APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 and are not based on a consideration of cancer effects. 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 no-observed-adverse-effect level/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 and longer) 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.

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 levels. 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 F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1-Bromopropane
CAS Numbers: 106-94-5
Date: August 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 10
Species: Rat

Minimal Risk Level: 1 [ ] mg/kg/day [X] ppm

Reference: Honma T, Suda M, Miyagawa M. 2003. Inhalation of 1-bromopropane causes excitation in the central nervous system of male F344 rats. Neurotoxicology 24(4-5):563-575.

Experimental design: The study examined the effects of 1-bromopropane on several neurobehavioral tests conducted in male F-344 rats. Groups of rats were exposed whole-body to 0, 10, 50, 200, or 1,000 ppm 1-bromopropane vapors 8 hours/day, 7 days/week for 3 weeks. All tests were conducted at various times after the 3-week exposure period except for a traction test that was also conducted on exposure days 1, 7, and 14. In the traction test, rats are forced to hang from a horizontal bar with the forelimbs and the time until the rat falls from the bar is recorded. The traction test is used to measure forelimb grip strength. Five rats per group were used in this test.

Effect noted in study and corresponding doses: No statistically significant differences in grip strength were observed between exposed rats and controls on days 1 or 7. On day 14, however, rats exposed to 1,000 ppm 1-bromopropane showed a statistically significant decrease in grip strength compared to lower exposure groups and controls, thus defining NOAEL and LOAEL values of 200 and 1,000 ppm, respectively, for neurological effects in an acute-duration inhalation study. Because all data were presented graphically, the means and standard error (SDs were subsequently calculated) for traction time (assessed on day 14) were extracted digitally using GrabIt! Software (version XP2) (see Table A-1).

Table A-1. Digitized Dataset for Traction Time in Male F-344 Rats Exposed to Vaporized 1-Bromopropane for 14 Days[a]

Exposure concentration (ppm)	Number of rats	Traction time (seconds)	Standard deviation
0	5	15.158	9.644
10	5	13.433	6.339
50	5	11.338	3.582
200	5	8.627	5.787
1,000	5	3.204[b]	2.480

[a]Data extracted from Figure 11 in Honma et al. (2003).
[b]$p<0.05$.

Dose and end point used for MRL derivation: $BMCL_{1SD}$ of 97.50 ppm for neurological effects in male rats.

[ ] NOAEL [ ] LOAEL [X] $BMCL_{1SD}$

The traction time data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.4.0) using a benchmark response of 1 SD change from control. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) was selected as the POD when the difference between the BMCLs estimated from these models were >3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling.

All but two BMD models provided adequate and nearly equivalent fits (see Table A-2) by the various statistical criteria. Because the BMCL estimates are not sufficiently close, the model with the lowest BMCL (Exponential model 4) was selected. The Exponential model calculates BMC_{1SD} and $BMCL_{1SD}$ values of 259.23 and 97.40 ppm, respectively, for decreased traction time (reduced grip strength) on day 14 (see Figure A-1).

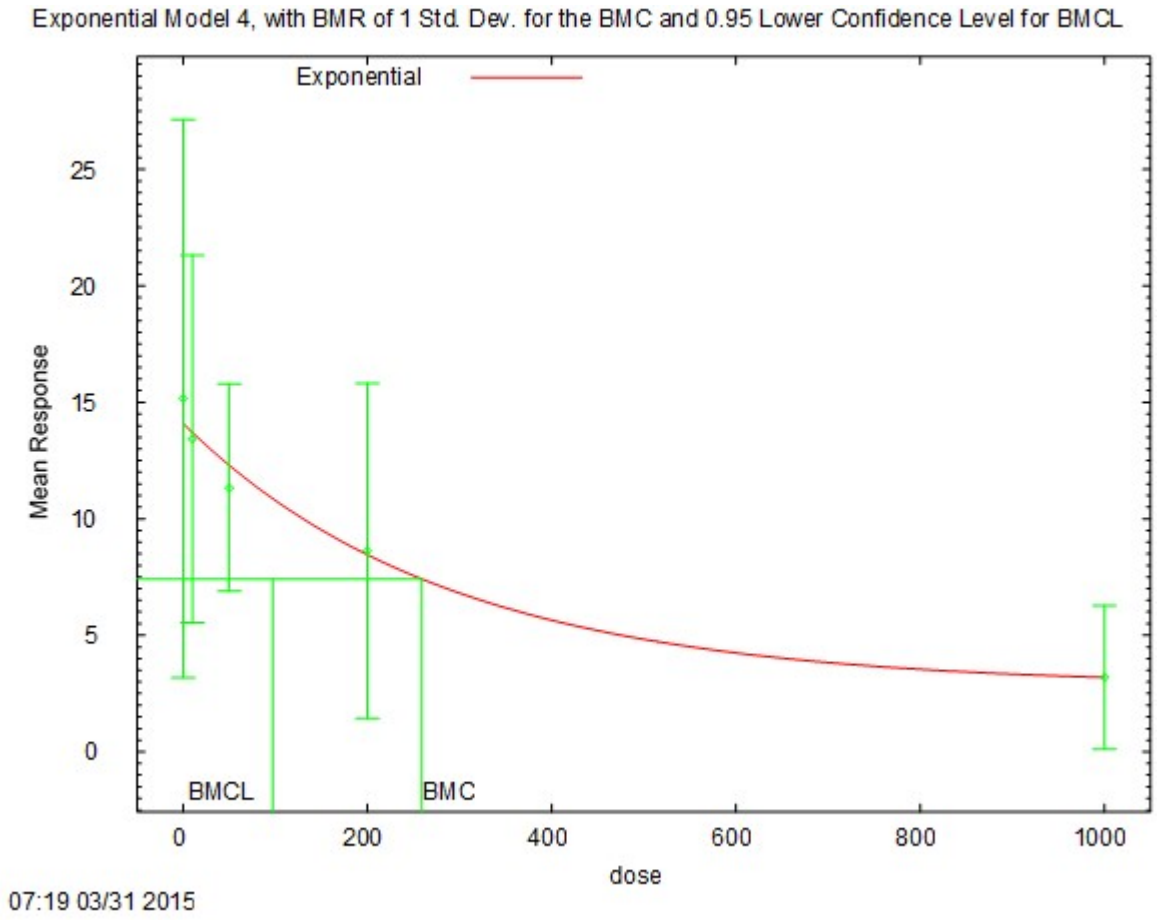
Table A-2. Model Predictions for Traction Time in Male F-344 Rats Exposed to Vaporized 1-Bromopropane for 14 Days (Honma et al. 2003)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMC	Scaled residuals[c] Dose above BMC	Scaled residuals[c] Overall largest	AIC	BMC_{1SD} (ppm)	$BMCL_{1SD}$ (ppm)
Constant variance									
Linear[d]	0.01	0.04	0.59	-0.89	0.20	-0.89	117.70	ND	ND
Nonconstant variance									
Exponential (model 2)[e]	0.01	0.46	0.51	-0.54	0.17	0.64	112.84	452.29	211.80
Exponential (model 3)[e]	0.01	0.46	0.51	-0.54	0.17	0.64	112.84	452.29	211.80
Exponential (model 4)[e,f]	**0.01**	**0.46**	**0.45**	**0.08**	**0.01**	**0.36**	**114.10**	**259.23**	**97.40**
Exponential (model 5)[e]	0.01	0.46	0.45	0.08	0.01	0.36	114.10	259.22	97.40
Hill[e]									ND
Linear[d]									ND
Polynomial (2-degree)[d]	0.01	0.46	0.34	-0.86	0.06	-0.86	113.85	673.69	461.93
Polynomial (3-degree)[d]	0.01	0.46	0.34	-0.86	0.06	-0.86	113.85	673.69	461.93
Polynomial (4-degree)[d]	0.01	0.46	0.34	-0.86	0.06	-0.86	113.85	673.69	461.93
Power[e]	0.01	0.46	0.34	-0.86	0.06	-0.86	113.85	673.69	461.93

