MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 17, 2017

TO: File for Diethylene Glycol Monobutyl Ether Acetate (CAS No. 124-17-4)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for Diethylene Glycol Monobutyl Ether Acetate (DGBEA) (CAS No. 124-17-4) is 1 µg/m³ with annual averaging time.

Previously (see attached memo by Marco Bianchi, September 30, 1993), the ITSL for DGBEA was 25 µg/m³ with a 24-hr averaging time. The ITSL for DGBEA was based on an ITSL of 20 µg/m^3 for diethylene glycol monobutyl ether (DGBE)(CAS No. 112-34-5). DGBE's ITSL was based on a U.S. Environmental Protection Agency (EPA) Reference Concentration (RfC) that was available at that time. The ethyl acetate group (see far right of Figure 1) of DGBEA is readily cleaved under biological conditions and becomes the alcohol, DGBE (see Figure 2).

Figure 1. Diethylene Glycol Monobutyl Ether Acetate (DGBEA)

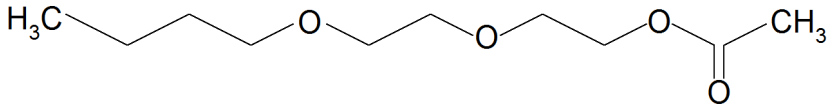
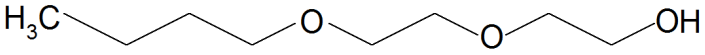


Figure 2. Diethylene Glycol Monobutyl Ether (DGBE)



Since the ITSL for DGBE changed recently (July 11, 2016), the ITSL for DGBEA needs to be updated. The basis for the ITSL for DGBE is as follows:

> EPA (2009) developed a chronic Provisional Peer-Reviewed Toxicity Value (PPRTV) for EGBE at 0.1 µg/m^3 based on a rat 5-week inhalation study (Gushow et al., 1984) with a critical effect of hepatocellular vacuolization. From an examination of the data for hepatocellular vacuolization, they determined a NOAEL at the lowest exposure level = 2 ppm (18 mg/m^3), in contrast to EPA (1992) which regarded the highest exposure level (18 ppm) to be a NOAEL, and ACGIH which noted liver effects at the highest exposure level in this key study. EPA (2009) derived a $NOAEL_{ADJ}$ HEC = 2.3 mg/m^3 and utilized benchmark dose modeling to derive $BMCL_{10}$ HEC = 0.32 mg/m^3. They applied a total UF = 3000 to derive the chronic PPRTV. The total UF of 3000 included: a subchronic-to-chronic UF_S = 10; UF_A = 3 (to account for potential pharmacodynamic differences, since dosimetric equations were used to account for pharmacokinetic differences); UF_H = 10; and, UF_D = 10 for database deficiencies due to: the database includes only one 5-week

study, and lacks chronic toxicity studies, developmental toxicity studies, and a multigeneration reproduction study.

The ITSL is being established at 1 µg/m^3 (annual AT) based on the EPA (2009) chronic PPRTV, but with removal of the UF_{DB} factor of 10 that was employed by EPA (2009). The chronic PPRTV is based on the same key study (Gushow et al, 1981, 1984) as the EPA (1992) withdrawn RfC which previously formed the basis for the ITSL. The chronic PPRTV differs from the EPA (1992) withdrawn RfC by utilizing benchmark dose modeling to derive a point-of-departure, and by the application of a larger UF_{DB} value (10 vs. 3). The UF_{DB} is based on the lack of additional studies rather than on chemical-specific data suggesting a critical effect at lower exposure levels than had been demonstrated experimentally. That is not considered a sufficient rationale for use in ITSL derivation in this particular case. Also, it is noted that EPA (2009) utilized a point-of-departure ($BMCL_{10HEC}$) = 0.32 mg/m^3) that is significantly more conservative than the $NOAEL_{HEC}$ = 2.3 mg/m^3. A total UF = 300, rather than 3000 as applied by EPA (2009), is considered appropriate in this case for ITSL development.

