MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: Dipropylene Glycol Dimethyl Ether file (CAS #111109-77-4)

FROM: Keisha Williams, Air Quality Division (AQD)

SUBJECT: Screening level update for dipropylene glycol dimethyl ether

DATE: February 1, 2016

The initial threshold screening level (ITSL) for dipropylene glycol dimethyl ether is 59 µg/m^3 (annual averaging time) based on United States Environmental Protection Agency's (USEPA's) guidance for derivation of reference concentrations (RfCs) (USEPA, 1994). The ITSL value was established on April 3, 1998 (MDEQ, 1998; see attached).

The ITSL was originally established with an averaging time set at 24 hours, the default averaging time, per AQD Rule 232 (2). It is being changed at this time to an annual averaging time, as allowed per AQD Rule 229 (2), because the derivation accounted for chronic exposure.

References

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

U.S. Environmental Protection Agency. 1994. Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Washington D.C. EPAI600/8-90/066F.

MDEQ. 1998. *Memo from Marco Bianchi to File for Dipropylene Glycol Dimethyl Ether (CAS #111109-77-4).* April 3, 1998. Michigan Department of Environmental Quality, Air Quality Division.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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April 3, 1998

TO: File for Dipropylene Glycol Dimethyl Ether (CAS #111109-77-4)

FROM: Marco Bianchi, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level (ITSL)

The ITSL for dipropylene glycol dimethyl ether (DPGDME) is 59 µg/m^3 based on an 24 hr. averaging time.

The following references or databases were searched to identify data to determine the ITSL:
IRIS, HEAST, NTP Management Status Report, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC, NIOSH Pocket Guide, and ACGIH Guide.

A detailed database search was conducted for DPGDME, but information was limited to a series of non-published Dow Chemical rat inhalation studies. These studies included LC50, 9-day, teratology and 13 week vapor inhalation investigations.

In the LC_{50} study, groups of 5 male and 5 female rats were whole-body exposed for 4 hours to 792 PPM DPGDME vapors, the maximum attainable concentration. All animals survived the exposure and 2-week observation period. Body weights initially decreased but recovered by day eight. There were no exposure-related observations at the gross necropsy conducted 14 days post exposure. Based on this study, the LC_{50} for DPGDME in rats is greater than 792 PPM (5227 mg/m^3).

