MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Diethylene glycol monomethyl ether (CAS# 111-77-3)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: February 2, 2017

SUBJECT: Diethylene glycol monomethyl ether (CAS# 111-77-3) ITSL remaining at 24-hour averaging time

The initial threshold screening level (ITSL) for diethylene glycol monomethyl ether (DGME) is 190 µg/m^3 based on a 24-hour averaging time. The ITSL was originally established on 2/28/1996 and was based on a 13-week vapor inhalation study on male and female rats from Miller et al, (1985). This study found no significant effects from inhalation at the highest dose of 1,061 mg/m^3, which is considered the no observed effect level (NOEL). In a yamano et al, (1993) developmental study, DGME was found to be fetotoxic. The fetotoxic effects included; a dose-dependent significant decrease in fetal body weights; external malformations were seen that correlated to skeletal malformations. These malformations may have been related to impaired ossification which occurred in a dose-dependent manor. DGME also caused significantly elevated visceral malformations such as aortic arch defects, thymic remnants in the neck, and dilated renal pelvises. AS DGME is a developmental toxicant, it is appropriate for the ITSL to remain at a 24-hour averaging time.

References:

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

Miller RR, Eisenbrandt DL, Gushow TS, and Weiss SK. 1985. Diethylene glycol monomethyl ether 13-week vapor inhalation toxicity study in rats. *Fund Appl Toxicol* 5(6, part 1):1174-1179.

Yamano T, Noda T, Shimizu M, Morita S, and Nagahama M. 1993. Effects of diethylene glycol monomethyl ether on pregnancy and postnatal development in rats. *Arch Environ Contam Toxicol* 24(2):228-235.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 28, 1996

TO: File for Diethylene Glycol Monomethyl Ether (DGME) [CAS # 111-77-3]

FROM: Dan O'Brien

SUBJECT: Initial Threshold Screening Level for DGME

The initial threshold screening level (ITSL) for diethylene glycol monomethyl ether is 190 $\mu g/m^3$ based on a 24 hour 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 -November 6, 1995), CESARS, Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

DGME is a colorless mild-smelling liquid (Verschueren, 1983). Its uses are listed by Hawley (1981) and Merck (1983) as a high boiling point solvent, a component of brake fluids, and as a intermediate in chemical synthesis.

Gingell *et al.* (1994) characterize the compound as "low in oral toxicity, painful but not seriously injurious to the eyes, and not irritating to the skin. ...Hazardous amounts are not likely to be inhaled under ordinary conditions, but where heated material is encountered, care is warranted." On dermal exposure, it is "not especially irritating to skin, but on extensive and prolonged contact, it can be absorbed in toxic and even lethal amounts" (Opdyke, 1974). The same author notes that no sensitization reactions occurred in 25 human volunteers exposed to DGME at a 20% concentration in petrolatum. Dermal LD_{50}s are listed as ranging from 9.4 - 20 g/kg (Gingell *et al.*, 1994).

DGME is one of the glycol ethers whose toxicity has been reviewed and summarized in a health effects assessment document by EPA (EPA, 1984). This reference tabulates two longer term oral studies with DGME, those of Smyth and Carpenter (1948) and Kersten *et al.* (1939), but neither is recent, and EPA notes that the experimental protocol in the former is "incompletely reported". The two studies report no effect levels of 190 mg/kg body weight/day for 30 days, and 1000 mg/kg body weight/day for 110 days, respectively, both with exposure *via* the drinking water. Effects reported at higher doses included reduced growth at 1830 mg/kg/day by Smyth and Carpenter, and hydropic tubular degeneration of the kidney at 3000 - 5000 mg/kg/day in Kersten *et al.* EPA did not

consider either study adequate for use in calculating Acceptable Intake concentrations, which suggests limited usefulness for quantitative risk assessment. An unpublished acute inhalation study is available from the U.S. Environmental Protection Agency's Office of Toxic Substances (EPA-OTS, 1989). This study, conducted in 1977, exposed 10 male Wistar rats to a nominal DGME concentration of 200 mg/L (200 g/m^3) for 1 hour, after which they were removed from exposure and observed daily for 14 days. Body weights were recorded prior to exposure and at necropsy fourteen days post-exposure. There was no mortality nor any clinical signs during exposure or the post-exposure period, and all animals continued to gain weight over the course of the study. Necropsy findings reported were "three dark kidneys and three dark livers". The authors concluded that DGME was "Not toxic by this route of administration".