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model did not fit variance data, but non-constant variance model did. With non-constant variance model applied all models, except for the Hill and the Linear (BMCL computation failed), provided adequate fit to the variance data. BMCLs for models providing adequate fit were not sufficiently close (differed by >2–3-fold), so the model with the lowest BMCL was selected (Exponential 4 model; the Exponential 5 converged onto the Exponential 4).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{1SD}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated to a change in the mean response equal to one control standard deviation from the control mean); ND = not determined (BMCL computation failed or the BMC was higher than the highest dose tested)

Figure A-1. Selected Model (Exponential Model 4) for Decreased Grip Strength Following Exposure to 1-Bromopropane (Honma et al. 2003)



Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability

MRL = $BMCL_{[HEC]}$ / 30 (UF)
MRL = 32.3 ppm / 30 = 1 ppm

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

$$BMCL_{1SD[HEC]} = BMCL_{1SD[ADJ]} \times (H_{b/g}A / H_{b/g}H)$$

where:

$BMCL_{1SD[ADJ]}$ = 97.40 ppm x 8 hours/24 hours = 32.3 ppm

$H_{b/g}A$ = animal blood:air partition coefficient = 11.7 (NTP-CERHR 2004)

$H_{b/g}H$ = human blood:air partition coefficient = 7.08 (NTP-CERHR 2004)

$$(H_{b/g}A / H_{b/g}H) = 11.7/7.08 = 1.653$$

Because the ratio of the partition coefficients is >1, a default value of 1 was used.

$$BMCL_{[HEC]} = 32.3 \text{ ppm} \times 1 = 32.3 \text{ ppm}$$

Was a conversion used from intermittent to continuous exposure? Yes, see above.

Other additional studies or pertinent information that lend support to this MRL: Limited information from a few case studies showed that workers exposed to 1-bromopropane for a few weeks reported subjective symptoms including respiratory irritation, headache, nausea, and lower extremity numbness, pain, and weakness; the geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm) (Raymond and Ford 2007). An acute-inhalation study in rats reported decreased activity and ataxia after single exposures to ≥1,800 ppm, but not 300 ppm; however, only qualitative data were provided (Kim et al. 1999). Intermediate-duration inhalation studies have shown that concentrations as low as 50 ppm can induce changes in neurobehavior, muscle strength, electrophysiology, morphology, and biochemistry (Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2000b; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Ueno et al. 2007; Wang et al. 2002, 2003; Yu et al. 2001).

Agency Contact (Chemical Manager): Nickolette Roney

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1-Bromopropane
CAS Numbers: 106-94-5
Date: August 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 55
Species: Rat

Minimal Risk Level: 0.1 [ ] mg/kg/day [X] ppm

Reference: Honma T, Suda M, Miyagawa M. 2003. Inhalation of 1-bromopropane causes excitation in the central nervous system of male F344 rats. Neurotoxicology 24(4-5):563-575.

Experimental design: The study examined the effects of 1-bromopropane on several neurobehavioral tests conducted in rats. Tests included locomotor activity, open field behavior, passive avoidance test, water maze test, traction test and rota-rod tests. Body weight and temperature were also monitored. Groups of male F-344 rats (4 per group) were exposed whole-body to 0, 10, 50, 200, or 1,000 ppm 1-bromopropane vapors 8 hours/day, 7 days/week for 3 weeks. All tests were conducted at various times after a 3-week exposure period except for a traction test that was also conducted on exposure days 1, 7, and 14.

Effect noted in study and corresponding doses: Rats in the 1,000 ppm lost weight during the 3-week exposure period. At termination of exposure, body weight in the 1,000 ppm group was about 12% lower than in controls. However, it recovered over the next 25 days. Body temperature also was significantly reduced in 1,000 ppm group, especially during exposure days 1–7, but recovered when exposure ceased. Spontaneous locomotor activity was significantly increased in rats exposed to 50 ppm 1-bromopropane on post-exposure days 1, 2, and 3 and in the group exposed to 200 ppm on post-exposure days 1, 2, 3, and 4 (locomotor activity was not tested in rats exposed to 1,000 ppm 1-bromopropane). The open field test showed that exposure to 1-bromopropane reduced freezing time (all doses, but not significantly), significantly increased ambulation and rearing at 200 ppm, had no significant effect on preening, and significantly reduced defecation/urination at 1,000 ppm. Exposure to 1-bromopropane did not affect passive avoidance behavior. 1-Bromopropane increased latency time in the water maze test in the 1,000 ppm group. In addition, 1-bromopropane at 200 and 1,000 ppm decreased traction performance indicating decreased muscle strength. Performance in the rota-rod test (motor coordination) was not significantly affected. Of all the parameters examined, locomotor activity appeared to be the most sensitive and a NOAEL and LOAEL of 10 ppm and 50 ppm, respectively can be defined based on this test.

Dose and end point used for MRL derivation: NOAEL of 10 ppm for neurological effects in male rats.