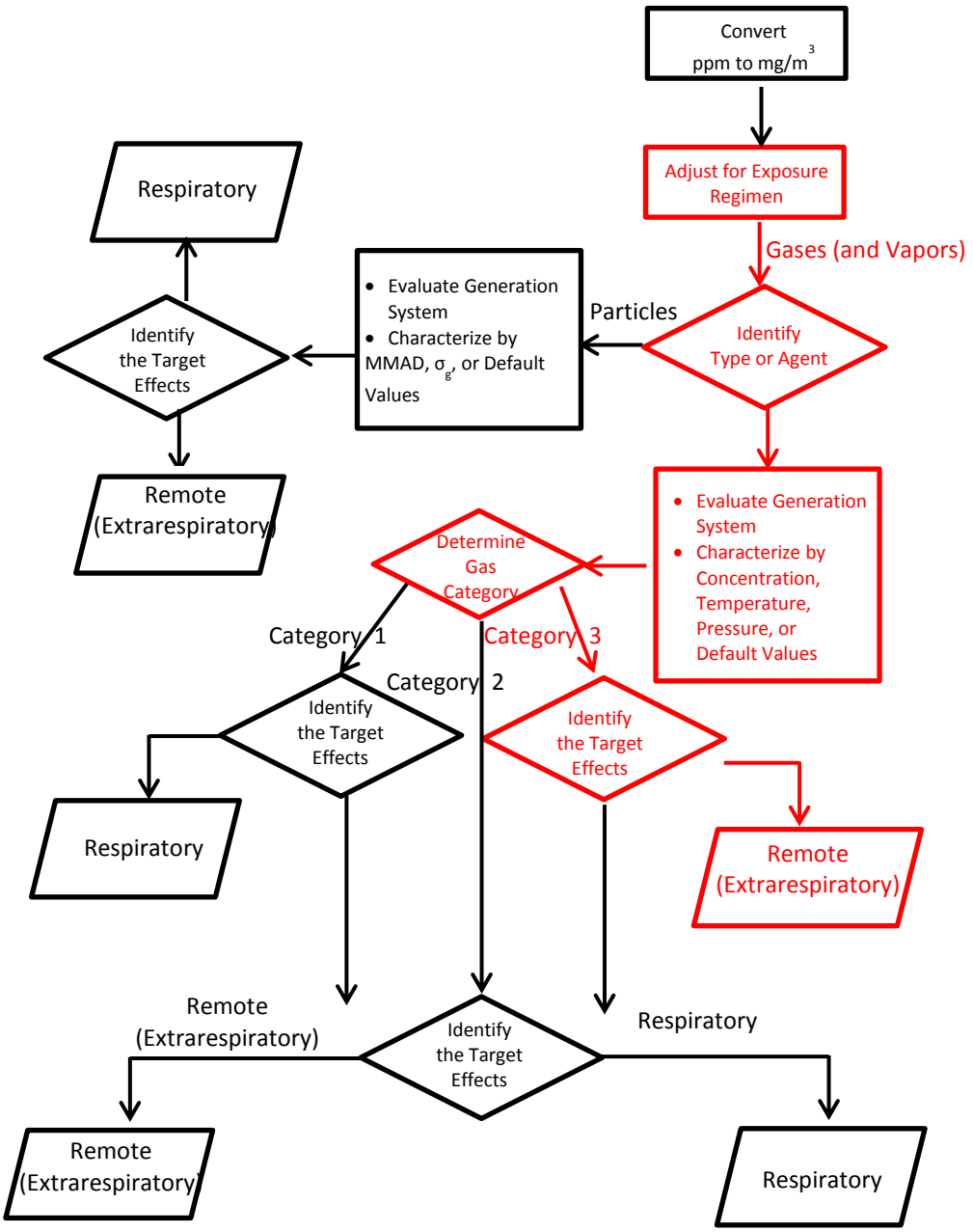
A total of 5 rats/sex/dose were whole-body exposed in a 9-day inhalation study to 0, 70, 225 or 700 PPM DPGDME vapors 6 hrs/day, 5 days/wk. A kidney lesion, protein droplet nephropathy was observed in males only, at 225 or 700 PPM. Liver weights were increased in both sexes at the same dose levels, The no-observed-effect level (NOEL) for male and female rats in this study was 70 PPM (462 mg/m^3).

In the inhalation teratology study, rats were exposed to 0, 70, 225, and 700 PPM DPGDME vapors on days 6-15 of gestation. Results indicate maternal toxicity (slight decrease in food consumption and body weight, with an increase in absolute/relative liver weight) and suggest fetotoxicity at 700 PPM (a statistically identified increase in the incidence of delayed ossification of skull bones and cervical centra). No maternal toxicity or fetal effects were seen at either of the lower exposure levels. The NOEL for fetotoxicity was 225 PPM (1485 mg/m^3) and the NOEL for teratogenicity and embryolethality is 700 PPM (4620 mg/ m^3)

Male and female rats were exposed to 0, 50, 100, and 700-PPM DPGDME vapors 6 hrs/day, 5 days/week for 13 weeks in a subchronic inhalation study. High dose animals were uncoordinated on day 1 of the study but subsequently appeared normal. There was a very slight, statistically identified decrease in red cell parameters in males necropsied immediately after 13 weeks of exposure to 700 PPM. Very slight

decreases were also seen in male rats allowed to recover for 4 weeks. There were no effects on urinalysis, clinical chemistry, or gross pathology. Effects were seen in kidneys of males exposed to 100 or 700 PPM. The kidney lesion was characterized as a male rat specific, alpha 2u-globulin mediated protein droplet neuropathy. Increased liver weights and centrilobular hepatic hypertrophy were observed in both sexes at 100 and 700 PPM. Morphologic changes in the liver appear to be reversible, although the liver weights remained elevated after 4 weeks of recovery. The adrenal gland of male rats exposed to 700 PPM had slightly increased cortical vacuolation that partially reversed in the 4-week recovery period. The NOEL for male and female rats was 50 PPM (330 mg/ m^3).