A more recent thirteen week vapor inhalation study is available (Miller *et al.*, 1985). Fischer 344 rats, 6-8 weeks of age, were randomly assigned (10 males and 10 females per group) to exposure groups of 0, 30, 100 or 216 ppm (0, 147, 491 or 1061 mg/m^3, resp.) and exposed to DGME vapor 6 hours per day, 5 days per week (excluding holidays) for thirteen weeks. The authors note that "the 216 ppm exposure level was the maximum concentration which was practically attainable". All animals were weighed and those with statistically outlying body weights were excluded from the study prior to group assignment. Endpoints monitored included observations for clinical signs (daily); body weights (at initiation of exposure, then weekly thereafter, and immediately prior to termination); hematology and urinalysis (after 12 weeks exposure); clinical chemistry (after 13 weeks exposure); gross pathology, [including absolute and relative liver, kidney, brain, heart, thymus and testes weights (all animals)] and histopathology (all control and high dose animals). Statistical analyses consisted of evaluation of homogeneity of variance (Bartlett's test), followed by analysis of variance (ANOVA)/Dunnett's multiple comparison test (where variances were homogeneous) or by non-parametric ANOVA/Wilcoxon's rank sum test with Bonferroni's correction (where variances were not homogeneous). Outlier detection for body weights was accomplished using the sequential procedure of Grubbs.

The time-weighted average (TWA) exposure concentrations (mean ± S.D.) for the 30, 100 and 216 ppm exposure groups were 30.5 ± 1.8, 101.5 ± 3.9 and 216 ± 17 ppm, respectively (149.8, 498.4 and 1060.6 mg/m^3, resp.), as measured *via* daily gas chromatography analysis of chamber samples. Nominal concentrations for the 30 and 100 ppm groups were within 10% of TWA concentrations, but the nominal concentration in the high dose group (343 ppm) was much higher than the measured concentration in that group. The authors attributed this to vapor condensation. There was no mortality, nor any exposure-related clinical signs at any dose. A single female in the 100 ppm group was injured during cage movement and was removed from the study. The only significant difference between any of the exposed animals and controls for any of the studied endpoints was significantly depressed mean body weight for the 100 ppm females after the first 4 weeks of the study. This was not seen in males at that exposure level, nor in animals at the high dose level, and was consequently not considered to be exposure-related. All gross and

histopathologic observations were considered common background changes in Fischer 344 rats of similar age. Consequently, an effect threshold for subchronic DGME inhalation exposure was not identified in this study, and by default the highest concentration studied, 1061 mg/m^3, can be considered the no observed effect level (NOEL).

Literature concerning the disposition and metabolism of DGME is limited. Hansen and Andersen (1988) carried out a computer simulation study to predict the solubility of organic solvents in various biological matrices. Their results found DGME to be soluble in lard (considered analogous to human fat in that study) at human body temperature (37°C), but not in lard at room temperature (23°C), nor in human serum. While these data could be interpreted as suggestive that DGME could accumulate in fat tissue, no studies have shown this to be the case in actual animal or human systems. The effects of DGME on hepatic metabolizing enzymes have been studied by Kawamoto and coworkers (1990). The compound has also been investigated as (and found not to be) a proximate testicular toxicant *via* gavage at a dose of 5.1 mmol/kg/d for 20 days in one metabolism study (Cheever *et al.*, 1988). Hardin *et al.* (1986) note that "the metabolism of diEGME [DGME] has not been investigated, but if it is a substrate for the alcohol dehydrogenase system, 2-methoxyethoxy acetaldehyde and 2-methoxyethoxy acetic acid are the presumptive metabolites and could act much like the corresponding EGME [ethylene glycol monoethyl ether] metabolites". Kawamoto *et al.*, while agreeing that 2-methoxyethoxy acetic acid is a likely DGME metabolite, also suspect that "the enzyme which takes part in the metabolism of diEGME is different from that of EGME although diEGME is a structural homologue of EGME". The only metabolic data located in our searches specific for diethylene glycol ethers pertained to diethylene glycol monoethyl ether [DGEE] (Johanson, 1988) and diethylene glycol monobutyl ether [DGBE] (Miller, 1987). The latter author has reviewed the metabolism and disposition of the glycol ethers as a class and notes that with the exception of the triethylene glycols, available evidence suggests that they are oxidized to alkoacetic acid metabolites. Once formed, these alkoacetic acids are either excreted unchanged in urine or conjugated with glycine and then eliminated in urine; this excretion "accounts for the majority of a given dose." Available data place the oral uptake of DGEE at about 68% in humans and the inhalation uptake of ethylene glycol monoethyl ether (EGEE) at between 53 and 64% in humans (Johanson, 1988). The same review estimates the excretion half-life of ethylene glycol ethers at 21-48 hours for humans exposed by inhalation. In summary then, there is almost no pharmacokinetic or metabolic data specific to DGME. However, assuming that DGME is likely to be metabolized in a manner similar to the ethylene glycol ethers, the data that are available suggest that 1) it would be rapidly excreted and unlikely to accumulate in the body and; 2) DGME may share a common mechanism of toxicity with other glycol ethers (being metabolized *via* the alcohol/aldehyde dehydrogenase system), although some evidence is conflicting.

