MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Diethylene Glycol (CAS No. 111-46-6)

FROM: Robert Sills, Toxics Unit Supervisor, Air Quality Division

SUBJECT: ITSL Basis

DATE: August 31, 2017

The Initial Threshold Screening Level (ITSL) for diethylene glycol (DEG) is 1,600 ug/m^3 with annual averaging time (AT).

The previous ITSL for DEG was 21,000 µg/m^3, with 24-hr averaging time, established on May 21, 1996 (O'Brien, 1996). The basis for that ITSL was an 18-week continuous breeding study with male and female Swiss mice receiving DEG via drinking water at 0, 0.35%, 1.75%, or 3.5% (w/v) (Williams et al., 1990). Those dose groups equated to 0, 0.61, 3.06, 6.13 g/kg bw/d. The Lowest Observed Adverse Effect Level (LOAEL) was 1.75% (3.06 g/kg/d); the critical effects were reproductive / developmental (R/D) including decreased litters per pair, decreased live pups per litter, and decreased pup weights. The No Observed Adverse Effect Level (NOAEL) was 0.35%, or 610 mg/kg/d. Using that NOAEL as the Point of Departure (POD), AQD used a total uncertainty factor (UF_T) = 100 (consisting of animal-to-human uncertainty factor (UF_A) = 10 and human intrapecies variability uncertainty factor (UF_H) = 10) and a route-to-route conversion of 70 kg bw / 20 m^3 daily inhalation, to derive the ITSL = 21,000 ug/m^3. Because the critical effects were R/D, a subchronic-to-chronic uncertainty factor (UF_S) = 1 was utilized for this 18-week study. A 24 hour averaging time was assigned for the ITSL at that time (O'Brien, 1996), and later affirmed in a review by Air Quality Division (AQD) on February 1, 2017, as appropriate given that the critical effects were R/D (Lehner, 2017). It was noted (O'Brien, 1996) that a chronic 108-week rat drinking water study (Hiasa, et al., 1990) was available for risk assessment, providing a NOAEL = 1088 mg/kg/d with a LOAEL based on a 10% decrease in survival. However, the authors did not report the incidences of non-neoplastic lesions at any site; O'Brien (1996) therefore reasoned that the apparent absence of signs of renal toxicity suggests that any toxicity at the NOAEL dose level was relatively mild. O'Brien (1996) cited evidence that nephrotoxicity was a sensitive indicator of DEG toxicity, and that while DEG exposure can have R/D effects, the maternal effects occur at lower doses. O'Brien (1996) also noted that the stringency of the R/D NOAEL = 610 mg/kg/d was much lower than the R/D LOAEL = 3060 mg/kg/d due to the dose spacing. Given these considerations, O'Brien (1996) derived a

prospective health-based limit of 21,000 ug/m^3 based on the R/D NOAEL, and another prospective health-based limit = 38,000 ug/m^3 for potential nephrotoxicity and the NOAEL from Hiasa et al. (1990) which reported decreased survival at the LOAEL and did not adequately report histopathology or other indicators of potential renal toxicity. The value of 21,000 ug/m^3 was thus relatively more stringent and was reasoned to be protective for potential nephrotoxicity as well as R/D effects, and was adopted as the ITSL.

The present assessment is largely based on a recent review of DEG toxicity data (Snellings et al., 2017) and detailed reporting of an unpublished key study by Gaunt el al. (1976) that was not available for the previous (O'Brien, 1996) AQD risk assessment. Although that key study (Gaunt et al, 1976) is still not available for AQD review, it is described in detail in Snellings et al. (2017). In a subchronic dietary study, Gaunt et al. (1976) administered DEG to groups of Wistar rats for 14 weeks at 0, 0.4%, 2%, or 4% in diet, and for 32 weeks to groups at 0, 0.085%, 0.17%, 0.4%, and 2% in diet. Critical effects were found to be renal toxicity and body weight depression, with a LOAEL = 2% in diet (1550 mg/kg bw/d) and a NOAEL = 0.4% in diet (300 mg/kg bw/d). The authors (Snellings et al., 2017) regarded kidney lesions (renal hydropic degeneration) as the critical effect for risk assessment; they derived a $BMDL_{10}$[1] [1]= 448 mg/kg. They utilized a UF_T = 1000, consisting of UF_A = 10, UF_H = 10, and UF_S = 10. They derived a Reference Dose (RfD) = 0.3 mg/kg/d from ($NOAEL/UF_T$ = 300 mg/kg/d / 1000). They chose to use as the Point of Departure (POD) the NOAEL of 300 mg/kg/d rather than the $BMDL_{10}$ of 448 mg/kg/d, "…in keeping with the conservative approach established for this assessment…" (Snellings et al., 2017). Alternatively, utilizing the $BMDL_{10}$ = 448 mg/kg/d, and a UF_T = 1000, an RfD could be derived as 0.448 mg/kg/d. It may also be noted that the determination that the 2% dietary dose level was a LOAEL may be regarded as conservative because it is supported by a prevalence of only 1/15 male rats expressing renal hydropic degeneration in the 14 week study and no such effects at that dose level in the 32 week study (although the next higher dose level, 4% in diet, resulted in enlarged kidneys and tubular necrosis). The authors (Snellings et al., 2017) also considered that a lesser UF_S = 3 may be justified, given the key study duration of up to 32 weeks and the availability of other chronic studies that did not report histologic renal effects; however, they questioned how thoroughly those other studies performed renal evaluations of the particular effects observed by Gaunt et al. (1976). The calculation of the representative dose at the NOAEL of 0.4% in feed is another decision point that the authors (Snellings et al., 2017) considered; they opted to utilize a more conservative approach of the average of the weekly dosages, rather than the average of the first 2 weeks which they reasoned may be a more realistic dosage to represent the effective treatment-related dosage for the critical renal effects.

[1] $BMDL_{10}$ = lower confidence limit of the benchmark dose for a 10% response.

The weight of evidence supports a focus of the risk assessment on the critical effect of nephrotoxicity. The ITSL is derived from the key study by Gaunt et al. (1976) and the POD = $BMDL_{10}$ = 448 mg/kg and UF_T = 1000. This is consistent with the approach of Snellings et al. (2017), except that the $BMDL_{10}$ is utilized for the POD rather than the NOAEL because it better accounts for the dose-response information. An annual averaging time will be used with this ITSL. The ITSL derivation is as follows:

$$ITSL = \frac{BMDL_{10}\ (mg/kg/d) \times 70\ kg \times 1000\ ug}{20\ m^3/d \times UF_T \times mg}$$

$$ITSL = \frac{448\ (mg/kg/d) \times 70\ kg \times 1000\ ug}{20\ m^3/d \times 1000 \times mg}$$

ITSL = 1568 ug/m^3 ~ 1600 ug/m^3 (annual averaging time)

Given this ITSL, the previous ITSL based on R/D effects with a 24-hour averaging time does not appear to be necessary as a 2nd ITSL to ensure protection from R/D effects. This position is supported by a more recent developmental effects study (Ballantyne and Snellings, 2005). They found that gavage dosing of mice and rats on gestation day (gd) 6-15 resulted in a maternal toxicity No-Observed-Effect-Level (NOEL) of 559 mg/kg/d in mice and 1118 mg/kg/d in rats, and a developmental effects NOEL of 2795 mg/kg/d with mice and 1118 mg/kg/d in rats. Although developmental toxicity (fetotoxicity) was induced in this study, there were no indications of embryotoxicity or teratogenic effects in either species (Ballantyne and Snellings, 2005).

References:

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