The series of studies that Dow used to comprehensively evaluate DPGDME justifies deriving an RfC for this compound using the U.S. Environmental Protection Agency's (EPA's) Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry guidance document (EPA/600/8-90/066F; October 1994). According to this guidance document, a key element in extrapolating laboratory animal inhalation data to humans is estimating the human equivalent concentration (HEC) or "dose" (i.e., agent mass deposited per unit surface area or tissue volume) delivered to specific target sites in the respiratory tract or made available to uptake and metabolic processes for systemic distribution. This is considered with mechanistic determinants of toxicant-target interactions and tissue responses. The HEC is the basis for comparison and choice of the critical effect and study. Calculating a HEC is a stepwise procedure. First adjustment factors are used to determine the observed exposure effect levels (i.e., NOAELs) in laboratory animals to estimate a concentration that would be an equivalent exposure to humans (i.e., NOAEL[HEC]). The next step is converting the exposure regimen of the experiment to that of the human exposure scenario; that is, a continuous (24-h/day) lifetime (70-year) exposure. Then, dosimetric adjustments are appropriately applied for the type of toxicant being assessed (particle or gas, and if a gas, what category) and the effect to be assessed (respiratory tract or extra-respiratory toxicity) resulting from an inhalation exposure. Identification of the target effect(s) is also used to further define the gas category. (*Category 1 gases are defined as gases that are highly water-soluble and/or rapidly reactive in the respiratory tract. Reactivity is defined to include both the propensity for dissociation as well as the ability to serve as a substrate for metabolism in the respiratory tract. Gases in Category 1 are distinguished by the property that the gas does not significantly accumulate in the blood which would reduce the concentration driving force into the respiratory tract tissue and hence reduce the absorption rate. Gases in Category 2 are defined as gases that are moderately water- soluble that may be rapidly reversibly reactive or moderately to slowly irreversibly reactive in respiratory tract tissue. These gases are "transitional" gases that have the potential for significant accumulation in the blood and thus have the potential for both respiratory and remote (extrarespiratory) toxicity. The accumulation in the blood will reduce the concentration driving force during inspiration and thereby reduce the absorption rate or dose upon inhalation. These types of gases also have the potential for significant desorption during exhalation. Gases or vapors in Category 3 are relatively water insoluble and unreactive in the Extrathoracic and Tracheobronchial regions. Thus, the relatively limited dose to these respiratory tract regions does not appear to result in any significant toxicity, although some respiratory tract toxicity may be related to recirculation. The uptake of these gases is predominately in the pulmonary region and is perfusion limited. The site of toxicity is generally remote to the principal site of absorption in the pulmonary region. For gases in Category 3 that exhibit their toxic effects outside of the respiratory tract, an approach for the scenario when the concentrations of the gas in the animals is periodic with respect to time is recommended*). For gases, the determination of the appropriate gas category is required to determine which dosimetric adjustment would apply to calculate an HEC. A flowchart presented below, better describes the decision making process used to determine the methodology to calculate the HEC for DPGDME.



