MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Dimethyl Ether (CAS#115-10-6)

FROM: Keisha Williams, Air Quality Division

DATE: February 3, 2017

SUBJECT: Screening Level Review for Dimethyl Ether

The initial threshold screening level (ITSL) for dimethyl ether (DME) is 740 µg/m^3 (annual averaging time), and 1900 µg/m^3, 24-hour averaging time.

The following references or databases were searched to identify data to determine the screening level: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, MDEQ Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1986- September 2014), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Aggregated Computational Toxicology Resource (ACToR) Database, EPA TSCATS database, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels for Airborne Chemicals, EPA High Production Volume Database, Agency for Toxic Substances and Disease Registry's (ATSDR's) Toxicological Profiles, United States Department of Labor Occupational Safety and Health Administration Permissible Exposure Limits, Spacecraft Maximum Allowable Concentrations, California Office of Environmental Health Hazard Assessments Reference Exposure Levels, Chemical Safety Program Protective Action Criteria, Texas Commission on Environmental Quality Effects Screening Levels, and European Chemicals Agency Registered Substances Dossiers.

Background Information

DME (Figure 1.) is used as an aerosol propellant, fuel, refrigerant, and to produce other chemicals (DuPont, 2012). It is a colorless gas, with a faint ether-like odor (Pubchem database). Table 1 lists chemical properties. Synonyms include methoxymethane; methyl ether; methane,oxybis-; dimethyl oxide; oxybismethane; and methyl oxide.

Figure 1. Chemical structure of DME

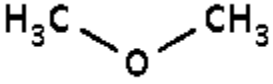

Table 1. Chemical properties of DME

- Molecular weight: 46.07 grams/mole
- Melting point: -141.5°C
- Boiling point: -24.8°C
- Vapor pressure: 4450 mmHg at 25°C
- Vapor density: 1.6, where air=1

Reference: PubChem database, http://pubchem.ncbi.nlm.nih.gov/compound/dimethyl_ether

The American Industrial Hygiene Association (AIHA) has established a Workplace Environmental Exposure Level at 1000 ppm (1900000 µg/m^3) for an 8 hour averaging time (AIHA, 2013). The Texas Commission on Environmental Quality (TCEQ) has established interim health effects screening levels at 19000 µg/m^3 for short term and 1900 µg/m^3 for long term exposure (TCEQ, 2014).

Evaluation of Cancer Risk

An unpublished 2 year rat reproductive toxicity study was performed under GLP conditions to also evaluate cancer risk (DuPont Co, 1986). Only the summary was available (High Production Volume Robust Summary, 2001). Male and female Crl:CD (Sprague Dawley) BR rats were exposed to 0, 2000, 10000, or 20000 ppm DME for 6 hours/ day, 5 days/ week for 3, 6, 9, 18, and 24 months. Reproductive organs were collected for histopathology. An increase in mammary tumors was reported but not considered biologically significant, because 1) the rats in the control group had an unusually low occurrence of at least 1 benign or malignant tumor, 2) a dose-response relationship was not established as both the lowest dose and the highest dose gave the same significant increase in incidence of at least one benign mammary tumor (Table 2), and 3) there was difficulty identifying tumors as benign or malignant. The results are as follows:

Table 2. Mammary tumor identification in female rats exposed to DME

Exposure (ppm)	0	2000	10000	20000
# rats histologically examined	75	77	74	70
# rats with at least one benign tumor	16	30*	24	29*
# rats with at least one malignant tumor	14	16	16	20
# rats with at least one benign or malignant tumor	27	34	35	37*
% rats with at least one benign or malignant tumor[a]	36.0	44.2	47.3	52.9

*****, statistically different from the control group ($p < 0.05$) by the Fischer's Exact test
a, not analyzed statistically

Masses were observed more in female rats at every exposure level as compared to the control group; however, the unusually low incidence of masses in the control group as compared to historical controls suggested that this increase was not biologically significant. The authors reported that the historical incidence rate of benign or malignant mammary tumors in female rats was 53 %, which was similar to the percentage observed in the highest exposure group. The researchers reported that DME-related lesions were not consistently observed.

Review of relevant studies

Study used in 1986 to establish the former ITSL, 66 ug/m3 (annual AT):

