MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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October 16, 2017

To: File for Butyl Acetates, all isomers
N-Butyl Acetate (CAS No. 123-86-4)
Iso-Butyl Acetate (CAS No. 110-19-0)
Sec-Butyl Acetate (CAS No. 105-46-4)
Tert-Butyl Acetate (CAS No. 540-88-5)

From: Michael Depa, Air Quality Division, Toxics Unit

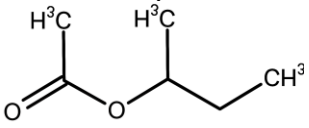
Subject: Screening Level Derivation

The initial threshold screening level (ITSL) for all isomers of butyl acetate is 2400 µg/m³ with eight-hour averaging time. Footnote: The combined ambient impact of all butyl acetate isomers must be below the ITSL.

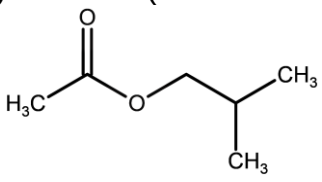
The following databases were search in order to establish a screening level:

- U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS)
- EPA Acute Exposure Guideline Levels (AEGLs)
- Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRLs)
- U.S. EPA Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV)
- California Office of Environmental Health Hazard Assessment (OEHHA)
- American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs)
- ECHA (European Chemical Agency)

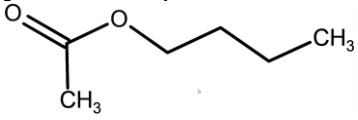
Sec-Butyl Acetate (CAS No. 105-46-4)



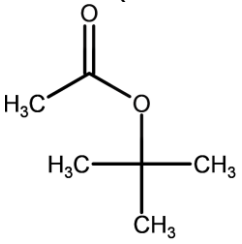
Isobutyl acetate (CAS No. 110-19-0)



n-Butyl acetate (CAS No. 123-86-4)



tert-Butyl acetate (CAS No. 540-88-5)



From ChemIDplus (2017): The molecular weight (MW) of butyl acetates is 116.16g. The vapor pressure of sec-butyl acetate is 17 mmHg. The vapor pressure of Isobutyl acetate17.8 mmHg. The vapor pressure of n-butyl acetate is 11 mmHg. The vapor pressure of tert-butyl acetate is 47 mmHg.

Bus et al. (2015) calculated acute and chronic reference concentrations (RfCs) for tert-butyl acetate (TBA) of 1.5 and 0.3 ppm, respectively. The acute and chronic 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 dose[1] (BMDL) of 150 parts per million (ppm) for neurological effects in mice. The Air Quality Division (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-TWA[2] 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 anosmics[3] suggest that n- and sec-butyl acetate have similar thresholds for nasal pungency and irritation and that for tert-butyl acetate is somewhat 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 at 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 RD50[4] 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 (Stouten and Bogaerts, 2002) and in rats for tert-butyl acetate of 15,750 ppm (Stouten and Bogaelts, 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

[1] Benchmark Dose at 95% lower confidence limit of the BMD10 (the 10% response rate).
[2] Time weighted average of 8-hrs
[3] A person who has lost or has an impairment of the sense of smell.
[4] RD50 is the concentration inducing a 50% decrease in the respiratory rate.

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:

ITSL = OEL/100

Where the OEL is the ACGIH TLV of 50 ppm

ITSL = 50 ppm/100
ITSL = 0.50 ppm

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

$\mu g/m^3$ = (ppm x MW)/24.45 x (1000 µg/mg)
$\mu g/m^3$ = (0.50 ppm x 116g)/24.45 x (1000µg/mg)
$\mu g/m^3$ = 2372

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

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

In agreement with ACGIH (2016), it was determined that all isomers of butyl acetate are sufficiently toxicologically similar 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 $\mu g/m^3$ (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 $\mu g/m^3$ with 8-hr averaging time.

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, Pourreau 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.

ChemIDplus. Toxnet database. U.S. National Library of Medicine. Accessed 10/16/17. https://chem.nlm.nih.gov/chemidplus/chemidlite.jsp

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.