The remaining DGME literature largely concerns developmental toxicity. Gingell *et al.* (1994) have noted that "DGME has been shown to be embryo toxic and teratogenic by the oral route, and fetotoxic and embryo toxic

by the dermal route in experimental animals. No adverse human experience has been reported". The potential for reproductive and developmental effects due to DGME exposure has been investigated (Hardin *et al.*, 1987; Schuler *et al.*, 1984), apparently because of the demonstrated teratogenic effects of structurally-related compounds such as EGME. There is some suggestion that a metabolite common to both DGME and EGME, methoxyacetic acid, is the proximate teratogen (Gingell *et al.*, 1994; Brown *et al.*, 1984). The reproductive toxicity of glycol ethers as a class has been reviewed by Hardin (1983). DGME has been evaluated in a short-term screening assay (Hardin *et al.*, 1987; Schuler *et al.*, 1984) in which pregnant CD-1 mice, 6 to 8 weeks old, were exposed daily during the period of organogenesis [Gestation Days (GDs) 7-14] *via* gavage to a dose of 4000 mg/kg/day. The dose was deliberately chosen at a level expected to result in 10% maternal mortality (the LD_{10} determined in a preliminary dose-finding study). At this exposure level, 5/50 dams died, and those that survived experienced significant weight loss compared to controls. Four out of five measured indices of reproductive toxicity (number of viable litters, number of liveborn pups/litter, percentage survival, and neonatal weight gain) were statistically significantly lower than controls; only birth weight was comparable. Toxicity was marked; only 5/32 (16%) litters were viable, and of those born, only 23% survived three days postpartum. These results led Schuler *et al.* to classify DGME as a "high priority" for further developmental toxicity testing, which it has since received. Two recent teratology studies were reviewed in our search (Yamano *et al.*, 1993; Hardin *et al.*, 1986), both of which utilized the oral route of exposure.

In the earlier study, Hardin and coworkers randomly assigned time-mated female Sprague-Dawley rats, weighing 207-216 g, to one of three groups (12 or 13 rats per group), where they were exposed to either 0, 720 or 2165 mg/kg/day DGME in distilled water *via* gavage on GDs 7 to 16. All animals had access to feed and water *ad libitum*. Dose levels for the teratology study were arrived at based on the results of an initial dose-finding study, also described in Hardin *et al.* (1986). Maternal body weights were recorded on GDs 6-16 and at termination (GD21); maternal food consumption was determined over GDs 7-12, 12-17 and 17-21. At termination, fetuses were weighed, examined for gross external defects, then preserved in alcohol or Bouin's fluid for subsequent internal examinations. Statistical analyses of food consumption, body weights, numbers of implantations and percentage of live implants were conducted by non-parametric m-ranking procedures, corrected for multiple comparisons. Proportions of litters affected were analyzed for inter-treatment group independence using χ^2, with pairwise comparisons between controls and individual treatment groups by one-tailed Fisher's Exact tests.

With respect to maternal effects, food consumption was reduced in the first five days of dosing in the 2165 mg/kg/day group, and gross maternal body weights were significantly reduced in that group on GD21. However, extra gestational weight gain was not significantly influenced by DGME exposure, and maternal toxicity was thus not considered significant by the authors. In contrast, both fetal weight and litter

size were significantly reduced at 2165 mg/kg/day and 2/23 litters were completely resorbed at that dose. There was no gross evidence of fetotoxicity at 720 mg/kg/day, although fetal body weight was slightly lower than the control average. The incidence of fetal malformations was clearly related to dose; the percentages of litters with at least one malformed fetus (combining gross, skeletal and visceral observations) were significantly increased in both treatment groups (23% in controls versus 52% at 720 mg/kg/day and 91% at 2165 mg/kg/day). Significant skeletal malformations included rudimentary cervical ribs and bilateral wavy ribs (each significantly elevated at the high, but not the low, dose), abnormal vertebrae and unilateral wavy ribs (χ^2 suggested a significant exposure effect), and ossification deficiencies (cranial, axial and appendicular; significantly increased at both 720 and 2165 mg/kg/day). In addition, visceral malformations (primarily of the cardiovascular (CV) system) were highly ($p < 0.001$) significantly increased in the high dose group. Prominent CV abnormalities included aortic arch malformations and cardiac septal defects. The incidence of dilated renal pelvises was also significantly increased over controls at both exposure levels. Notably, in the discussion, Hardin *et al.* mention that "this marked similarity of EGME and diEGME fetal effects suggests a mechanistic commonality". Elsewhere, Hardin (1989) states that "mechanistic studies indicate that metabolism by the alcohol dehydrogenase system is a necessary prelude to both testicular and teratogenic effects" of the glycol ethers. Miller (1987) has noted that like the ethylene glycol ethers, the diethylene glycol ethers as a class are "also metabolized *via* the alcohol/aldehyde dehydrogenase pathway if disposition studies with DGBE acetate are representative of the group". So, while Hardin *et al.* (1986) also note that "the potency of diEGME on a molar basis is considerably less than that of EGME", the potential for additivity of effects from simultaneous exposure to DGME and other glycol ethers is plausible, and should be borne in mind.

