MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Ethylene glycol dimethyl ether (CAS# 110-71-4)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 31, 2017

SUBJECT: Ethylene glycol dimethyl ether (CAS# 110-71-4) remaining at 24-hour averaging time

The initial threshold screening level (ITSL) for ethylene glycol dimethyl ether will remain at 24 µg/m^3 based on a 24-hour averaging time. The ITSL was originally established on 7/15/2005 and is based on reproductive study on rats by Leonhardt et al, (1991). The critical effects included an increase in stillborn deaths, delayed parturition, and maternal toxicity. As ethylene glycol dimethyl ether is a reproductive and 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.

Leonhardt DE, Coleman LW, and Bradshaw WS. 1991. Perinatal Toxicity of Ethylene Glycol Dimethyl Ether in the Rat. *Reproductive Toxicology*. 5:157-162.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 15, 2005

TO: File for ethylene glycol dimethyl ether (CAS #110-71-4)

FROM: Anne Kim, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for ethylene glycol dimethyl ether is 24 ug/m^3 based on a 24-hour averaging time.

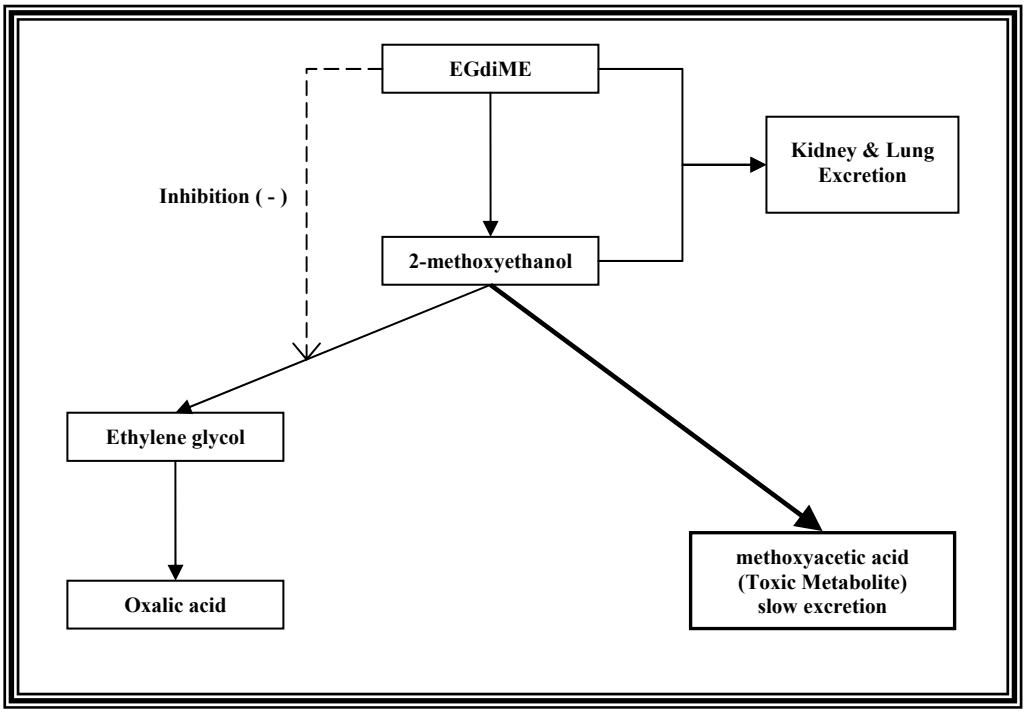
The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2005), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. There are no occupational exposure limits for ethylene glycol dimethyl ether. The EPA has not established a reference concentration or reference dose for ethylene glycol dimethyl ether. There is no information on ethylene glycol dimethyl ether from ATSDR. The molecular weight of ethylene glycol dimethyl ether is 90.12 g. The molecular structure of ethylene glycol dimethyl ether is shown in Figure 1.