[X] NOAEL [ ] LOAEL

The spontaneous locomotor activity results were presented graphically; however, the data were not amenable for extraction using GrabIt! Software (version XP2). Thus, the NOAEL/LOAEL approach was used to identify the POD for the MRL. The data (Figure 3 in the study) are presented as changes in spontaneous locomotor activity relative to pre-exposure levels (assigned as 100% activity) for each day post-exposure that the test was performed (up to 6 days post-exposure). The selection of which post-exposure day (1–6) to model to compare treated and controls would have been entirely arbitrary.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability

MRL = 3.33 ppm / 30 (UF) = 0.1 ppm

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times (H_{b/g}A / H_{b/g}H)$$

where:
$NOAEL_{[ADJ]}$ = 10 ppm x 8 hours/24 hours = 3.33 ppm
$H_{b/g}A$ = animal blood:air partition coefficient = 11.7 (NTP-CERHR 2004)
$H_{b/g}H$ = human blood:air partition coefficient = 7.08 (NTP-CERHR 2004)

$$(H_{b/g}A / H_{b/g}H) = 11.7/7.08 = 1.653$$

Because the ratio of the partition coefficients is >1, a default value of 1 was used.

$$NOAEL_{HEC]} = 3.33 \text{ ppm} \times 1 = 3.33 \text{ ppm}$$

Was a conversion used from intermittent to continuous exposure? Yes, see above.

Other additional studies or pertinent information that lend support to this MRL: No human data suitable for MRL derivation. However, the human data available suggests that the nervous system is a target for 1-bromopropane toxicity. There are two publications of human cases exposed for intermediate durations (from weeks to months) that provide exposure levels. A case discussed by Ichihara et al. (2002) (case 3) was a woman who showed signs of staggering and numbness and paresthesias in the feet, thighs, lower back, and hips, and complained of headaches after 2 months of using 1-bromopropane as a solvent with a spray gun. Estimates of the exposure levels using a passive sampler indicated that the daily TWA concentration ranged from 60 to 261 ppm with an average of 133±67 ppm (SD). Raymond and Ford (2007) reported that four workers developed severe ataxia, sensory motor, and cognitive impairments soon after the introduction of 1-bromopropane into their workplace as a furniture adhesive. A survey conducted by NIOSH 9 months after the four workers became ill showed that the workers could have been exposed to a mean concentration of 1-bromopropane of 107 ppm (range 58–254 ppm).

Agency Contact (Chemical Manager): Nickolette Roney

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1-Bromopropane
CAS Numbers: 106-94-5
Date: August 2017
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 89
Species: Human

Minimal Risk Level: 0.02 [ ] mg/kg/day [X] ppm

Reference: Li W, Shibata, E, Zhou Z, et al. 2010. Dose-dependent neurologic abnormalities in workers exposed to 1-bromopropane. J Occup Environ Med 52(8):769-777.

Experimental design: The study examined the exposure-dependent effects of 1-bromopropane in a population of workers and age-, sex-, and region-matched controls in three 1-bromopropane production plants in China. The purity of the 1-bromopropane manufactured was >96% in one factory and ≥99% in the other two factories. The factories were evaluated at different times, but within the 2001–2005 year period. The final analysis comprised 120 women (60 exposed, 60 referents) and 52 men (26 exposed, 26 referents). The referents were randomly recruited from various factories not involved with 1-bromopropane; however, no monitoring data were available in the control factories. Workers from 1-bromopropane production plants could potentially be exposed to 1-bromopropane during: adding the chemical into the reaction pots; sitting close to the reaction pots to observe and record the temperature; taking out the crude product; adding hydroxy carbonate and stirring; or pouring the product into drums. No protective masks were worn in any of the factories studied, but in one of the factories investigated in 2001, the workers wore plastic gloves. The exposure periods ranged from 35.9 to 47.0 months. Workers were asked to fill out a questionnaire that included age, sex, smoking or drinking habits, education, past or present illnesses, and previous exposure to other chemicals and duration of exposure to 1-bromopropane. Electrophysiological studies measured motor nerve conduction velocity, distal latency, F-wave conduction velocity in the tibial nerve, sensory nerve conduction velocity in the sural nerve, and amplitude of the electromyography (EMG) elicited by stimulation of the motor nerve, and F-wave and potential of sensory nerve. Vibration sense was measured in the big toe, and reflexes and muscle strength were scored in four limbs. Various neurobehavioral tests, including Santa Ana, simple reaction time, digit symbol, Benton test, digit span, and pursuit aiming tests, were conducted. The report, however, does not indicate how often the tests were conducted. Comprehensive hematological and clinical tests were also conducted in addition to measuring serum TSH, LH, FSH, estradiol (females), and testosterone (males). Assessment of individual exposure to 1- and 2-bromopropane was done by analyzing the content of passive samplers attached to each worker during one 8- or 12-hour shift. This was done twice for two shifts and the average exposure level was used as the representative exposure level. Individual TWA exposure to 1-bromopropane ranged from 0.07 to 106.4 (median ± interquartile range, 6.6±16.3) ppm for females and from 0.06 to 114.8 (median ± interquartile range, 4.6±11.6) ppm for males. Females were classified into low-, mid-, and high-exposure groups (median exposures of 1.28, 6.6, and 22.58 ppm, respectively) and males into low- and high-exposure groups (median exposures of 1.05 and 12.5 ppm, respectively). Data were analyzed in three different ways. Continuous variables were analyzed with ANOVA followed by Dunnett's multiple comparison and scores of reflex and muscle strength were compared using nonparametric Wilcoxon test. Linear regression analysis was performed to confirm the trend with the exposure level or the product of exposure level and period of exposure (cumulative exposure). The median value of each exposure group (rather than individual exposures) was used for regression analysis or analysis of covariance (ANCOVA) on the exposure level.

Effect noted in study and corresponding doses: Dunnett's multiple comparison following ANOVA showed significant differences between controls and exposed female groups for tibial distal latency (increase), sural sensory nerve conduction velocity (decrease), vibration sense threshold (increase), fatigue, serum LDH (increase), serum TSH (increase), serum FSH (increase), estradiol (decrease), white blood cell (decrease), red blood cells (decrease), and hemoglobin and hematocrit (decrease). The most sensitive effect was increased vibration sense threshold, which showed significant effects in all exposure groups. No differences between controls and exposed men were seen except for increased BUN in exposed men. Regression analysis adjusting for alcohol exposure and pair-matching for age, sex, and region in selecting controls showed significant trends in tibial distal latency, vibration sense in toes, Benton test (test for visual perception and memory), BUN, LDH, TSH, red blood cells, hematocrit, and platelets in females. In males, only BUN showed a significant trend. The same regression analysis on the product of exposure levels and duration of exposure (cumulative exposure) showed significant increases in tibial distal latency, vibration sense threshold, BUN, LDH, CK, TSH, MCV, MCH, red blood cells, and hematocrit in female workers and in BUN and Santa Ana non-preferred hand in male workers. Because estimation of vibration loss is influenced by the examining neurologist and body weight, which were not controlled for in the regression analysis, an ANCOVA analysis on 1-bromopropane exposure level (or 1-bromopropane cumulative exposure level), neurologist, age, height, body weight, and alcohol consumption was conducted in female workers (n=60/group; body weight data was unavailable for five age-matched pairs, so these pairs were assigned the average body weight of the group). The results showed that the effect of 1-bromopropane and cumulative 1-bromopropane were significant; however, the effect of examining neurologist was also significant.

