

**STATE OF MICHIGAN
Rick Snyder, Governor**



DEPARTMENT OF ENVIRONMENTAL QUALITY

**AIR QUALITY DIVISION
Constitution Hall • 525 WEST Allegan Street • P.O. Box 30260 • Lansing,
MICHIGAN 48909-7760
www.michigan.gov/air**

August 1, 2017

**Response to Public Comments for
Ethyl Tertiary Butyl Ether (CAS # 637-92-3)**

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the Initial Threshold Screening Level (ITSL) for ethyl tertiary butyl ether. As a result of that review, AQD agrees with the commenter that the ITSL basis is not the most appropriate in light of more recent toxicology studies. Therefore, the ITSL is changed from 373 ug/m³ (annual averaging time) to 9,000 ug/m³ (annual averaging time).

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), AQD solicited and received public comments on these screening levels for 60 days: February 14 through April 14th, 2017. AQD must respond to these comments within 180 days; the latest date for response is October 11th, 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)

Comments and Responses:

Comment:

AQD received comments from one party regarding the ITSL for ethyl tertiary butyl ether (ETBE). The commenter noted that the ITSL (373 ug/m³) was derived by AQD in 2001 based on a key rodent bioassay by Medinsky et al. (1999) who reported testicular effects of ETBE. (In 2016, AQD retained this ITSL value but changed the averaging time (AT) from 24 hours to annual.) However, the commenter indicated that multiple more recent toxicity bioassays did not find such testicular effects. They reported that ACGIH had reviewed this issue and agreed with them, and then developed a revised Threshold Limit Value (TLV). They also recommended that we consider a review article on this issue (de Peyster, 2010). The commenter requested that AQD consider more recent toxicity data and update the ITSL. They also provided a lengthy list of references, dated from 2003 to 2016. They did not suggest a specific key study, critical effect, or revised ITSL.

Response:

AQD agrees with the commenter that the ITSL basis is not appropriate based on the more recent toxicology literature for ETBE. The review by de Peyster (2010) concludes that more recent, well-conducted studies were unable to confirm the findings of Medinsky et al. (1999), possibly because the latter study did not preserve testes according to methods currently considered optimal, and also possibly because of differences in how the pathologists scored severity and how they staged germ cells. As indicated by the commenter, the ACGIH (2013) found that the testicular effects reported by Medinsky et al (1999) were not observed in other studies. ACGIH (2013) relaxed the TLV-TWA from 5 ppm to 25 ppm (105 mg/m³), based on protection from respiratory tract irritation as found in a human study. They noted that the key human study demonstrated a LOAEL of 50 ppm and a NOAEL of 25 ppm (105 mg/m³) in 8 healthy male volunteers exposed for 2 hours during light exercise, with increased complaints of discomfort of the throat and airways. They also noted that the same study found slight but statistically significant decreases in objective pulmonary function measures (Vital Capacity and Forced Vital Capacity) at both concentrations, however these were within the range of normal variability and thought to be of little clinical significance (ACGIH, 2013). It may be noted that a potential ITSL based on this TLV-TWA would be 1000 ug/m³ (8 hr AT), derived as (TLV ÷ 100), per Rule 232(1)(c). The AQD review also found that health-based criteria for ETBE were not currently available from CalEPA, the ATSDR, or the Texas CEQ.

AQD is tracking EPA's ongoing IRIS assessment process for ETBE. The IRIS assessment is currently at "step 4": public comment and external peer review. In June

2017, the EPA (2017) Toxicological Review was released for external peer review by the EPA's Science Advisory Board's (SAB) Chemical Assessment Advisory Committee (CAAC). EPA (2017) describes the search strategy for the assessment; the literature searches were most recently updated in November, 2015, and December, 2016, depending on the specific database. The EPA (2017) documentation is very thorough. They noted the Medinsky et al. (1999) study providing suggestive evidence of ETBE-induced testicular degeneration and effects on sperm count, sperm mobility, and sperm DNA damage. They also noted that several other well-conducted studies did not support that study's finding. "Collectively, the available evidence is considered inadequate to draw conclusions regarding the male reproductive toxicity of ETBE, and male reproductive effects are not carried forward as a hazard." (EPA, 2017). EPA (2017) developed an RfC = 9,000 ug/m³ based on a chronic male rat bioassay and a critical effect of urothelial hyperplasia. They utilized benchmark dose modeling to derive the point-of-departure, and applied a total uncertainty factor = 30 (consisting of UF = 10 for intraspecies variability, and UF = 3 for interspecies extrapolation). They stated that confidence is "high" for the principal study, the database, and the RfC.

Summary and Conclusions:

AQD agrees with the commenter that the ITSL basis is not appropriate, because the key study and critical effect have not been supported by other relevant studies and the validity of the reported finding is questionable. The ACGIH TLV provides an alternate approach to deriving an ITSL, however, the key study involved only 8 healthy male subjects, focused on irritancy effects, and was not the preferred data utilized by EPA (2017) for draft RfC derivation. Although the EPA (2017) RfC is in draft form and awaits completion of the peer review process, it appears to be appropriately and transparently derived, it has EPA's "high" confidence rating, it has a relatively small composite uncertainty factor of 30, and, it would be much more restrictive than the LOAEL for human irritancy effects utilized by ACGIH (2013) to derive the TLV. The EPA (2017) also reflects a very recent and thorough literature search. Therefore, AQD will adopt an ITSL of 9,000 ug/m³ (annual averaging time) consistent with EPA's draft RfC. If EPA finalizes a different RfC, AQD will re-evaluate the ITSL basis at that time. It is noted that EPA (2017) also reported *suggestive evidence of carcinogenic potential* for ETBE. AQD will await finalization of the IRIS process and review the outcome of this assessment.

The primary AQD reviewer for these comments was Robert Sills, AQD Toxics Unit Supervisor. The secondary (peer) reviewer was Doreen Lehner, AQD Toxicologist.

References:

ACGIH. 2013. Documentation of the TLVs and BEIs. Ethyl tertiary butyl ether.

de Peyster, A. 2010. Ethyl t-butyl ether: review of reproductive and developmental toxicity. Birth Defects Research (Part B) 89: 239-263.

EPA. 2017. Toxicological Review of Ethyl Tertiary Butyl Ether (CASRN 637-92-2). External Review Draft. EPA/635/R-17/016a. www.epa.gov/iris.