MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Diisopropyl ether (CAS# 108-20-3)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 25, 2017

SUBJECT: Diisopropyl ether (CAS# 108-20-3) remaining at 24-hour averaging time

The initial threshold screening level (ITSL) for diisopropyl ether is now set at 360 µg/m^3 based on a 24-hour averaging time. The ITSL was originally established on 3/19/2001 and was set at 358 µg/m^3 based a 24-hour averaging time. The ITSL is based on a Dalbey and Feuston (1996) subchronic and developmental inhalation studies on rats. In the 13 week inhalation study the effects included: increased liver and kidney weights in male rats and increased liver weight in female rats. In the developmental study the effects included: reduction in body weight gain in pregnant females and a significant increase in rudimentary or short 14th ribs in fetuses at the lowest exposure concentration. The ITSL has been rounded to 2 significant figures. As diisopropyl ether 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.

Dalbey W and Feuston M. 1996. Subchronic and developmental toxicity studies of vaporized diisopropyl ether in rats. J. Tox. Env. Health 49:29-43.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

March 19, 2001

TO: File for diisopropyl ether (108-20-3)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for diisopropyl ether (DIPE), is 358 $\mu g/m^3$ based on a 24-hour averaging time. The following references or databases were searched to identify data to determine the ITSL/IRSL: IRIS-online, HEAST, NTP Management Status Report-online, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC-online, NIOSH Pocket Guide, and ACGIH Guide.

DIPE is used mainly as a solvent for mineral, vegetable, and animal oils; for waxes, resins, dyes, and paints; and for varnish removers. Recently, this compound has been used as an additive for gasolines, similar to other oxygenates such as ethanol and methyl t-butyl ether (MTBE).

According to the American Council of Governmental Hygienists (ACGIH) documentation, DIPE has an anesthetic action very much like diethyl ether but is somewhat more toxic. The minimal lethal dose of DIPE for rabbits was 5 to 6.5 g/kg. A rapid, intense intoxication was produced. Death was due to respiratory failure caused by depressant action. Acute oral LD_{50} values for DIPE in rats ranged from 4.6 to 11.4 g/kg.

Data further presented in the ACGIH documentation stated that one investigator exposed a group of human subjects for 15 minutes at 500 ppm. The subjects did not consider the exposure to be irritating. At a concentration of 300 ppm, however, about one-third of the subjects objected to the unpleasant odor, while at 800 ppm for 5 minutes, most subjects reported irritation of the eyes and nose. The ACGIH based their Threshold Limit Value (TLV) on these human exposures. The TLV is listed at 250 ppm or 1040 mg/m^3.

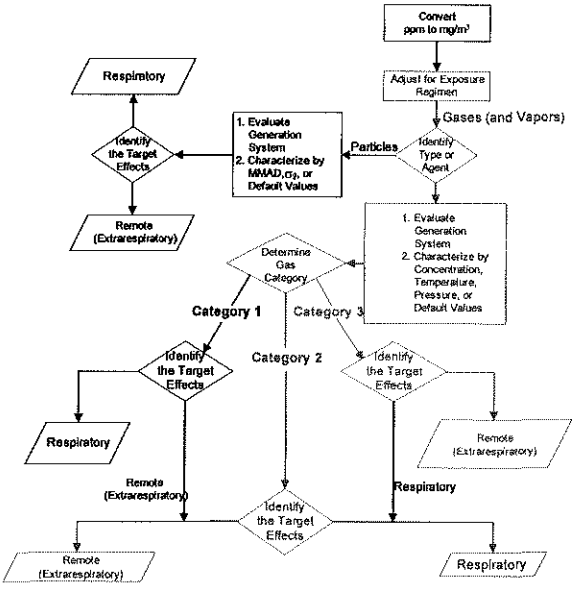
The available mammalian subchronic toxicity studies for diisopropyl ether (DIPE) were subchronic, developmental, and neurotoxicity inhalation studies utilizing rats. Rodriguez and Dalbey (1997), exposed Sprague-Dawley rats (10/sex) to 0, 450, 3250, or 7060 ppm DIPE for 5 d/wk, 6 h/d for 13 weeks. The neurotoxicity potential of DIPE was assessed using a functional observational battery test, automated motor activity, and neuropathology. The neuropathological assessment consisted of microscopic examination of the brain, spinal cord, gasserian, dorsal root ganglia and sciatic nerve in the control and high dose group. The results reported a significant reduction in cage activity in low and high dose female rats during week four. Additionally, high dose females had a significant decrease in motor activity at 8 weeks, while low-dosed females had a significant increase in motor activity at 4 weeks. Low-dose males had a significant decrease in pinna reflex and a significant increase in rectal temperature compared to controls, but fluctuated within the normal range. No pathological effects were observed in the high dose group. The behavioral endpoints observed in did not exhibit a dose-dependent response and only occurred at certain time periods, thus the biological significance of these effects are unclear. The authors concluded that exposure to the concentrations of

DIPE in the present study caused only minor neurological changes which indicated that the neurological effects of DIPE in rats were minimal.