Figure 1

Background

Ethylene glycol dimethyl ether (EGdiME) is a colorless, volatile liquid with a vapor pressure of 50 mmHg at 20ºC that is mainly used as a solvent in the resin, lacquer, and dye industries. The toxic metabolite of EGdiME, methoxyacetic acid, is produced from the intermediate metabolite, 2-methoxyethanol (Figure 2.). The relatively rapid pathway for methoxyacetic acid production is further advanced with greater accumulation of EGdiME, which inhibits other less toxic metabolic pathways. The toxicity of methoxyacetic acid has been studied extensively. This compound is a known reproductive toxicant that causes testicular atrophy and is also a known developmental toxicant that results in fetotoxicity. Thus, studies have been conducted to determine if similar reproductive and developmental adverse effects from EGdiME exposure occur. (ChemFinder.com, 2005; EPA, 2001)

Figure 2. Metabolism of EGdiME



Reproductive Studies

A study conducted by Nagano et al. (1984) reported the effects of EGdiME exposure in mice. Male JCL-ICR mice, six weeks old, were given 0, 250, 500, or 1000 mg/kg EGdiME by oral gavage 5 days per week for 5 weeks. Concurrent controls were fed water by gavage. At the end of the study, the animals were necropsied and analyzed for reproductive toxic effects. Neither data nor statistical analyses were reported, but qualitative results were available. The investigators observed a dose-related decrease in testicular weight as well as a smaller decrease in the weight of seminal vesicles and coagulating gland combined in the high dose group. EGdiME exposure also showed a significant decrease in white blood cell count.

Developmental Studies

Female CRJ:CD-1 pregnant mice were given 0, 250, 350, or 490 mg/kg by oral gavage from gestational day 7 to gestational day 10 (gd 7 to gd 10) (Uemura, 1980). On gd 18, dams were sacrificed to collect the litters which were examined in terms of litter survival, weight values, and gross abnormalities. Maternal toxicity was also assessed. Results indicated there were no significant maternal toxicity effects from EGdiME exposure. There were, however, significant developmental effects seen in the fetal measurements. At all doses, fetal weight in treated groups were significantly lower than control, and dose dependent skeletal malformations were observed starting from the 250 mg/kg dose level; skeletal malformations included cervical vertebrae malformations, rib fusions, and retarded skeletal ossification. Mice treated with 350 mg/kg EGdiME or higher exhibited exencephaly, caudal defects, and umbilical hernia.

Pregnant CD-1 mice were exposed to 0 mg/kg or 361 mg/kg EGdiME on gd 11 (Hardin et al., 1987). On gd 18, fetuses were removed, weighed, and examined for malformations. Maternal toxicity was not seen, but treatment-related effects were seen in fetuses. Fetal weights in the treated group were significantly lower than control fetal weights, and developmental toxicity was seen in the occurrence of paw malformations in the 361 mg/kg dose group.

An oral gavage study exposed 50 pregnant CD-1 female mice to doses of either 0 mg/kg or 2000 mg/kg EGdiME for 7 days from gd 7 to gd 14 (Schuler et al., 1984). The toxic endpoints studied included litter survival and litter weight. Mice exposed to 2000 mg/kg EGdiME produced no viable pups.

In another study, Sprague-Dawley pregnant rats were exposed to 0, 30, 60, 120, 250, 500, or 1000 mg/kg EGdiME by oral gavage from gd 8 to gd 18 (Leonhardt, 1991). Under a randomized process, the rats were either sacrificed on gd 19 or allowed to give birth at term. Rats treated with 120 mg/kg to 1000 mg/kg EGdiME produced no viable litters and showed signs of maternal toxicity. Decreases in maternal weight gain were observed at doses of 120 mg/kg and above compared to that of control. Deaths occurred at the 1000 mg/kg exposure level. Maternal toxicity was also seen at the lowest exposure dose of 30 mg/kg; delayed parturition was evidenced by the significant increase in gestation length compared to control ($P \leq 0.01$). Toxic effects observed in fetuses included increased number of resorptions (prenatal), increased number of stillborns (postnatal), and increased incidence of edema and skeletal malformation. The most sensitive toxic effect was the greater incidence of stillborn fetuses in the 30 mg/kg dosage group ($P \leq 0.05$).