This study has a number of limitations, some of which were identified by the investigators or pointed out by others (Smith et al. 2011). Of particular concern for the chronic inhalation MRL derivation are the following limitations: (1) the cross-sectional study design; (2) potential selection bias for the control group; (3) potential underestimation of 1-bromopropane exposure levels; (4) lack of biomonitoring data for controls; and (5) concerns regarding the vibration sense measurement method utilized in the study.

1. ATSDR acknowledges that use of a cross-sectional study design limits the ability to identify a cause-effect relationship between 1-bromopropane and observed effects. However, supporting evidence from two other cross-sectional studies and several case-reports supported an association between neurotoxic effects and exposure to 1-bromopropane (Ichihara et al. 2002; Majersik et al. 2007; NIOSH 2002, 2003a; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999; Wang et al. 2015).

2. ATSDR acknowledges that there may be selection bias in the identification of the age-, sex-, and region-matched controls. While the investigators stated that controls were “randomly” selected from adjacent factories, it is unclear what methods were used to randomly select controls.

3. ATSDR acknowledges that estimated 1-bromopropane exposures provided by the study investigators may be lower than actual exposures. The study authors indicated that windows and doors were wide open during the working hours, but it is reasonable to assume that windows and/or doors may have been closed during rainy or cold weather. If monitoring was conducted with windows and doors open, the exposure levels would be greater if windows and doors were closed. Study authors also indicate uncertainties in the cumulative exposure assessment, as measurements were taken over a 1–3-day period and presumed to be the same level for entire duration of employment. Additionally, no details for the sampling rate on personal monitors was provided and indoor air temperature during monitoring was not reported (temperature is essential to convert the mass concentration in mg/m^3 to ppm). Furthermore, exposure levels were not reported by factory or job description, which would have led to a more meaningful evaluation of

results. Also, potential dermal exposure from lack of wearing gloves and oral exposure if hands were not properly washed prior to eating may have contributed to exposure levels beyond measured air levels (Smith et al. 2011). In response, the study investigators clarified that plastic gloves were worn in at least one of the factories, decreasing the potential for dermal/oral exposure (Ichihara et al. 2011), but it does not appear that gloves were worn in other factories.

4. Smith et al. (2011) raised concerns regarding lack of biomonitoring data for controls from nearby factories not using 1-bromopropane, particularly the lack of exposure data for other potentially neurotoxic chemicals. However, ATSDR agrees with the study investigators, who proposed that if neurotoxic chemical exposure did occur at control factories it would only serve to underestimate the neurotoxic effects in the bromopropane-exposed group of workers (Ichihara et al. 2011).

5. ATSDR acknowledges that the 128 Hz tuning fork is not the best choice for quantitative analysis of vibration sense between individuals, as more specialized equipment is available that would have produced more quantitatively accurate results (such as the quantitative Rydel-Seiffer 64 Hz tuning fork, bio/neurothesiometer, or Computer Assisted Sensation Examination IV [CASE IV]) (Burns et al. 2002; Levy 2010; Nizar et al. 2014; Pestronk et al. 2004; Willits et al. 2015). Identification of clinical vibration impairment using a tuning fork has been shown to overestimate the quantitative vibration threshold (identified by the CASE IV system), and the discordance was associated with age, height, and body surface area of the subject (Burns et al. 2002). However, the study authors acknowledged that clinical assessment of vibration threshold using a tuning fork is inherently inaccurate due to examiner bias and subject characteristics (age, weight, height), and reported that findings remained significant after statistical adjustment for examiner and subject characteristics. A follow-up letter to the editor by the study investigators clarified that examiners were blinded to the exposure group (Ichihara et al. 2011), which was an initial concern raised by Smith et al. (2011). Other studies evaluating the 128 Hz tuning for the ability to accurately detect loss of vibration sense in patients with diabetic neuropathy reported a sensitivity (ability to diagnose condition if present) of 40–69% and a specificity (ability to diagnose lack of condition) of 90–100%, compared with detection using the neurothesiometer (which is considered the diagnostic tool of choice) (Nizar et al. 2014; Willits et al. 2015). These values indicate that use of a 128 Hz tuning fork to clinically identify loss of vibration sense will most likely underestimate (rather than overestimate) the presence of dysfunction. Additionally, by placing the tuning fork on the examiner's foot (once subjects indicated they could no longer feel vibration), the study investigators deviated from the standard protocol (as described by Gilman 2002), which involves removing the tuning fork from the subject and placing it on the examiner's fingers (which are much more sensitive). This deviation would also most likely underestimate (rather than overestimate) the presence of dysfunction. Taking into consideration all available evidence, while the 128 Hz tuning fork is not the most sensitive or quantitative assessment tool, it was able to detect statistically significant differences between control and exposed groups after adjusting for examiner and subject characteristics (age, weight, height). Therefore, ATSDR considered data obtained using this method adequate for the derivation of the chronic inhalation MRL.

Other limitations of the study identified by Smith et al. (2011) or the study authors include: (1) lack of control of the temperature of the skin of the legs may have impacted measurements of nerve conduction velocity; (2) abnormally high control values for tibial nerve distal latency; (3) co-exposure to low levels of 2-bromopropane in the exposed group of workers (which has been shown to have reproductive and hematopoietic effects on workers and animals); and (4) no data on menstrual cycle of females (which could have influenced some hematology and some clinical chemistry results). While these limitations are acknowledged by ATSDR, they do not directly impact end points used in the MRL derivation because

they relate either to neurological end points not selected as the basis for the MRL (limitations 1 and 2) or to non-neurological end points (limitations 3 and 4).

Despite the limitations of this study, ATSDR still considers the study by Li et la. (2010) as the most appropriate study for deriving the chronic inhalation MRL (see further discussion in *Other additional studies or pertinent information that lend support to this MRL* section below). However, it is noted that the confidence in this MRL is low due to the acknowledged limitations.

