MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Dipropylene glycol methyl ether acetate (CAS # 88917-22-0)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Dipropylene glycol methyl ether acetate ITSL change in the averaging time from 24 hrs to annual

DATE: January 17, 2017

The current ITSL for Dipropylene glycol methyl ether acetate is 930 ug/m^3, with annual averaging time (AT).

Previously, the ITSL was established on April 12, 2006 at 930 ug/m^3 with 24 hr averaging time (see attached justification memo). The averaging time (AT) assigned to the ITSL previously was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The ITSL derivation applied a total uncertainty factor (UF) = 300, which consisted of a UF = 3 for interspecies extrapolation, UF = 10 for intraspecies variability, and UF = 10 for subchronic-to-chronic conversion. The current file review concludes that the AT for the ITSL may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b).

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Dipropylene Glycol Methyl Ether (DPGME), [CAS# 34590-94-8]
File for Dipropylene Glycol Methyl Ether Acetate [CAS# 88917-22-0]

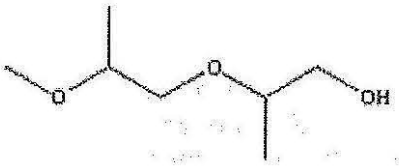
FROM: Margaret M Sadoff, Air Quality Division, Toxics Unit

DATE: April 12, 2006

SUBJECT: Update of Screening Level

The initial threshold screening level for DPGME is 720 ug/m3, 24-hour average.
The initial threshold screening level for DPGMEA is 930 ug/m2, 24-hour average.

A search of the literature and the following databases was performed for health effects information regarding DPGME and its acetate: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Integrated Risk Information System (IRIS), Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, and CalEPA's Toxicity Values Database.



DPGME is a clear, colorless liquid with an ether-like odor. The reported odor threshold is 35 ppm (210 mg/m3) *(CCOHS ChemInfo, 2005)*. Its miscibility with water, as well as a number of organic liquids (e.g., benzene), make this chemical a widely used industrial solvent. It is also used as an intermediate in chemical synthesis. DPGME is used as a solvent in hard-surface household cleaners, water-based paints and coatings, synthetic resins and hydraulic brake fluid among other products. Due to its high solubility and low vapor pressure, DPGME is expected to partition to the aquatic phase of the environment. Half-life in air is estimated at approximately 3.4 hours. *(Patty's Toxicology 5th ed, Toxline's HSDB).*

The previous ITSL is based on the ACGIH TLV-TWA of 100ppm (606 mg/m3) and was set in 1992 according to Rule 232(1)(c) at 6,060 ug/m3 with an 8-hour averaging time. At that time, no literature search was conducted to determine whether there were adequate data from which to derive an ITSL based on EPA RfC methodology. The occupational level is set to protect against eye, nose and throat irritation and, therefore, is also protective against CNS effects such as narcosis that can occur at higher exposure concentrations. ACGIH also has a TLV-STEL value of 150ppm (909 mg/m3) with a skin notation based on reported transient weight loss and

narcosis in rabbits following dermal application of DPGME. OSHA/NIOSH standards are equivalent *(ACGIH. 2001. Documentation of the threshold limit values and biological exposure indices. 7th ed.)*

A 13-week inhalation study in rats and rabbits exists and is of sufficient quality to derive an RfC. An RfC- based ITSL supersedes an OEL-based ITSL according to the hierarchy established in Rule 232.

General Toxicity Information

DPGME has been reported to be disagreeable to humans at concentrations around 300 ppm. A probable minimum concentration of 35 ppm (212 mg/m3) has been reported to cause minor nasal irritation. This minimal concentration also coincides with the low end of the odor threshold range. The level at which exposure to DPGME is considered to be immediately dangerous to life and health is 600 ppm. Inhalation toxicity tests have been conducted in a number of animal species. Most report little to no toxicity up to about 800 ppm. *(Patty's Toxicology 5th edition, HSDB Online).*

In general, propylene glycols are much less toxic than the ethylene glycols. As a group, the ethylene glycols have been found to be reproductive toxicants, mainly by the oral route. Teratogenicity is not expected for the propylene glycol ethers due to different metabolic pathways (see Reproductive/Developmental Effects section for more detail).

Subchronic Animal Inhalation Studies

Rats, rabbits guinea pigs, and monkeys exposed 7 hrs/day, 5 days/wk over a 6 to 8 month period in a "saturated" atmosphere of 300-400 ppm DPGME exhibited slight increases in liver weights but this was considered an adaptive rather than a toxic response. Rats experienced transient narcosis during the first few weeks of the study *(Patty's Toxicology, 5th ed.)*

A single 7-hour exposure to 500 ppm caused temporary mild narcosis in male rats (Rowe et al., 1954 as cited in Landry & Yano, 1984).

