crossings (females: 31%, p≤0.01), decreased novel side crossings (females: 55%, p≤0.01); deceased locomotor activity (females: 28%, p≤0.01) (no assessment in males due to excessive mortality) **NOAEL/LOAEL: X/10 ppm**
9 Months 0, 10, 33, or 100 ppm	–	Control: 18/86 deaths in males; 23/85 deaths in females 10 ppm: 22/85 deaths in males; 18/86 deaths in females 33 ppm: 18/85 deaths in males; 18/86 deaths in females decreased hindlimb grip strength (males: 21%, p≤0.01) 100 ppm: 55/86 deaths in males; 22/86 deaths in females; no assessment due to excessive mortality (males) **NOAEL/LOAEL: 10 ppm/33 ppm**

[a]Incidence data for mortality were not reported.

LOAEL = lowest observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; X = NOAEL or LOAEL value not identified

Source: NTP 1992

Selection of the Point of Departure for the MRL: In selecting the POD for derivation of the intermediate-duration inhalation MRL, an important consideration is that death was observed in rats continuously exposed to 10 ppm bromomethane for 3 weeks; no mortality was observed at 0, 1, or 5 ppm (Sato et al. 1985). Therefore, adverse effects associated with $LOAEL_{adj}$ values >5 ppm (adjusted for intermittent exposure) were not considered as the basis of the intermediate-duration inhalation MRL. The $LOAEL_{adj}$ value of 1.8 ppm for decreased locomotor activity in mice (a NOAEL value was not identified) is the only $LOAEL_{adj}$ value ≤5 ppm (NTP 1992); therefore, this was selected as the critical effect.

To determine the POD for derivation of the intermediate-duration inhalation MRL, data sets for decreased locomotor activity in male and female mice (summarized in Table A-3) were analyzed by continuous variable models in the EPA Benchmark Dose Software (BMDS, version 3.1.1). The benchmark response (BMR) for continuous models is defined as a change equal to 1 standard deviation (SD) from the control

mean. Adequate model fit is judged by three criteria: goodness-of-fit (p>0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (the lower limit of a one-sided 95% CI on the BMC) is selected as a reasonably conservative POD when differences between the BMCLs estimated from these models are >3-fold; otherwise, the BMCL from the model with the lowest Akaike's information criterion (AIC) is chosen.

For male and female mice, none of the BMC models provided adequate fit to the locomotor activity data. Therefore, the minimal LOAEL of 10 ppm in male mice was selected as the POD for derivation of the intermediate-duration inhalation MRL.

Table A-3. Decreased Locomotor Activity in Male and Female Mice Exposed to Inhaled Bromomethane for 6 Months

Exposure level (ppm)	Number	Mean activity (in instrument units)	SE	SD
Male mice				
0	13	184	4.3	15.5
10	16	155[a]	10.8	43.2
33	16	158[a]	4.2	16.8
100	X	X	X	X
Female mice				
0	12	187	3.5	12.1
10	15	168[b]	5.0	19.4
33	16	166[b]	8.5	34
100	10	135[a]	9.5	30

[a]p≤0.01.
[b]p≤0.05.

SD = standard deviation; SE = standard error; X = due to significant mortality in male mice, neurobehavioral assessments were not conducted

Source: NTP 1992

Calculations

Intermittent Exposure: The LOAEL of 10 ppm identified in male mice was adjusted for intermediate exposure:

$LOAEL_{adj}$ = [(LOAEL of 10 ppm) (6 hours/24 hours) (5 days/7 days) = 1.8 ppm

Human Equivalent Concentration: The HEC for mice for extrathoracic effects ($RGDR_{ET}$) was calculated by multiplying the $LOAEL_{adj}$ by the regional gas dose ratio (RGDR) for extrarespiratory effects. In the absence of available blood:gas partition coefficients for humans and mice, the default ratio for the $RGDR_{ET}$ of 1 was used:

$LOAEL_{adj}$ x RGDR = $LOAEL_{HEC}$
1.8 ppm x 1 = 1.8 ppm

Uncertainty Factor: The total uncertainty factor was 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability):

$LOAEL_{adjHEC}$/total uncertainty factor = intermediate-duration inhalation MRL
1.8 ppm/90 = 0.02 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Specific information regarding effects of intermediate-duration inhalation exposure of humans is limited to a case report of two workers; no exposure data were reported (O'Malley et al. 2011). Signs and symptoms of neurotoxicity (difficulty with concentration and memory, dizziness, visual disturbances, difficulty with speech, ataxia, and abnormal gait) were reported. Although available data on intermediate-duration exposure of humans is limited, it is well established that exposure to inhaled bromomethane is neurotoxic to humans (Bulathsinghala and Shaw 2014; de Souza et al. 2013).

Several animal studies have evaluated the effects of intermediate-duration inhalation exposure to bromomethane. Results show that bromomethane affects several organ systems, with adverse effects observed in the respiratory tract (Eustis et al. 1988; Irish et al. 1940; Kato et al. 1986; NTP 1992), heart (Eustis et al. 1988; Kato et al. 1986), liver (Eustis et al. 1988; Kato et al. 1986), immunological system (Eustis et al. 1988), nervous system (EPA 1988a; Eustis et al. 1988; Honma et al. 1982; Ikeda et al. 1980; Irish et al. 1940; Kato et al. 1986; NTP 1992), reproductive system (EPA 1988a; Eustis et al. 1988), and the developing fetus (Mayhew et al. 1986, as cited in EPA 1986a; Kato et al. 1986). The lowest effect levels adjusted for intermittent exposure ($LOAEL_{adj}$) identified for each outcome were 10 ppm for pulmonary hemorrhage (Sato et al. 1985), 17.9 ppm for focal fibrosis of the heart (Kato et al. 1986), 28.6 ppm for thymus inflammation and atrophy (Eustis et al. 1988), 1.79 ppm for decreased locomotor activity (NTP 1992), 21.4 ppm for decreased sperm density (EPA 1984), and 5.36 ppm for decreased pup weight (Mayhew et al. 1986, as cited in EPA 1986a).

