MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY
_____

INTEROFFICE COMMUNICATION
_____

TO: File for Trimethyl Borate (CAS # 121-43-7)

FROM: Keisha Williams, Air Quality Division

DATE: January 18, 2019

SUBJECT: Screening Level for Trimethyl Borate and Borates

The initial threshold screening level (ITSL) for acute exposure to borates is 80 µg/m^3 as boron (1-hour averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1233 (1) and (2). With molecular weight adjustment, the ITSL for trimethyl borate is 770 µg/m^3 (1-hour averaging time).

Based on information summarized for trimethyl borate (CAS # 121-43-7) in the Hazardous Substances Data Bank (HSDB), this toxic air contaminant (TAC) is commonly grouped with boric acid and other boron compounds in terms of its toxicity and expected fate in the environment (MDNR, 1991; HSDB, 2005a). As a result, it was determined that this TAC should be grouped with borates.

The following references or databases were searched to identify data to determine the screening level for borates: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), ChemView: the EPA's database on chemical health and safety data for chemicals subject to the Toxic Substances Control Act (TSCA), the TSCA documents in the National Technical Reports Library (NTRL) database, 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, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels, International Agency for Research on Cancer (IARC) Monographs, the American Chemical Society's SciFinder database, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels (AEGLs) for Airborne Chemicals, EPA High Production Volume Database, United States Department of Labor Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs), the Organisation for Economic Co-operation and Development's Existing Chemicals Database, the Canadian Centre for Occupational Health and Safety's Registry of Toxic Effects of Chemical Substances (RTECS), the Toxnet databases: Hazardous Substances Data Bank and Toxline, Spacecraft Maximum Allowable Concentrations (SMACs), California Office of Environmental Health Hazard Assessments Reference Exposure Levels, Texas Commission on Environmental Quality (TCEQ) Effects Screening Levels (ESLs), German maximale Arbeitsplatz-Konzentration (MAK) values, and European Chemicals Agency Registered Substances Dossiers.

Background Information

Borates, as classified as boron-containing oxyanions, are used in glass and ceramic products, soaps and detergents, pesticides, and fire retardants (ACGIH, 2005; ATSDR, 2010). Borates are often grouped toxicologically. In the European Centre for Ecotoxicology and Toxicology of Chemicals' (ECETOC's) technical report on some inorganic borates, it is noted, "Of particular interest in a toxicological review is an understanding of what species of chemical interacts with biological tissue and the consequences of any such interaction. Because boric acid is stable and a very weak acid (pKa 9.15), the undissociated acid (H_3BO_3) is the predominant species in aqueous solution at physiological pH. This applies also to boric acid and sodium borates. As a consequence, the toxicology of all these substances is likely to be similar on an equivalent boric acid basis (as boron)" (ECETOC, 1995). Figure 1 shows boric acid, the parent compound to other borates. Table 1 provides chemical and physical properties of two different borates.

Figure 1. Chemical structure of boric acid
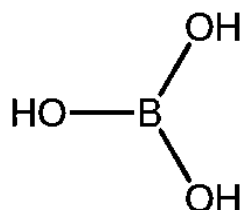
Table 1. Chemical and physical properties of select borates

	Boric Acid (CAS # 10043-35-3)	Pentahydrate Sodium Borate (CAS # 12179-04-3)	Sodium Perborate (CAS # 7632-04-4)	Trimethyl borate (CAS # 121-43-7)
Molecular weight (g/mol)	61.63	291.4	81.80	103.912
Melting point	171 °C	200 °C	63 °C	-29.3 °C
Boiling point	300 °C	---	---	67.5 °C
Physical state at room temp.	Solid, particle	Solid, particle	Solid, particle	Liquid

References: ACGIH, 2005; HSDB, 2005b; NCBI

As noted in the ATSDR toxicological profile, "boron is a trace element and is not metabolized in the body. Borates exist in the body as boric acid, the only form of boron recovered in the urine" (ATSDR, 2010). As shown in Table 2, boric acid and other inorganic borate compounds are regularly classified together for evaluation through health-based benchmarks.