A 13-week inhalation study in rats and rabbits reported a NOAEL of 200ppm (1,212 mg/m3). Fischer 344 rats (10/sex/group) and New Zealand White rabbits (7/sex/group) were exposed to 0, 15, 50, or 200 ppm (0, 91, 303, or 1212 mg/m3) of DPGME for 6 hrs/day, 5 days/wk for 13 weeks. The highest concentration used in this study is approximately 40% of a saturated atmosphere of DPGME. According to most reports, 300 to 400 ppm is the maximum vapor concentration practically attainable at room temperature and pressure. Health parameters examined included general observations, body weights, clinical chemistry and hematology, urinalyses (for rats only), organ weights, and histopathology. There were no adverse effects attributed to DPGME at any exposure concentration in either male or female rats or rabbits. Therefore the NOAEL for this study is 1,212 mg/m3. *(Landry TD & Yano, BL (1984). Fundamental & Applied Toxicology 4: 612-617).*

In a 2-week inhalation study conducted by Landry & Yano prior to the 13-week study, statistically significant increases in absolute liver weights were noted in both male rats and female mice exposed to 330 ppm for 6 hrs/day for 9 days. Although these changes were statistically significantly different from controls, they were not believed to be indicative of adverse health effect since there were no reported gross or histopathologic changes indicating

hepatotoxicity. Given the data from both the 2-week and 13-week studies, the true NOAEL is likely between 200 and 330 ppm. *(Landry TD & Yano, BL (1984). Fundamental & Applied Toxicology 4: 612-617).*

Human Inhalation Exposure

Human subjects exposed to DPGME vapor concentrations between 50 and 2,000 ppm experienced eye, nose and throat irritation before the onset of CNS impairment, which occurred at 1,000 ppm in one of two subjects. *(NIOSH Toxicologic Review of Selected Chemicals).*

Dermal Absorption/Skin Sensitization

One study reported a significant number of deaths in rabbits who were subjected to 65 repeated dermal applications of DPGME at concentrations of 3 ml/kg or higher during a 90-day period. Another reported that topical administration of 10 mg/kg DPGME 5 times per week for 13 weeks in rabbits caused death in 6 of 7 animals. Patch tests on the skin of 250 human subjects produced neither irritation nor sensitization. No human study has been conducted to determine adverse effects from repeated or prolonged dermal exposure, but based on the dermal toxicity results in rabbits, the occupational standards have retained the skin notation. *(NIOSH Toxicologic Review of Selected Chemicals).*

Reproductive/Developmental Effects

For the propylene glycol group as a whole, there are no reports of teratogenicity. One study did report that the monomethyl ether acetate form, PGMEAc, was teratogenic in rabbits (Hellwig et al. 1994 as cited in Chemically Induced Birth Defects). However, several other repro/developmental studies in rats and rabbits have shown that PGME and its acetate are not teratogenic up to the highest reported NOAEL of 4160 ppm (EPA, IRIS). Reproductive effects of the propylene monomethyl glycol ethers is not expected since the metabolism of PGME is substantially different than that of EGME. Propylene series glycol ethers are predominantly secondary alcohols and are biotransformed via microsomal enzymes to metabolites that are relatively innocuous. Propylene glycols follow a metabolic pathway that does not include oxidation to 2-methoxyacetic acid, the primary metabolite of ethylene glycols ethers responsible for their teratogenic activity. *(Schardein, JL. (1993). Chapter 28 Industrial Solvents in "Chemically Induced Birth Defects).*

Pregnant New Zealand White rabbits and Fischer 344 rats were exposed via inhalation to 0, 50, 150, or 300 ppm commercial-grade DPGME for 6 hrs/day on days 7 through 19 (rabbits) or days 6 through 15 (rats) of gestation. Females were evaluated for general toxicity and various reproductive parameters. Fetuses were removed on gestation day 28 (rabbits) or day 21 (rats), weighed and examined for external, visceral, and skeletal abnormalities. No significant treatment related effects were noted for any maternal, embryonic or fetal parameters at any exposure level. The reproductive/developmental NOAEL for rabbits and rats from this study is 300 ppm *(Breslin et al. 1990, 1996).* Therefore, an ITSL based on a NOAEL of 200 ppm is assumed to be protective against any potential reproductive or developmental effects from DPGME exposure in humans.

Mutagenicity/Genotoxicity Testing

There has been limited testing for mutagenicity/genotoxicity. Several TSCATs submissions by DOW indicate that DPGME is not mutagenic in bacteria or yeast.