Numerous studies in laboratory animals support identifying the nervous system as a critical target of toxicity. Overt signs of neurological effects have been observed in animals, including paralysis, tremors, and curling and crossing of limb in monkeys exposed to ≥66 ppm (Irish et al. 1940), rats exposed to 300 ppm (Kato et al. 1986), mice exposed to ≥80 ppm (EPA 1988a), and rabbits exposed to ≥33 ppm (Irish et al. 1940). A dog study reported that during a neurological examination, one dog appeared depressed and one dog was unresponsive and motionless (EPA 2001b). Both dogs were exposed to 5.3 ppm 7 hours/day, 5 days/week for 7 weeks; these symptoms were not observed in the remaining six dogs in this group. The investigators considered the significance of this finding as unclear. However, in a subsequent study, no overt signs of neurotoxicity were observed in eight dogs exposed to 5.3 ppm (EPA 2002); alterations in proprioceptive placing were sporadically observed in dogs exposed to 10 or 20 ppm.

Although there is some uncertainty regarding the toxicological significance of the findings in the two dogs exposed to 5.3 ppm for 7 weeks (EPA 2001b), the findings were not confirmed in a subsequent 6-week dog study (EPA 2002) and the MRL is 250 times lower than this exposure concentration and is likely to be protective of the effect.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL: 0.001 ppm
Critical Effect: Respiratory effects (basal cell hyperplasia of the olfactory epithelium)
Reference: Reuzel et al. 1991
Point of Departure: $LOAEL_{(HEC)}$ of 0.110 ppm
Uncertainty Factor: 90
LSE Graph Key: 50
Species: Rat

MRL Summary: The chronic-duration inhalation MRL for bromomethane was derived from a minimal LOAEL value of 3.1 ppm (adjusted for intermittent exposure and converted to a $LOAEL_{(HEC)}$ of 0.108 ppm) for basal cell hyperplasia of the olfactory epithelium. A total uncertainty factor of 90 was applied (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

Selection of the Critical Effect: The most sensitive effects of chronic exposure of animals to inhaled bromomethane are lesions of the respiratory epithelium in male and female rats (Reuzel et al. 1987, 1991) and mild neurotoxicity in female mice (NTP 1992). Basal cell hyperplasia of the olfactory epithelium was selected as the critical effect because the $LOAEL_{adj}$ of 0.55 ppm (a NOAEL was not identified) for respiratory lesions is lower than the $LOAEL_{adj}$ of 1.79 ppm (a NOAEL was not identified) for neurotoxicity reported by NTP (1992).

Selection of the Principal Study: The Reuzel et al. (1991) study was selected as the principal study because it reported the lowest $LOAEL_{adj}$ value of 0.55 ppm (a NOAEL was not identified) for lesions of the olfactory epithelium in male and female rats. In addition, the study demonstrated exposure-related increases of hyperplasia of the olfactory epithelium in both male and female rats after 128 weeks of exposure. Severity of nasal lesions increased with exposure concentration and duration.

Summary of the Principal Study:

Reuzel PG, Dreef-van der Meulen HC, Hollanders VM, et al. 1991. Chronic inhalation toxicity and carcinogenicity study of methyl bromide in Wistar rats. Food Chem Toxicol 29(1):31-39. (Data also reported in Reuzel PG, Kuper CF, Dreef-Van Der Meulen HC, et al. 1987. Initial submission: Chronic (29-month) inhalation toxicity and carcinogenicity study of methyl bromide in rats with cover letter dated 081092. DuPont Chem Co. Submitted to the U.S. EPA under TSCA Section 8ECP. EPA Document No. 88-920008788.OTS0546338.)

Groups of 60 male and female Wistar rats were exposed to target concentrations of 0, 3, 60, or 90 ppm (actual concentrations were 3.1, 29.6, and 89.1 ppm) bromomethane for 6 hours/day, 5 days/week for 128 weeks (males) and 129 weeks (females). Animals were examined daily for clinical signs and mortality, and rats were weighed weekly for the first 12 weeks of the study, then monthly for the remainder of the study. Assessments for hematology, clinical chemistry, and urinalysis were conducted at weeks 12–14 and 52–53. Gross pathological examination was performed on all animals at the end of

treatment or upon early death. At the end of the treatment period, organ weights were recorded for selected tissues and histopathological examination was conducted on comprehensive tissues.

Cumulative mortality was significantly increased in the 89.1 ppm group at exposure week 114 in male rats (36/60; $p<0.05$) and at exposure week 121 in female rats (38/50; $p<0.05$); significant increases were not observed at other time points. Body weights were also decreased throughout the study in males and females exposed to 89.1 ppm. No treatment-related effects were observed for hematology, clinical chemistry, or urinalysis. Significant, exposure-related histopathological changes were observed in the nasal cavity (basal cell hyperplasia of the olfactory epithelium) at all bromomethane concentrations tested, with changes classified as very slight or slight at 3.1 ppm, slight at 29.6 ppm, and slight to moderate at 89.1 ppm. Hyperkeratosis of the esophagus was observed in male rats in the 89.1 ppm group. Microscopic examination of the heart showed cartilaginous metaplasia in males, thrombi in males and females, and moderate to severe myocardial degeneration in females exposed to 89.1 ppm. The incidences of neoplastic lesions in treatment groups were similar to controls.