The more recent study (Yamano *et al.* 1993) referenced the work of Hardin and coworkers, and expanded their experimental design to include lower exposure levels and assessment of postnatal development and non-pregnant animals. Three month old Wistar rats, both pregnant and non-pregnant, were exposed by gavage to DGME in water in a dose-finding study, the details of which are related in the same publication. As a result, dose levels of 0, 200, 600 and 1800 mg/kg/day were chosen for the larger scale teratology and postnatal study. Pregnant rats were sorted into groups of 22 rats each and exposed to DGME in water by daily gavage on GDs 7 to 17 at the above dose levels. Body weights, food consumption, general condition and behavior were monitored daily throughout gestation. On GD20, 14 dams from each group were sacrificed, and the number and position of live, dead, and resorbed fetuses, and *corpora lutea* recorded. Live fetuses were weighed, sexed, and examined for external malformations. Half of these were fixed in Bouin's solution, and the other half in alcohol, for subsequent visceral and skeletal evaluations, respectively. Also, maternal thymic weights were recorded; this organ's weight was considered by the authors the most sensitive maternal organ weight monitored in the dose-finding study. The remaining dams' (eight per group) litters were allowed to go to term, and at delivery, evaluated for size, number liveborn, sex, and external

anomalies. On day 4 postpartum (PPD4), litters were culled to leave eight pups per litter and approximately equal numbers of males and females. These remaining pups were then nursed by their own dams for 21 days more; during this time pups were examined for growth and external differentiation, and body weights recorded on PPD7, 14 and 21. On PPD21, pups were sacrificed and radiographed for skeletal observations; dams were also killed and the number of implants from the previous pregnancy noted. Statistical analyses consisted of multiple comparisons *via* Dunnett's or Scheffé's methods "in a parametric or non-parametric manner".

All dams survived throughout the trial and gave birth to live young, although maternal body weight gain, food consumption, and thymic weight were significantly decreased at 1800 mg/kg/day. Fetal body weights were significantly decreased compared to controls in the 600 and 1800 mg/kg/day groups, and the decrease was clearly dose-related. External malformations were limited to the high dose group, where their incidence was significantly elevated. Visceral malformations were significantly increased in the 1800 mg/kg/day group as well, consisting mainly, as in Hardin *et al.* (1986), of aortic arch defects. The proportion of fetuses with visceral variations was increased at all exposure levels (and significantly so in the top two dose levels) versus controls (3.5% in the controls versus 5%, 35% and 100% in the 200, 600 and 1800 mg/kg/day groups, respectively). The variation most sensitive to exposure was the occurrence of thymic remnants in the neck; these were significantly increased in the top two dose groups. The occurrence of dilated renal pelvises was significantly increased at the high dose level as well, again replicating the findings of Hardin and coworkers. Unlike that study though, the incidence of rib malformations was not increased, and skeletal malformations in general were found only in those fetuses with external malformations (which were limited to the 1800 mg/kg/day group). The degree of ossification, however, was significantly impaired at the 600 and 1800 mg/kg/day levels, the vertebral ossification centers being most sensitive. As for postnatal endpoints, gestation was two days longer and the number of pups delivered significantly decreased compared to controls at the 1800 mg/kg/day level. The viability of the neonates was markedly affected by exposure; the number of live pups on PPD4 ÷ the number of live born was 92/100, 95/101, 58/93 and 2/37 in the 0, 200, 600 and 1800 mg/kg/day groups, respectively. Body weight gain in the neonates up to PPD21 was unaffected in the 200 mg/kg/day group and slightly decreased in the 600 mg/kg/day group. The one high dose group pup still alive at PPD21 weighed only about half that of the control mean. Postnatal development (ear detachment, eyelid opening, tooth eruption, etc.), however, was about the same in all groups, and there were no significant exposure-related skeletal observations at PPD21. Under the conditions of this study, the no observed adverse effects level (NOAEL) for fetal effects was 200 mg/kg/day. The authors also note in their discussion that the thymus gland was the most sensitive organ to DGME exposure, and consequently, "the immunotoxicity of DGME and the other glycol ethers deserves further examination".