ITSL = $BMCL_{10HEC}$ / UF = [0.32 mg/m^3 X 1000 ug/mg] / 300 = 1.07 ug/m^3 ~ 1 ug/m^3
(from Sills, 2016)

A molecular weight adjustment was used to derive an ITSL for DGBEA (mol. weight is 204.27g), based on the ITSL for DGBE (mol. weight is 162.26g)

(ITSL for DGBE)/(Mol. Weight for DGBE) = (ITSL for DGBEA)/(Mol. Weight of DGBEA)

Solving for “ITSL for DGBEA”

ITSL for DGBEA = (ITSL for DGBE × Mol. Weight of DGBEA))/(Mol. Weight for DGBE)

Where,

ITSL for DGBE is 1 µg/m³
Mol. Weight for DGBEA is 204.27g
Mol. Weight of DBBE is 162.26g

ITSL for DGBEA = (1 µg/m³ × 204.27 g/mole)/(162.26 g/mole)

ITSL for DGBEA = 1.259 µg/m³, rounded to 1 significant figure is ~ 1 µg/m³

Rounding to 1 significant figure, the ITSL for DGBEA is 1 µg/m³. The averaging time for DGBEA is annual, because the ITSL for DGBE has annual averaging, pursuant to Rule 232(2)(b).

References

Sills, R. 2016. File for Diethylene glycol monobutyl ether (CAS # 112-34-5). Interoffice memorandum. State of Michigan. Michigan Department of Environmental Quality. Air Quality Division. Toxics Unit. Lansing, MI

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

September 30, 1993

TO: File for diethylene glycol monobutyl ether acetate (CAS No. 124-17-4)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for diethylene glycol monobutyl ether acetate (DGBA) is 25 µg/m³ based on annual averaging time.

A previous literature search conducted in February 1992, provided LD50 data on DGBA to tentatively derive an ITSL. However, further investigation of the literature revealed an EPA verifiable RfC for diethylene glycol monobutyl ether (DOBE), a metabolite of DGBA. The applicability of using the DGBE-RfC as a surrogate to obtain a DGBA ITSL is supported by a metabolic study by Deisinger et al.

According to Deisinger (Xenobiotica, 1989), DGBA is metabolized to DGBE in both in vivo and in vitro studies. Deisinger, also stated that DGBA hydrolyzes fast enough to "suggest that the biological effects of DGBA and DGBE would be indistinguishable." This study provides support for using DGBE data to derive a DGBA ITSL. The principal study used by EPA to derive a DGBE-RfC was a rat inhalation study described below.

Gushow et al., (Dow Chemical, 1981) exposed four groups of F344 rats (15/sex/group) to 0, 2, 6, or 18 ppm DGBE for 6 hours/day, 5 days/week for 5 weeks, totaling 22 exposures. After the final exposure, the rats were sacrificed and received gross histopathologic and microscopic examinations of major organs including the liver, kidneys, spleen, nasal turbinates, lungs and testes. Hematologic effects were the most sensitive endpoints of toxicity. The NOAEL was determined to be 18 ppm, with a corresponding RfC of 2E-2 mg/m³ or 20 µg/m³. The RfC for DGBE is not listed in IRIS, but was presented internally as a verified RfC on April 16, 1992 in a document presented by the Environmental Criteria and Assessment Office (ECAO). This document stated that despite major deficiencies in the DGBE data base e.g., lack of a 90-day or chronic inhalation study, ethylene glycol butyl ether (EGBE) inhalation studies in rats, mice, and dogs, and an oral two generation reproductive in mice exposed to EGBE all provide supporting evidence that hematologic effects are the most sensitive endpoints of toxicity for these two compounds. ECAO spokesperson, Jeff Gift, said DGBE is not listed in IRIS because new data for EGBE may impact this RfC. Preliminary results have indicated that human red blood cells (RBCS) are not as adversely effected as animal RfCs.

A molecular weight adjustment was used to derive an ITSL for DGBA, based on the DGBE-RfC.

$(20\ mg/m^3)/(162.26\ g/mole) \times (X\ \mu g/m^3)/(204.27\ g/mole)$

$x = 25.2\ \mu g/m^3$

ITSL for diethylene glycol monobutyl ether acetate = 25 $\mu g/m^3$ based on 24 hour averaging.

References:

1. Deisinger P.J., D. Guest. 1989. Metabolic studies with diethylene glycol monobutyl ether acetate (DGBA) in rat. Xenobiotica, Vol. 19, No. 9, 981-989.

2. Gushow, T.S., R.R. Miller, and B.L. Yano. 1981. DOWANOL DB: A 5-week repeated vapor inhalation study in rate. Dow Chemical U.S.A. report.

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