Selection of the Point of Departure for the MRL: The most sensitive effect identified in the Reuzel et al. (1991) study is nasal lesions (basal cell hyperplasia of the olfactory epithelium) in male and female rats, with a LOAEL of 3.1 ppm at the lowest concentration tested; data are summarized in Table A-4. To determine the POD to derive the chronic-duration inhalation MRL, incidence data were fit to all available dichotomous models in EPA's BMDS (version 3.1.1) using the extra risk option. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (the lower limit of a one-sided 95% CI on the BMC) is selected as a reasonably conservative POD when differences between the BMCLs estimated from these models are >3-fold; otherwise, the BMCL from the model with the lowest AIC is chosen (EPA 2012).

Table A-4. Incidence and Severity Data for Basal Cell Hyperplasia of the Olfactory Epithelium in Male and Female Rats Exposed to Inhaled Bromomethane for 29 Months

Exposure level (ppm)	Number of rats affected/number of rats examined	Severity (number of rats)
Male rats		
0	4/46	Very slight: 2 Slight: 2 Moderate: 0
3.1	13/48[a]	Very slight: 9 Slight: 3 Moderate: 1
29.6	23/48[b]	Very slight: 7 Slight: 12 Moderate: 4
89.1	31/48[b]	Very slight: 8 Slight:14 Moderate: 9

Table A-4. Incidence and Severity Data for Basal Cell Hyperplasia of the Olfactory Epithelium in Male and Female Rats Exposed to Inhaled Bromomethane for 29 Months

Exposure level (ppm)	Number of rats affected/number of rats examined	Severity (number of rats)
Female rats		
0	9/58	Very slight: 7 Slight: 2 Moderate: 0
3.1	19/58[a]	Very slight: 17 Slight: 2 Moderate: 0
29.6	25/59[a]	Very slight: 13 Slight: 9 Moderate: 3
89.1	42/59[b]	Very slight: 10 Slight: 23 Moderate: 9

[a]p≤0.05
[b]p≤0.01

Source: Reuzel et al. 1987, 1991

Only the LogLogistic model provided adequate fit to the incidence data for basal cell hyperplasia of the olfactory epithelium in male rats (BMC_{10} 5.81 ppm; $BMCL_{10}$ 3.65 ppm) (Table A-5). The goodness of fit (p-value) was <0.1 for all other models. The selected model fit is shown in Figure A-1. For basal cell hyperplasia of the olfactory epithelium in female rats, dichotomous models provided adequate fit to the incidence data, except for the Hill and probit models (Table A-6). Using the criteria for model selection, the LogLogistic model (BMC_{10} 6.41 ppm; $BMCL_{10}$ 4.13 ppm) was selected as the best fit model. The selected model fit is shown in Figure A-2. None of the models provided adequate fit for the combined male and female data sets.

Table A-5. Benchmark Dose Model (Version 3.1.1) Predictions for Bromomethane, Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Male Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
All doses									
Gamma[c]	2	5.47	0.06	1.25	1.03	-1.50	221.83	ND-0.10	ND-0.10
Hill	1	0.11	0.74	-0.02	-0.12	0.17	218.22	ND-10	ND-10
Logistic	2	8.65	0.01	0.73	1.71	-2.11	225.61	ND-0.10	ND-0.10
LogLogistic[d,e]	***2***	**3.56**	**0.17**	**1.35**	**0.29**	**1.35**	**219.68**	**5.67**	**3.56**
LogProbit[d]	1	0.14	0.71	-0.02	0.12	-0.29	218.25	ND-10	ND-10

Table A-5. Benchmark Dose Model (Version 3.1.1) Predictions for Bromomethane, Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Male Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]			AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Multistage (1-degree)[f]	2	5.47	0.06	1.25	1.03	-1.61	221.83	ND-0.10	ND-0.10
Multistage (2-degree)[f]	2	5.47	0.06	1.25	1.03	-1.61	221.83	ND-0.10	ND-0.10
Multistage (3-degree)[f]	2	5.47	0.06	1.25	1.03	-1.61	221.83	ND-0.10	ND-0.10
Probit	2	8.48	0.01	1.78	-2.08	-2.08	225.31	ND-0.10	ND-0.10
Weibull[c]	2	5.47	0.06	1.25	1.03	-1.50	221.83	ND-0.10	ND-0.10

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The only model that provided adequate fit to the data was the Log-Logistic.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND-0.10 = not determined, goodness-of-fit criteria, p<0.10; ND-10 = not determined, BMDL is 10-fold lower than the lowest non-zero dose; Hill model $BMCL_{10}$ = 0.028; LobProbit model $BMCL_{10}$ = 0.043

Figure A-1. Selected Model (LogLogistic) for Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Male Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)

