MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

July 15, 2015

To: File for 1-Bromopropane (CAS No. 106-94-5)

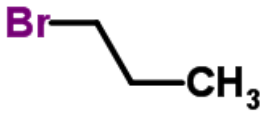
From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Update

The Initial Threshold Screening Level (ITSL) for 1-bromopropane (1-BP; also known as n-propyl bromide) is 32 µg/m³ with 24-hr averaging time. Previously, the ITSL was 49 µg/m³ with annual averaging time. An Initial Risk Screening Level (IRSL) is being established at 1.1 µg/m³ with annual averaging time. The Secondary Risk Screening Level (SRSL) is 11 µg/m³ with annual averaging time.

The following information sources were searched in order to support the development of screening levels for 1-bromopropane (1-BP): United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS, 2013), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration (RfC) for 1-BP. California Office of Environmental Health Hazard Assessment (Cal-OEHHA) has not established reference exposure levels for 1-BP; however, it is known to cause reproductive toxicity (OEHHA, 2013). The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) has not established minimal risk levels for 1-BP. The ACGIH has a TLV of 10 ppm (49 mg/m³); however, there is a notice of intended change for a TLV of 0.1 ppm (parts per million)(0.1 ppm = 0.5 mg/m³ for 1-bromopropane based on MW of 123g). NIOSH has not established occupational exposure levels. See Figure 1 for chemical and physical information for n-propyl bromide.

Figure 1. Chemical and Physical Information for 1-Bromopropane



Molecular Formula = C_3H_7Br [$Br\text{-}CH_2\text{-}CH_2\text{-}CH_3$]
Molecular Weight = 122.99g
Melting Point = -110 ℃, -167 ℉
Boiling Point = 70-71 ℃, 158-160 ℉
Vapor Pressure = 19.5 kPa (at 20 ℃)
(*for reference*: the vapor pressure of H_20 is 17.5 kPa @ 20℃)

1-BP is slightly soluble in water at 2.5 g/L (at 20 ℃). The blood:gas partition coefficient was described in a National Toxicology Program Report (NTP, 2002):

> Empirical evidence from rodent toxicity studies indicates that 1-BP is absorbed by the inhalation route. However, animal studies that characterize and quantify absorption and distribution of 1-BP by any route were not found. The blood:air partition coefficients for humans (7.08) and rats (11.7) indicate that 1-BP is readily soluble in blood; the fat:air partition coefficient for humans is 128 and for rats is 236.

Summary of Human Health Studies

Several human case studies have reported polyneuropathy (Sclar. 1999) and neurotoxicity (Ichihara et al., 2002, 2004, Li et al., 2010; Majersik et al., 2007; Perrone et al., 2008) in 1-BP-exposed workers. Symptoms included headache, nausea, incontinence, and subacute spastic paraparesis with distal sensory loss. Diminished vibration sensation and lower scores in memory and mood tests were reported in workers exposed to time-weighted average exposures of 0.34 ppm (1.7 mg/m^3) to 49.19 ppm (247 mg/m^3) 1-BP (Ichihara et al., 2004).

Li *et al.* (2010) investigated 60 female workers and 26 male workers in four 1-BP associated factories in China, including the factory investigated in a previous study (Ichihara et al., 2004). Age, sex, and region- matched controls were randomly selected from a beer factory, a refrigeration equipment factory, a knitting workshop, and a steel operation factory. The workers and controls were examined by questionnaire and by electrophysiological, neurological, neurobehavioral, and blood tests. The ambient concentration of 1-BP in the factories was measured by a kitagawa-type detection tube while individual worker exposure was assessed using passive samplers and gas chromatographic-mass spectral analysis. The purity of the 1-BP product produced in the factories ranged from >96% to ≥ 99% 1-BP. The ambient concentrations of 1-BP ranged from 3.3 to 5.5 ppm at reaction pot sites and from 16.5 to 58.3 ppm at raw product collection sites. Individual time-weighted average exposures to 1-BP ranged from 0.07 to 106.4 ppm (median 6.6 ppm) for female workers (n=60) and from 0.06 to 114.8 ppm (median 4.6 ppm) for male workers. The female workers could be classified into three 1-BP exposure groups: low (0.07-3.35 ppm), middle (3.39-14.13 ppm), and high (15.28 - 106.4 ppm), while the male workers could be classified into low (006-3.5 ppm) and high (5.7-114.8 ppm) 1-BP exposure groups. The duration of 1-BP exposure (39.8 ± 18.8 months for females and 41.5 ± 20.7 months for males) was not significantly different among the 1-BP exposure groups. None of the workers investigated had diabetes mellitus or a history of neurological diseases. Dose-dependent adverse effects of 1-BP were observed in the exposed workers. 1-BP exposure produced prolongation of the distal latency of the tibial nerve, decreased sensory nerve conduction velocity and vibration sense in toes, and decreased scores in the Benton cognitive test. Exposed female workers had increased LDH, TSH and FSH, and decreased red blood cell count and hematocrit, while exposed male workers had increased blood urea nitrogen. Analysis based on the product of 1- BP exposure level and exposure duration showed cumulative dose-dependent changes in the neurological, endocrinological, hematological and biochemical endpoints given above in female workers. The results suggest a lowest observed-adverse-effect level (LOAEL) of 1.28 ppm (6.44 mg/m^3) 1-BP for loss of vibration sense in toes and lowered red blood cell count in exposed female workers (Li *et al.,* 2010).

Selected Animal Toxicity Results
The following summaries of animal toxicity studies provides an overview of the toxicity database available for assessing risk from exposure to 1-BP.

