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Rick Snyder, Governor



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September 22, 2017

Response to Public Comments for
Tert-Butyl Acetate (CAS No. 540-88-5)

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the Initial Threshold Screening Level (ITSL) for tert-butyl acetate. As a result of that review, a new ITSL for tert-butyl acetate, including isomers of butyl acetate, is being established at 2400 $\mu\text{g}/\text{m}^3$ with an eight-hour averaging time. A new footnote is assigned to all isomers of butyl acetate, such that their combined impact cannot exceed 2400 $\mu\text{g}/\text{m}^3$ with eight-hour averaging time. The ITSL is based on the American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Time Weighted Average (TWA) for butyl acetates, all isomers. The previous ITSL of 9500 $\mu\text{g}/\text{m}^3$ with eight-hour averaging time is now rescinded.

Background:

Revisions to the Air Pollution Control Rules¹ were promulgated December 22, 2016. Subsequently, the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) published toxic air contaminant screening levels and their basis as required by Rule 230(1). Pursuant to Rule 230(2), the AQD solicited and received public comments on these screening levels for 60 days: February 14 through April 14, 2017. The AQD must respond to these comments within 180 days; the latest date for response is October 11, 2017.

¹ Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources And Environmental Protection Act, 1994. PA 451, as amended (NREPA).

Comment and Response:

Comment: The 2000 AQD assessment of tertiary butyl acetate is outdated and should be updated. A list of study reports and publications available since 2000 is provided. Summaries of unpublished toxicity reports were prepared for the EU REACH registration of tertiary butyl acetate and are available online. The ACGIH recently updated their TLV for all the butyl acetate isomers. A recently published review article by Dr. James Bus calculated acute and chronic reference concentrations based on recent toxicity evaluations. The toxicology database for tertiary butyl acetate supports that tertiary butyl acetate as a low concern to human and environmental health.

Response: AQD reviewed the reports referenced in the comment, including the Bus et al. (2015), and the documentation for the ACGIH Threshold Limit Value (TLV) for “butyl acetates, all isomers” (ACGIH, 2016). AQD also reviewed the toxicological information contained in the European Chemical Agency (ECHA) registration dossier for tert-butyl acetate.

The acute and chronic reference values (RfCs) derived by Bus et al. (2015) were based on a 13-week inhalation study by Faber et al. (2014), where clinical observations of hyperactivity, excessive grooming, impaired equilibrium, and excessive chewing were noted in mice during the post-exposure observations. Bus et al. (2015) calculated a benchmark dose² (BMDL) of 150 parts per million (ppm) for neurological effects in mice. AQD reviewed the methodology that Bus et al. (2015) used to calculate the benchmark dose and the resulting RfCs, and found that the RfCs were appropriately derived using U.S. Environmental Protection Agency methodology (U.S. EPA, 1994). AQD also reviewed the ACGIH TLV (ACGIH, 2016) recommendation, where ACGIH stated:

A TLV-TWA³ of 50 ppm (238 mg/m³) is recommended for butyl acetate isomers to minimize the potential risk of irritation reported in volunteers exposed to 147 ppm of acetate for 4 hours (Iregren et al., 1993) and confirmed by experimentally determined eye irritation thresholds of 113 and 177 ppm for 10-second exposures to n-butyl acetate and tert-butyl acetate (Cain and Schmidt, 2009). Data from anosmics⁴ suggest that n- and sec-butyl acetate have similar thresholds for nasal pungency and irritation and that for tert-butyl acetate is some-what higher (Abraham et al., 1996). Therefore, all butyl acetates are being treated as similarly potent.

The TWA should protect against transient hyperactivity seen in mice subchronically exposed to 400 ppm tert-butyl acetate and increased motor activity in male rats seen at 1600 ppm (Faber et al., 2014) and against possible reproductive effects of n- and tert-butyl acetate where the adverse effects on development of the fetus are probably secondary to maternal toxicity (Saillenfait et al., 2007; Yang et al., 2007).

This TLV should also be protective against the hepatic effects seen at doses over 440 ppm for tert-butyl acetate (Kenney, 2000 as cited in Copestake and Heath, 2005).

Data are limited in respect of iso- and sec-butyl acetate but based on the RD50⁵ values, they do not appear to be more acutely toxic than the n- and tert- isomers. RD50s have been reported in mice for n-butyl acetate of 730 ppm (Schaper, 1993) and 720 ppm

² Benchmark Dose at 95% lower confidence limit of the BMD10 (the 10% response rate).

³ Time weighted average of 8-hrs

⁴ A person who has lost or has an impairment of the sense of smell.

