MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 12, 2017

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

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 185 µg/m³ with annual averaging time. A footnote for the screening levels is to read, "The combined ambient impacts for the isomers of trimethylbenzene or any mixture thereof, cannot exceed the screening levels."

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, and US EPA (epa.gov).

Physical Properties

The molecular weight of TMB is 120.19g. If released to the atmosphere, 1,2,3-TMB, 1,2,4-TMB, and 1,3,5-TMB will exist solely in the vapor phase in the atmosphere under ambient conditions, based on measured vapor pressures of 1.69, 2.10, and 2.48 mm Hg at 25℃, respectively (HSDB, 2011a, b, c). Degrada tion of TMB isomers in the atmosphere occurs by reaction with hydroxyl radicals; the half-life is 11−12 hours (HSDB, 2011a, b, c). The commercially available substance known as trimethylbenzene, Chemical Abstracts Service number (CAS) 25551-13-7, is a mixture of three isomers in various proportions, namely CAS 526-73-8 (1,2,3-TMB or hemimellitene), CAS 95-63-6 (1,2,4-TMB or pseudocumene), and CAS 108-67-8 (1,3,5-TMB or mesitylene).

AIHA (1995) reported odor detection levels of 2.4 ppm (11.8 mg/m³) for 1,2,4-TMB and 2.2 ppm (10.8 mg/m³) for 1,3,5-TMB after a review and critique of the available data.

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. EPA (U.S. EPA, 2016a) stated that, [D]ata support the conclusion that the TMB isomers are very similar to one another regarding their toxicokinetic characteristics." Both NIOSH and ACGIH regulate the combination of TMB isomers with one exposure limit. It was deemed appropriate to use a single ITSL for derivation of a health-protective benchmark for all three isomers of TMB as long as the cumulative ambient air levels of all TMB isomers was used to evaluate the total potential exposure and compared to the ITSL.

Summary of Health Effects

> Effects on the nervous, respiratory, and hematological (i.e., blood) systems have been reported in occupationally- and residentially-exposed humans, but these effects were observed following exposure to complex mixtures containing TMB isomers, thus making it difficult to determine the contribution of each TMB isomer to the observed health effects. Health effects that are roughly analogous to those seen in humans have been observed in animals exposed to the individual isomers. Effects on the nervous system, including cognitive effects and decreased pain sensitivity, are the most widely observed effects in animals. Effects on other systems, including the respiratory and hematological systems, have also been observed in animals. Both 1,2,4-TMB and 1,3,5-TMB have been observed to elicit effects on pregnant animals and developing fetuses, but at exposure levels greater than those that cause effects on the nervous system. There is inadequate information to evaluate the carcinogenicity of TMBs. (U.S. EPA, 2016a)

Neurotoxicity is the most consistently observed endpoint in the toxicological database for TMBs, and decreased pain sensitivity was observed in multiple studies following exposures to 1,2,3- or 1,2,4-TMB for short-term or subchronic durations. Given the consistency of this effect, and the determination that decreased pain sensitivity is an appropriate adverse effect with which to derive reference values, decreased pain sensitivity was selected as the critical effect and Korsak and Rydzyński (1996) was selected by EPA (2016a) as the principal study for derivation of the RfC for TMBs.

Summary of Principal Study

Groups of 10 male wistar rats were exposed to 0, 25, 100, and 250 ppm (0, 123, 492, and 1229 mg/m³) mixtures of TMBs (pseudocumene, mesitylene and hemimellitene; 1,2,4-TMB, 1,3,5-TMB and 1,2,3-TMB, respectively) for 6/hrsday, 5 days/week for 3 months (Korsak and Rydzyński, 1996). Neurological effects were measured using a rotarod. The rotarod apparatus consisted of a 8-cm diameter wooden rod rotating at 12 rpm and suspended horizontally 20 cm above the floor which was constructed from metal bars connected to a power source of 80 V and 2 mA. The ability of rats to remain on the rotating rod for 2 min was taken as an index of normal neuromuscular function. Significant decreases in rotarod performance were observed at 1,230 mg/m^3 1,2,4-TMB (40% response) and ≥492 mg/m^3 1,2,3-TMB (50−70% response) when tested immediately after exposure for 13 weeks. This impaired function was still evident at 2 weeks post-exposure, indicating a persistence of this effect. Specifically, failures in 70% and 40% of animals after 13 weeks of exposure to 1,230 mg/m^3 1,2,3-TMB and 1,2,4-TMB, respectively (compared to 0% of animals in control groups at any time), were 50% and 30% at 2 weeks post-exposure, although 30% failure at 15 weeks for 1,2,4-TMB was no longer significantly different from controls (note: statistical comparisons did not appear to include a repeated measures component and comparisons to the 13-week time-point were not performed). The observations of substantial decrements in rotarod