Other Studies

Trained female rats were tested for avoidance and escape responses in a behavioral experiment conducted by Goldberg et al. (1964). For 2 weeks, the animals were exposed in inhalation chambers to concentrations of 1000, 2000, 4000, or 8000 ppm 4 hours/day, 5 days/week. The 8000 ppm dose group showed a significant decrease in the avoidance response with no change in the escape response. After five days of exposure, half of the rats exposed to this high dose died. Severe hemorrhage of the lung and gastrointestinal tract were observed at autopsy. At the 4000 ppm dose level, rats did not begin to die until after the tenth exposure day. Autopsy revealed the same toxic effects noted in the 8000 ppm dose group. The lower dose groups, 1000 ppm and 2000 ppm, had no deaths, but significant decreases in the avoidance response only were observed. Following the 2 weeks of exposure, rats in the 1000 ppm and 2000 ppm dose groups fully recovered within a few days from their impaired behavioral responses.

Rats were exposed to 20 mg/L (20,000 mg/m^3) or 63 mg/L (63,000 mg/m^3) EGdiME vapor for 6 hours (Kodak, 1979). The sex and number of rats were not specified. After a 14-day post-exposure observation period, a LC50 of >20 mg/L was established based on 100% mortality at the 63 mg/L dose level. All rats in this high dose group died within 72 hours after exposure. In the 20 mg/L dose group, irritation and ataxia was observed but no deaths occurred.

Groups of 4 female rats were exposed to 500, 1000, 2000, or 4000 mg/kg EGdiME by oral gavage (DuPont, 1992). Duration of exposure was not indicated. An LD50 of >4000 mg/kg was established based on raw mortality values. No rat died in the 500 mg/kg and 2000 mg/kg dose groups. One rat each died in the 1000 mg/kg and 4000 mg/kg groups during the 14-day post-observation period.

Table 1. Summary of studies.

	Species	Route	Exposure Dosage	Sensitive Effects	Effect Level	Study
Reproductive	Mice	Oral gavage	0, 250, 500, 1000 mg/kg	Decrease in testicular weight and WBC count	Not specified by authors	Nagano et al., 1984
Developmental	Mice	Oral gavage	0, 250, 350, 490 mg/kg	Skeletal malformations, decrease in fetal weight	LOAEL = 250 mg/kg	Uemura, 1980
	Mice	Oral gavage	0, 361 mg/kg	Decrease in fetal weight; paw malformations	LOAEL = 361 mg/kg	Hardin et al., 1987
	Mice	Oral gavage	0, 2000 mg/kg	No viable pups	LOAEL = 2000 mg/kg	Schuler et al., 1984
	Rats	Oral gavage	0, 30, 60, 120, 250, 500, 1000 mg/kg	Increase in stillborn deaths; delayed parturition; maternal toxicity	LOAEL = 30 mg/kg	Leonhardt, 1991
Behavioral	Rats	Inhalation	1000, 2000, 4000, 8000 ppm	Decrease in avoidance response	LOAEL = 1000 ppm	Goldberg et al, 1964
Lethal	Rats	Inhalation	20, 63 mg/L	Death	LC50>20 mg/L (20,000 mg/m^3)	Kodak, 1979
	Rats	Oral gavage	500, 1000, 2000, 4000 mg/kg	Death	LD50>4000 mg/kg	DuPont, 1992

Discussion

The lowest dose at which toxic effects were seen – in both adult and fetal animals – was 30 mg/kg from the Leonhardt (1991) study. 30 mg/kg EGdiME caused an increase in gestational length in dams ($P \leq 0.01$) and an increase in the incidence of stillborn fetuses ($P \leq 0.05$). An increase in gestational length is considered an indicator of maternal toxicity because it may be a sign of a chemical-induced effect on the parturition process (EPA, 1991). Thus, the lowest-observed-adverse-effect level (LOAEL) of 30 mg/kg would be used to derive an initial threshold screening level (ITSL) for developmental effects.