There are well-designed, controlled human studies on the effects of borate inhalation (Cain et al., 2004; Cain et al., 2008). Irritation and respiratory symptoms have been identified as critical effects after acute exposure. Because of concern for the portal of entry effects from inhaling borates, route to route extrapolation has been deemed inappropriate for acute exposures (ACGIH, 2005; ATSDR, 2010). At the same time, it is important to note that developmental/ reproductive effects are the critical effects from borate ingestion (ECETOC, 1995, ATSDR, 2010) and there is limited information regarding developmental and reproductive effects after

borate inhalation. The appropriateness of the current ITSL should be re-evaluated when developmental and reproductive toxicity studies via the inhalation route of exposure become available for review.

Table 2. Health benchmarks protecting against adverse effects after inhalation to borates

Agency	Benchmark Value	Regulated under
ACGIH	TLV: 2.0 mg/mg^3 -time weighted average (TWA) 6 mg/m^3-short-term exposure limit (ACGIH, 2005)	Inorganic borate compounds, inhalable particle mass
ATSDR	MRL: 300 μg/m^3 (ATSDR, 2010)	Boron
US EPA HEAST	RfC: 20 μg/m^3 for subchronic exposure 20 μg/m^3 for chronic exposure (US EPA, 1997)	Elemental boron, but specifically for anhydrous borax
NIOSH	Recommended Exposure Limit (REL): 5 mg/m^3 for TWA for sodium borate decahydrate 1 mg/m^3 for TWA for sodium borate (anhydrous) 1 mg/m^3 for TWA for sodium borate pentahydrate (NIOSH, 2018)	Borates, tetra, sodium salts
German MAKs	MAK: 10 mg/m^3 for TWA for boric acid (1.8 mg/m^3 as boron) 5 mg/m^3 for TWA for sodium tetra pentahydrate (0.75 mg/m^3 as boron) 0.75 mg/m^3 for TWA for tetraborates (as boron) (MAK, 2017)	Boric acid and tetraborates
ECHA	Derived no effect level (DNEL): 4.15 mg/m^3 for long-term exposure (ECHA, 2018)	Boric acid
TCEQ	Effect Screening Level (ESL): 2 μg/m^3 for long-term exposure 20 μg/m^3 for short-term exposure (TCEQ, 2013)	Borates, not otherwise specified (based on the ACGIH TLV)

NOTE: Inhalation studies for boron and compounds were reviewed under US EPA's IRIS, but RfCs were not derived (US EPA, 2004).

Evaluation of Cancer Risk

There are no known inhalation studies that evaluate borate-induced carcinogenicity. In oral studies, borate administration has not led to increased tumors (ATSDR, 2010). As a result, borates will not be classified as carcinogens.

Discussion of Previous ITSL for Trimethyl Borate

The previous ITSL for trimethyl borate is based on a LD50 study (MDNR, 1994).

It is expected that trimethyl borate will transform into boric acid and methanol in the atmosphere (HSDB, 2005a). Therefore, as described above, it is considered appropriate to group this TAC with other borates. However, the use of an LD50 study is not appropriate since borate-induced portal of entry effects have been shown. As a result, the previous ITSL is being rescinded and trimethyl borate is being grouped with other borates.

Review of Relevant Studies for Non-carcinogen Effects

The 2010 acute MRL is the most recently developed inhalation health benchmark for borates and is based on the studies from Cain et al. (2004 and 2008). These studies are well-designed, controlled human studies. Furthermore, the MRL is derived to protect against effects in the general public, including for sensitive populations. As a result, the acute MRL is well suited for use with ITSL derivation.