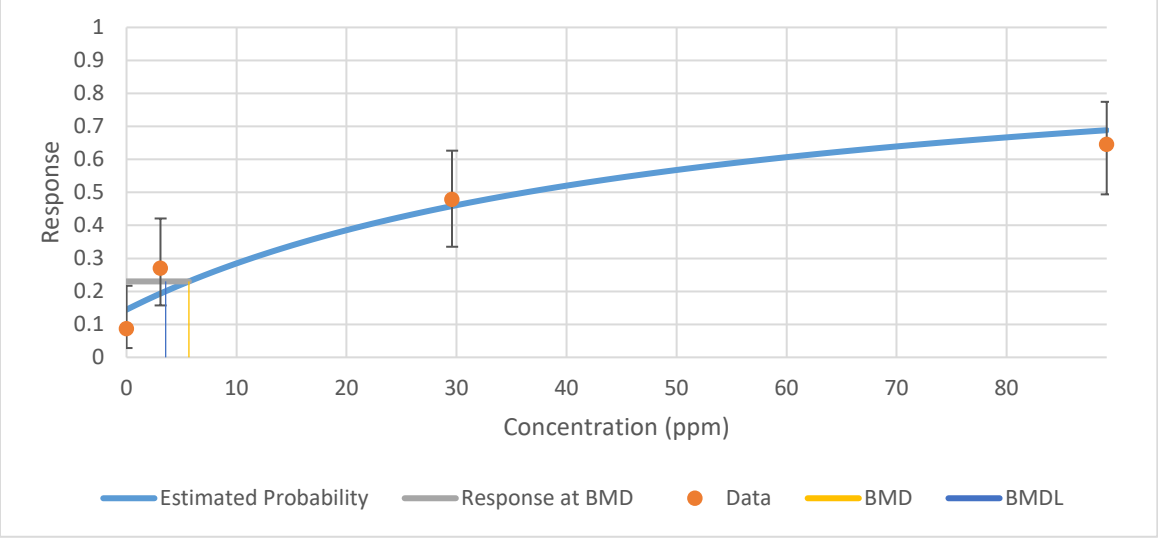


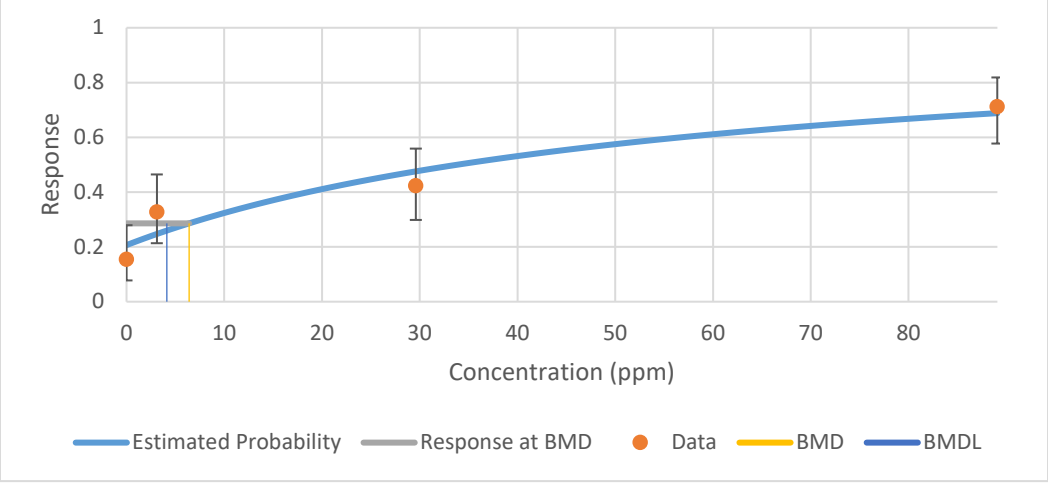
Table A-6. Benchmark Dose Model (Version 3.1.1) Predictions for Bromomethane, Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Female Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Scaled residuals[b] Dose above BMC	Scaled residuals[b] Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[c]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00
Hill	1	3.16	0.07	0.83	-1.31	0.83	283.86	ND-0.10	ND-0.10
Logistic	2	4.24	0.12	1.22	0.48	-1.57	283.12	15.94	13.01
LogLogistic[d,e]	***2***	**3.75**	**0.15**	**1.42**	**-0.80**	**1.42**	**282.39**	**6.41**	**4.13**
LogProbit[d]	1	3.40	0.06	1.48	0.20	-1.56	284.11	ND-0.10	ND-0.10
Multistage (1-degree)[f]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00
Multistage (2-degree)[f]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00
Multistage (3-degree)[f]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00
Probit	2	4.19	0.12	1.24	0.47	-1.55	283.06	15.56	12.83
Weibull[c]	2	3.53	0.17	1.44	-0.24	1.44	282.22	9.44	7.00

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >2–3-fold). Therefore, the model with lowest BMCL was selected (Log-Logistic).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND-0.10 = not determined, goodness-of-fit criteria, p<0.10

Figure A-2. Selected Model (LogLogistic) for Incidence of Basal Cell Hyperplasia of the Olfactory Epithelium in Female Rats Following Chronic Inhalation Exposure (Reuzel et al. 1991)



The $BMCL_{10}$ values of 3.56 and 4.13 ppm for olfactory epithelial basal cell hyperplasia in male and female rats, respectively, which are theoretical no-effect levels, are higher than the empirical LOAEL of 3.1 ppm, suggesting that the BMD models are not predictive of low-concentration effects. Therefore, to determine the POD for derivation of the chronic inhalation MRL, $LOAEL_{adj}$ value for olfactory epithelial hyperplasia was converted to a HEC ($LOAEL_{HEC}$) by multiplying the $LOAEL_{adj}$ by the RGDR values for extrathoracic effects, as shown in Table A-7.

Table A-7. Possible PODs for the Chronic-Duration Inhalation MRL

Species	Exposure	Effect	LOAEL (ppm)	$LOAEL_{adj}$ (ppm)[a]	RGDR	$LOAEL_{HEC}$ (ppm)[b]	Reference
Male rats	29 Months, 6 hours/day, 5 days/week	Basal cell hyperplasia of the olfactory epithelium	3.1	0.55	0.280[c]	0.154	Reuzel et al. 1991
Female rats	29 Months, 6 hours/day, 5 days/week	Basal cell hyperplasia of the olfactory epithelium	3.1	0.55	0.200[c]	0.110	Reuzel et al. 1991

[a]Adjusted for intermittent exposure. See details below under *Calculations*.
[b]HEC: $LOAEL_{adj\text{-}HEC}$ = ($LOAEL_{adj}$)(RGDR). See details below under *Calculations*.
[c]RGDR for rats for extrathoracic respiratory effects ($RGDR_{ET}$). See details below under *Calculations*.