The primary metabolite of EGdiME is 2-methoxyethanol, also known as ethylene glycol monomethyl ether (EGME). The breakdown of this primary metabolite leads to the formation of the toxic compound, methoxyacetic acid (Figure 2). EGME has been extensively tested in reproductive and developmental studies. These well-conducted studies measuring EGME toxicity at low ranges of dosages allowed NOAELs to be established for a number of endpoints. Comparing the levels at which EGME caused reproductive or developmental toxicity, reproductive effects were a more sensitive endpoint. EPA has already performed a thorough analysis of all these different studies and developed an inhalation reference concentration (RfC) of 20 ug/m^3 for EGME (Figure 3). The RfC basis comes from a study finding reproductive effects in rabbits and rats, with the former being the most sensitive.

Figure 3. Calculation of EPA's RfC – NOAEL = 93 mg/m^3

Note: NOAEL = 93 mg/m^3 (30 ppm)
NOAEL(HEC) = 17 mg/m^3

Derivations of RfC (EPA)

$$RfC = \frac{NOAEL}{UF}$$

>where: NOAEL = no-observed-adverse-effect level
UF = uncertainty factors
UFs that apply: 1) variation in sensitivity among members of the human population = 10
2) extrapolation from animal data to humans and database uncertainty = 10
3) extrapolation from subchronic study to chronic study = 10

$$RfC = \frac{17\ mg/m^3}{10 \times 10 \times 10}$$

$$RfC = 0.017\ mg/m^3$$

$$RfC = 0.02\ mg/m^3$$

$$RfC = 20\ ug/m^3$$

EGdiME has not been studied as thoroughly as EGME. Developmental studies have been conducted on EGdiME, however, none involved testing at low enough doses to determine levels at which no adverse effects occur. It is important to note that, in addition to less extensive developmental data, there is a lack of adequate reproductive toxicity tests for EGdiME.

A developmental study conducted by Hardin et al. (1987) demonstrated support for the occurrence of EGdiME and EGME toxicity by the same toxic metabolite, methoxyacetic acid. (EGdiME effects only from this study were discussed previously.) Hardin and colleagues measured the developmental toxicity of both EGdiME and EGME, which, again, is the primary metabolite of EGdiME. Pregnant CD-1 female mice were given a single dose of 4 mmol/kg of each compound on gestational day 11. The corresponding doses equivalent to 4 mmol/kg were 361 mg/kg and 304 mg/kg for EGdiME and EGME, respectively. Seven days after exposure, on gd 18, the fetuses were collected and examined. Paw malformations were observed in both the EGdiME-treated and EGME-treated litters, where the percent of litters affected were 86.7% and 87.5%, respectively. The percentages of fetuses affected within the litters were 33.8% for EGdiME-treated and 68.5% for EGME-treated groups. The percent of litters affected is of greater relevance than the percent of fetuses as indicated by EPA in a 1991 guidance document:

> Because the maternal animal, and not the conceptus, is the individual treated during gestation, data generally are calculated as incidence per litter or as number and percent of litters with particular endpoints…. Since the litter is generally considered the experimental unit in most developmental toxicity studies, and fetuses or pups within litters do not respond independently, the statistical analyses are generally designed to analyze the relevant data based on incidence per litter or on the number of litters with a particular endpoint.
> (EPA, 1991)

EGME reproductive effects were determined to be the most sensitive, and since the toxicity of both EGME and EGdiME are due to the same toxic metabolite, methoxyacetic acid, there is much support for assuming that the critical effect for EGdiME would be the same – reproductive.

The calculation of a potential initial threshold screening level (ITSL) based on the Leonhardt's LOAEL of 30 mg/kg results in a value of 105 ug/m^3 (Figure 4).

