MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 26, 2012

TO: File for Trimethylbenzene (CAS No. 25551-13-7)
File for 1,3,5-Trimethylbenzene (CAS No. 108-67-8)
File for 1,2,4-Trimethylbenzene (CAS No. 95-63-6)
File for 1,2,3-Trimethylbenzene (CAS No. 526-73-8)

FROM: Michael Depa, Toxics Unit, Air Quality Division MD

SUBJECT: Acute and Chronic Screening Levels for Isomers of Trimethylbenzene

The acute initial threshold screening level (ITSL) for all trimethylbenzene (TMB) isomers combined is 1200 µg/m³ with 8-hr averaging time. The chronic ITSL for all TMB isomers combined is 50 ug/m³ with annual averaging time. A footnote for the two screening levels is to read, "The combined ambient impacts for the isomers of trimethylbenzene or any mixture thereof, cannot exceed the screening level(s)."

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR) and the California Office of Environmental Health Hazard Assessment (Cal OEHHA). Other on-line databases or search-engines were queried, including National Library of Medicine's TOXNET, US EPA (epa.gov) and Google. Table 1. has a list of relevant health benchmarks for trimethylbenzene.

INDIVIDUAL ISOMERS VS MIXTURE OF TMB ISOMERS

In order to derive candidate health benchmarks for TMB, the toxicity database for all three isomers was searched. It was decided to regulate TMB with a screening level that would protect against adverse effects for any one or all isomers. Support for this approach is found in EPA (2007):

> Little difference in toxicity has been observed between the TMB isomers. Since occupational exposure are likely to involve more than one isomer, regulatory standards that have been established are for the individual isomers and any mixture thereof. ... Therefore, even though the point of departure may be based on data from an individual isomer, the resulting [health benchmark] values are considered applicable to all three TMB isomers.

Both NIOSH and ACGIH regulate the combination of TMB isomers with one exposure limit.

Table 1. Health Benchmarks for Trimethylbenzene in the U.S.

Organization (Benchmark) *Year established/recently reviewed*	Value ($\mu g/m^3$)	Averaging Time	Protected Population
MDEQ (ITSL) *2006 (rescinded Feb. 2012)*	220	24-hr	All populations
EPA (PPRTV p-cRfC*) *2010 and 2007 (for 1,2,3- and 1,2,4-TMB, respectively)*	5 and 7**	Annual***	All populations
EPA (AEGL-1****)(Interim) *2007*	890,000 890,000 690,000 440,000 220,000	10 minute 30-minute 1-hr 4-hr 8-hr	General populations ("could experience notable discomfort")
ACGIH (TLV) *2001*	123,000	8-hr	Occupational
NIOSH (REL) *1997*	123,000	10-hr	Occupational

* PPRTV = Provisional Peer-Reviewed Toxicity Value; p-cRfC = provisional chronic reference concentration
** 5 $\mu g/m^3$ for 1,2,3-trimethylbenzene (EPA, 2010); 7 $\mu g/m^3$ for 1,2,4-trimethylbenzene (EPA, 2007)
*** Assumed/not specified. Both 1,2,3- and 1,2,4-TMB benchmarks are for "chronic" exposures; usually interpreted as annual averaging time (EPA, 2004)
**** AEGL: Acute Exposure Guidance Level-1 for protection of mild reversible effects

The ACGIH-TLV and NIOSH-REL are based on an occupational exposure investigation in paint workers exposed to "Fleet-X-DV-99" containing 30% 1,3,5-TMB and 50% 1,2,3-TMB and 20% other solvents (possibly some benzene). Hydrocarbon vapor concentrations ranged from 10 to 60 parts per million (ppm) (49.9 mg/m^3 to 294.6 mg/m^3) for a "number of years" (Battig et al. 1956). A significant number of workers complained of nervousness, tension, anxiety, and asthmatic bronchitis. ACGIH stated, "In addition, the peripheral blood showed a tendency to hypochromic anemia and a deviation from normal in the coagulability of the blood." The ACGIH-TLV of 25 ppm was recommended to protect for central nervous system (CNS) depression , asthmatic bronchitis and blood dyscrasias. NIOSH used similar reasoning for their Recommended Exposure Limit (REL) for TMB (NIOSH, 1989).