⁵ RD50 is the concentration inducing a 50% decrease in the respiratory rate.

(Stouten and Bogaerts, 2002) and in rats for tert-butyl acetate of 15,750 ppm (Stouten and Bogaerts, 2002) and 4200 ppm (Copestake and Heath 2005). For isobutyl acetate, the RD50 was 817 ppm in mice (Copestake and Heath, 2005)

See ACGIH (2016) for citations

The ACGIH derived the TLV of 50 ppm to be protective of eye and upper respiratory tract irritation in humans, as stated above. The TLV of 50 ppm was described as protective of neurological, liver and reproductive effects in animals. The AQD agrees that the TLV is protective for occupationally exposed individuals for the stated adverse effects. Typically, an appropriately derived RfC would take precedence as the basis for an ITSL over an occupational exposure limit (OEL) such as the TLV. However, in this case, the OEL derived by ACGIH (2016) is based on human data, whereas the RfCs are based on animal data. Furthermore, the TLV would be protective of the effects observed in animals as described in ACGIH (2016). Therefore, AQD deemed the TLV as the most appropriate basis for the ITSL for tert-butyl acetate. Using the equation in Rule 232(1)(c) the ITSL is calculated as follows:

$$\text{ITSL} = \text{OEL}/100$$

Where the OEL is the ACGIH TLV of 50 ppm

$$\text{ITSL} = 50 \text{ ppm}/100$$

$$\text{ITSL} = 0.50 \text{ ppm}$$

The ITSL was converted to micrograms per cubic meter as follows:

$$\mu\text{g}/\text{m}^3 = (\text{ppm} \times \text{MW})/24.45 \times (1000 \mu\text{g}/\text{mg})$$

$$\mu\text{g}/\text{m}^3 = (0.50 \text{ ppm} \times 116\text{g})/24.45 \times (1000\mu\text{g}/\text{mg})$$

$$\mu\text{g}/\text{m}^3 = 2372$$

Where MW of 116 grams is the molecular weight of butyl acetate isomers.

Rounding to 2 significant figures results in an ITSL of 2400 $\mu\text{g}/\text{m}^3$. Pursuant to Rule 232(2)(a) the averaging time is eight-hours.

AQD also agrees with ACGIH that the isomers of butyl acetate are sufficiently toxicologically similar to tert-butyl acetate so that all isomers should be evaluated using the same exposure limit. Therefore, AQD will establish new screening levels for all isomers of butyl acetate at 2400 $\mu\text{g}/\text{m}^3$ (eight-hour average), each with a footnote:

The combined impact of all butyl acetate isomers must be evaluated together such that the impacts cannot exceed 2400 $\mu\text{g}/\text{m}^3$ with 8-hr averaging time.

Summary and Conclusions:

AQD reviewed the current literature and references that the commenter submitted and determined that a new ITSL based on the ACGIH TLV for “butyl acetates, all isomers” is the most appropriate basis for protection of adverse effects from exposure to tert-butyl

acetate. AQD is also establishing screening levels for all butyl acetate isomers at 2400 $\mu\text{g}/\text{m}^3$ with 8-hour averaging time.

The primary AQD reviewer for these comments was Mike Depa, AQD Toxics Unit Toxicologist. The secondary (peer) reviewer was Doreen Lehner, AQD Toxics Unit Toxicologist.

References:

American Conference of Governmental and Industrial Hygienists (ACGIH). 2016. Butyl Acetate, All Isomers. Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition - 2016 Supplement. 14 pages. ISBN: 978-1-607260-79-0. ACGIH®. 1330 Kemper Meadow Drive, Cincinnati, Ohio 45240

Bus JS, Marcy I, Banton MI, Faber WD, Kirman CR, McGregor DB, Poureau DB. 2015. Human health screening level risk assessments of tertiary-butyl acetate (TBAC): Calculated acute and chronic reference concentration (RfC) and Hazard Quotient (HQ) values based on toxicity and exposure scenario evaluations. *Critical Reviews in Toxicology*. 45(2): 142–171

ECHA (European Chemical Agency). Registration file for tert-butyl acetate (CAS No. 540-88-5). <https://www.echa.europa.eu/information-on-chemicals/registered-substances>

Faber W, Kirkpatrick D, Coder P, Li A, Borghoff S, Banton M. 2014. Subchronic, reproductive, and maternal toxicity studies with tertiary butyl acetate (TBAC). *Regul Toxicol Pharmacol*, 68, 332 – 342.

U.S. Environmental Protection Agency (EPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry, EPA/600/8–90/066F.