The acute MRL is more broadly applied to boron-containing compounds. However, sodium tetraborate pentahydrate and boric acid specifically were used in the research studies on which the acute MRL is based. In the 2010 ATSDR toxicological profile, exposures were molecular-weight adjusted to the mass of boron for comparison across various types of borates. In the 2004 study by Cain et al., male volunteers were exposed to approximately 0, 0.8, 1.5, 3.0, 4.5 or 6.0 mg boron/m^3. The exposure lasted for 20 minutes. Volunteers were trained to recognize and characterize boron exposure in relation to chemesthetic feel (in the eye, nose and throat) of various levels of CO_2. Changes in nasal secretions, mucociliary clearance, nasal resistance, heart rate and ventilation rate were also measured. The presence of the dust was felt at the lowest concentration given in the throat; however, irritation was felt at 4.5 mg boron/m^3 in the nose. Thus, ATSDR identified a no observable adverse effect level (NOAEL) for irritation in the nose at 3 mg boron/m^3. A statistically significant increase in nasal secretions was measured at 1.5 mg boron/m^3 as compared to the control exposure, and the associated NOAEL was determined to be 0.8 mg boron/m^3. Similar results for chemesthetic feel and measurements of nasal secretions were obtained in the 2008 study by Cain et al., where exposures were intentionally performed at levels not expected to induce irritation.

Using the 0.8 mg boron/m^3 as a point of departure, an uncertainty factor of 3 was applied for human variability to derive the MRL. ATSDR noted, "an uncertainty factor of 3 for human variability was based on the fact that inhaled borates and boric acid exert their adverse effects on respiratory tract tissues as portal-of-entry irritants. For portal-of-entry inhalation toxicants, the variability between humans in pharmacokinetics (i.e., toxicant deposition in the respiratory tract) is minimal. Thus, half ($10^{0.5}$, or 3) of the composite uncertainty factor for pharmacokinetic and pharmacodynamic variability in humans should be applied to the identified NOAEL."

For derivation of the acute ITSL, certain aspects of the acute MRL will be modified to adhere to US EPA guidance and AQD Rule 336.1233. Specifically, US EPA guidance indicates that research does not support use of half of the composite uncertainty factor for pharmacokinetic and pharmacodynamic variability in humans (US EPA, 1994; US EPA, 2002). In the 1994 guidance on inhalation reference concentration derivation, it is noted that "Hattis et al. (1987) also suggest that a value of 10 is generally appropriate for this UF based on an analysis of human variability for key pharmacokinetic parameters." This description identifies pharmacokinetic variability as potentially influencing a 10-fold factor alone. In the 2002 update to the 1994 guidance, it is noted that "the intraspecies UF is applied to account for variations in susceptibility within the human population (interhuman variability) and the possibility (given a lack of relevant data) that the database available is not representative of the dose/exposure-response relationship in the subgroups of the human population that are most sensitive to the health hazards of the chemical being assessed. Because the RfD/RfC is defined to be applicable to "susceptible subgroups," this UF was established to account for uncertainty in that regard. In general, the Technical Panel reaffirms the importance of this UF, recommending that reduction of the intraspecies UF from a default of 10 be considered only if data are sufficiently representative of the exposure/dose-response data for the most susceptible subpopulations (s)."

Given that those with lung disease, e.g. asthmatics, may represent the most susceptible subpopulations, and the research studies on which the acute MRL were derived with relatively healthy adults with no known history of chronic disease of the upper or lower airways, an uncertainty factor of 10 for human variability will be used for ITSL derivation as seen in Equation 1 per AQD Rule 336.1233.

Equation 1.

$$ITSL = \frac{POD}{UF_h \, x \, UF_A \, x \, UF_L} \, x \, \frac{hours \; exposed}{AT}$$

Where:
- POD=NOAEL=0.8 mg/m^3
- UF$_h$=10
- UF$_A$=1
- UF$_L$=1
- hours exposed/AT is not applicable since boric acid and borates are considered sensory irritants that have dose-dependent not time-dependent irritation effects

$$ITSL = \frac{0.8 \frac{mg}{m^3}}{10 \, x \, 1 \, x \, 1} \, x \, 1 \, x \, \frac{1000 \frac{\mu g}{m^3}}{\frac{mg}{m^3}} = 80 \, \frac{\mu g}{m^3}, 1 \; hour \; averaging \; time$$

The ITSL is based on molecular-weight adjustment, so care should also be taken to do molecular weight adjustment for any related borates. The specific example with trimethyl borate is shown in Equation 2. Furthermore, since this ITSL applies to several different borates, multiple forms of borates must be accounted for additively to ensure that the combined ambient air impact does not exceed a hazard index of one. It is also important to use discretion with grouping toxic air contaminants under this family of chemicals as some borates may also be composed of relatively more toxic moieties.