HEC = human equivalent concentration; LOAEL = lowest observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; RGDR = regional gas dose ratio

Calculations

Intermittent Exposure: The LOAEL of 3.1 ppm in female rats was adjusted for intermittent exposure (6 hours/day, 5 days/week):

$LOAEL_{adj}$ = [(LOAEL of 3.1 ppm) (6 hours/24 hours) (5 days/7 days) = 0.55 ppm

Human Equivalent Concentration: The RGDR for rats for extrathoracic respiratory effects ($RGDR_{ET}$) was calculated using the following equation (EPA 1994b):

$$RGDR_{ET} = \frac{\left(V_E / SA_{ET}\right)_{Rat}}{\left(V_E / SA_{ET}\right)_{Human}}$$

where V_E is the ventilation rate (m^3/day; humans: 20; male Wistar rats: 0.42; female Wistar rats: 0.30; EPA 1988b), and SA_{ET} is surface are of the extrathoracic region of the respiratory tract (cm^2; humans: 200; male and female rats: 15) (EPA 1994b).

$LOAEL_{adj}$ x RGDR = $LOAEL_{HEC}$
0.55 ppm x 0.20 = 0.110 ppm

Uncertainty Factor: The total uncertainty factor was 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability):

$LOAEL_{adjHEC}$/total uncertainty factor = Chronic-duration inhalation MRL
0.11 ppm/90 = 0.001 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Information regarding effects of chronic-duration inhalation exposure of humans is limited to occupational survey studies (Akca et al. 2009; Anger et al. 1986) and case reports (Geyer et al. 2005; Greenberg 1971; Hine 1969) in bromomethane workers. Results show that chronic inhalation exposure to bromomethane produces signs and symptoms of neurotoxicity (headache, dizziness, decreased upper extremity sensation, decreased recall, uncoordinated movements, ataxia, seizures, confusion), respiratory effects (nasal irritation, dyspnea, cough, increased phlegm), nausea, and vomiting. The Anger et al. (1986) survey study conducted in 32 bromomethane workers employed as fumigators showed increased muscle ache and fatigue and mild neurotoxic effects (headache, dizziness, decreased upper extremity sensation, and decreased recall). However, exposure levels were not determined for these workers. The reported mean exposure level of 2.3 ppm was determined from personal monitoring data collected in different populations of fumigators. However, since exposures of workers in the survey study are unknown, the outcomes observed cannot quantitatively be related to exposure levels.

Results of animal studies show that chronic exposure to bromomethane produces toxicity to the respiratory tract in rats (Gotoh et al. 1994; Reuzel et al. 1987, 1991) and mice (NTP 1992;), heart in rats (Reuzel et al. 1987, 1991) and mice (NTP 1992), gastrointestinal tract in rats (Reuzel et al. 1987, 1991), skeleton in mice (NTP 1992), and neurological system in mice (NTP 1992). In addition, decreased body weight gain was observed in rats (Reuzel et al. 1987, 1991) and mice (NTP 1992). The lowest effect levels adjusted for continuous exposure ($LOAEL_{adj}$) were 1.79 ppm for decreased locomotor activity (NTP 1992), 17.9 ppm for dysplasia of the sternum (NTP 1992), 0.54 ppm for basal cell hyperplasia of the olfactory epithelium (Reuzel et al. 1987, 1991), 16.1 ppm for myocardial degeneration (Reuzel et al. 1987, 1991), and 16.1 ppm for hyperkeratosis of the esophagus (Reuzel et al. 1987, 1991).

Identification of the respiratory tract as one of the most sensitive targets of toxicity is supported by findings of nasal irritation and cough noted in cases reports and a rat study by Gotoh et al. (1994). Non-neoplastic lesions of the nasal cavity were observed in a 2-year study in male and female F344 rats exposed to 0, 4, 20, or 100 ppm bromomethane 6 hours/day, 5 days/week (Gotoh et al. 1994). Inflammation of the nasal cavity was observed in males exposed to 4, 20, and 100 ppm and in females exposed to 100 ppm, and necrosis of the olfactory epithelium was observed in males exposed to 100 ppm.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: The oral toxicity of this compound has not been thoroughly studied because bromomethane tends to volatilize and exists mainly as a gas at room temperature. One acute-duration oral study was identified (Kaneda et al. 1998). This study exposed pregnant rats to 0, 3, 10, or 30 mg/kg/day and pregnant rabbits to 0, 1, 3, or 10 mg/kg/day bromomethane in corn oil by gavage on gestation days 6–15. In rats, erosion and thickening of the wall of the non-glandular stomach or adhesion of the stomach to the spleen, liver, or diaphragm was seen in all rats in the 30 mg/kg/day dose group. No clinical signs of toxicity, effects on reproductive function, or developmental effects in fetuses were observed. The only effects observed in rabbits were significant decreases in body weight and decreased food consumption in the 10 mg/kg/day group. Effects on body weight gain in rats and rabbits were considered to be secondary to the decreased food consumption.

It is unclear if effects observed in the glandular stomach are due to the bolus administration of a very reactive chemical, and if gavage administration would be an appropriate model for human exposure to bromomethane. In chronic-duration dietary studies, no gastrointestinal lesions were observed in rats (EPA 1999) or dogs (Wilson et al. 2000). 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 and, therefore, would not mimic the gavage exposure in animal studies. Given the uncertainty of whether the observed forestomach lesions are unique to gavage administration of bromomethane, an acute-duration oral MRL was not derived.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: The oral toxicity of this compound has not been thoroughly studied because bromomethane tends to volatilize and exists mainly as a gas at room temperature. Two intermediate-duration gavage studies conducted male rats were identified (Boorman et al. 1986; Danse et al. 1984). These studies administer bromomethane by gavage at doses of 0, 0.4, 2, 10, or 50 mg/kg/day (Boorman et al. 1986) for 13 weeks and 0 or 50 mg/kg/day for 13–25 weeks (Danse et al. 1984). Mild focal hyperemia in the forestomach was observed at 2 mg/kg/day (Danse et al. 1984) and forestomach ulceration was observed at 50 mg/kg/day (Boorman et al. 1986; Danse et al. 1984). A 4-week feeding study in rats did not identify any adverse effects of dietary exposure to microencapsulated bromomethane at doses up to 7.98 mg/kg/day (EPA 1996). Although mean body weight gain was decreased by 14% in males during the first week of exposure and by 33% in females during weeks 1–2, but not during other weeks (EPA 1996). These changes were accompanied by decreased food intake and, therefore, are not considered adverse.