Animal studies have shown that subchronic non-continuous inhalation exposure to various pure concentrations of 1,2,3- or 1,2,4-TMB cause hematopoietic toxicity and analgesia/behavioral neurotoxicity as low as 25 ppm. Korsak et al., (2000) exposed male and female rats 0, 25, 100, or 250 ppm 1,2,3-TMP for 6 hrs/day, 5 days/week for 3 months. At 25 ppm, Korsak et al. (2000) found statistically significant changes in % reticulocytes, decrease in % segmented neutrophils, decrease in red blood cell counts and an increase in % lymphocytes. Lower respiratory tract histopathological changes were statistically different from controls at 100 ppm and higher (Korsak et al., 2000). All three TMB isomers cause an impairment of active avoidance response at 100 ppm (Gralewicz and Wiadrna, 2001) and the spike-wave discharge activity from an electroencephalogram recording showed a progressive increase during a 4-month post-exposure period from exposure to 25 ppm 1,2,4-TMB for 28 days. Korsak and Rydzynski (1996) examined neurobehavioral effects in rats exposed to 0, 25, 100, and 250 ppm 1,2,3-TMB for 6 hrs/day, 5 days/week for 3 months. Latency of the paw-lick response was statistically increased compared to control in all dose groups in a dose-dependent manner.

Subchronic exposures in animal studies were able to identify a Lowest Observed Adverse Effect Level (LOAEL) of 25 ppm (123 mg/m^3). The critical effects from these studies ranged from neurobehavioral to hematopoietic toxicity. The ACGIH-TLV and NIOSH-REL are set at 25 ppm, and based on a study where worker exposures lasted for a subchronic time-period (8-hr per day for a "number of years"). The effects in workers were similar to animals (CNS depression

and blood dyscrasias). It seems possible that the occupational exposure level is not fully protective for workers because the animal effect levels and occupational benchmarks are the same (25 ppm or 123 mg/m³). However, in several pharmacokinetic studies in humans with all three isomers of TMB, no irritation or central nervous system effects were reported in volunteers exposed to up to 25 ppm for 2 hours (Jarnberg et al., 1996) or 4 hours (Jones et al., 2006) or up to 30 ppm for 8 hours (Kostrzewski et al., 1997). These studies support the conclusion that exposures up to 25 ppm are probably protective of healthy adults during short work-place exposure scenarios. While some uncertainty remains as to the protectiveness of the occupational exposure limit (OEL) for TMB (e.g., ACGIH-TLV and NIOSH REL), when deriving an ITSL from OELs, several factors are used to diminish the likelihood of adverse effects. An uncertainty factor (UF) of 10 is used to account for potential effects from sensitive individuals. Also, the TLV is converted to continuous life-time exposure as follows:

$$\text{Continuous Exposure} = OEL \times \frac{40\ hours\ per\ workweek}{168\ hours\ per\ week} \times \frac{30\ years\ occupational\ time}{70\ year\ lifetime}$$

$$\text{Continuous Exposure} = OEL \times 0.1$$

The continuous exposure TLV is one 10^{th} (40/168 x 30/70 = 0.1), which when coupled with the UF of 10 for sensitive individuals results in a candidate ITSL that is 100 times lower than the TLV.

ACUTE ITSL

An acute ITSL was derived from the OEL for TMB of 25 ppm, pursuant to Rule 232(1)(c):

ITSL = OEL/100

Where, the OEL is the ACGIH-TLV and NIOSH REL

ITSL = 25 ppm/100
ITSL = 0.25 ppm

The following was used to convert ppm to mg/m³, and mg/m³ to µg/m³:
mg/m³ = (molecular weight x ppm)/24.45; and mg/m³ = 1000 µg/m³
mg/m³ = (120.19g x 0.25 ppm)/24.45
mg/m³ = 1.2
µg/m³ = mg/m³ x 1000 µg/m³ per mg/m³
µg/m³ = 1.2 x 1000
Therefore,
ITSL = 1200 µg/m³

Pursuant to Rule 232(2)(b), the averaging time is 8-hr.

CHRONIC ITSL

After evaluating the toxicity data and developing candidate RfCs for all three isomers, the EPA's derivation of a PPRTV for 1,2,3-TMB (EPA, 2010) was deemed to be the most appropriate. This was based on two points. First, the candidate RfC for 1,2,3-TMB was slightly lower than the benchmarks for other isomers. And second, since the AQD screening level is designated for

all three or any combination thereof, even 100% 1,2,3-TMB, a screening level based on 1,2,3-TMB would also be protective for exposures to the other TMB isomers, but that their screening levels would not be protective of adverse effects from 1,2,3-TMB. If a process emits only 1,2,4- or 1,3,5-TMB then a facility or process-specific evaluation of the TMB emissions could be done on a case-by-case basis.