Figure 4. Calculation of potential ITSL using Leonhardt et al.'s study – LOAEL = 30 mg/kg

Note: LOAEL = 30 mg/kg

Derivations of a Potential Screening Level

ITSL = RfD_{DT} x (70 kg)/(20 m^3)

>where: RfD_{DT} = developmental reference dose

$$RfD_{DT} = \frac{\text{LOAEL (mg/kg/day)}}{\text{UF}}$$

>where: LOAEL = lowest-observed-adverse-effect level

UF = uncertainty factors

UFs that apply: 1) variation in sensitivity among members of the human population = 10

2) extrapolation from animal data to humans = 10

3) extrapolation from LOAEL to NOAEL = 10

$$RfD_{DT} = \frac{\text{30 mg/kg/day}}{\text{10 x 10 x 10}}$$

RfD_{DT} = 0.03 mg/kg/day

ITSL = 0.03 mg/kg x (70 kg)/(20 m^3)

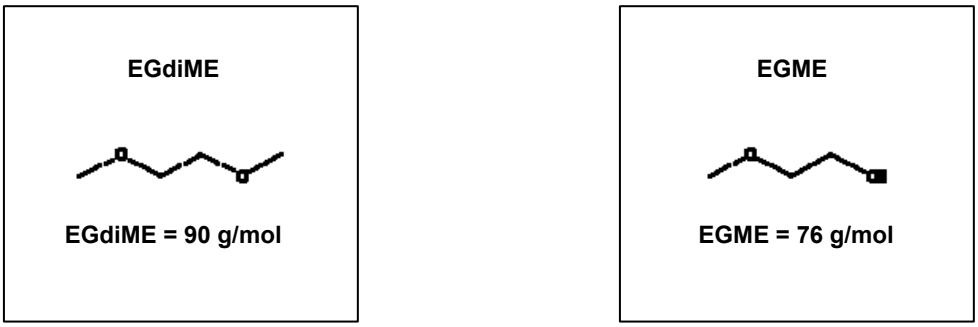
ITSL = 0.105 mg/m^3

ITSL = 105 ug/m^3 - based on a 24-hour averaging time

This may not be adequately protective, as this ITSL is derived from a developmental study, and as emphasized before, there is not enough data on reproductive effects from EGdiME exposure.

Therefore, under the well-supported assumption that EGME and EGdiME produce similar toxicity by the same toxic metabolite, the RfC already established by EPA for EGME will be adjusted accordingly to determine the RfC for EGdiME.

Figure 5. EGdiME and EGME structures and molecular weights



Note: RfC for EGME = 20 ug/m^3:

Derivations of Screening Level

The molar masses used to adjust the EGME RfC proportionally to EGdiME are shown in Figure 5.

$$\frac{20\ \text{ug EGME}}{m^3} \times \frac{1\text{x}10^{-6}\ \text{g EGME}}{1\ \text{ug EGME}} \times \frac{1\ \text{mol EGME}}{76\ \text{g EGME}} \times \frac{1\ \text{mol EGdiME}}{1\ \text{mol EGME}} \times \frac{90\ \text{g EGdiME}}{1\ \text{mol EGdiME}} \times \frac{1\ \text{ug EGdiME}}{1\text{x}10^{-6}\ \text{g EGdiME}}$$

$$= \frac{23.7\ \text{ug EGdiME}}{m^3} = 24\ \text{ug/m}^3 \text{ - based on a 24-hour averaging time}$$

The resulting ITSL is slightly higher than the ITSL for its primary metabolite, EGME, which is 20 ug/m^3 (24-hour averaging time), due to the adjustment for molecular weight. If the toxicity of both EGdiME and 2-methoxyethanol are due to the common toxic metabolite, methoxyacetic acid, the ITSL for EGdiME may be conservative since the derivation assumes complete conversion to the toxic metabolite without mitigation due to the formation of the intermediate, 2-methoxyethanol.

Therefore, the ITSL for ethylene glycol dimethyl ether (110-71-4) is 24 ug/m^3 based on a 24-hour averaging time.

References

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