It is unclear if effects observed in the forestomach of rats are due to the bolus administration of a very reactive chemical, and if gavage administration would be an appropriate model for human exposure to bromomethane. 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 and, therefore, would not mimic the gavage exposure in animal studies. Given the uncertainty of whether the observed forestomach lesions are unique to gavage administration of bromomethane, an acute-duration oral MRL was not derived.

Agency Contacts (Chemical Managers): Sam Keith

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Bromomethane
CAS Numbers: 74-83-9
Date: March 2020
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: The oral toxicity of this compound has not been thoroughly studied because bromomethane tends to volatilize and exists mainly as a gas at room temperature. Two chronic-duration oral studies were identified: one study exposing dogs to dietary bromomethane at doses up to in 0.28 mg/kg/day in males and 0.27 mg/kg/day in females for 1 year (Wilson et al. 2000) and one study exposing rats to microencapsulated bromomethane at doses up to 11.10 and 15.12 mg/kg/day in males and females, respectively, for 12–24 months (EPA 1999). No adverse effects were observed in the study in dogs (Wilson et al. 2000). In rats, decreases in body weight gain were observed in the first 12–18 months at the highest dose levels. However, decreased food consumption were also observed at these doses during the same time period; therefore, decreased body weight gain is not considered adverse (EPA 1999). No other compound-related effects were observed.

This database was not considered adequate for derivation of a chronic-duration oral MRL because the targets of toxicity have not been established.

Agency Contacts (Chemical Managers): Sam Keith

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR BROMOMETHANE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to bromomethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for bromomethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of bromomethane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of bromomethane are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

	Other noncancer effects
	Cancer
Toxicokinetics	
	Absorption
	Distribution
	Metabolism
	Excretion
	PBPK models
Biomarkers	
	Biomarkers of exposure
	Biomarkers of effect
Interactions with other chemicals	
Potential for human exposure	
	Releases to the environment
	Air
	Water
	Soil
	Environmental fate
	Transport and partitioning
	Transformation and degradation
	Environmental monitoring
	Air
	Water
	Sediment and soil
	Other media
	Biomonitoring
	General populations
	Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for bromomethane released for public comment in 2018. The following main databases were searched in May 2019:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for bromomethane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to bromomethane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
05/2019	(74-83-9[rn] OR "methyl bromide"[nm] OR "Bercema"[tw] OR "Brom-O-Gas"[tw] OR "Brom-O-Sol"[tw] OR "BROMO METHANE"[tw] OR "Bromomethane"[tw] OR "Celfume"[tw] OR "Curafume"[tw] OR "Dawson 100"[tw] OR "Detia gas EX-M"[tw] OR "Dowfume MC-2"[tw] OR "Dowfume MC-2R"[tw] OR "Dowfume MC-33"[tw] OR "Drexel Plant Bed Gas"[tw] OR "Edco"[tw] OR "Embafume"[tw] OR "F 40B1"[tw] OR "Halon 1001"[tw] OR "Haltox"[tw] OR "Iscobrome"[tw] OR "Kayafume"[tw] OR "M-B-C Fumigant"[tw] OR "M-B-R 98"[tw] OR "MBC Soil Fumigant"[tw] OR "Mbc-33 Soil Fumigant"[tw] OR "MBX"[tw] OR "Metafume"[tw] OR "Meth-O-Gas"[tw] OR "Methane, bromo"[tw] OR "Methogas"[tw] OR "Methybrom"[tw] OR "Methyl bromide"[tw] OR "Methyl fume"[tw] OR "Methylbromide"[tw] OR "Monobromomethane"[tw] OR "Pestmaster"[tw] OR "Profume"[tw] OR "R 40B1"[tw] OR "Terabol"[tw] OR "Terr-O-Cide II"[tw] OR "Terr-O-Gas"[tw] OR "Tri-Brom"[tw] OR "Zytox"[tw]) AND (2014/12/01 : 3000[dp] OR 2015/12/01 : 3000[edat] OR 2015/12/01 : 3000[crdt] OR 2015/12/01 : 3000[mhda])
Toxline	
05/2019	(74-83-9[rn] OR "Bercema" OR "Brom-O-Gas" OR "Brom-O-Sol" OR "BROMO METHANE" OR "Bromomethane" OR "Celfume" OR "Curafume" OR "Dawson 100" OR "Detia gas EX-M" OR "Dowfume MC-2" OR "Dowfume MC-2R" OR "Dowfume MC-33" OR "Drexel Plant Bed Gas" OR "Edco" OR "Embafume" OR "F 40B1" OR "Halon 1001" OR "Haltox" OR "Iscobrome" OR "Kayafume" OR "M-B-C Fumigant" OR "M-B-R 98" OR "MBC Soil Fumigant" OR "Mbc-33 Soil Fumigant" OR "MBX" OR "Metafume" OR "Meth-O-Gas" OR "Methane, bromo" OR "Methogas" OR "Methybrom" OR "Methyl bromide" OR "Methyl fume" OR "Methylbromide" OR "Monobromomethane" OR "Pestmaster" OR "Profume" OR "R 40B1" OR "Terabol" OR "Terr-O-Cide II" OR "Terr-O-Gas" OR "Tri-Brom" OR "Zytox") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 2015 through 2019
Toxcenter	
05/2019	FILE 'TOXCENTER' ENTERED AT 14:16:04 ON 01 MAY 2019 CHARGED TO COST=EH011.10.LB.01.05 L1 5026 SEA FILE=TOXCENTER 74-83-9 L2 4155 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 4039 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 243 SEA FILE=TOXCENTER L3 AND ED>=20150101 ACT TOXQUERY/Q ---