Equation 2.

$$sodium \; perborate \; equivalent \; ITSL = 80 \, \frac{\mu g}{m^3} \, x \, \frac{molecular \; weight \; of \; trimethyl \; borate}{molecular \; weight \; of \; boron}$$

$$= 80 \, \frac{\mu g}{m^3} \, x \, \frac{103.912}{10.8}$$

$$= 769.7185 \, \frac{\mu g}{m^3} \approx 770 \frac{\mu g}{m^3}, 1 \; hour \; averaging \; time$$

Since oral studies have shown developmental and reproductive toxicity to be the critical effects, a potential ITSL based on oral studies is described here. Table 2 presents health benchmarks that protect against adverse effects from borate ingestion. All three agencies cite the research studies that were published following the NTP study on developmental toxicity after boric acid administration (US EPA, 2004; ATSDR, 2010; ECHA, 2018). In these animal studies, decreased fetal weight, increased malformations and prenatal mortality were observed as the critical effects. A potential ITSL can be derived as shown in Equation 3 based on AQD Rule 232 (1) (b).

Table 2. Health benchmark protecting against adverse effects after oral ingestion of borates

Agency	Benchmark Value	Regulated under
IRIS	RfD: 0.2 mg/kg per day (US EPA, 2004)	Boron and compounds
ATSDR	Acute and Intermediate oral MRL: 0.2 mg/kg per day (ATSDR, 2010)	Boron and compounds
ECHA	DNEL: 0.98 mg/kg per day for long-term exposure (ECHA, 2018)	Boric acid

Equation 3.

$$Potential\ ITSL = Oral\ RfD\ x\ \frac{70kg}{20m^3}$$

Where:

   Oral RfD is 0.2 mg/kg per day

$$Potential\ ITSL = 0.2\frac{mg}{kg}\ per\ day\ x\ \frac{70kg}{20m^3}\ x\ \frac{10^3\ \mu g}{mg} = 700\frac{\mu g}{m^3}, 24\ hr\ averaging\ time$$

The potential ITSL based on oral studies is higher than the acute ITSL based on inhalation data, so the acute ITSL is expected to be health protective of developmental toxicity, as well. However, the appropriateness of this ITSL to protect against developmental toxicity should be reviewed if developmental toxicity data from inhalation exposure become available.

Therefore, the ITSL for borates is 80 µg/m^3, 1-hour averaging time and the trimethyl borate-specific ITSL related to this is 770 µg/m^3, 1-hour averaging time.

References

ACGIH. 2005. Documentation of the Threshold Limit Values and Biological Exposure Indices-Borate compounds, inorganic. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

ATSDR. 2010. Toxicological Profile for Boron. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Services.

ECHA. 2018. Registration dossier: Boric acid. Toxicological Information: Toxicological Summary. https://echa.europa.eu/registration-dossier/-/registered-dossier/15472. Accessed December 2018.

Hazardous Substances Data Bank (HSDB) [Internet]. 2005a. Bethesda (MD): National Library of Medicine (US); [Last Revision Date September 2005; cited on January 3, 2019]. Trimethyl Borate; Hazardous Substances Databank Number: 5589. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+5589

Hazardous Substances Data Bank (HSDB) [Internet]. 2005b. Bethesda (MD): National Library of Medicine (US); [Last Revision Date September 2005; cited on January 3, 2019]. Sodium Perborate; Hazardous Substances Databank Number: 1676. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+1676

MAK. 2017. BAT Value Documentation: Boric acid and tetraborates [MAK Value derived in 2010]. The MAK-Collection for Occupational Health and Safety: Annual Thresholds and Classifications for the Workplace, 2(1), 189-197.