Dalbey and Feuston (1996) performed two inhalation studies with a vaporized sample of commercial-grade DIPE. In the subchronic study, Sprague-Dawley rats (14/sex) were exposed to 0, 480, 3300, or 7100 ppm DIPE for 6 h/d, 5 d/wk, for approximately 13 weeks. At 3300 ppm, weights of liver and kidney were increased in males and only liver weight increased in females compared to control. Exposure to males at 7100 ppm resulted in hypertrophy of liver cells and increased kidney weights, whereas, females exposed to 7100 ppm had increased liver and kidney weights with no morphological changes observed in either organ. No adverse effects on clinical signs, body weights, serum chemistry, hematology, or the number of sperm or spermatids were observed following exposure to 480 ppm DIPE. In the developmental toxicity study, pregnant Sprague-Dawley rats (22/group) were exposed to 0, 430, 3095, and 6745 ppm for 6 h/d on gestation d 6-15. At 6745 ppm, dams had a slight reduction in body weight gain and a significant decrease in food consumption. There was a significant increase in rudimentary or short 14th ribs in fetuses exposed to DIPE at 3095 and 6745 ppm. There was no apparent toxicity, either maternal or fetal, at the lowest exposure concentration (430 ppm). At first it would seem the NOAEL presented in the developmental study would be the most appropriate to derive an ITSL because it is the lowest value based on the studies examined. The EPA has used developmental studies to derive RfCs. Their rationale is that a single exposure at a critical time in development may produce an adverse developmental effect, i.e., repeated exposure is not a necessary prerequisite for developmental toxicity to be manifested. However, the EPA further states that 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. Because the NOAELs are very similar, (430 ppm vs. 480 ppm) using the developmental NOAEL of 430 ppm without the adjustment for different time frames would produce an ITSL greater than deriving an ITSL using the NOAEL of 480 ppm. Therefore, following Rule 232(1)(a), *the RfC is determined from the best available information sources,* in this case, the 13-week study by Dalbey and Feuston is the best study to use for an ITSL derivation. The NOAEL of 430 ppm from the developmental study (Dalbey and Feuston, 1996) and the minimal neurotoxic potential of DIPE (Rodriguez and Dalbey, 1997) provides supporting data for the ITSL derivation.

The quality of the Dalbey and Feuston study used to evaluate DIPE justifies deriving an RfC for this compound using the U.S. Environmental Protection Agency's Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry guidance document (EPA/600/8-90/066F; October 1994) (hereafter referred to as 1994 Methods document). 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 in laboratory animals to estimate a concentration that would be an equivalent exposure to humans). 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 DIPE.



Utilizing the above guidance, DIPE was classified in the following manner in order to determine a HEC. The first assumption was determining whether the compound is a particle or gas. Study data indicated that DIPE is a gas. Next, a determination was made as to what category

of gas DIPE is. In reviewing the bioassay, it was determined that DIPE is a Category 2 gas; or a gas that has the potential for significant accumulation in the blood and thus have the potential for both respiratory and remote (extrarespiratory) toxicity. Study results indicated that this compound affected the eyes and nose of test subjects in addition to causing central nervous system (CNS) depression. Therefore, this compound was classified as a Category 2 gas. However, derivation of equations regarding Category 2 gases in the 1994 Methods document are in error. The U.S. EPA (Mark Greenberg, Hazardous Pollutant Assessment Group; National Center for Environmental Assessment) recommends a default for chemicals that would be expected to have only extrarespiratory or remote effects to use Category 3. 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). It was impossible to tell from the study the exact time course for periodicity. According to the guidance document, if the periodicity is unknown, the default value will be equal to 1 (one).

Adjust for Exposure Regimen

$NOAEL_{[ADJ]}$ = E (mg/m^3) x D (h/24h) x W (days/7 days)

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

$NOAEL_{[ADJ]}$ = 2006 mg/m^3 x 6h/24h x 5days/7days

$NOAEL_{[ADJ]}$ = 358 mg/m^3

Dosimetric Adjustments and Calculation of $NOAEL_{[HEC]}$

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

$NOAEL_{[HEC]}$ = 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 $(H_{b/g})_A > (H_{b/g})_H$.

$$NOAEL_{[HEC]} = 358\ mg/m^3 \times \frac{1}{1}$$

$NOAEL_{[HEC]}$ = 358 mg/m^3

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

$$\frac{358\ mg/m^3}{10 \times 10 \times 10} = 0.358\ mg/m^3$$

Conversion of mg/m³ to ug/m³

$$0.358\ mg/m^3 \times \frac{1{,}000\ \mu g}{1\ mg} = 358\ \mu g/m^3$$

The ITSL for isopropyl ether = 358 μg/m³ based a 24-hr. averaging time.

Reference:

1. Dalbey, W. and M. Feuston 1996. Subchronic and developmental toxicity studies of vaporized diisopropyl ether in rats. J. Tox. Env. Hlth. 49:29-43.

2. Documentation of Threshold Limit Values and Biological Exposure Indices. 1992. Diisopropyl ether. American Conference of Governmental Industrial Hygienists (ACGIH), 6th Edition.

3. Rodriguez, S.C., and Dalbey, W.E. 1997. Subchronic neurotoxicity of vaporized diisopropyl ether in rats. Internat. J. Tox. 16:599-610.

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