The ITSL was derived from a subchronic rat, inhalation study (Collins et al, 1978). Groups of male and female Wistar rats were exposed to 0, 0.02%, 0.2% and 2% for 6 hours/day, 5 days/week for 30 weeks (n=25). The lowest concentration produced no treatment-related

effects, and was therefore considered a no observable adverse effect level (NOAEL). The 0.2% group was the only group that showed a significant increase in serum glutamic oxaloacetic transaminase (SGOT) in the blood serum of male rats as compared to controls. This increase is indicative of liver or heart damage. However, both male and female rats in the high dose groups did show a significant increase in serum SGPT levels. This increase is more specifically indicative of liver damage. High dose male rats also showed a significant reduction in liver weight. No histological abnormalities were observed in liver for any treatment groups.
Since the SGOT levels were increased in the rats exposed to 0.2% but nor 2% DME, it was not clear to the reviewer for the 1986 ITSL derivation whether 0.2% should be considered an "effect level" or not. However, 0.02% was identified as a clear NOAEL in this study. Thus, the ITSL was derived using 0.02% as the NOAEL. The mean exposure concentration from the 0.02% level was found to be 197 ppm based upon analytical results in the study, and the ITSL was derived as:

$$former\ ITSL = \frac{NOAEL\ x \frac{hours\ exposed\ per\ day}{24\ hours\ per\ day} x \frac{days\ exposed\ per\ week}{7\ days\ per\ week}}{uncertainty\ factors},$$

where uncertainty factors that were applied included 10 for intraspecies uncertainty, 10 for interspecies uncertainty, and 10 for subchronic to chronic uncertainty.

$$former\ ITSL = \frac{197\ ppm\ x \frac{6\ hrs\ per\ day}{24\ hrs\ per\ day} x \frac{5\ days\ exposed\ per\ week}{7\ days\ per\ week}}{10\ x\ 10\ x\ 10} = 0.035\ ppm$$

$$= 66 \frac{\mu g}{m^3}, annual\ averaging\ time$$

In the present review, it may be noted that the 1986 ITSL derivation utilized some conservatism in the UFs that may not be employed using current risk assessment practices. First, a subchronic-to-chronic UF of 3, rather than 10, may be more appropriate given the duration of the study (30 weeks, while being less than chronic, is significantly longer than a 90 day duration where the full 10-fold UF is routinely employed). Secondly, using current EPA guidance for dosimetric conversion, an interspecies UF of 3 may be more appropriate than 10, based on toxicodynamic differences (UF=3) with systemic effects of gases defaulting to a toxicokinetic UF = 1 (EPA, 2012 dosimetry guidance pp. 2-19 and 2-20; EPA, 1994 dosimetry guidance, p. 4-78).

With this in mind, the ITSL would be calculated thusly:

$$chronic\ ITSL = \frac{197\ ppm\ x \frac{6\ hrs\ per\ day}{24\ hrs\ per\ day} x \frac{5\ days\ exposed\ per\ week}{7\ days\ per\ week}}{3x\ 3\ x\ 10} = 736\ \frac{\mu g}{m^3}$$

$$\approx 740 \frac{\mu g}{m^3}, annual\ averaging\ time$$

Human inhalation study
For ITSL derivation, well-designed human studies are more relevant and are preferred to animal studies. For that reason, a neurobehavioral toxicity study that used human subjects (Davidson, 1925) is discussed here. The lowest exposure concentration was 5% (≈94,000 mg/m^3), in which the subject(s) experienced feelings of intoxication, were inattentive, and had a reaction time that was 3 times longer than without DME inhalation.

Simple arithmetic problems were performed without difficulty after inhalation of the lowest concentration, but at 10% DME, there was difficulty with arithmetic problems. Slight incoordination and analgesic effects were also observed at 10% DME after 50 minutes of inhalation and feelings of sickness were reported after nearly 2 hours of exposure. Higher concentrations of 14 and 20% DME exposure led to similar adverse responses but in shorter periods of time, indicating a dose-response effect. Furthermore, the more severe effect of unconsciousness occurred at these higher doses.

There are major limitations to this study: sample size is not given, there are no descriptions of the human subjects (besides the description of one subject being male), and the results were not evaluated with consideration for statistical significance. Since essential information to characterize the study population and evaluate the robustness of the results is missing, this study will not be used to calculate the ITSL. However, qualitatively, this study identifies potential neurological effects from DME.

Developmental toxicity study in rats with inhalation administration
Only the summary was obtained (High Production Volume Robust Summary, 2001). This study focused on developmental toxicity of DME via a 6 hour per day inhalation exposure for 10 days with pregnant Crl:CD (Sprague Dawley) BR rats (DuPont, 1981). The rats were exposed to 0, 1250, 5000 or 20000 ppm DME.

There was little to no effect on the dams, except a decreased response to sound at the highest DME concentration. There were skeletal malformations observed in fetuses at all DME exposure levels as shown in Table 2. While skeletal abnormalities largely presented a dose-response relationship, a significant increase in one abnormality (unossified hyoid) was observed exclusively with the lowest DME exposure group. Four non-skeletal malformations were observed in the lowest exposure group. In comparison, no non-skeletal malformations were reported in the control group, and only one malformed fetus was observed in the highest exposure group. However, the non-skeletal malformations in the lowest concentration group were not reported as being significantly increased.