MDEQ. 2013. *Memo from Cathy Simon to File for Methanol (CAS# 67-56-1). Subject: Update of the Initial Threshold Screening Level for Methanol*, November 26, 2013. AQD, MDEQ.

MDNR. 1994. *Memo from George Eurich to File for Trimethoxyborine (CAS# 121-43-7). Subject: Screening Level for Trimethoxyborine*, March 28, 1994. AQD, MDNR.

NCBI: National Center for Biotechnology Information. PubChem Compound Database; CID=8470, https://pubchem.ncbi.nlm.nih.gov/compound/8470 (accessed Jan. 3, 2019).

NIOSH. 2018. Borates. Accessed December 2018. The page was last reviewed on November 29, 2018. http://www.cdc.gov/niosh/npg/npgd0507.html

TCEQ. Texas Air monitoring Information System Web Interface. Tox-ESL Summary Report-Boric Acid. Accessed December 5, 2018. https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=home.welcome

US EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC, EPA/600/8-90/066F.

US EPA. 1997. HEAST Table 1: Subchronic and chronic toxicity (other than carcinogenicity) - Boron, elemental. Oak Ridge National Laboratory. https://rais.ornl.gov/epa/heast/table1.htm. Accessed December 2018.

US EPA. 2002. A review of the reference dose and reference concentration processes. In Risk Assessment Forum EPA/630/P-02 F (Vol. 2).

US EPA. 2004. IRIS database. Boron and compounds (CASRN 7440-42-8). Accessed in December 2018. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0410_summary.pdf

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

March 28, 1994

TO: File for Trimethoxyborine (CAS # 121-43-7)

FROM: George Eurich

SUBJECT: Screening Level for Trimethoxyborine

The ITSL for Trimethoxyborine is set at 18 ug/m³ based on annual average time.

The following sources were searched for information on this compound:

RTECS	NIOSH REL
IRIS	NTP MANAGEMENT STATUS REPORT
EPB LIBRARY	IARC MONOGRAPHS
ACGIH	EPB CHEMICAL CRITERIA DATABASE
HEAST	CAS ONLINE (1967-1994)
NLM (1981-1994)	

The ITSL is based on an LD50 of 6.14 ml/kg taken from a range finding study (Smyth, et al.). No details of the study were available other than the LD50 dose and 95% confidence interval. The ITSL is calculated according to Rule 232 (1) (h) as follows:

LD50 = 6.14 ml/kg
Specific Gravity of Trimethoxyborine = 0.915 (Patty's Indus. Hyg. and Toxicol.)
Density = d^{25} = d' = SF_{Bt} = 0.915 x 0.99705 = 0.912 g/cm³ : where d^{25} = d' = density at 25°C, S = specific gravity of trimethoxyborine, F_{Bt} = A function of the coefficient of cubical expansion of trimethoxyborine at temperature t. (Lange's Handbook of Chemistry)

LD50 = 6.14 ml/kg x 0.912 g/cm³ = 5.60 g/kg = 5600 mg/kg

$$ITSL = \frac{1}{500 \times 40 \times 100} \times \frac{5600 \text{ mg/kg}}{.167 \times .931} = 18 \text{ ug/m}^3 \text{ annual average}$$

References:

Lange's Handbook of Chemistry. Twelfth Edition. Editor: Dean, J. A. McGraw
- Hill Book Company, New York.   1979.   pg. 10-89.

Patty's Industrial Hygiene and Toxicology.   Third Revised Edition.   Vol.
IIB.   Editors: Clayton, G.D., and F.E. Clayton.   John Wiley & Sons, New
York. 1981.

Smyth H.F. et al. (1962) Range-finding toxicity data: list VI.   American
Ind. Hyg. Assoc. J. 23:95.

GE:ma