MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Diethylene glycol monoethyl ether (CAS# 111-90-0)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: February 2, 2017

SUBJECT: Diethylene glycol monoethyl ether (CAS# 111-90-0) ITSL change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for diethylene glycol monoethyl ether (DGEE) is 1750 µg/m^3 based on an annual averaging time. The ITSL was originally established on 2/5/1996 and was based on a Hall et al, (1966) 90-day feeding study in male and female rats. The effects of exposure to DGEE included: a decrease in mean body weight in male rats with increases in relative kidney and testes weights; renal tubular cell dilatation and hydropic degeneration with inflammatory cell infiltration in male and female rats; proteinuria; slight to moderate fatty hepatocellular changes seen in male and female rats; and testicular edema in male rats. The oral reference dose (RfD) for diethylene glycol monoethyl ether was calculated at 5 mg/kg/day. As the key study used to derive the ITSL is a 90-day feeding study, the averaging time is being changed from 24 hours to annual.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

Hall DE, Lee FS, Austin P, and Fairweather FA. 1966. Short-term feeding study with diethylene glycol monoethyl ether in rats. *Food Cosmet Toxicol* 4:263-268.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 5, 1996

TO: File for Diethylene Glycol Monoethyl Ether (DGEE) [CAS # 111-90-0]

FROM: Dan O'Brien

SUBJECT: Initial Threshold Screening Level for DGEE

The initial threshold screening level (ITSL) for diethylene glycol monoethyl ether is 1750 $\mu g/m^3$ based on a 24 hr averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967 -October 18, 1995), CESARS, Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

DGEE is a colorless hygroscopic liquid at ambient temperature (Gingell *et al.*, 1994). The chemical has been used as a solvent for dyes, nitrocellulose, and resins; in non-aqueous wood stains and lacquers; for the setting and conditioning of yarns and cloth; in textile printing; in soap production; in organic synthesis; and as a brake fluid diluent (Hawley, 1981).

Little data was found in the course of our search that documents toxic effects of DGEE in human populations, and no Occupational Exposure Limits (OELs) were found for the compound. Gingell *et al.* (1994) simply note that "Experience with human subjects has been uneventful". A review has been published assessing the safety of DGEE for use as an ingredient in cosmetics (Cosmetic, Toiletry and Fragrance Association, 1985). The effects of DGEE exposure have also been considered as part of a health effects assessment document for the glycol ethers as a class, by the U.S. Environmental Protection Agency (EPA, 1984).

Acute toxicity of the compound has been summarized as "low in oral toxicity and not appreciably irritating to the eyes or skin, but may be absorbed in toxic amounts through the skin. Its volatility is sufficiently low that acutely hazardous vapor concentrations do not occur at ordinary temperatures" (Gingell *et al.*, 1994). The RTECS (1995) and CESARS (1995) databases list oral LD_{50}s ranging from 5.4 - 8.7 g/kg in the rat, from 3.7 - 3.8 g/kg in the guinea pig, 6.6 g/kg in the mouse, and 3.6 g/kg in the rabbit. Dermal LD_{50}s in mice and rats are both reported to be 6 g/kg. The primary clinical signs reported

were somnolence, ataxia and coma in all species. No published inhalation LC_{50}s were found in the listed references.

There have been a number of subchronic and chronic oral studies investigating the effects of DGEE. The Health Effects Assessment Summary Tables [HEAST] (1994) list both chronic and subchronic Provisional Reference Doses ([RfDs]), though neither is listed in the IRIS Database, indicating that these concentrations have not received Agency-wide approval within EPA. The chronic provisional [RfD] of 2 mg/kg/day is based on the three generation oral study of Smyth *et al.* (1964), carried out in 1944, in which groups of eight weanling albino rats of each sex were exposed to concentrations of 1, 0.2, 0.04 or 0.01% of two different DGEE formulations in their drinking water for up to 718 days. The authors estimated daily dosages (*via* monitoring of water intake) to be 0.95, 0.2, 0.04 and 0.01 g/kg body weight/day. It is notable that neither of the two formulations was pure DGEE; the difference between them pertained to their respective concentrations of ethylene glycol (EG) as a contaminant. One formulation contained approximately 29.5% and the other < 0.2% ethylene glycol. A fairly wide variety of endpoints were assessed including hematology, some serum biochemistry, urinalysis and gross and histopathology. The primary lesions were in the urinary system, with tubular epithelial necrosis in the renal cortices, and calcium oxalate bladder calculi most prominent. Cloudy cellular swelling of the liver and desquamated intestinal villi were also reported. The authors propose 0.07 g/day and 1.4 g/day as permissible intakes of the two DGEE formulations for man, but the ethylene glycol contamination, coinciding with the prominence of the urinary lesions, cast doubt on the precision of these estimates, since ethylene glycol is known to be a potent nephrotoxicant. Moreover, even though the study is potentially quite useful because of its duration, the documentation available for our review consisted only of a brief summary which made it impossible to verify details of the experimental protocol, such as the accuracy of estimated doses. Also, the relatively small sample sizes (8 per sex per group) make the design less than optimal. Thus, the study, and the provisional [RfD] based on it, appear to be of limited usefulness for purposes of quantitative risk assessment of DGEE.