Inhalation exposure of rats to 1-BP produced developmental toxicity (Huntington Life Sciences. 2001). Pregnant Sprague Dawley rats were exposed 6 hours/day from gestational days 6 to 19 at 0, 100, 498, or 996 ppm 1-BP, and fetuses were removed at gestational day 20. Maternal weight gain and food were decreased at ≥ 498 ppm. Decreased fetal weight was observed at all doses. Embryotoxicity was not observed. A dose-related decrease in ossification in the litters was observed at ≥ 498 ppm with a significant increase in bent ribs at 996 ppm. The no-observed-adverse-effect-level (NOAEL) for maternal toxicity was 100 ppm. However, decreased fetal weights were observed at this dose. The dose of 100 ppm (503 mg/m^3) is therefore embryotoxic and designated as a lowest-observed-adverse-effect-level (LOAEL).

The National Toxicology Program (NTP, 2002) collected information on the potential for 1-bromopropane to adversely affect human reproduction or development. Also included in this monograph is an expert panel report, public comments on that report, and additional scientific information available since the expert panel public meeting (Dec. 5-7, 2001).

Additional short-term animal studies by the NTP (2011) are summarized in Appendix A.

Summary of NTP Carcinogenesis Bioassay (NTP, 2011)
Male and female rats (F344/N) and mice (B6C3F1) were exposed by inhalation to doses of 1-BP 6 hours per day, 5 days per week for 2 years (NTP, 2011). The exposure doses are shown in tables 1 and 2 below.

Table 1. Male and Female Rats
Exposure and Adjusted Doses of 1-BP

Exposure Dose		Adjusted Dose*
ppm	*mg/m^3*	*mg/m^3*
0	0	0.0
125	628.83	112.3
250	1257.67	224.6
500	2515.34	449.2
* Exposure duration adjusted; i.e., 5days/7days x 6hrs/24hrs (=0.17857)		

Table 2. Male and Female Mice
Exposure and Adjusted Doses of 1-BP

Exposure Dose		Adjusted Dose*
ppm	*mg/m^3*	*mg/m^3*
0	0	0.0
62.5	314.42	56.1
125	628.83	112.3
250	1257.67	224.6
* Exposure duration adjusted; 5days/7days x 6hrs/24hrs =0.17857		

Table 3. Evidence of Mutagenic Activity of 1-BP (NTP, 2011)

Bacterial gene mutations:	Negative in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535 +/- S9; negative in *E. coli* WP2 *uvrA*/pKM101 +/- S9
Micronucleated erythrocytes Mouse peripheral blood *in vivo*:	 Negative

A complete list of significant findings of the NTP (2011) bioassay can be found in Appendix B.

Cancer Effects: Derivation of Initial Risk Screening Level (IRSL)

The EPA's Benchmark Dose Model (BMDM)(EPA, 2013) was used to model the slope of the dose-response curve for carcinogenic effects observed in the NTP (2011) report. Duration adjusted air concentrations were used as exposure (dose). The incidence denominator was adjusted to account for animals alive at the time of the first tumor. Input data (dose and incidence) and some output data for multistage cancer modeling using Benchmark Dose Software (BMDS) are shown in Appendix C.

Dosimetric Adjustment Factors (DAFs) for animal to human dose equivalency is done by converting the animal adjusted dose of 1-BP to a human equivalent concentration (HEC). (US EPA, 2012b):

For pulmonary effects, the ratio of ventilation rate (V) to surface area (SA) of the pulmonary region (PU) for animal (A) to human (H) was used.

$$DAF = RGDR_{PU} = \frac{\left(V_A / SA_{PU_A}\right)}{\left(V_H / SA_{PU_H}\right)}$$

Where: RGDR = Regional Gas Dose Ratio, SA_{PU} = Pulmonary Surface Area

For systemic effects, the ratio of blood gas partition coefficients ($H_{b/g}$) from the animal to human were used.

$$DAF = (H_{b/g})_A / (H_{b/g})_H$$

The $H_{b/g}$ for rats $(H_{b/g})_A$ =11.7, and for humans $(H_{b/g})_H$ = 7.08. The DAF for systemic effects would normally equal the ratio of the blood:air partition coefficients for animal to human:

DAF = 11.7/7.08
DAF = 1.65

However, as stated by EPA (2012b), if the $(H_{b/g})_A$ is greater than $(H_{b/g})_H$, then a default DAF value of 1 is used.

The calculations for deriving the DAFs and their input values are shown in Appendices E and F.

Table 4. BMDS Multistage Cancer Modeling Results (Input Data from NTP, 2011)

Species, Sex and Cancer Type	AIC*	p-value	Animal IUR** (per mg/m³)	DAF	Human IUR (per mg/m³)	IRSL (µg/m³)
Rat Male: Skin	150.34	0.364	0.00092	1	0.000920	1.1
Rat Female: Lung Adenoma	130.63	0.31	0.00132	3.23	0.000409	2.4
Mouse Female: Lung Adenoma + Carcinoma	159.54	0.261	0.00227	5.48	0.000414	2.4
Rat Female: Intestine	59.053	0.988	0.00042	1	0.000420	2.4
Rat Female: Skin	52.839	0.811	0.0004	1	0.000400	2.5
Rat Male: Mesothelioma	64.031	0.866	0.00034	1	0.000340	2.9
Mouse Female: Lung Carcinoma	114.1	0.016	0.0011	5.48	0.000201	5.0

* Akaike's Information Criterion
** Inhalation Unit Risk $(mg/m^3)^{-1}$

US EPA Carcinogen Risk Assessment (Cancer Guidelines) and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (Supplemental Guidance) were reviewed in order to assess whether early-life exposures to 1-BP would increase the cancer incidence. The Supplemental Guidance advises that age-dependent adjustment factors (ADAFs) be used with the cancer slope factors and age-specific estimates of exposure in the development of risk estimates, if the weight of evidence (WOE) supports a mutagenic mode of action for carcinogenicity. NTP (2011) summarized 1-BP "genetic toxicology" as follows:

> 1-Bromopropane was not mutagenic in either of two independent bacterial mutagenicity assays, each conducted with and without induced rat liver activation enzymes. Bacterial strains tested included Salmonella typhimurium strains TA97, TA98, TA100, and TA1535, and Escherichia coli strain WP2 uvrA/pKM101. In addition, no increases in the frequencies of micronucleated normochromatic erythrocytes were seen in male or female B6C3F1 mice exposed for 3 months to 62.5 to 500 ppm 1-bromopropane via inhalation.