The results of the study by Li et al. (2010) suggest a minimal LOAEL of 1.28 ppm based on a statistically significant increase in the vibration sense threshold in female workers. Women in this exposure group also showed significantly slower sural nerve conduction velocity; however, this effect was not selected as the critical effect as it was not observed consistently in higher exposure groups and was not significant based on regression analysis. Other neurological effects observed in this study at higher exposures (≥6.6 ppm) in female workers included increased tibial nerve distal latency. Effects observed in hematology and clinical chemistry are not considered by ATSDR to be biologically relevant because they were small in magnitude and were generally within human reference ranges. No NOAEL was identified for this study.

Dose and end point used for MRL derivation: 1.28 ppm

[ ] NOAEL [X] LOAEL

A minimal LOAEL of 1.28 ppm was identified for mild neurological impairment in females (increased vibration sense threshold). No NOAEL was identified. BMD modeling was conducted on this end point; however, no models provided an adequate fit.

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

MRL = 1.28 x 5 days/7 days x 12 hours/24 hours = 0.46 ppm
MRL = 0.46 ppm / 30 (UF) = 0.02 ppm

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? The exposure concentration was adjusted to continuous exposure basis as shown above. Although Li et al. (2010) report median exposure levels based on TWA concentrations for 8- or 12-hour work shifts, the majority of workers (65%) had 12-hour work shifts.

Other additional studies or pertinent information that lend support to this MRL: Candidate principal studies considered for deriving the chronic inhalation MRL are shown in Table A-3. Of the candidate human studies, only the Li et al. (2010) study was adequate for consideration. The NIOSH occupational health surveys (2002, 2003a) did not contain a reference group. Among the candidate animal studies, the lowest LOAEL was for various histological alterations in the respiratory tract of mice (Morgan et al. 2011; NTP 2011); LOAELs from other available studies occur at much higher concentrations. Therefore,

both the Li et al. (2010) study in humans and the Morgan et al. (2011) study in mice were further evaluated as potential principal studies. The critical effects, PODs, uncertainty factors, and candidate MRL for each option are presented in Table A-4. Candidate MRLs based on the key human and animal studies are almost the same (0.02 and 0.03 ppm, respectively); rationale for selection of the human study over the animal study as the critical study is discussed below.

Table A-3. Studies Considered for Deriving the Chronic-Duration Inhalation MRL

Study	End point(s) evaluated	Significant effects at LOAEL	NOAEL (ppm)	LOAEL (ppm)
Human studies				
Li et al. (2010) Cross-sectional occupational exposure study; average exposure duration ~40 months	Hematology, clinical chemistry (including thyroid and reproductive hormones), neurological evaluation (nerve conduction velocity, vibration sense, neurobehavioral testing)	Increased vibration threshold	ND	1.28
NIOSH (2003a) Cross-sectional occupational health survey; average exposure duration ~29 months	Hematology, clinical chemistry, questionnaire for neurological deficits, nerve conduction velocity	Subjective complaints of neurotoxicity	ND	45.7
NIOSH (2002) Cross-sectional occupational health survey; exposure duration 4–9 years	Hematology, questionnaire for neurological and reproductive deficits	Subjective complaints of neurotoxicity	ND	117.1
Animal studies				
Morgan et al. (2011); NTP (2011) B6C3F1 mice, 105 weeks	Comprehensive 2-year bioassay; neurological function not assessed	Various histological alterations in the nasal respiratory epithelium, larynx, trachea, and bronchioles	ND	62.5
Morgan et al. (2011); NTP (2011) F-344 rats, 105 weeks	Comprehensive 2-year bioassay; neurological function not assessed	Glandular hyperplasia in the nose (both sexes), chronic active nasal inflammation (females)	ND	125
BSOC (2001a) Sprague-Dawley rats, 2 generations (~16–18 weeks per generation)	Comprehensive 2-generation reproductive toxicity study; neurological function not assessed	Hepatocellular vacuolization in F0 and F1 males, reduced prostate weight in F0 males	100	250

LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Table A-4. Options for Derivation of Chronic-Duration Inhalation MRL Based on Principal Chronic Human and Animal Studies

Study	Critical effect	POD (ppm)	UF	MRL (ppm)
Human study Li et al. (2010)	Decreased vibration sense	0.46 ppm ($LOAEL_{CONV}$)	30 10 for human variability; 3 for use of minimal LOAEL	0.02
Mouse study Morgan et al. (2011); NTP (2011)	Respiratory lesions	0.78 ($BMCL_{10HEC}$)	30 10 for human variability; 3 for dosimetric adjustment	0.03

BMCL = lower limit on the benchmark concentration; CONV = converted to continuous exposure; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; POD = point of departure; UF = uncertainty factor

Decreased vibration sense was identified as the most sensitive effect in the human occupational study by Li et al. (2010). As discussed above, there are numerous limitations to this study; however, the identification of neurological impairment as the critical effect is supported by the NIOSH occupational surveys and several human case reports of workers exposed to 1-bromopropane at workplace air concentrations >45 ppm for weeks to years. No other available study evaluated the reportedly low exposure levels (median exposures of 4.6 ppm in men and 6.6 ppm in women) reported in the Li et al. (2010) study. Reported neurological effects in workers in these other studies ranged from mild neurological impairments and complaints, such as numbness and tremors, to frank neurotoxic effects requiring hospitalization, such as ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy (Ichihara et al. 2002; Majersik et al. 2007; NIOSH 2002, 2003a; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999; Wang et al. 2015). Several of the case studies reported decreased vibration sense, particularly in the lower extremities (Ichihara et al. 2002; Majersik et al. 2007; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999), supporting the selection of increased vibration sense threshold in the toe from the Li et al. (2010) study as the critical effect.

Animal studies provide supporting evidence that exposure to 1-bromopropane can result in neurotoxicity. Although neurological function has not been evaluated in animals following chronic exposure, observed effects in acute- and intermediate-duration inhalation rat studies at concentrations as low as 50 ppm included changes in neurobehavior, muscle strength, electrophysiology, morphology, and biochemistry (Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2000b; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Ueno et al. 2007; Wang et al. 2002, 2003; Yu et al. 2001).