In choosing a key study for derivation of a screening level for DGME, the well conducted and documented subchronic inhalation study of Miller

et al. (1985) is a justifiable choice, due to its duration, and continuity and route of exposure. However, when consideration is given to the developmental toxicity data, it appears that fetotoxicity may be a more sensitive endpoint on which to base risk assessment than are effects in non-pregnant adults (although the dissimilarity of the study protocols leads to some uncertainty). The NOAELs for adult toxicity in non-pregnant and pregnant rats from the dose-finding portion of the Yamano *et al.* study were 2000 and 1000 mg/kg/day, respectively, while the NOAEL for developmental toxicity was 200 mg/kg/day in the teratology portion of the same study, ≥ 5 times lower. While adult NOAELs might be lower in animals exposed for longer periods than the 11 days used by Yamano *et al.*, good longer term oral studies to support or refute such speculation are unfortunately not available. Both portions of the study were conducted with essentially the same experimental protocol, so these NOAELs may reasonably be compared directly. Pharmacokinetic studies addressing potential differences between the oral and inhalation routes of exposure were not found in our searches, so it is not possible to assess the magnitude of any such differences at this time[1]. Consistent with EPA's guidelines for Developmental Toxicity Risk Assessment (EPA, 1991, p. 63817), there is sufficient experimental animal evidence/limited human data for the developmental toxicity of DGME, based on positive evidence in two rat studies (Yamano *et al.*, 1993; Hardin *et al.*, 1986), and a mouse study (Hardin *et al.*, 1987; Schuler *et al.*, 1984). This categorization constitutes convincing evidence that a potential hazard for developmental toxicity in humans exists. It seems useful here to present calculations of what prospective health-based limits (PH-BLs) would be, based both on adult inhalation toxicity and on oral fetotoxicity, in order to compare the two prospective limits and discern if one limit is likely to be protective of both adult and fetal effects. Such a limit would then be a reasonable choice for the ITSL for DGME.

ITSL Derivation: If one considers fetotoxicity to be the critical health effect with respect to human risk assessment, the NOAEL for fetotoxicity (200 mg/kg/day) from Yamano *et al.* (1993) appears most suitable to drive derivation of a prospective health-based limit for developmental effects ($PH\text{-}BL_{[DEV]}$). It is necessary to understand that quantitative assessment of risks from exposure to developmental toxicants differs in a key respect from the assessment of risks due to chronic intoxications. EPA (1991; pp. 63816, 63819) states that

> For developmental toxic effects, a primary assumption is that a single exposure at a critical time in development may

---

[1] Although the differing exposure regimens preclude strict route-to-route comparison (since the gavage study rats were exposed for 11 consecutive days, compared to the thirteen week intermittent exposure in the inhalation study), conversion of the NOAELs of Yamano *et al.* to a mg/m^3 basis (assuming an inhalation rate of 0.969 $m^3/kg/day$, the Air Quality Division (MDNR, 1991) default for an adult female Wistar rat) allows a *crude* comparison to the NOAEL of Miller *et al* (1061 mg/m^3). The non-pregnant adult NOAEL converts to 2064 mg/m^3, the pregnant adult NOAEL to 1032 mg/m^3, and the NOAEL for fetotoxicity to 206 mg/m^3.

> produce an adverse developmental effect, *i.e.*, repeated exposure is not a necessary prerequisite for developmental toxicity to be manifested....Therefore, it is assumed that, in most cases, a single exposure at any of several developmental stages may be sufficient to produce an adverse developmental effect. Most of the data available for risk assessment involve exposures over several days of development. Thus, human exposure estimates...are usually not adjusted for duration or pattern of exposure. For example, it would be inappropriate in developmental toxicity risk assessments to use time-weighted averages or adjustment of exposure over a different time frame than that actually encountered [such as the adjustment of a 6-hour inhalation exposure to account for a 24-hour exposure scenario], unless pharmacokinetic data were available to indicate an accumulation with continuous exposure.

As noted earlier, in the case of DGME, no specific pharmacokinetic data are available at this time to indicate accumulation with continuous exposure. Moreover, if diethylene glycol ethers behave similarly pharmacokinetically to ethylene glycol ethers, there is evidence to suggest that they would not accumulate in man (Johanson, 1988). So, consistent with EPA's recommendations, the daily dose NOAEL is not adjusted here for exposure duration.