It was determined that there was insufficient information available to conclude that 1-BP acts through a mutagenic MOA. Therefore, ADAFs were not deemed appropriate to adjust the cancer inhalation unit risk for 1-BP.

Non-Cancer Effects: Derivation of Initial Threshold Screening Level (ITSL)
Several potential screening levels were evaluated in order to establish a screening level protective of sensitive effects. All of the non-cancer endpoints observed in the NTP bioassay were evaluated using EPA Benchmark Dose Software (BMDS) (U.S. EPA, 2013). A macro-enabled spreadsheet developed for the EPA by ICF International was used to assist in analyzing the data (ICF BMDS Wizard, 2013).

Incidence data for all of the statistically significant elevated non-cancer toxicity endpoints observed from NTP (2011) were used in the BMDS (See Appendix B for incidences of cancer and non-cancer data, and Appendix D for non-cancer data modeled using BMDS). All eight available "dichotomous" models (e.g., probit, log-logistic, multistage, etc.) were used by the BMDS to "fit" curves to the observed data. For each toxicity endpoint a single best fit model was chosen based on benchmark dose (BMD) technical guidance (US EPA, 2012a). The BMDS uses a default of 10% extra risk of the response (i.e., a

benchmark response or BMR of 10%). The software calculates a 95% lower bound on the BMD (i.e., the $BMDL_{10}$) at the BMR of 10% as the point of departure (POD). The PODs are shown in Table 6 below. PODs are used, along with uncertainty factors (UFs) to extrapolate from animals to humans and for limitations of the data to calculate a reference concentration (RfC) safe for the general public.

The Human Equivalent Concentration (HEC) of the Benchmark Concentration ($BMCL_{10\text{-}HEC}$) is calculated as follows:

$$BMCL_{10\text{-}HEC} = BMCL_{10} \times DAF$$

Table 6. BMDS Results for Non-Cancer Effects and Point of Departure (POD)

Sex*, Species and Lesion (NTP, 2010)	$BMCL_{10}$**	DAF***	POD**** (HEC of $BMCL_{10}$)
MR* Nose Inflammation Suppurative Chronic	240	1	240
MR Nose Inflammation Chronic Active	37.4	1	37.4
MR Nose Glands Hyperplasia	76.6	1	76.6
MR Larynx Inflammation Chronic Active	59.7	1	59.7
FR Nose Inflammation Suppurative Chronic	225	1	225
FR Nose Inflammation Chronic Active	27.2	1	27.2
FR Nose Glands Hyperplasia	19.8	1	19.8
FR Nose Respiratory Epithelium Hyperplasia	80.3	1	80.3
FR Nose Olfactory Epithelium Metaplasia Respiratory	46.1	1	46.1
FR Larynx Inflammation Chronic Active	30	1	30
FR Larynx Metaplasia Squamous	184	1	184
FR Lung Inflammation Suppurative Chronic	409	3.23	1321
FR Trachea Inflammation Chronic Active	221	2.5	553
FR Trachea Epithelium Hyperplasia	409	2.5	1023
MM Nose Respiratory Epithelium Vacuolization Cytoplasmic	29.8	1	29.8
MM Larynx Vacuolization Cytoplasmic	45.7	1	45.7
MM Trachea Vacuolization Cytoplasmic	12.8	4.12	52.7
FM Nose Respiratory Epithelium Vacuolization Cytoplasmic	82.2	1	82.2
FM Nose Respiratory Epithelium Hyperplasia Lowest POD➔	**14.3**	**1**	**14.3**
FM Nose Olfactory Epithelium Metaplasia Respiratory	37.1	1	37.1

*MR = male rat; FR = female rat; MM = male mouse; FM = female mouse
**$BMCL_{10}$* (mg/m^3) = Lower 95% Confidence Limit on the Benchmark Concentration (10% response). This is the duration adjusted animal dose.
***DAF = Dosimetric Adjustment factor to convert animal dose to human dose. See Appendices E and F for derivation of DAFs.
****Point of Departure

$$\text{Potential Initial Threshold Screening Level (ITSL)} = POD/(UF_H \times UF_A)$$

Where UF_H = Intrahuman (10); and UF_A = Animal to Human (3)

$$\text{Potential ITSL} = BMCL_{10\text{-}HEC}/(10 \times 3)$$
$$\text{Potential ITSL} = 14.3\ mg/m^3/30$$
$$\text{Potential ITSL} = 0.476\ mg/m^3 \times 1000\ \mu g/mg$$
$$\text{Potential ITSL} = 476\ \mu g/m^3$$

The total uncertainty factor (UF) of 30 was based on a default factor of 10 to account for intrahuman variability, 3 for extrapolation from an animal study for which effect levels were adjusted by appropriate animal-to-human dosimetry.

Annual averaging time would be appropriate for this potential ITSL because the screening level was adjusted for and based on data to account for chronic continuous inhalation exposure up to a lifetime.

Short-term Non-Cancer ITSL Derivation

As mentioned above the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV) for 1-BP is 10 ppm or 49 mg/m³ (ACGIH, 2012). Draft documentation for a Notice of Intended Change (NIC) of 0.1 ppm (0.5 mg/m³) was made available to the MDEQ-AQD in July of 2012 (ACGIH, 2012). The draft documentation of NIC contained several summaries of human studies, including the Li et al (2010) study that described the LOAEL of 1.28 ppm. Unlike the typical documentation of a TLV, this document did not contain a section on the basis of the TLV, simply stating the TLV numeric value. However, it seems likely that the TLV of 0.1 ppm was based on the Li *et al.* (2010) study which identified a LOAEL of 1.28 ppm. The TLV is roughly 10 times lower than the LOAEL. The TLV committee likely applied an uncertainty factor of 10 to extrapolate from a LOAEL to a NOAEL.