In the chronic mouse study, lesions in the lung and nasal epithelium were the most sensitive effects occurring at the lowest tested concentration, 62.5 ppm (Morgan et al. 2011; NTP 2011). Lesions in the lung and nasal epithelium were also found in F-344 rats at the lowest tested concentration, 125 ppm (Morgan et al. 2011; NTP 2011). In intermediate-duration animal studies, respiratory tract lesions were found in mice exposed to concentrations as low as 125 ppm for 2–14 weeks (NTP 2011), but were not found in F-344 rats at concentrations up to 1000 ppm for 14 weeks (NTP 2011), Sprague-Dawley rats at concentrations up to 1,800 ppm for 8–13 weeks (Albemarle Corporation 1997; Kim et al. 1999), or Wistar rats at concentrations up to 800 ppm for 12 weeks (Ichihara et al. 2000a). These results suggest that mice are more sensitive to respiratory effects than rats following intermediate-duration inhalation exposure. Several acute and intermediate-duration rat studies found neurological effects at concentrations lower

than those causing respiratory effects (as low as 50 ppm, see previous paragraph), providing support for neurological effects as the critical effects following acute and intermediate-duration exposure. In humans, the only evidence for respiratory effects was mild respiratory irritation reported in case studies of workers experiencing frank neurotoxicity following exposure to >100 ppm 1-bromopropane (Ichihara et al. 2002; Raymond and Ford 2007). The relative severities of the respiratory and neurotoxic effects in these cases suggest that humans are more susceptible to neurotoxic effects from 1-bromopropane than respiratory effects.

Based on available data, neurological effects appear to be the most sensitive effect for workers repeatedly exposed to 1-bromopropane and in animals exposed to 1-bromopropane for acute and intermediate durations. Neurological effects in chronically exposed animals, however, have not been adequately studied to characterize the relative sensitivity of neurological effects versus respiratory effects. In the absence of this information, a comparison was made of MRLs based on the minimal LOAEL for neurological effects in workers in the Li et al. (2010) study and the LOAEL for respiratory tract lesions in mice exposed for 2 years (Morgan et al. 2011; NTP 2011). The resultant MRLs were numerically equivalent (Table 3). Despite the limitations in the principal human study, ATSDR still considers Li et al. (2010) the best available study on which to base the MRL, principally because it is based on human data. ACGIH (2014) also used the same study to recommend a TLV-TWA of 0.1 ppm based on the LOAEL of 1.28 ppm for decreased vibration sense in toes from female workers in the Li et al. (2010) study. The TLV-TWA is TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect (AGCIH 2016). Confidence in the chronic MRL is low because of the limitations of the principal study, but could be improved with additional and better-designed neurological evaluations (cross-sectional or prospective) of workers exposed to 1-bromopropane in workplace air.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1-Bromopropane
CAS Numbers: 106-94-5
Date: August 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 7
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] ppm

Reference: Zhong Z, Zeng T, Xie K, et al. 2013. Elevation of 4-hydroxynonenal and malondialdehyde modified protein levels in cerebral cortex with cognitive dysfunction in rats exposed to 1-bromopropane. Toxicology 306:16-23.

Experimental design: The study examined the effects of 1-bromopropane on cognitive function in male Wistar rats and the possible role of oxidative stress. Groups of rats (10/group) were administered 0, 200, 400, or 800 mg 1-bromopropane/kg/day by gavage in corn oil for 12 consecutive days. On days 8–12, cognitive function (spatial learning and memory) was assessed with the Morris water maze test. Twenty-four hours after the last dose, the rats were killed, and the cerebral cortex was removed. The following were measured in cerebral cortex homogenates: GSH, oxidized glutathione (GSSG), total thiol (total -SH) content, GSH reductase and GSH peroxide (GSH-Px) activities, and MDA level, as well as 4-HNE and MDA modified proteins.

Effect noted in study and corresponding doses: Some rats in the 400 and 800 mg 1-bromopropane/kg/day groups showed irritability at the start of dosing. After 1 week of dosing, rats in the 800 mg 1-bromopropane/kg/day group showed slow response and sluggishness. Final body weight was reduced about 13% in the high-dose group; no data on food consumption were provided. Dose-related impairments were observed in learning and memory measures of the Morris water maze. During the 4-day learning phase, the escape latency was significantly increased in the 800 mg 1-bromopropane/kg/day group and the total swimming distance was increased at ≥200 mg 1-bromopropane/kg/day. Time spent in different swimming "search" patterns (direct finding, approaching target, random searching, and thigmotaxis) differed significantly in all exposed groups, compared with controls, with exposed animals showing increased thigmotaxis (time spent in periphery of tank). On day 5, when the escape platform was removed to assess memory, all exposure groups showed a significant decrease in the number of times they crossed the former location of the target platform; rats exposed to 800 mg 1-bromopropane/kg/day also showed a significant decrease in time spent in the target quadrant. Assessment of biochemical indices showed an increase in oxidative stress (increased MDA and GSSG, decreased GSH, and decreased GSH reductase activities), mostly observed in the mid- and high-dose groups. Tests with specific monoclonal antibodies also showed increased total levels of reactive aldehyde modified proteins in the cerebral cortex.

A LOAEL of 200 mg/kg/day was identified for this study based on impaired spatial learning and memory (increased swimming distance, altered search pattern, decreased number of crossings of the escape platform); no NOAEL was identified. All data were presented graphically. The SDs could not be extracted from day 1–4 figures either because they overlapped between dose-groups (total swimming distance) or they were not reported (distribution of search patterns); therefore, these data could not be used for BMD analysis. However, the means and SDs for the number of crossing of the escape platform

(assessed on day 5) were extracted digitally using GrabIt! software (version XP2) for BMD analysis (Table A-5). Alternate data extraction of the means and SDs using DigitizeIt software resulted in BMDLs that differed by <17% on average, which would yield the same MRL.

Table A-5. Digitized Dataset for Number of Crossings of Escape Platform Location on Day 5[a]

Dose (mg/kg/day)	Animal number	Mean (number)	Standard deviation
0	10	7.2	2.8
200	10	4.3[b]	2.6
400	10	3.7[c]	2
800	10	2.4[c]	2

[a]Data extracted from Figure 3B in Zhong et al. (2013).
[b]p<0.05.
[c]p<0.01.

Dose and end point used for MRL derivation: 19.75 mg/kg/day

[ ] NOAEL [ ] LOAEL [X] $BMDL_{1SD}$

All models provided an adequate and nearly equivalent fits (see Table A-6) by the various statistical criteria, but the BMDLs had a 15.4-fold range, indicating some model dependence of the BMDL estimates. The range of results is judged to be reasonable, because the range of the absolute differences between the individual BMDs and their corresponding BMDLs was comparable, ranging from about 111 to 130 mg/kg/day. Because the BMDL estimates are not sufficiently close, selecting the model with the lowest BMDL is recommended (EPA 2012b). Thus, the BMDL of 19.75 mg/kg/day from the Hill model is a reasonable conservative estimate. The Hill model calculates BMD_{1SD} and $BMDL_{1SD}$ values of 148.37 and 19.75 mg/kg/day, respectively, for decreased spatial memory in rats on day 5 of the Morris water test (see Figure A-2).