Table B-2. Database Query Strings

Database search date	Query string
	L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29

Table B-2. Database Query Strings

Database search date	Query string
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L35 QUE L33 OR L34 --------- L36 146 SEA FILE=TOXCENTER L4 AND L35 L37 133 DUP REM L36 (13 DUPLICATES REMOVED) ANSWERS '1-133' FROM FILE TOXCENTER L*** DEL 146 S L4 AND L35 L*** DEL 146 S L4 AND L35 L38 133 SEA FILE=TOXCENTER L37 L39 17 SEA FILE=TOXCENTER L38 AND MEDLINE/FS D SCAN L37

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
05/2019	Compounds searched: 74-83-9
NTP	
05/2019	"74-83-9" "Methyl bromide" "Methylbromide" "Bromomethane" "Monobromomethane" "BROMO METHANE" "Bercema" "Methane, bromo" "Edco" "MBX" "Terabol" "Halon 1001" "Brom-O-Gas" "Brom-O-Sol" "Celfume" "Curafume" "Dawson 100" "Detia gas EX-M" "Dowfume MC-2" "Dowfume MC-2R" "Dowfume MC-33" "Drexel Plant Bed Gas" "Embafume" "F 40B1" "Haltox" "Iscobrome" "Kayafume" "M-B-C Fumigant" "M-B-R 98" "MBC Soil Fumigant" "Mbc-33 Soil Fumigant" "Metafume" "Meth-O-Gas" "Methogas" "Methybrom" "Methyl fume" "Pestmaster" "Profume" "R 40B1" "Terr-O-Cide II" "Terr-O-Gas" "Tri-Brom" "Zytox"
Regulations.gov	
05/2019	74-83-9 "Methyl bromide" "Methylbromide" "Bromomethane" "Monobromomethane"
NIH RePORTER	
05/2019	Text Search: "Bercema" OR "Brom-O-Gas" OR "Brom-O-Sol" OR "BROMO METHANE" OR "Bromomethane" OR "Celfume" OR "Curafume" OR "Dawson 100" OR "Detia gas EX-M" OR "Dowfume MC-2" OR "Dowfume MC-2R" OR "Dowfume MC-33" OR "Drexel Plant Bed Gas" OR "Edco" OR "Embafume" OR "F 40B1" OR "Halon 1001" OR "Haltox" OR "Iscobrome" OR "Kayafume" OR "M-B-C Fumigant" OR "M-B-R 98" OR "MBC Soil Fumigant" OR "Mbc-33 Soil Fumigant" OR "MBX" OR "Metafume"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	OR "Meth-O-Gas" OR "Methane, bromo" OR "Methogas" OR "Methybrom" OR "Methyl bromide" OR "Methyl fume" OR "Methylbromide" OR "Monobromomethane" OR "Pestmaster" OR "Profume" OR "R 40B1" OR "Terabol" OR "Terr-O-Cide II" OR "Terr-O-Gas" OR "Tri-Brom" OR "Zytox" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 335
- Number of records identified from other strategies: 47
- Total number of records to undergo literature screening: 382

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on bromomethane:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

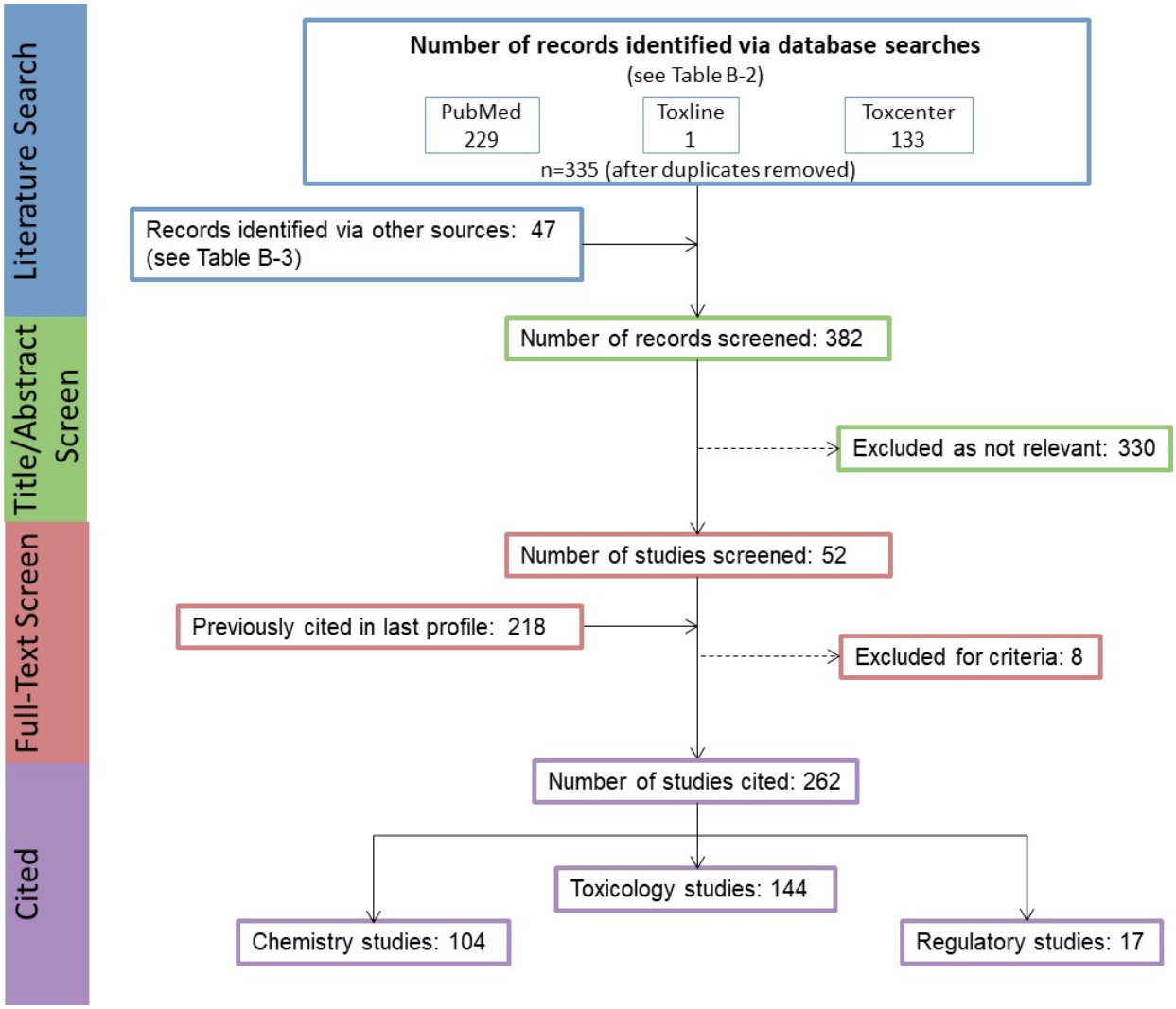
- Number of titles and abstracts screened: 382
- Number of studies considered relevant and moved to the next step: 52