The EPA Guidelines for Developmental Toxicity Risk Assessment (EPA, 1991; p. 63817) suggest calculation of an oral Reference Dose for Developmental Toxicity ($RfD_{[DT]}$) as the basis of a quantitative risk assessment approach for developmental effects, after the method of Barnes and Dourson (1988). An $RfD_{[DT]}$ is defined as "an estimate of a daily exposure to the human population that is assumed to be without appreciable risk of deleterious developmental effects". The [DT] subscript serves to distinguish this number from the more common RfD, which is calculated to reflect a chronic, rather than short-term, exposure situation. From Barnes and Dourson (1988), we have

$$\text{Oral RfD} = \frac{\text{NOAEL (mg/kg/day)}}{[\text{UF} \times \text{MF}]}$$

EPA (1991; pp. 63817-63818) suggests that "uncertainty factors (UFs) for developmental and maternal toxicity applied to the NOAEL generally include a 10-fold factor for interspecies variation and a 10-fold factor for intraspecies variation. In general, an uncertainty factor is not applied to account for duration of exposure". Consistent with these guidelines,

$$RfD_{[DT]} = \frac{200 \text{ mg/kg/day}}{[(10 \times 10) \times 1]}$$

$$= 2 \text{ mg/kg/day}$$

Here, the modifying factor (MF) takes on the default value of 1.

Applying Rule 232(1)(b) of Article II, Chapter 1, Part 55 of Act 451, to derive a $PH\text{-}BL_{[DEV]}$ by means that would be consistent with those for an RfD-based ITSL,

$$(\text{PH-BL}_{[\text{DEV}]}) = \text{Oral RfD} \times \frac{70\ \text{kg}}{20\ \text{m}^3}$$

$$= (2\ \text{mg/kg/day}) \times 3.5\ \text{kg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}}$$

$$= 7000\ \mu\text{g/m}^3$$

and consistent with 232(2)(b), a 24 hour averaging time would be considered appropriate for this $\text{PH-BL}_{[\text{DEV}]}$.

If one considers adult inhalation toxicity to be the critical health effect with respect to human risk assessment, the NOEL from Miller *et al.*, (1985) [1061 mg/m^3] appears most suitable to drive derivation of a prospective health-based limit for adult toxicity ($\text{PH-BL}_{[\text{AT}]}$). At 13 weeks duration, Miller's study satisfies the minimum criteria necessary for derivation of an inhalation RfC (EPA, 1990)[2], which will be used here to derive a $\text{PH-BL}_{[\text{AT}]}$ by means that would be consistent with those for an RfC-based ITSL.

Human Equivalent Concentration (HEC) Calculation:

a) The key study NOEL (based on the mean of the actual hourly chamber concentrations) of 216 ppm, is converted to mg/m^3, using the chemical-specific conversion factor (1 ppm = 4.91 mg/m^3) of Gingell *et al.* (1994). Thus, the NOEL = 1061 mg/m^3.

b) Dose adjustment is necessary to account for discontinuous exposure regimens used in the key study. Per EPA (1990), section 4.1.1.2, p. 4-13:

$$\text{NOEL}_{[\text{ADJ}]}\ (\text{mg/m}^3) = 1061\ \text{mg/m}^3 \times \frac{6\ \text{hrs/day}}{24\ \text{hrs/day}} \times \frac{5\ \text{days/week}}{7\ \text{days/week}}$$

$$= 1061\ \text{mg/m}^3 \times 0.25 \times 0.71 = 189\ \text{mg/m}^3$$

c) The next step in the calculation of a $\text{PH-BL}_{[\text{AT}]}$ involves choice of an appropriate dosimetry equation [EPA, (1990), section 4.1.1.2, Fig. 4-1]. Exposures in Miller *et al.* were to DGME vapors. With respect to target effects, there were none under the conditions of Miller's inhalation exposures. It is not possible with the data available to tell whether inhalation exposures at higher concentrations may have elicited effects. However, if one

---

[2] The 1990 Interim RfC Methods are used in this case, even though the more recent Final Methods (EPA, 1994) are currently available. Methodological inconsistencies have become apparent during application of the 1994 guidelines to inhalation risk assessments. These inconsistencies have been communicated to EPA, which has promised review of the issues involved and guidance once the review is complete. When these issues have been resolved satisfactorily, the RfC and ITSL calculated here may be re-evaluated in light of that guidance.

assumes that given sufficient exposure the effects on inhalation are likely to be similar to those seen following ingestion, then the target effects of DGME exposure can be assumed to be extrarespiratory (fetotoxicity, and decreases in maternal body weights, food consumption and thymus weights). It is also assumed here that the concentration of the inhaled compound within the animals in Miller *et al.* achieved periodicity with respect to time for the majority of the experiment duration[3]. The NOAEL Human Equivalent Concentration ($NOAEL_{[HEC]}$) is derived using the model for extrarespiratory effects (per EPA (1990), section 4.1.1.2), subject to the assumptions above. The default equation (4-10) is used here. So,

$$NOEL_{[HEC]}\ (mg/m^3) = NOEL_{[ADJ]}\ (mg/m^3) \times \frac{\lambda_{animal}}{\lambda_{human}}$$

$$= 189\ mg/m^3 \times 1$$

$$= 189\ mg/m^3$$

where $\lambda_{animal}/\lambda_{human}$ is the ratio of blood-to-air partition coefficients for rats to humans. Although two articles referenced by EPA (Jepson et al., 1994; Gargas et al., 1989) were reviewed in an effort to define partition coefficients for DGME, these parameters were not found in these references nor in any of our other searches. Consequently, the ratio assumes the EPA default value of 1 in the absence of data to the contrary.