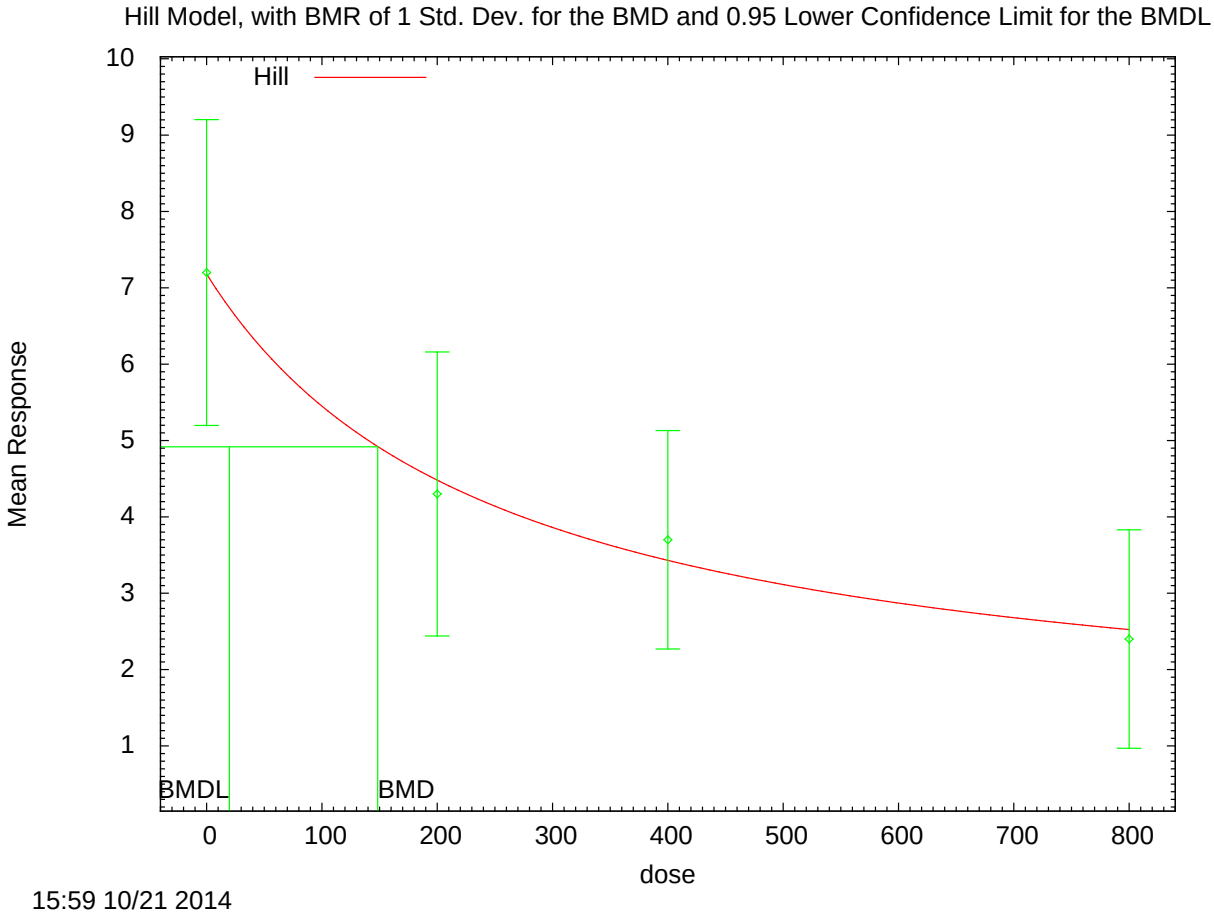
Table A-6. Model Predictions for Effects of 1-Bromopropane on the Spatial Memory Ability of Rats

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
All doses									
Constant variance									
Exponential (model 2)[d]	0.002	0.61	0.45	-0.9692	0.0365	0.579	112.63	266.03	154.01
Exponential (model 3)[d]	0.002	0.61	0.45	-0.9692	0.0365	0.579	112.63	266.04	154.01
Exponential (model 4)[d]	0.002	0.61	0.52	0.0777	-0.3698	0.4757	113.46	165.96	55.12
Exponential (model 5)[d]	0.002	0.61	0.52	0.0777	-0.3698	0.4757	113.46	165.96	55.12
Hill[d,e]	***0.002***	***0.61***	***0.63***	***0.0291***	***-0.247***	***0.384***	***113.29***	***148.37***	***19.75***
Linear[r]	0.002	0.61	0.15	-1.22	-0.573	1.2	114.85	435.59	305.49
Polynomial (2-degree)[r]	0.002	0.61	0.15	-1.22	-0.573	1.2	114.85	435.59	305.49
Polynomial (3-degree)[r]	0.002	0.61	0.15	-1.22	-0.573	1.2	114.85	435.59	305.49
Power[d]	0.002	0.61	0.15	-1.22	-0.573	1.2	114.85	435.59	305.49

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. With constant variance applied, all the models provided an adequate fit to means. BMDLs for models providing adequate fit differed by >threefold, so the model with the lowest BMDL (Hill) was selected. The Hill model also provided the best fit in the low-dose range (based on scaled residuals).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated to a change in the mean response equal to one control standard deviation from the control mean)

Figure A-2. Selected Model (Hill) for Impaired Spatial Memory Following Exposure to 1-Bromopropane (Zhong et al. 2013)



Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

MRL = 19.75 mg/kg/day ÷ 100 = 0.2 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Marked decreases in spontaneous activity (sedation), piloerection, and dyspnea were reported in rats exposed once to 2,000 mg 1-bromopropane/kg in a lethality study by Elf Atochem S.A. (1993). Clinical signs were observed within 4 hours of dosing; surviving animals (9/10) fully recovered by day 2 of the 14-day observation period. Of

direct relevance to the results of Zhong et al. (2013) are the results of a recent study by the same groups of investigators, which confirmed the previous results and reported that treatment of male Wistar rats with ≥200 mg 1-bromopropane/kg/day for 12 days impaired spatial memory and spatial learning ability (Guo et al. 2015). In this study, rats exposed to ≥200 mg 1-bromopropane/kg/day tested in the Morris Water Maze showed a significantly dose-related decreased percent of time at the target platform; the NOAEL was 100 mg 1-bromopropane/kg/day. Modeling these data yielded a $BMDL_{1SD}$ (POD) of 77.94 mg 1-bromopropane/kg/day, which is higher than the $BMDL_{1SD}$ of 19.75 mg 1-bromopropane/kg/day used to derive the current MRL. Therefore, it is still more appropriate (more protective) to use data from Zhong et al. (2013) to derive an acute-duration oral MRL for 1-bromopropane. Also relevant is another study from the same group of investigators that reported motor abnormalities in rats administered ≥200 mg 1-bromopropane/kg/day for up to 16 weeks (Wang et al. 2012). Only limited data from this study were available for review.