An acute ITSL can be derived from the TLV based on Rule 232(1)(c) as follows:

Potential ITSL = OEL/100

Where OEL is the occupational exposure limit of 0.5 mg/m³ proposed by the TLV committee.

Potential ITSL = 0.5 mg/m³/100
Potential ITSL = 0.005 mg/m³ x 1000µg/mg
Potential ITSL = 5 µg/m³

The averaging time for this ITSL would be 8 hours according to Rule 232(2)(a).

An alternate acute ITSL can be derived directly from the Li *et al.* (2010) study using the LOAEL of 1.28 ppm. The units of ppm were converted to mg/m³ using the equation:

mg/m³ = (ppm x MW)/24.45
mg/m³ = (1.28 x 123)/24.45
mg/m³ = 6.44

Assuming a typical workday exposure, a duration adjusted dose can be calculated as follows:

$$LOAEL_{ADJ} = LOAEL \times \frac{\text{Human occupational default minute volume per 8 hours} = 10\text{m}^3}{\text{Human ambient default minute volume per 24 hours} = 20\text{m}^3}$$

$LOAEL_{ADJ}$ = 6.44 mg/m³ x 10m³/20m³

$LOAEL_{ADJ}$ = 3.22 mg/m³

Using the $LOAEL_{ADJ}$ of 3.22 mg/m³ as the point of departure (POD), an acute ITSL can be derived, such that:

Potential ITSL = $POD/(UF_L \times UF_H)$

Where,

UF_L is an uncertainty factor of 10 for the conversion of a LOAEL to NOAEL, and
UF_H is 10 for the extrapolation of sensitive individuals.

The ITSL then becomes:

Potential ITSL = (3.22 mg/m³)/(10 x 10)
Potential ITSL = 0.0322 mg/m³ x 1000 µg/mg
Potential ITSL = 32 µg/m³ (rounded to 2 significant figures)

The averaging time associated with this acute ITSL is 24-hours.

The potential chronic ITSL of 476 µg/m³ (annual averaging time) will not be established at this time. The human data indicates that 1-BP is neurotoxic at much lower doses than identified in animals. The human LOAEL was 1.28 ppm, whereas the animal NOAEL was 125 ppm in rats and 62.5 ppm in mice (NTP, 2010).

At the present time, the updated TLV is in draft format; therefore, the acute ITSL of 32 µg/m³ (24-hr avg.) is being established based on the Li *et al.* (2010) study.

References

ACGIH (2012a) Booklet of Threshold Limit Values (TLV) and Biological Exposure Indices (BEI). American Conference of Governmental and Industrial Hygienists (ACGIH). ISBN: 978-1-607260-48-6. 1330 Kemper Meadow Drive, Cincinnati, OH, 45240-4148.

ACGIH (2012b) Documentation of TLV for 1-Bromopropane: Notice of Intended Change. Revision: 10/26/2011. 12 page document, in electronic format (PDF). Personal Communication from David Gustafson, The Dow Chemical Company (dwgustofson@dow.com), Regulatory Affairs Leader, EH&S Global Regulatory Services, Midland Michigan. (forwarded email attachment from Robert Sills to Joy Taylor Morgan with CC to Michael Depa, MDEQ-AQD; 7/10/2012. Subject: n-propylbromide)

Huntington Life Sciences (2001) A developmental toxicity study in rat via whole body inhalation exposure. Study Number 98.4141; 2001. Document ID Title OAR-2002-0064. Document available in public docket A-2001 07, OAR-2002-0064. and A-91-42. US EPA, Washington, DC (2001). [A summary is available from EPA: (8EHQ-98-14346, 89990000147.pdf) (8EHQ-0601-14672, 89010000246.pdf)]

ICF BMDS Wizard (2013) BMDS Wizard v1.7-dichotomous.xlsm. (Microsoft Excel spreadsheet, macro enabled). Beta Version 1.7 March 18, 2013. By ICF International. wizard@icfi.com http://www.icfi.com/insights/products-and-tools/bmds-wizard. Downloaded from EPA in conjunction with Benchmark Dose Software (BMDS) Version 2.4 R70 [Build: 04/01/2013] http://www.epa.gov/NCEA/bmds/index.html (Accessed 02/01/2013)

Ichiliara G, Miller JK, Ziolkowska A*, et al.* (2002) Neurological disorders in three workers exposed to 1-bromopropane. J Occup Health 44: 1—7 (2002).

Ichihara G: LW: Shibata E, *et al.* (2004) Neurologic abnormalities in workers of a 1-bromopropane factory. Environ Health Perspectives 112:1319—1325 (2004).

ICSC (2004) International Chemical Safety Cards. 1-BROMOPROPANE. ICSC: 1332. International Programme on Chemical Safety & the Commission of the European Communities. IPCS CEC. October 28, 2004 Validated. Downloaded August 2, 2013. http://www.cdc.gov/niosh/ipcsneng/neng1332.html

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

Majersik JJ, Caravati EM, Steffens JD (2007) Severe neurotoxicity associated with exposure to the solvent 1-bromopropane (n-propyl bromide). Clin Toxicol 45: 270— 276

NTP (2002) Monograph on the Potential Human Reproductive and Developmental Effects of 1-Bromopropane. National Toxicology Program. NTP-Center for the Evaluation of Risks to Human Reproduction (CERHR) NIH Publication No. 04-4479 p. II-7. MARCH 2002 NTP-CERHR-1-BP-02. Downloaded January 29, 2013: http://ntp.niehs.nih.gov/ntp/ohat/bromopropanes/1-bromopropane/1-BP_final.pdf

NTP (2011) NTP technical report on the toxicology and carcinogenesis Studies of 1-bromopropane (CAS NO. 106-94-5) in F344/N Rats and B6C3F1 mice (inhalation studies) National Toxicology Program Research Triangle Park, NC. NTP TR 564. NIH Publication No. 11-5906. National Institutes of Health, Public Health Service, U.S. Department Of Health And Human Services

OEHHA (2013) Chemicals Known To The State To Cause Cancer Or Reproductive Toxicity, January 4, 2013. State Of California, Environmental Protection Agency, Office Of Environmental Health Hazard Assessment (OEHHA). Downloaded January 29, 2013: http://oehha.ca.gov/prop65/prop65_list/files/P65single010413.pdf

Perrone J, Marcus SM, Blando JD, *et al.* (2008) Neurologic illness associated with occupational exposure to the solvent 1-bromopropane— New Jersey and Pennsylvania. 2007-2008. Morbid Mortal Week Rep 57: 1300—1302 (2008).