Table 2. Skeletal abnormalities in fetuses

Variation:	0 ppm	1250 ppm	5000 ppm	20000 ppm
Number given skeletal exams*	325/25	343/24	370/27	350/25
Rib -rudimentary	2/1	3/3	7/4	21/11[t]
Rib -extra	0	0	4/2	4/2
Rib -thickened	0	0	0	2/1
Rib -wavy	1/1	0	0	0
Rib -extensive wavy	1/1	0	1/1	0
Rib -extra ossification center	19/12	32/15	76/23[#]	117/23[#]
Centrum –dumb belled	12/7	14/6	29/13	37/15[#]
Centrum -bipartite	5/3	8/6	16/9	13/8
Hyoid -partially ossified	12/7	6/6	9/7	6/6
Hyoid -unossified	2/2	14/8[t]	5/3	8/5
Hyoid -bipartite	1/1	0	0	0

*Results represented as number of fetuses with abnormality/number of litters with positive fetuses
# = Significantly different from control incidence by two tailed Mann-Whitney U test (p<O.05).
t = Significantly different from control incidence by Fisher's exact test (p<0.05).

The inconsistent dose-response relationship observed here parallels what was seen in the Collins study.

Statistically significant increases in “rib – extra ossification center” were observed at 5000 ppm and 20000 ppm, and in “rib-rudimentary” and “centrum–dumbelled” at 20000 ppm. Unossified hyoid may be regarded as a critical effect, with 1250 ppm being the lowest observable adverse effect level (LOAEL) based on the significantly elevated number of fetuses and litters with this defect at 1250 ppm compared to the control group even though the responses across all treatment groups did not follow a dose-response relationship. As also seen in the Collins study, responses to dimethyl ether do not consistently follow a typical dose-response relationship.

For our purposes and application to the permitting process, an ITSL with a 24 hour averaging time would better protect against the high, short term exposures of concern to fetuses. Furthermore, under EPA Guidance (EPA, 1991, pg. 42) reference concentrations derived from developmental toxicity studies are considered on a daily basis of exposure to provide protection against acute exposures that would cause damage on during this critical window of time. Also, note that the LOAEL of 1250 ppm (≈2300 mg/m^3) is a lower than the LOAEL identified in the controlled human study (Davidson, 1925). With this in mind, the acute ITSL would be derived thusly:

$$acute\ ITSL = \frac{\text{LOAEL}}{(UFs)}\ x\ \frac{hrs\ exposed\ per\ day}{24\ hrs\ per\ day},$$

where UFs are 10 for LOAEL to NOAEL, 10 for intraspecies differences, and 3 for interspecies differences

$$acute\ ITSL = \frac{2.3\ \text{x}\ 10^6 \mu\text{g/m}^3}{(10x3x10)}\ x\ \frac{6\ hrs\ per\ day}{24\ hrs\ per\ day} = 1917\ \mu\text{g/m}^3$$

≈*1900* µg/m^3, 24-hour averaging time

The two ITSLs for DME are being established at 1900 µg/m^3 (24-hour averaging time) and 740 µg/m^3 (annual averaging time).

References

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MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

May 22, 1986

TO: File

FROM: Catherine Simon

SUBJECT: Dimethyl Ether (CAS No. 115-10-6)

No human epidemiology studies or lifetime exposure animal bioassays were available to evaluate the health effects from exposure to dimethyl ether (DME). One subchronic animal study was found which could be used to derive an acceptable ambient concentration (AAC) for dimethyl ether. In this study (Collins, et al, 1978), groups of 25 male and 25 female Wistar rats were exposed to 0.02 %, 0.2%, and 2% v/v of DME in air for 6 hour per day, 5 days per week, for 30 weeks. The results of this study showed that exposure to the lowest dose (0.02%) of DME produced no treatment related effects in either male or female rats. This dose level was considered a no observable effect level (NOEL). For the dose group exposed to 0.2% DME, the only effect observed was a statistically significant increase in serum SGOT levels in male rats. This effect was not observed in the high dose (2% DME) rats. Both male and female high dose rats did show, however, a statistically significant increase in serum SGPT levels. In addition, high dose male rats showed a significant reduction in liver weight. No histological abnormalities were observed in the liver or any other organ for any treatment group when compared to control animals.

Because the SGOT levels were increased in the rats exposed to 0.2% DME but not 2% DME, it is not clear whether 0.2% should be considered an “effect level” or not. Since no other data are available to clarify the dose response data for DME, the NOEL of 0.02% is used to derive an AAC. Based upon analytical results presented in the study (Collins, et al, 1978), the exposure level of 0.02% corresponded to a mean concentration of 197 ppm. The AAC is derived as follows:

$$AAC = 197\ ppm\ x\ \frac{6\ hours}{24\ hours} x\ \frac{5\ days}{7\ days} x\ \frac{1}{1000}$$

AAC = 0.035 ppm

At 25°C and 1 atmosphere pressure, the AAC of 0.035 ppm is equivalent to 66 µg/m3.

References

Collins, Christopher J. et al. 1978. Effects of chronic inhalation of dimethyl ether in the rat. Toxicology 11:65-71.

CAS : mh