While evidence for neurotoxicity following oral exposure is limited, human and animal evidence from inhalation studies indicate that the nervous system is a target for 1-bromopropane toxicity. Mild neurological symptoms have been reported in humans at median TWA workplace air levels as low as 1.28 ppm (Li et al. 2010), and two NIOSH health surveys and several case reports of workers exposed for months to years indicate that higher exposure levels (>45 ppm) can lead to more severe, even permanent, effects (Ichihara et al. 2002; Majersik et al. 2007; NIOSH 2002; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999). Neurological effects ranged from mild neurological impairments and complaints with acute exposure, such as headache, numbness and weakness, to frank neurotoxic effects requiring hospitalization following exposure for months or years, such as ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy. Evidence from animal studies supports that exposure to 1-bromopropane can result in neurotoxic effects. Observed effects in acute and intermediate-duration inhalation studies at concentrations as low as 50 ppm included changes in neurobehavior, muscle strength, electrophysiology, morphology, and biochemistry (Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2002; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Suda et al. 2008; Ueno et al. 2007; Wang et al. 2002, 2003; Yu et al. 2001; Zhang et al. 2013).

All other effects observed in acute studies occurred at or above the LOAEL of 200 mg 1-bromopropane/kg/day identified in the neurobehavioral study by Zhong et al. (2013). Observed effects included reduced antibody responses to the T-dependent SRBC antigen at ≥200 mg 1-bromopropane/kg/day (Lee et al. 2007); congestion, hemorrhage, cellular swelling and vacuolization of hepatocytes in mouse liver at ≥500 mg 1-bromopropane/kg/day, but not 200 mg 1-bromopropane/kg/day (Lee et al. 2007); degeneration of spermatocytes in mouse testes at 600 mg 1-bromopropane/kg/day (only dose tested) (Yu et al. 2008); and a 13% decrease in body weight at 800 mg 1-bromopropane/kg/day, but not ≤400 mg 1-bromopropane/kg/day (Zhong et al. 2013). While the LOAEL of 200 mg 1-bromopropane/kg/day for immune effects was considered as the basis of the MRL, the evidence supporting that 1-bromopropane is an immunosuppressant (Anderson et al. 2010; Lee et al. 2007) is far less than the evidence indicating that 1-bromopropane is a neurotoxicant (discussed above).

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points 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?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" 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 end point 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 end point 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 (UF) 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.

Chapter 3

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, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures 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 Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is 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) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. 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 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "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.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(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 end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A 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.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects 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) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

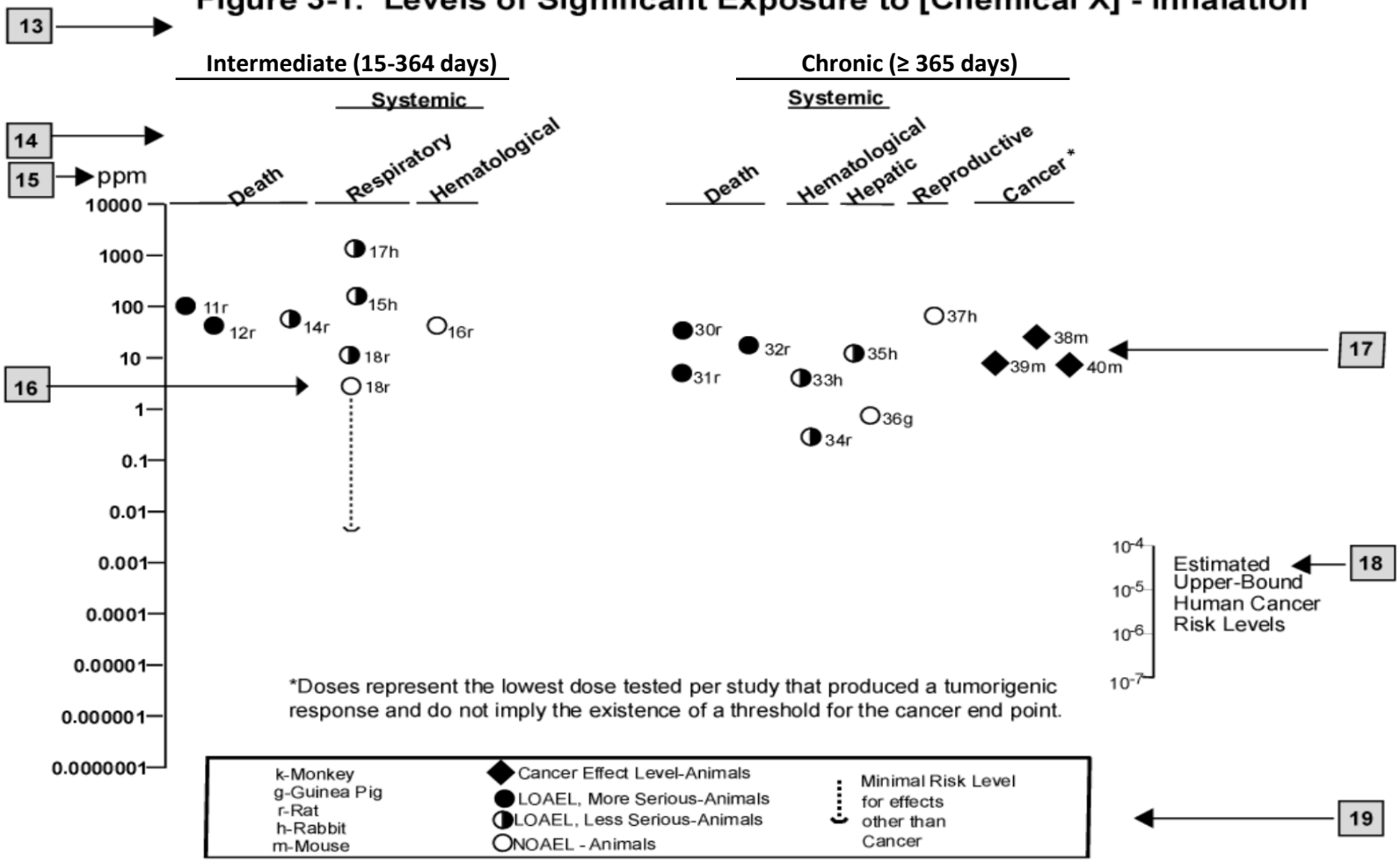
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
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
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
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	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
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
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TOC	total organic carbon
TPQ	threshold planning quantity
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
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