The subchronic provisional [RfD] (5 mg/kg/day) is based on a ninety day feeding study by Hall *et al.* (1966). As was the case in the three generation study of Smyth *et al.* (1964), the test article was contaminated with ethylene glycol, in this case, at a concentration of 0.4%; this concentration was determined by gas-liquid chromatography. Briefly, the experiment exposed groups of 12 male and 12 female specific pathogen-free (SPF) Wistar rats to concentrations of 0.0, 0.25, 1 or 5% DGEE for periods up to 90 days. Health endpoints monitored included body weights and food intake (weekly), hematology (weeks 6 and 12), urinalysis and blood urea nitrogen (BUN) (week 12) and gross and histopathology of some major organs at termination. The only fatality was a high dose group male; otherwise there were no clinical signs in any of the studied animals. Effects considered to be significantly adverse were confined to the 5% dose level and were more prominent in the males; these included decreases in mean body weight, increases in relative kidney and testes weights, renal tubular cell dilatation and

hydropic degeneration with inflammatory cell infiltration (seen in 2/12 males and 1/12 females only at the 5% dose level), proteinuria, slight to moderate fatty hepatocellular changes ("seen in most of the animals on the highest level") and testicular edema (in 5/11 males at 5%). The kidney lesions (with the exception of hydropic change) were present in all dose groups including the controls, but were "accentuated in the 5% group". The fact that BUN concentrations remained normal and not significantly different from controls even in the high dose groups suggests that the adverse renal effects were not severe. The only hematological changes were decreases in leukocyte counts after 12 weeks exposure in both sexes of the high dose group compared to the other dose levels. These decreases were not regarded as significant and are within or close to historical normal limits. These authors suggested that "there is general agreement that the adverse effects of diethylene glycol monoethyl ether are largely attributable to the presence of ethylene glycol as an impurity. The authors identified a no effect level of 1% in the diet, "corresponding to approximately 0.8 g/kg/day". EPA (1984) assumes a feed intake of 5% of body weight per day for rats to derive its no effect level of 0.5 g/kg/day, which appears to be conservative, since the food consumptions reported by Hall *et al.* are consistently greater than 5% of body weight for both sexes throughout the study, averaging 7.5% in males and 8.1% in females at the 1% dietary level.

Gaunt and colleagues (1968) justified another 90 day dietary study by questioning the accuracy of the EG concentration in the test article reported by Hall *et al.* (1966). According to Gaunt, the actual EG concentration was not the 0.4% reported, but rather 0.6%. Since the British Standards Institution at that time had set a maximum level of 0.4% for food additives and contaminants, Gaunt *et al.* re-tested DGEE containing "less than 0.4% ethylene glycol" in three species: rat, mouse and pig. Groups of 15 male and 15 female weanling SPF CFE strain rats were fed diets containing 0, 0.5 or 5% DGEE for 90 days; groups of 20 male and 20 female weanling SPF CD-1 mice were fed diets containing 0, 0.2, 0.6, 1.8 or 5.4% DGEE for 90 days; and groups of 3 male and 3 female "Large White" hogs were fed doses of 0, 167, 500 or 1500 mg/kg/day for 90 days. The top dose level in the pig portion of the study was decreased to 1000 mg/kg/day after 3 weeks "as severe toxic effects were seen". Body weight in all species, and food consumption in the rodents, was recorded weekly. Hematology was carried out on some rats after week 6, and terminally in all studied animals. Additional endpoints examined included serum urea nitrogen, alanine transaminase and aspartate transaminase, and urinalyses, as well as gross and histopathologic examinations of major organs. A wider variety of tissues were sampled in the rats than in the other two species, but the principal organs (brain, liver, kidney, heart, and spleen) were examined in all. Fatalities were recorded in 10/20 male mice in the high dose group and 2/3 female and 1/3 male hogs at the 1500 mg/kg/day level. On necropsy of these pigs, liver and kidney histopathology noted lesions similar to those described by Hall *et al.* (1966) and Smyth *et al.* (1964), *viz.*, destruction of renal tubular cells and hydropic hepatocellular degeneration, although some of the reported gross lesions (pleural and pericardial effusion, fibrinous abdominal exudates, subcutaneous edema, petechial renal hemorrhages) are consistent with