RTECS® (2013) Registry of Toxic Effects of Chemical Substances. Canadian Centre for Occupational Health and Safety. www.ccohs.ca. On-line database. Subscription necessary. http://ccinfoweb.ccohs.ca/rtecs/search.html

Sclar G. (1999) Encephalomyeloradiculoneuropathy following exposure to an industrial solvent. Clin Neurol Neurosurg. Sep;101(3):199-202.

U.S. EPA (Environmental Protection Agency) (1988) Recommendations for and documentation of biological values for use in risk assessment. National Technical Information Service PB 88-179874.

U.S. EPA (1994) Methods for derivation of inhalation RfCs and application of inhalation dosimetry. EPA, Office of Research and Development, Washington DC 20460. EPA/600/8-90/066F. October 1994.

U.S. EPA (2012a) Benchmark Dose Technical Guidance. U.S. Environmental Protection Agency, Washington, DC. Risk Assessment Forum. EPA/100/R-12/001. http://www.epa.gov/raf/publications/pdfs/benchmark_dose_guidance.pdf (Accessed 02/01/2013).

U.S. EPA (2012b) Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment (Final Report). ORD; NCEA-RTP, U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-12/044. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=508055.

U. S. EPA (2013) Benchmark Dose Software (BMDS) Version 2.4 R70 [Build: 04/01/2013]. National Center for Environmental Assessment. Developed for EPA by Lockheed Martin Corp. Available from: http://www.epa.gov/NCEA/bmds/index.html (Accessed 02/01/2013).

APPENDIX A

National Toxicology Program (NTP, 2011) Short-Term Studies

3-MONTH STUDY IN RATS
Groups of 10 male and 10 female rats were exposed to 1-bromopropane vapor at concentrations of 0, 62.5, 125, 250, 500, or 1,000 ppm, 6 hours plus T90 (10 minutes) per day, 5 days per week for 14 weeks. Liver weights of males exposed to 250 ppm or greater and of females exposed to 125 ppm or greater were significantly increased. Spleen and kidney weights of 1,000 ppm females were significantly increased. Exposure concentration-related decreases of 28% in sperm motility and 37% in sperm counts were seen in the 1,000 ppm group of male rats. Female rats in all three exposure groups evaluated exhibited altered estrous cycles, spending significantly more time in extended estrus and less time in extended diestrus. The incidences of cytoplasmic vacuolization of the liver were significantly increased in males exposed to 250 ppm or greater and in females exposed to 500 ppm or greater. Hepatocyte degeneration was also observed in 1,000 ppm females.

3-MONTH STUDY IN MICE
Groups of 10 male and 10 female mice were exposed to 1-bromopropane vapor at concentrations of 0, 62.5, 125, 250, or 500 ppm, 6 hours per day, 5 days per week for 14 weeks. One 250 ppm male and four males and five females in the 500 ppm groups died early. Mean body weights of exposed groups were similar to those of the chamber controls. Lethargy was observed in males and females exposed to 500 ppm, and abnormal breathing was observed in moribund mice. The kidney, liver, and lung weights of 500 ppm females were significantly greater than those of the chamber controls. The kidney weights of 500 ppm males were significantly decreased. Sperm counts in the 500 ppm group of male mice were 28% less than that in the chamber controls. Female mice exhibited altered estrous cycles, with females in the 500 ppm group spending significantly more time in extended diestrus and those in the 250 ppm group spending significantly more time in extended estrus compared to the chamber controls. Nonneoplastic lesions were observed in the nose, larynx, trachea, lung, and liver of 500 ppm males and females and in the adrenal cortex of 500 ppm females.

Appendix B
1-Bromopropane Inhalation Bioassay Results (NTP, 2011)

Male F344N Rats

Non-neoplastic Effects:

Nose: inflammation, suppurative, chronic (0/50, 1/48, 2/48, 7/50); inflammation, chronic active (29/50, 33/48, 34/48, 35/50); glands, hyperplasia (5/50, 14/48, 14/48, 15/50)

Larynx: inflammation, chronic active (21/50, 28/50, 31/50, 26/50)

Neoplastic Effects:

Large intestine: adenoma (0/50, 0/50, 2/50, 1/50)

Skin: keratoacanthoma (0/50, 3/50, 6/50, 6/50); keratoacanthoma or squamous cell carcinoma (1/50, 4/50, 6/50, 8/50); keratoacanthoma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma (1/50, 7/50, 9/50, 10/50)

Equivocal Findings:

Malignant mesothelioma: (0/50, 2/50, 2/50, 4/50)

Pancreatic islets: adenoma (0/50, 5/50, 4/50, 5/50) adenoma or carcinoma (3/50, 10/50, 9/50, 8/50)

Level of Evidence of Carcinogenic Activity: Some Evidence

Female F344N Rats

Non-neoplastic Effects

Nose: inflammation, suppurative, chronic (0/50, 1/50, 3/49, 7/50); inflammation, chronic active (24/50, 37/50, 37/49, 36/50); glands, hyperplasia (6/50, 23/50, 28/49, 30/50); respiratory epithelium, hyperplasia (5/50, 13/50, 9/49, 18/50); olfactory epithelium, metaplasia, respiratory (3/50, 4/50, 6/49, 9/50)