The EPA chronic PPRTV (p-cRfC) for 1,2,3-TMB was based on Korsak and Rydzynski (1996), described above. The LOAEL was 123 mg/m³ (25 ppm), and the critical effect identified was neurobehavioral toxicity: latency (delay) of the paw-lick response when placed on a hot-plate. EPA used benchmark dose software to derive the 95% lower confidence limit on the benchmark dose concentration at 1 standard deviation ($BMCL_{1SD}$). The $BMCL_{1SD}$ of 97 mg/m³ was used as a point of departure. This was duration adjusted for continuous exposure as follows:

$BMCL_{adj} = BMCL_{1SD} \times 6/24 \times 5/7$
for exposure to 6 hours per day and 5 days per week.
$BMCL_{adj} = 17$ mg/m³

EPA derived the Human Equivalent Concentration (HEC) for animal to human dose equivalency using the rat and human blood gas partition coefficient $H_{b/g}$ for 1,2,3-TMB from Meulenberg and Vijverberg (2000). The animal $H_{b/g} = 62.6$, and the human = 66.5 for TMB, so the $BMCL_{HEC}$ is calculated as follows:

$BMCL_{HEC} = BMCL_{adj} \times 0.94$
$BMCL_{HEC} = 17$ mg/m³ $\times 0.94$
$BMCL_{HEC} = 16$ mg/m³

AQD used the $BMCL_{HEC}$ as a point of departure (POD) for derivation of RfC as follows:

$RfC = (BMCL_{HEC})/(UF_1 \times UF_2 \times UF_3)$
Where $UF_1 = 3$ for animal to human, $UF_2 = 10$ for subchronic to chronic and $UF_3 = 10$ for sensitive individuals.
RfC = (16 mg/m³)/300
RfC = 0.05 mg/m³
RfC = 50 µg/m³

The derivation of the RfC as described above, differs from the derivation of EPA's p-cRfC as described in EPA, 2010. AQD decided not to use a database uncertainty factor (UF_{db}) of 10. EPA's justification for using 10 for database deficiency UF_{db} was as follows:

> No subchronic human studies are available. The relevant inhalation database includes one 3-month comprehensive systemic toxicity study and one-3-month and two 4-week neurobehavioral studies, all in rats. Developmental and reproductive toxicity studies are lacking for both the inhalation and oral routes, as are subchronic studies in a second species, therefore a full factor of 10 is applied.

AQD does not believe that the absence of a subchronic human study should be a relevant factor for application of 10 for database deficiencies because these data are rarely available, and almost all RfCs would require a 10 fold UF if this criteria were applied uniformly in the derivation of other health benchmarks. EPA states, "all in rats" implying that because a second species, such as mice, were not tested using TMB, a more sensitive critical effect could be missing from the

database. However, in another report EPA (2007) seems to contradict the assertion that a more sensitive species would show a lower effect level, when it states that:

> From the data available, it appears that rats are slightly more sensitive than mice to the toxic effects of the TMB isomers.

As for the point that "Developmental and reproductive toxicity studies are lacking," AQD found that Saillenfait et al., (2005) performed developmental toxicity studies using 1,3,5- and 1,2,4-TMB and found that fetal weight was decreased at 600 ppm and higher, but no external, visceral, or skeletal malformation were observed at any dose level. A three-generation reproductive study was performed using C-9 hydrocarbon inhalation exposure, which contained 8.4% 1,3,5-TMB, 40.5% 1,2,4-TMB and 6.2% 1,2,3-TMB (total TMB ≈ 55%) with the remainder being a mixture of o-xylene, cumene, n-propyl benzene, and 4-, 3-, and 2-ethyltoluene. F2 generation animals had reduced body weight at 100 ppm. Although this study used a mixture of TMB with a substantial exposure to other hydrocarbons (~45%) it still provides some information on the reproductive toxicity of TMB, namely, that TMB inhalation exposure is not exceptionally toxic to the reproductive system. Given that the database is generally better than other toxicity databases AQD has used to derive ITSLs, AQD believes that the application of the UF_{db} is not appropriate for ITSL derivation.

An annual averaging time was used for the chronic ITSL of 50 µg/m³ for TMB. Typically, a 24-hr averaging time would be applied to an RfC derived ITSL pursuant to Rule 232(2)(b),

> If the initial threshold screening level is derived as in subrule (1)(a) and (b) of this rule, then the averaging time is 24 hours.

However, since the RfC was derived using Rule 229(2)(b) and not Rule 232(1)(a), AQD is not strictly limited to a 24-hr averaging time. Since the RfC was derived to protect against health effects from long-term exposure, it was deemed appropriate to use an annual averaging time. EPA (2004) provides justification for using an annual averaging time for chronic benchmarks:

> In screening inhalation risk assessments, which are routinely built around a particular year's estimate of emissions, the exposure estimate is usually based on an assumption of continuous long-term exposure using an annual average as the estimate of exposure concentration.

It follows that long-term exposures should be assessed using a health benchmark with annual averaging time.

SUMMARY

- The acute ITSL for all isomers of trimethylbenzene (TMB) is 1,200 µg/m³ with 8-hr averaging time.
- The chronic ITSL for all isomers of TMB is 50 µg/m³ with annual averaging time.
- Footnote: "The combined ambient impacts for the isomers of trimethylbenzene or any mixture thereof, cannot exceed the screening level(s)."

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