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 52
- Number of studies cited in the pre-public draft of the toxicological profile: 218
- Total number of studies cited in the profile: 262

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. April 2018 Literature Search Results and Screen for Bromomethane



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

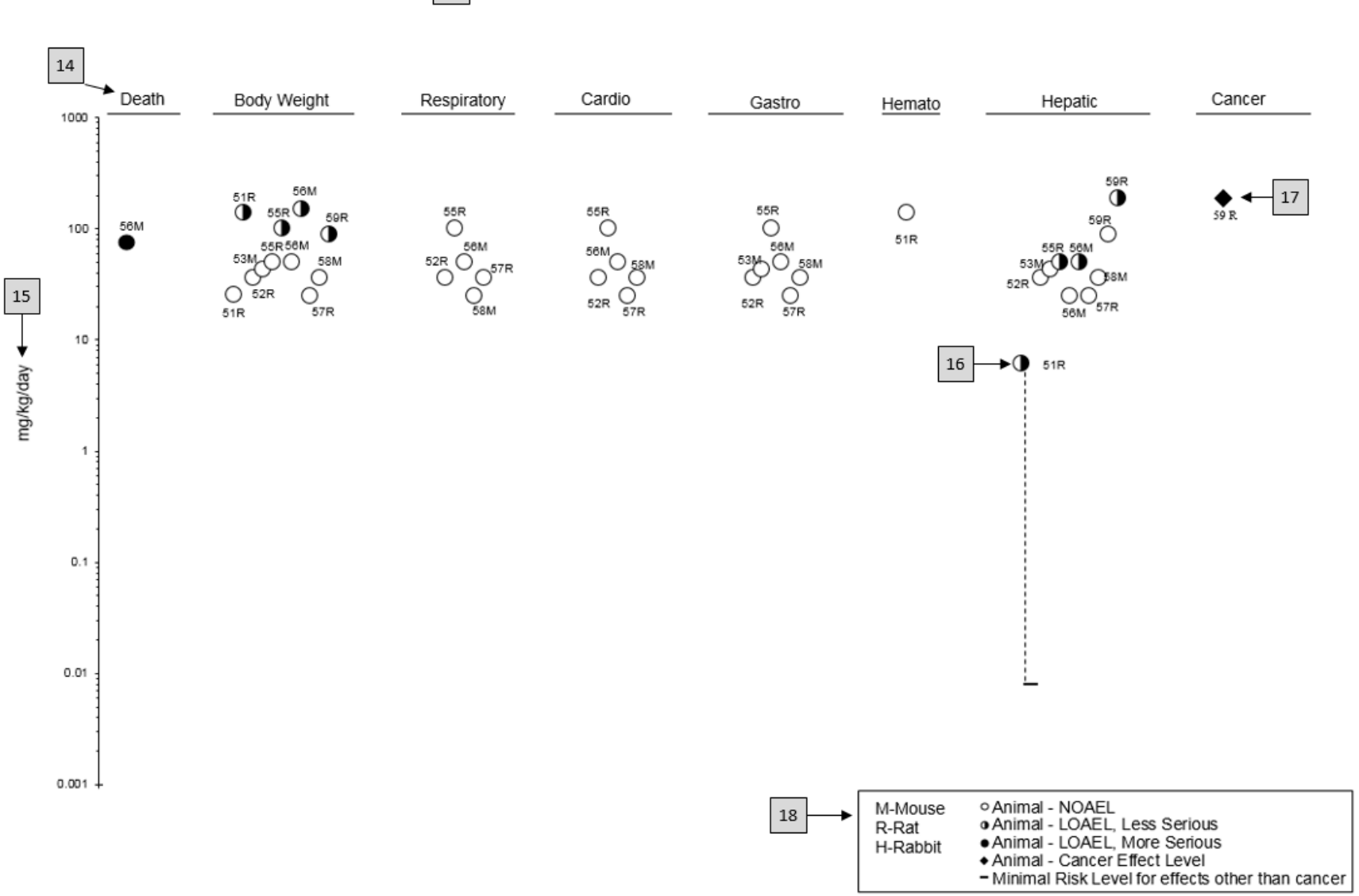
Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
(2) **CHRONIC EXPOSURE**									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
(10) **Aida et al. 1992**									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
QPS	quarantine and preshipment
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result