Larynx: inflammation, chronic active (18/50, 25/50, 30/50, 32/50); metaplasia, squamous (3/50, 2/50, 6/50, 21/50)

Lung: inflammation, suppurative, chronic (0/50, 0/50, 0/50, 4/50)

Trachea: inflammation, chronic active (0/50, 4/50, 1/50, 6/50); epithelium, hyperplasia (0/50, 0/50, 0/50, 4/50)

Neoplastic Effects:

Large Intestine Adenoma (0/50, 1/50, 2/50, 5/50)

Equivocal Findings:

Skin squamous cell papilloma, keratoacanthoma, basal cell adenoma, or basal cell carcinoma (1/50, 1/50, 1/50, 4/50)

Level of Evidence of Carcinogenic Activity: Clear Evidence

Male B6C3F1 Mice

Non-neoplastic Effects

Lung: bronchiole, vacuolization cytoplasmic (0/50, 18/50, 19/49, 17/49); bronchiole, regeneration (1/50, 44/50, 38/49, 47/49)

Nose: respiratory epithelium, vacuolization cytoplasmic (0/50, 12/50, 19/50, 20/50); respiratory epithelium, hyperplasia (16/50, 29/50, 23/50, 26/50); olfactory epithelium, metaplasia, respiratory (0/50, 7/50, 6/50, 3/50)

Larynx: vacuolization cytoplasmic (0/48, 5/50, 10/48, 11/50)

Trachea: vacuolization cytoplasmic (0/49, 15/50, 24/47, 24/50)

Neoplastic Effects: None

Equivocal Findings: None

Level of Evidence of Carcinogenic Activity: No Evidence

Female B6C3F1 mice

Non-neoplastic effects:

Lung: bronchiole regeneration (0/50, 45/50, 43/50, 49/50)

Nose: respiratory epithelium, vacuolization cytoplasmic (0/50, 3/50, 5/50, 8/50);
respiratory epithelium hyperplasia (11/50, 25/50, 28/50, 27/50):
olfactory epithelium metaplasia respiratory (0/50, 4/50, 5/50, 14/50)

Trachea: vacuolization cytoplasmic 0/50, 8/49, 7/50, 4/50)

Neoplastic Effects:

Lung: alveolar/ bronchiolar adenoma (1/50, 6/50, 4/50, 10/50);
alveolar/bronchiolar carcinoma (0/50, 7/50, 5/50, 4/50);
alveolar/bronchiolar adenoma or carcinoma (1/50, 9/50, 8/50, 14/50)

Equivocal Findings: None

Level of Evidence of Carcinogenic Activity: Clear Evidence

Appendix C

Multistage Cancer Model: Dose, Incidence and Model Results

	Female Mouse lung adenoma and carcinoma				
Dose*	**Est._Prob.**	**Expected**	**Observed**	**Size**	**Residual**
0	0.0432	1.77	1	41	-0.592
56.1	0.1261	5.801	9	46	1.421
112.3	0.202	8.483	8	42	-0.186
224.6	0.3344	15.719	14	47	-0.531

	Female Mouse lung carcinoma (FAILED p)				
Dose	**Est._Prob.**	**Expected**	**Observed**	**Size**	**Residual**
0	0.0393	1.964	0	50	-1.43
56.1	0.0629	3.146	7	50	2.244
112.3	0.086	4.302	5	50	0.352
224.6	0.1305	6.526	4	50	-1.06

	Female Mouse lung adenoma				
Dose	**Est._Prob.**	**Expected**	**Observed**	**Size**	**Residual**
0	0.0287	1.433	1	50	-0.367
56.1	0.0742	3.712	6	50	1.234
112.3	0.1178	5.889	4	50	-0.829
224.6	0.1987	9.936	10	50	0.023

	Female Rat large intestine adenoma with adjusted dose groups				
Dose	**Est._Prob.**	**Expected**	**Observed**	**Size**	**Residual**
0	0	0	0	48	0
112.3	0.0207	0.91	1	44	0.096
224.6	0.0504	2.165	2	43	-0.115
449.2	0.1332	4.927	5	37	0.035

	Female Rat skin carc				
Dose	**Est._Prob.**	**Expected**	**Observed**	**Size**	**Residual**
0	0.0228	0.775	1	34	0.258
112.3	0.0311	1.027	1	33	-0.027
224.6	0.0557	1.67	1	30	-0.534
449.2	0.1478	3.547	4	24	0.26

	Female Rat mesothelioma				
Dose	**Est._Prob.**	**Expected**	**Observed**	**Size**	**Residual**
0	0	0	0	50	0
112.3	0.0234	1.147	2	49	0.806
224.6	0.0463	2.313	2	50	-0.211
449.2	0.0904	4.518	4	50	-0.256

	Male Rat skin				
Dose	**Est._Prob.**	**Expected**	**Observed**	**Size**	**Residual**
0	0.0333	1.632	1	49	-0.503
112.3	0.1	4.902	7	49	0.999
224.6	0.1622	7.947	9	49	0.408
449.2	0.2739	12.325	10	45	-0.777

* Duration adjusted animal dose; 6hrs/24hrs x 5days/7days

Appendix D: Number of Animals as Input for Non-cancer Modeling Using BMDS, and Resulting Lowest $BMCL_{10}$