relatively common infectious disease lesions in pigs. Growth rates in rats and mice and food consumption in rats were significantly decreased at the high dose level. There was a significant decrease in erythrocyte counts in male mice and male rats at the end of the study at their respective high dose levels. There were no differences in serological indices measured in any of the species; the only urologic abnormality noted was the appearance of oxalate crystals at the high dose levels in both rats and mice. Terminal body weights were significantly decreased only in the high dose male rats. There were no statistically significant differences from control in any of the species with respect to absolute organ weights. The only significantly increased relative organ weights were 1) kidneys in male and female rats and spleen and thyroid in female rats at the 5.0% dose level; 2) kidneys only in male mice at the 1.8% dose level, brain in male mice only and liver and heart in female mice only at the 5.4% dose level, and 3) kidneys of both sexes of mice at the 5.4% dose level. There were no organ weight differences in any of the pigs at any exposure level. Histopathological changes reported included 1) hepatocellular enlargement (centrilobular and midzonal) and fatty degeneration (periportal) in all examined hogs of both sexes in the high exposure group, and in 1/2 females at the 500 mg/kg/day level; 2) centrilobular hepatocellular enlargement in 2/20 male mice at the 1.8% dose level and 8/16 males and 5/20 females at the 5.4% dose level; 3) hydropic kidney tubular cell degeneration in 7/16 male mice at the 5.4% level; 4) hydropic kidney tubular cell degeneration in 6/15 and 1/15 male and female rats (respectively) at the 5.0% dose; 5) hydropic kidney tubular cell degeneration in 2/3 male and 3/3 female hogs at the high exposure level, and in 1/2 female hogs at the 500 mg/kg/day dose level. Other lesions were randomly distributed amongst the control and exposed animals. The authors summarized the lowest levels of exposure at which various effects were observed as follows:

Table 1: Summary of effect levels in various species as reported in Gaunt et al. (1968).

Effect	**Rat (% *diet*)**	**Mouse (% *diet*)**	**Pig (*mg/kg/day*)**
Growth reduction	5.0	5.4	Not observed
Anemia	5.0	5.4	1000
↑ Relative kidney wt.	5.0	1.8	1000
Hydropic degeneration of kidneys	5.0	5.4	500
Liver changes	Not observed	1.8	500
Oxaluria	5.0	5.4	Not observed

Consequently, the authors report that "the no-effect levels established from this study are 0.5% of the diet(approximately equivalent to 250 mg/kg/day) for rats, 0.6% (approximately equivalent to 850-1000 mg/kg/day) for mice and 167 mg/kg/day for pigs". Empirically, the physiological similarity of swine to humans makes them desirable as animal models of risks to humans, helping to minimize the uncertainty associated with interspecies extrapolation. While the lowest no-effect level in this study is associated with swine, EPA (1984) notes that "Pigs may be more sensitive to diethylene glycol monoethyl ether than rats or mice, however, only 2 -3 pigs per treatment group were tested

making these data difficult to interpret". Consequently, even though data collected from the most sensitive species would ordinarily be used to derive a screening level, in this case, the potential instability of the pig data due to small sample sizes suggests that the use of the next most sensitive species, the rat, may be more appropriate.

EPA (1984) also cites a study by Butterworth et al. (1976) which exposed ferrets to DGEE orally at concentrations between 500 and 3000 mg/kg body weight/day. EPA cites the study as reporting no adverse effects, but virtually no details of the study are available; EPA also notes that the "protocol (was)incompletely reported" and that exposure "duration and method (were) not reported". Too little information is thus available for this study to utilize it for screening level development.

No reports of carcinogenic effects were located among any of the sources consulted. Gingell et al (1994) report that the compound has "little or no carcinogenic potential".