performance are interpreted as a biologically relevant response in light of the lack of failures in controls and the similarities in response magnitude across isomers. Inhalation studies of acute TMB exposure support this observation. Hotplate tests were used to evaluate pain sensitivity. Decreased pain sensitivity is clearly observed immediately after termination of subchronic exposure to either 1,2,4-TMB or 1,2,3-TMB. Hot plate (exposure-dependent increase in paw-lick latency, which recovers by 2 wks post-exposure) were statistically elevated for all dose levels of 1,2,3-TMB; therefore, a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 123 mg/m³ (25 ppm) was identified.

Information on another study supports the designation of 123 mg/m³ as a subchronic LOAEL. Korsak et al. (1997) observed that bronchoalveolar lavage (BAL) fluid showed that protein (total protein, mucoprotein) and enzyme activities (lactate dehydrogenase, acid phosphatase) were increased significantly ($p<0.05$) at 123, 492 and 1230 mg/m³.

Derivation of Chronic Inhalation Reference Concentration (RfC)

The EPA based the RfC for TMB on Korsak and Rydzynski (1996), described above. The 95% lower confidence limit on the benchmark concentration at 1 standard deviation ($BMCL_{1SD}$) of 97 mg/m³ was used as the Point of Departure (POD). The POD was then "duration adjusted" for continuous exposure as follows:

POD_{adj} = POD x hours exposed per day x days exposed per week
POD_{adj} = 97 mg/m³ x 6/24 x 5/7
POD_{adj} = 17 mg/m³

EPA derived the Human Equivalent Concentration (HEC) for animal to human dose equivalency using a Physiologically Based Pharmacokinetic (PBPK) Model. The PBPK model predicts average venous blood concentrations (mg/L) at various exposure levels in rats and humans, given a 6-hour/day, 5-day/week exposure. The PBPK equations used to predict the human equivalent concentration are presented in U.S. EPA (2016b) and are not presented here. However, a generalized equation (see below) shows how the PBPK model is used to derive the HEC from the adjusted dose:

POD_{HEC} = POD_{adj} x *PBPK*
POD_{HEC} = 17 mg/m³ x *PBPK*
POD_{HEC} = 18.5 mg/m³

The POD_{HEC} was used to derive the RfC as follows:

$RfC = (POD_{HEC})/(UF_1 \times UF_2 \times UF_3)$
Where
UF_1 = 3 for animal to human,
UF_2 = 3 for subchronic to chronic and
UF_3 = 10 for sensitive individuals.
RfC = (18.5 mg/m³)/100
RfC = 0.185 mg/m³ x 1000µg/mg
RfC = 185 µg/m³

The Air Quality Division's (AQD's) derivation of the RfC as described above, specifically for use in establishing an ITSL, differs from EPA's derivation of a chronic inhalation RfC as described in EPA (2016a), because it was decided by AQD not to use a database

uncertainty factor (UF_{db}) of 3. EPA's (2016a) justification for using a 3-fold UF for UF_{db} was as follows:

- lack of a developmental toxicity study for any individual isomer
- lack of a multi-generation reproductive toxicity study for TMB isomers is a possible deficiency in the TMB database
- lack of a developmental neurotoxicity study

However, it should be noted 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 inhalation concentrations of 600 ppm and higher, but no external, visceral, or skeletal malformations 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 (McKee et al., 1990). 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 that have been used to derive ITSLs, it is believed that the application of the UF_{db} is not appropriate for ITSL derivation.

The current file review concludes that the averaging time may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as directed under Rule 232(2)(b). Therefore, the averaging time is set to annual.

Derivation of Acute ITSL

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/m³ to 294.6 mg/m³) for a "number of years" (Battig et al. 1956). A significant number of workers complained of nervousness, tension, anxiety, and asthmatic bronchitis. ACGIH (2001) 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).

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). 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:

Continuous Exposure =

OEL x (40hrs per work-week)/(168hrs per week) x (30yrs work)/(70yrs lifetime)

Continuous Exposure = OEL x 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 an ITSL that is 100 times lower than the TLV.

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;
mg/m³ = (120.19g x 0.25 ppm)/24.45
mg/m³ = 1.2
ITSL = 1.2 mg/m³ x 1µg/1000mg
ITSL = 1200 µg/m³

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

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 185 µg/m³ with annual averaging time.
- Footnote: “The combined ambient impacts for the isomers of trimethylbenzene or any mixture thereof, cannot exceed the screening levels.”

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