	Sex-Species _ Lesion	Number of Animals in Each Dose Group				Incidence of Specific Lesions				$BMCL_{10}$
		cont.	low	med	high	cont	low	med	high	
1	**MR_Nose_inflammation_suppurative_chronic**	50	48	48	50	0	1	2	7	**240**
2	**MR_Nose_inflammation_chronic_active**	50	48	48	50	29	33	34	35	**37.4**
3	**MR_Nose_glands_hyperplasia**	50	48	48	50	5	14	14	15	**76.6**
4	**MR_Larynx_inflammation_chronic_active**	50	50	50	50	21	28	31	26	**59.7**
5	**FR_Nose_inflammation_suppurative_chronic**	50	50	49	50	0	1	3	7	**225**
6	**FR_Nose_inflammation_chronic_active**	50	50	49	50	24	37	37	36	**27.2**
7	**FR_Nose_glands_hyperplasia**	50	50	49	50	6	23	28	30	**19.8**
8	**FR_Nose_respiratory_epithelium_hyperplasia**	50	50	49	50	5	13	9	18	**80.3**
9	**FR_Nose_olfactory_epithelium_metaplasia_respiratory**	50	50	49	50	3	4	6	9	**46.1**
10	**FR_Larynx_inflammation_chronic_active**	50	50	50	50	18	25	30	32	**30**
11	**FR_Larynx_metaplasia_squamous**	50	50	50	50	3	2	6	21	**184**
12	**FR_Lung_inflammation_suppurative_chronic**	50	50	50	50	0	0	0	4	**409**
13	**FR_Trachea_inflammation_chronic_active**	50	50	50	50	0	4	1	6	**221**
14	**FR_Trachea_epithelium_hyperplasia**	50	50	50	50	0	0	0	4	**409**
15	*MM_Lung_bronchiole_vacuolization_cytoplasmic*	50	50	49	49	0	18	19	17	*x*
16	*MM_Lung_bronchiole_regeneration*	50	50	49	49	1	44	38	47	*x*
17	**MM_Nose_respiratory_epithelium_vacuolization_cytoplasmic**	50	50	50	50	0	12	19	20	**29.8**
18	*MM_Nose_respiratory_epithelium_hyperplasia*	50	50	50	50	16	29	23	26	*x*
19	*MM_Nose_olfactory_epithelium_metaplasia_respiratory*	50	50	50	50	0	7	6	3	*x*
20	**MM_Larynx_vacuolization_cytoplasmic**	48	50	48	50	0	5	10	11	**45.7**
21	**MM_Trachea_vacuolization_cytoplasmic**	49	50	47	50	0	15	24	24	**12.8**
22	*FM_Lung_bronchiole_regeneration*	50	50	50	50	0	45	43	49	*x*
23	**FM_Nose_respiratory_epithelium_vacuolization_cytoplasmic**	50	50	50	50	0	3	5	8	**82.2**
24	**FM_Nose_respiratory_epithelium_hyperplasia**	50	50	50	50	11	25	28	27	**14.3**
25	**FM_Nose_olfactory_epithelium_metaplasia_respiratory**	50	50	50	50	0	4	5	14	**37.1**
26	*FM_Trachea_vacuolization_cytoplasmic*	50	49	50	50	0	8	7	4	*x*

Duration Adjusted Exposure Concentrations (mg/m^3): Rats: 0.0, 112.3, 224.6, 449.2 for control, low, medium and high dose groups
Duration Adjusted Exposure Concentrations (mg/m^3): Mice: 0.0, 56.1, 112.3, 224.6 for control, low, medium and high dose groups

Appendix E

Calculation of Ventilation Rates for Rats and Mice

For the calculation of minute volume for rats and mice, the equation (4-4) from EPA (1994) was used.

Equation 4-4 $ln(V_E) = b_O + b_1(ln BW)$

Where *ln* is the natural log, V_E is the minute volume, b_O is the intercept, b_1 is the coefficient, and BW is body weight in kilograms (kg).

Intercept (b_O) and Coefficient (b_1)

Species	b_O	b_1
Rat	-0.578	0.821
Mouse	0.326	1.050

From: EPA (1994) p 4-29. Table 4-6, referenced from EPA (1988)

RAT

Female Rat Body Weight (BW) = 370g *(page 45, Figure 5. From: NTP, 2011)*

$ln(V_E) = -0.578 + 0.821$ (ln[0.37kg])

$ln(V_E) = -0.578 + 0.821(-0.9942)$

$ln(V_E) = -0.578 - 0.8163$

$ln(V_E) = -1.394$

$V_E = e^{-1.394}$

$V_E = 0.248$ Liters/minute (L/min)

MOUSE

Female Mouse BW = 58g *(page 67, Table 20 From: NTP, 2011)*

$ln(V_E) = 0.326 + 1.050(ln 0.058kg)$

$ln(V_E) = 0.326 + 1.050(-2.8473)$

$ln(V_E) = 0.326 + (-2.989)$

$ln(V_E) = -2.6637$

$V_E = e^{-2.6637}$

$V_E = 0.070$ L/min

Male Mouse BW = 52g *(page 66, Table19 From: NTP, 2011)*

$ln(V_E) = 0.326 + 1.050(ln 0.052kg)$

$ln(V_E) = 0.326 + 1.050(-2.9565)$

$ln(V_E) = 0.326 + (-3.104)$

$ln(V_E) = -2.778$

$V_E = e^{-2.778}$

$V_E = 0.0621$ L/min

References

NTP, 2011. NTP technical report on the toxicology and carcinogenesis Studies of 1-bromopropane (CAS NO. 106-94-5) in F344/N Rats and B6C3F1 mice (inhalation studies)
National Toxicology Program Research Triangle Park, NC. NTP TR 564. NIH Publication No. 11-5906. National Institutes of Health, Public Health Service, U.S. Department Of Health And Human Services

U.S. EPA. (Environmental Protection Agency) 1988. Recommendations for and documentation of biological values for use in risk assessment. EPA/600/6-87/008, February 1988. Blackburn, K. Also available from the National Technical Information Service (NTIS): PB 88-179874.

U.S. EPA, 1994. Methods for derivation of inhalation RfCs and application of inhalation dosimetry. EPA, Office of Research and Development, Washington DC 20460. EPA/600/8-90/066F. October 1994.

