MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Diethylene glycol monobutyl ether (CAS # 112-34-5)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Diethylene glycol monobutyl ether ITSL justification

DATE: July 11, 2016

The ITSL for diethylene glycol monobutyl ether (a.k.a., DGBE; butyl carbitol; diethylene glycol butyl ether) is 1 ug/m^3 with an annual averaging time (AT). DGBE is an EPA HAP, as a member of the glycol ethers group listing.

The structure of DGBE is:

$C_4H_9OCH_2CH_2OCH_2CH_2OH$

Previously, on 10/19/92 AQD established an ITSL of 20 ug/m^3 based on the EPA RfC that was available at that time. The averaging time (AT) assigned was 24 hours, which was the standard default AT at that time under Rule 232(2)(b). An AQD re-evaluation of the toxicological literature (6/9/95) found no new key studies and the ITSL was not changed. The AQD Scientific Advisory Panel (1995) recommended that AQD retain this ITSL based on and equivalent to the EPA RfC of 20 ug/m^3 , which was once verified by EPA but at that time (1995) was under EPA workgroup review. Based on the SAP (1995) recommendation, the ITSL was retained at 20 ug/m^3 (24 hr AT).

For the current re-evaluation of the ITSL, a limited review was conducted. EPA does not have a current IRIS database file for DGBE, nor does ATSDR have a toxicological profile or Minimal Risk Levels (MRLs) for DGBE. Cal OEHHA does not have RELs for DGBE. Texas CEQ does not have benchmarks for DGBE.

EPA (IRIS database) does not currently have a chemical file or RfC for DGBE. However, EPA (1992) had previously derived an IRIS RfC of 20 ug/m^3 which has since been rescinded (a hard copy is available in the AQD Toxics Unit files). This previous RfC was based on a 5 week rat inhalation study (Gushow et al., 1981), in which 4 groups of F344 rats (15/sex/group) were exposed to 0, 2, 6, or 18 ppm DOWANOL DB (98.6% DGBE, 1.3% diethylene glycol, 0.06% diethylene glycol isobutyl ether) for 6 hrs/d, 5 ds/wk, for a total of 22 exposures. EPA (1992) noted that the 18 ppm exposure level is close to the highest sustainable vapor concentration, given DGBE's low vapor

pressure (0.06 mmHg at 25C). Test animals were evaluated for hematology and histopathology. There was a “minor, but statistically significant” increase in alkaline phosphatase activity in the 18 ppm group males over controls (EPA, 1992). Relative liver weights of the 18 ppm females were significantly increased, and a slight paleness of the liver was observed in 3/10 females of the 18 ppm group. Hepatocyte vacuolization consistent with fatty change was increased in the female rats exposed to 6 and 18 ppm. These exposure levels may be adaptive physiologic responses (EPA, 1992). However, studies at higher exposure levels and durations would be necessary to confirm that they could not develop into a more severe, adverse effect (EPA, 1992). Liver changes were not observed for male rats of any exposure group. No effects were observed in the other organs or tissues examined. The NOAEL from this study is 18 ppm (119 mg/m^3) (EPA, 1992). EPA (1992) determined the NOAEL (ADJ) = NOAEL (HEC) = 21 mg/m^3. EPA (1992) applied a total UF = 1000 in deriving the RfC = 20 ug/m^3. A LOAEL was not established in this study. The total UF of 1000 consisted of values of: 10x for sensitive human populations; 10x for subchronic to chronic extrapolation; 3x for interspecies extrapolation (with dosimetric adjustments); and, 3x for database deficiencies. EPA (1992) noted that DGBE did not affect red blood cell fragility in this key study (with 15 exposures at 18 ppm), which was, “not surprising considering red blood cell fragility was not observed in rats exposed to EGBE until after the 30th exposure at 54 ppm (Carpenter et al., 1956)”. EPA (1992) noted that database deficiencies are significant, however they regarded hematologic effects as the presumed most sensitive toxicity endpoint for DGBE, as with EGBE.

For the NATA (2005) assessment, EPA (2011) utilized an RfC of 20 ug/m^3 for “glycol ether compounds”, based on the toxicity of ethylene glycol methyl ether. This RfC is noted to be from EPA OAQPS with a target system of “reproductive”. The rationale is as follows (EPA, 2011):
“Glycol ethers. Most of the emission inventory information for the glycol ether category reports only the total mass for the entire group without distinguishing between individual glycol ether compounds. These individual compounds, however, vary substantially in toxicity. In order to avoid underestimating the health hazard associated with glycol ethers, EPA has protectively applied the RfC for ethylene glycol methyl ether (the most toxic for which an assessment exists) to the entire group.”

ACGIH (2013) has an occupational exposure level (OEL) for DGBE: the TLV-TWA is 10 ppm (67.5 mg/m^3) for inhalable fraction and vapor. This is based on a subchronic study where rats were administered water containing DGBE and at 1000 mg/kg/day showed statistically significant increases in liver and kidney weights, in hepatic cytochrome P450 and uridine glucuronyl transferase (UGT), and decreases in RBC counts, hemoglobin, and in hematocrit. The NOAEL was 250 mg/kg/day. This is equivalent to a 70 kg human inhaling 10 m^3 air per day containing 260 ppm DGBE (ACGIH, 2013). This is supported by a 90-day rat inhalation study where the NOAEL was 94 mg/m^3 (14 ppm); a 2-week inhalation study where exposure to 100 mg/m^3 (15 ppm) caused a reduction in spleen weight in male rats and histopathological changes in the lungs; and a 5-week inhalation study where liver effects were seen in female rats exposed to 117 mg/m^3 (17 ppm) DGBE for 6 hrs/day, 5 ds/week (ACGIH, 2013). The original study citations are provided

in ACGIH (2013), but it may be noted that the latter study was Gushow et al. (1981) as reviewed in European Chemicals Bureau (1999) and was regarded as providing a LOAEL; as previously discussed, EPA (1992) noted the effects observed but regarded that dose group from that study as a NOAEL. A candidate (potential) ITSL based on the ACGIH TLV-TWA would be 680 ug/m^3 (8 hr averaging time; derived as: OEL/100 = 67,500 ug/m^3 / 100 = 675 ug/m^3 ~ 680 ug/m^3).

EPA (2009) developed a chronic Provisional Peer-Reviewed Toxicity Value (PPRTV) for EGBE at 0.1 ug/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 ug/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

An annual AT is applied to this ITSL as allowed under Rule 229, which is more appropriate than a 24 hr AT in this case because the derivation of the chronic PPRTV and the ITSL account for chronic exposures.

References:

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