$PH\text{-}BL_{[AT]}$ calculation:

Consistent with EPA (1990), section 4.1.1, pp. 4-4 to 4-5:

$$PH\text{-}BL_{[AT]} = NOEL_{[HEC]} / (UF \times MF)$$

$$= \frac{189\ mg/m^3}{([10 \times 10 \times 10] \times 1)} = 0.19\ mg/m^3$$

where the total UF of 300 is composed of 3 10-fold uncertainty factors to account for 1) extrapolation from healthy humans to sensitive humans; 2) extrapolation from the subchronic NOEL of Miller *et al.* (1989) to a chronic NOAEL; and 3) interspecies extrapolation from rats to humans. The use of the more traditional 10-fold interspecies factor is considered appropriate here, since there was no dosimetric adjustment of the $NOEL_{[HEC]}$ (since $\lambda_{animal}/\lambda_{human}$ was unknown in this case). The MF assumes the default value of 1.

---

[3] Unfortunately, neither arterial concentrations of the test agent over time in the exposed animals, nor tissue/air partition coefficients are available to assess the appropriateness of this assumption. Consequently, the assumption is considered reasonable here in the absence of data to the contrary.

Applying Rule 232(1)(a) of Article II, Chapter 1, Part 55 of Act 451, to derive a PH-$BL_{[AT]}$ by means that would be consistent with those for an RfC-based ITSL,

$$PH\text{-}BL_{[AT]} = 0.19\ mg/m^3 \times \frac{1000\ \mu g}{1\ mg} = 190\ \mu g/m^3$$

and consistent with 232(2)(b), a 24 hour averaging time would be considered appropriate for this PH-$BL_{[AT]}$.

Derivation of the ITSL:

In comparing the calculations above, it can be seen that the PH-$BL_{[AT]}$ < the PH-$BL_{[DEV]}$. Adoption of the PH-$BL_{[AT]}$ as the ITSL for DGME should protect against fetotoxic effects of DGME as well as effects on adult animals, while adoption of the PH-$BL_{[DEV]}$ as the ITSL would theoretically protect against only developmental effects. Given this, it seems reasonable and prudent to adopt the PH-$BL_{[AT]}$ calculated here as the ITSL. Consequently, the **ITSL** for DGME = **190 $\mu g/m^3$**, and a **24 hour averaging** time applies.

As a final point, it should be mentioned that as pharmacokinetic data regarding DGME become available, attention should be paid to 1) the specific mechanism of DGME fetotoxicity, with an eye toward assessing the risk of additive effects from simultaneous exposure to other glycol ethers; and 2) the absorption, bioavailability and tissue accumulation of DGME, as they might potentially effect adjustment of the daily dose developmental NOAEL for duration of exposure. Significant new data in either sphere may necessitate re-examination of the ITSL.

REFERENCES

Barnes, D.G. and Dourson, M. (1988). Reference dose (RfD): Description and use in health risk assessments. *Reg Toxicol Pharmacol* **8**:471-486.

Brown, N.A., Holt, D. and Webb, M. (1984). The teratogenicity of methoxyacetic acid in the rat. *Toxicol Lett* **22**:93-100.

Cheever, K.L., Richards, D.E., Weigel, W.W., Lal, J.B., Dinsmore, A.M. and Bernard, F. (1988). Metabolism of bis(2-methoxyethyl)ether in the adult male rat: Evaluation of the principal metabolite as a testicular toxicant. *Toxicol Appl Pharmacol* **94**(1):150-159.

EPA (1994). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC, Document # EPA/600/8-90/066F (10/94).

EPA (1991). Guidelines for Developmental Toxicity Risk Assessment. *Fed Register* **56**(234):63798-63826 (12/5/91).

EPA (1990). Interim Methods for Development of Inhalation Reference Concentrations (Review Draft). EPA Document No. 600/8-90/066A. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, N.C.

EPA (1984). Health effects assessment for glycol ethers. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, Washington, DC. EPA Doc # EPA/540/1-86/052, NTIS PB86-134632, (9/84), 78 pp.

EPA-OTS (1989). Inhalation toxicity of Poly-Solv DM in rats with cover letter dated 3/30/89. MB Research Labs, Inc., for Olin Corporation. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC, Doc. #86-890000166.

Gargas, M.L., Burgess, R.J., Voisard, D.E., Cason, G.H. and Andersen, M. (1989). Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. *Toxicol Appl Pharmacol* **98**:87-99.