Appendix F

Calculation of the Dosimetric Adjustment Factors for Deriving Human Equivalent Concentrations

The animal dose was scaled to the human dose using EPA (1994, 2012b) methodology.

Table E-1. Input Data for Regional Gas Dose Ratio (RGDR) Used in the Inhalation Unit Risk Calculations		
Species	**Pulmonary (Lung) Surface Area (SA)**	**Ventilation Rate (V)**
Human	54 m^2	13.8 L/min
Female Rat	0.3 m^2	0.248 L/min
Female Mouse	0.05 m^2	0.070 L/min

$$RGDR_{PU} = \frac{V_A / SA_{PU_A}}{V_H / SA_{PU_H}}$$

$RGDR_{PU\text{-}FemaleRat}$ = (0.248/0.3)/(13.8/54) = 0.82666/0.2555 = 3.23
$RGDR_{PU\text{-}FemaleMouse}$ = (0.07/0.05)/(13.8/54) = 1.4/0.2555 = 5.48

Table E-2. Input Data for Regional Gas Dose Ratio (RGDR) Used in the Non-cancer Dose-Response Calculations		
Species	**Tracheobronchial Surface Area (SA)**	**Ventilation Rate (V)**
Human	3200 cm^2	13.8 L/min
Female Rat	22.5 m^2	0.248 L/min
Male Mouse	3.5m^2	0.0621 L/min

$$RGDR_{TB} = (V_A/SA_{TB\text{-}Animal})/(V_H/SA_{TB\text{-}Human})$$

$RGDR_{TB\text{-}FemaleRat}$ = (0.248/22.5)/(13.8/3200) = 0.011/0.0043 = 2.5
$RGDR_{TB\text{-}MaleMouse}$ = (0.0621/3.5)/(13.8/3200) = 0.0177/0.0043 = 4.12

Appendix G

American Conference of Governmental Industrial Hygienists (ACGIH)
Threshold Limit Values (TLV)
Notice of Intended Change (NIC)
Draft TLV NIC Documentation for 1-Bromopropane
(revision: 10/26/2011)

This Documentation is in DRAFT format, and its content is subject to change. We are providing it as such because we believe it is important to provide access as early as practical to the data and technical information cited herein which are the basis for the proposed TLV(s)®, BEI(s)®, and related notations.

1-BROMOPROPANE

CAS number: 106-94-5

Synonyms: n-Propylbromide; Propylbromide

Molecular structure: C_3H_7Br

Chemical structure: 

TLV–TWA, 0.1 ppm (0.5 mg/m^3)

A3 — Confirmed Animal Carcinogen with Unknown Relevance to Humans

TLV® Recommendation

A TLV–TWA of 0.1 ppm (0.5 mg/m^3) should provide protection against the potential for neurotoxicity, hepatotoxicity, and reproductive and developmental toxicity in 1-bromopropane-exposed workers. 1-Bromopropane (1-BP) is a potential substitute for solvents used in cleaning, adhesive, and aerosol propellant applications. This document applies to commercial grade bromopropane (99% 1-BP with 0.1%–0.2% 2-bromopropane), not to 2-bromopropane. The recommended TLV–TWA for 1-BP should *never* be applied to 2-bromopropane.

1-BP exhibited low acute toxicity in rats but produced neurotoxicity, (Ichihara et al., 2000b) hepatotoxicity, (ClinTrials, 1997a) and reproductive (WIL, 2001) and developmental (Huntingdon Life Sciences, 2001) toxicity after repeated exposure. Several human case studies have reported polyneuropathy (Sclar, 1999) and neurotoxicity (Ichihara et al., 2002, 2004a, b; Li et al., 2010b; Majersik et al., 2007; Perrone et al., 2008) in 1-BP-exposed workers. Symptoms included headache, nausea, incontinence, and subacute spastic paraparesis with distal sensory loss. Diminished vibration sensation and lower scores in memory and mood tests were reported in workers exposed to time-weighted average exposures of 0.34 to 49.19 ppm 1-BP (Ichihara et al., 2004a). A study of 60 female workers in four 1-BP factories demonstrated dose-dependent neurological and hematological effects of 1-BP exposure with a lowest-observed-adverse-effect level (LOAEL) of 1.28 ppm 1-BP for loss of vibration sense in toes and lowered red blood cell count (Li et al., 2010b). A no-observed-adverse-effect level (NOAEL) for 1-BP-induced neurological effects was not identified in this study (Li et al., 2010b). The NOAEL for hepatotoxicity in the chronic rat study was 200 ppm (ClinTrials, 1997a). Decreased fetal weights were observed after exposure of pregnant rats at 100 ppm 1-BP (Huntingdon Life Sciences, 2001). All other adverse effects, including neurotoxic and reproductive effects, occurred at higher exposure concentrations in laboratory animals. The TLV–TWA for 1-BP should also protect against the potential for all adverse effects, including reproductive or hematopoietic toxicity from the contaminant 2-bromopropane. Inhalation exposure of rats (125, 250, or 500 ppm) or mice (62.5, 125, or 250 ppm) to 1-BP 6 hours/day, 5 days/week for 2 years produced cancer of the large intestine in both sexes of rats and lung tumors in female mice (NTP, 2011), supporting a cancer designation of A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans. There is no basis for a skin notation because the dermal LD_{50} of 1-BP was > 2 g/kg (Elf AtoChem, 1995b) and no basis for a SEN notation (Elf AtoChem, 1995a). There are no data to support a TLV–STEL for 1-BP.

TLV® Basis

Central nervous system (CNS) impairment; peripheral neuropathy; hematological effects; reproductive toxicity (male, female); developmental toxicity.

Reference: Personal Communication from David Gustafson of The Dow Chemical Company (dwgustafson@dow.com), Regulatory Affairs Leader, EH&S Global Regulatory Services, Midland Michigan (from a forwarded email with attachment of a PDF, forwarded by Robert Sills, MDEQ-AQD; 7/10/2012), (only page 1 of 12 is shown above).