Carcinogenicity

There are no studies reporting the carcinogenicity of DPGME in humans or animals.

Derivation of Initial Threshold Screening Level (ITSL)

Derivation of an RfC-based ITSL using EPA methodology requires determining whether a vapor phase chemical is a Category 1, 2, or 3 gas. This decision is based on a chemical's solubility and reactivity in the upper airway as well as potential for extrarespiratory effects. On the basis of solubility, DPGME could be considered a Category 1 or 2 gas due to its miscibility with water. Since Landry & Yano report no adverse effects in any health parameter, determination of a critical endpoint becomes problematic. DPGME is a known irritant, but no irritancy effects were noted in the key study. A 2-week study by Landry & Yano reported increased liver weights in male rats and female mice exposed to 330 ppm DPGME, indicating a potential for extra-respiratory effect at higher exposure concentrations. Landry & Yano also cite the 1954 study by Rowe et al. in which temporary mild narcosis was observed in male rats exposed to 500 ppm for 7 hours. Since there is some ambiguity with regard to choice of a critical endpoint for RfC derivation, we refer to EPA's IRIS review for propylene glycol monomethyl ether (PGME). The RfC for PGME was based on yet another inhalation study by Landry et al. (1983) in rats and rabbits with a reported NOAEL of 1,000 ppm. In that review, the critical effect was mild reversible sedation. Given the weight-of-evidence, it seems appropriate to derive an RfC based on potential for extrarespiratory effects. The resulting ITSLs are well below the noted probable minimum concentration for irritation (35 ppm or 210 mg/m3).

The minimum database requirement for deriving an RfC is a 13-week (90 day) study. According to Rule 232(1)(a), an ITSL is derived from the NOAEL of 1,212 mg/m3 reported by Landry & Yano as follows:

NOAEL [ADJ] = 1,212 mg/m3 x (5/7 days/wk) x (6/24 hours/day) = 216 mg/m3

NOAEL [HEC] = NOAEL [ADJ] x DAF (dosimetric adjustment factor)

DAF for extrarespiratory effects = $\frac{(Hb/g)A}{(Hb/g)H}$ where...

(Hb/g)A/(Hb/g)H = the ratio of the blood:gas (air) partition coefficient for the chemical in laboratory animals and humans. Where these values are unknown, the ratio defaults to 1.0.

NOAEL [HEC] = 216 mg/m3 x 1.0 = 216 mg/m3

216 mg/m3 / 300 Total UF = 0.721 mg/m3 = **720 ug/m3, 24-hour averaging time.**

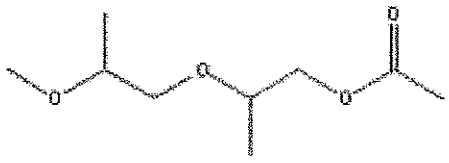
300 Total UF includes:

1) Factor of 3 for interspecies variability (extrapolating from animal to human)
   Note: Use of default DAF addresses the toxicokinetic aspects of the animal:human UF which reduces the UF for the remaining toxicodynamic factor to $10^{0.5}$or 3.
2) Factor of 10 for interindividual variability extrapolating from human to sensitive human)
3) Factor of 10 for subchronic to chronic exposure duration.

The acetate form, DPGMEA, would be expected to readily hydrolyze to DPGME and acetic acid by carboxyl esterase activity in nasal mucosal tissue, liver, kidneys, and blood. Therefore, the ITSL for DPGME can also be used for DPGMEA, after adjusting for differences in molecular weight between the two compounds. Converting 200 ppm to mg/m3 gives a NOAEL for DPGMEA of 1554 mg/m3. Taking that NOAEL through the above calculation gives an RfC-based ITSL of **930 ug/m3, 24-hour averaging time**.

***The ITSL for DPGME is 720 ug/m3, with a 24-hour averaging time.**
***The ITSL for DPGMEA is 930 ug/m3, with a 24-hour averaging time.**

***ITSLs have been rounded to 2 significant figures.**



DPGMEA

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2. EPA IRIS, RfC Documentation for Propylene Glycol Monomethyl Ether (PGME), CAS #107-98-2, last updated 1991.
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4. Breslin et all 1990. Developmental toxicity of inhaled DPGME in rabbits and rats. Toxicologist, 10(1): 39.
5. Breslin et al. 1996. Evaluation of the developmental toxicity of inhaled DPGME in rabbits and rats. Occup Hyg 2: 161-170
6. Schardein JL. 1993. in Chemically Induced Birth Defects 2nd ed., Chapter 28 Industrial Solvents, 909-940.