Gingell, R., Boatman, R.J., Bus, J.S., Cawley, T.J., Knaak, J.B., Krasavage, W.J., Skoulis, N.P., Stack, C.R. and Tyler, T.R. (1994). 19. Diethylene Glycol Monomethyl Ether. *In*: Patty's Industrial Hygiene and Toxicology, 4th Ed. (Clayton, G.D and Clayton F.E., Eds.), Volume II, Part D, Chapter Thirty One: Glycol Ethers and other Selected Glycol Derivatives. John Wiley and Sons, Inc., New York, pp. 2831-2834.

Hansen, C.M. and Andersen, B.H. (1988). The affinities of organic solvents in biological systems. *Am Ind Hyg Assoc J* **49**(6):301-308.

Hardin, B.D. (1989). Glycol ether hazards to reproductive health: An update. *In*: Hazard Assessment and Control Technology in Semiconductor Manufacturing, pp. 91-93. Industrial Hygiene Science Series. Lewis Publishers, Chelsea, MI, 1989, 322 pp.

Hardin, B.D. (1983). Reproductive toxicity of the glycol ethers. *Toxicology* **27**:91-102.

Hardin, B.D., Goad, P.T., and Burg, J.R., (1986). Developmental toxicity of diethylene glycol monomethyl ether (diEGME). *Fund Appl Toxicol* **6**(3):430-439.

Hardin, B.D., Schuler, R.L., Burg, J.R., Booth, G.M., Hazelden, K.P., MacKenzie, K.M., Piccirillo, V.J. and Smith, K.N. (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratogen Carcinogen Mutagen* **7**:29-48.

Hawley, G.G. (1981). The Condensed Chemical Dictionary. Tenth Ed. Van Nostrand Reinhold Company, New York, p. 347.

Jepson, G.W., Hoover, D.K., Black, R.K., McCafferty, J.D., Mahle, D.A. and Gearhart, J.M. (1994). A partition coefficient determination method for nonvolatile chemicals in biological tissues. *Fund Appl Toxicol* **22**:519-524.

Johanson, G. (1988). Aspects of biological monitoring of exposure to glycol ethers. *Toxicol Lett* **43**(1-3):5-21.

Kawamoto, T., Matsuno, K., Kayla, F., Hirai, M., Arashidani, K., Yoshikawa, M. and Kodama, Y. (1990). Effect of ethylene glycol monomethyl ether and diethylene glycol monomethyl ether on hepatic metabolizing enzymes. *Toxicology* **62**(3):265-274.

Kersten, H.D., Mulinos, M.G. and Pomerantz, L. (1939). Pathologic effects of certain glycols and related compounds. *Arch Pathol* **27**:447-465 [cited in EPA, 1984].

Michigan Department of Natural Resources (MDNR), 1991. Default animal data for risk assessment (as based on U.S. EPA, 1988, Recommendations for and documentation of biological values for use in risk assessment, EPA Document # PB 88-179874).

Merck (1983). The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, (Windholz, M., Ed.) Tenth Ed. Merck and Company, Rahway, N.J., p. 866.

Miller, R.R. (1987). Metabolism and disposition of glycol ethers. *Drug Metab Rev* **18**(1):1-22.

Miller, R.R., Eisenbrandt, D.L., Gushow, T.S. and Weiss, S.K. (1985). Diethylene glycol monomethyl ether 13-week vapor inhalation toxicity study in rats. *Fund Appl Toxicol* **5**(6, part 1):1174-1179.

Opdyke, D.L.J. (1974). Monographs on fragrance raw materials. Diethylene glycol monomethyl ether. *Food Cosmet Toxicol* **12**(4):519.

RTECS (1995). 2-(2-methoxyethoxy)ethanol (111-77-3). *In*: Registry of Toxic Effects and Chemical Substances Database. National Institute for Occupational Safety and Health, Public Health Service, Centers for Disease Control, U.S. Department of Health and Human Services, and Canadian Centre for Occupational Safety and Health.

Schuler, R.L., Hardin, B.D., Niemeier, R.W., Booth, G., Hazelden, K., Piccirillo, V. and Smith, K. (1984). Results of testing fifteen glycol ethers in a short-term *in vivo* reproductive toxicity assay. *Environ Health Persp* **57**:141-146.

Smyth, H.F., Jr. and Carpenter, C.P. (1948). Further experience with the range finding test in the industrial toxicology laboratory. *J Ind Hyg Toxicol* **30**:63-68 [cited in EPA, 1984].

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd Ed. Van Nostrand Reinhold Company, New York, p. 526.

Yamano, T., Noda, T., Shimizu, M., Morita, S. and Nagahama, M. (1993). Effects of diethylene glycol monomethyl ether on pregnancy and postnatal development in rats. *Arch Environ Contam Toxicol* **24**(2):228-235.

DO:ma

cc: W. Presson