Utilizing the above guidance, DPGDME was classified in the following manner in order to determine a $NOAEL_{[HEC]}$. The first assumption was determining whether the compound is a particle or gas. Study data indicated that DPGDME is a vapor (as compared to a particle). Next, a determination was made as to what category of gas DPGDME is. In discussions with a Dow Chemical representative, it was agreed that DPGDME is a Category 3 gas; or a gas that exhibits its toxic effect outside of the respiratory tract. Questions were raised as to whether this compound could also be considered a Category 2 gas because of its high water solubility, versus a Category 3 gas, which is relatively water insoluble. However, after re-evaluating the study results from all of the studies that Dow submitted (LC_{50}, 9-day, teratology and 13 week vapor inhalation) it was deemed more important to categorize the compound on the location of its toxics effects rather than its solubility. Not one of the studies Dow presented gave any indication that this compound effects the respiratory system. Therefore, this compound was classified as a Category 3 gas rather than a Category 2. An added assumption when considering a Category 3 gas is to determine whether the concentration of the inhaled compound within the animal achieved periodicity with respect to time (i.e., periodic steady state - the concentration versus time profile is the same for every week).

The Dow representative stated that they were uncertain to the exact time course for periodicity but assumed that it was for over 90% of the study. According to the guidance document, if the periodicity is unknown, the default value will be equal to 1 (one).

According to Rule 232(1)(a); if an RfC can be determined from best available information sources, the ITSL equals the inhalation RfC. Clearly, the 13-week study presented by Dow Chemical is sufficient in length and scope to be evaluated using the EPA RfC guidance methodology described above. With this in mind, an RfC (and ITSL) was determined using a NOAEL of 50 PPM (331 mg/m^3) based on the 13-week rat inhalation study presented by Dow Chemical.

NOAEL=50 PPM
MW of DPGDME=162

Conversion of PPM to mg/m^3

$$\frac{MW\ x\ PPM}{24.45} = \qquad \frac{mg}{m^3}$$

$$\frac{162\ x\ 50\ PPM}{24.45} = 331.3\frac{mg}{m^3}$$

Adjust for Exposure Regimen

$$NOAEL_{[ADJ]} = E\ \left(\frac{mg}{m^3}\right) x\ D\ \left(\frac{hr}{24hr}\right) x\ W\ (\frac{days}{7\ days})$$

E=experimental dose level
D=number of hours exposed/24 hr; and
W=number of days of exposure/7 days

$$NOAEL_{[ADJ]} = \ 331.3\frac{mg}{m^3} x \frac{6hr}{24hr} x \frac{5\ days}{7\ days}$$

$$NOAEL_{[ADJ]} = 59.1\frac{mg}{m^3}$$

Dosimetric Adjustments and Calculation of NOAEL

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]}\ x\ \left(H_{\frac{b}{g}}\right)_A / \left(H_{\frac{b}{g}}\right)_H$$

$NOAEL_{[HEC]}$ = the NOAEL or analogous effect level obtained with an alternative approach, dosimetrically adjusted to an HEC;

$NOAEL_{[ADJ]}$ = described above; and

$(H_{b/g})_A/(H_{b/g})_H$ = the ratio of the blood: gas (air) partition coefficient of the chemical for the laboratory animal species to the human value. The value of 1.0 is used for the ratio if $(H_{b/g})_A > (H_{b/g})_H$.

$NOAEL_{[HEC]}$ = 59.1 mg/m^3 x 1/1

$NOAEL_{[HEC]}$ = 59.1 mg/m^3

Uncertainty Factors
10 = interspecies
10 = sensitive populations
10= subchronic to chronic study

$$\frac{59.1\frac{mg}{m^3}}{10\ x\ 10\ x\ 10} = 0.0591\ \frac{mg}{m^3}$$

Conversion of mg/m^3 to µg/m^3

$$0.0591\frac{mg}{m^3}\ x\frac{1{,}000\ \mu g}{1\ mg} = 59\ \frac{\mu g}{m^3}$$

The ITSL for dipropylene glycol dimethyl ether = 59 µg/m^3 based on a 24 hour averaging.

References:

Cieszlak JW et al. 1993. *Dipropylene glycol dimethyl ether: a thirteen-week vapor inhalation toxicity study in Fischer 344 rats.* Toxicology Research Laboratory Health and Environment Sciences — Dow Chemical Company.

U.S. Environmental Protection Agency. 1994. Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Washington D.C. EPAI600/8-90/066F; October 1994.

MB:SLB
cc: Mary Lee Hultin, AQD