The potential for reproductive and developmental effects due to DGEE exposure has been investigated extensively (Williams *et al.*, 1990; Morrissey *et al.*, 1989; Hardin *et al.*, 1987; EPA, 1984; Nelson *et al.*, 1984; Reel and Lawton, 1984; Schuler *et al.*, 1984; Nelson *et al.*, 1982), apparently because of the demonstrated teratogenic effects of structurally-related compounds, such as ethylene glycol monoethyl ether. These investigations have included the only inhalation exposure experiments found in the literature reviewed (Nelson *et al.*, 1984; Nelson *et al.*, 1982); these noted neither maternal nor fetal toxicity on exposure to 102 ppm (560 mg/m^3) DGEE 7 hrs/day during days 7-15 of gestation (Nelson *et al.*, 1984), nor at 700 ppm (3843 mg/m^3) 6 hrs/day during days 7-15 of gestation (Nelson *et al.*, 1982) [A note from the investigators in the 1984 study stating that the low vapor pressure of DGEE prevented generation of vapor concentrations > 100 ppm suggests that the 700 ppm exposure reported was likely to an aerosol]. These results lead to the conclusion that DGEE "is likely not a teratogenic hazard after inhalation exposure" (Nelson *et al.*, 1984). Similarly, DGEE was assigned a low priority for further reproductive/developmental toxicity testing based on short-term screening (Schuler *et al.*, 1984). Results of that assay reported that DGEE "did not adversely affect any of the reproductive indices" even at exposure levels which resulted in 14% maternal mortality [5.5 g/kg/day by gavage, days 7-14 of gestation] (Hardin *et al.*, 1987). Utilizing a continuous breeding protocol and exposure *via* drinking water, oral exposures of up 2.5% (≅ 6.2 g/kg body weight/day) produced no significant adverse effects on reproduction, despite a 34% decrease in caudal epididymal sperm motility in the F_1 generation. Hardin (1983) cites a report which found DGEE exposures of 1000 ppm to cause an increased incidence of abnormal mouse sperm head morphology after five weeks exposure, and to result in "dramatically reduced" fertility in male rats exposed to that concentration, 3 - 8 weeks post-exposure. Fertility was again normal at 10 weeks post-exposure. Although these reproductive studies comprise most of the available recent literature on the toxicological effects of DGEE (and, as mentioned, the only inhalation studies), the fact that they employed only short exposure durations and failed to monitor endpoints suspected

to be sensitive indicators of DGEE toxicity (notably, nephrotoxicity) precludes their use in the derivation of an ITSL.

Selection of a key study for risk assessment of DGEE is by no means straightforward. There are no adequate inhalation studies available, and the adequate oral studies available are all at least 27 years old. In all of those, the test articles were contaminated to at least some extent with ethylene glycol, and the primary adverse effects exhibited in all of them are consistent with EG intoxication. Consequently, it is not clear what, if any, effects reported in these studies are actually due to DGEE, and the use of any of these studies may overestimate the risk of DGEE exposure. On the other hand, a screening level based on these studies also seems quite likely to be protective of possible risks to health from DGEE. Both Hall *et al.* (1966) and Gaunt *et al.* (1968) appear adequate in design to allow their use in screening level development. Both identified the same LOAEL (5% in the diet), and while the renal effects reported at that concentration were not severe, the fact that significant alterations in relative renal weights, histopathologic renal changes and abnormal urinalysis results all occurred simultaneously clearly suggests that this is an adverse effect level. The two studies identified different no effect levels in rats (1% in Hall *et al.* and 0.5% in Gaunt *et al.*), but Gaunt did not study the 1% level. Since neither of the two adequate studies is obviously of higher quality than the other, the study used by EPA to derive their provisional subchronic [RfD] (based on a subchronic Acceptable Intake (AIS)) from EPA (1984) is used to derive the ITSL.

ITSL Derivation: Applying Rules 232(1)(b) and 230(8)(b) of Article II, Chapter 1, Part 55 of Act 451,

$$\text{ITSL} = \text{Oral RfD} \times \frac{70\ \text{kg}}{20\ \text{m}^3}$$

$$= (5\ \text{mg/kg/day} \div 10) \times 3.5\ \text{kg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}}$$

$$= 1750\ \mu\text{g/m}^3$$

Since the oral RfD used here is based on a *subchronic* provisional [RfD], the provisional [RfD] is divided by a standard 10-fold uncertainty factor to account for extrapolation from a subchronic exposure to lifetime exposure. The provisional [RfD] already incorporates 10-fold uncertainty factors to account for extrapolation between species and for sensitive subgroups in the human population.

Consistent with 232(2)(b), a **24 hr averaging** time is considered appropriate.

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cc: W. Presson