MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Methanol (CAS No. 67-56-1)

FROM: Cathy Simon, Toxics Unit, Air Quality Division

DATE: November 26, 2013

SUBJECT: Update of the Initial Threshold Screening Level for Methanol

The initial threshold screening level (ITSL) for methanol has been updated. The revisions include two new ITSLs based on two different averaging times. The new ITSLs are as follows:

ITSL (24-hour averaging time) = 20,000 µg/m^3
ITSL (1-hour averaging time) = 28,000 µg/m^3

The background information, relevant data and bases for the new ITSLs are summarized below.

Background

In August 1992, the Michigan Department of Natural Resources (MDNR), Air Quality Division (AQD) first established an ITSL for methanol at 3250 µg/m^3 based on a 1-hour averaging time (MDNR, 1992). This ITSL was derived from the Threshold Limit Value-Short Term Exposure Limit (TLV-STEL) for methanol of 325 mg/m^3, established by the American Council of Governmental Industrial Hygienists (ACGIH), and the National Institute of Occupational Safety and Health (NIOSH) Recommended Exposure Level-Short Term (REL-ST), also set at 325 mg/m^3. The ITSL of 3250 µg/m^3 was derived by dividing these occupational exposure levels by a factor of 100.

In 2012, the Toxics Unit of the AQD, Michigan Department of Environmental Quality (MDEQ), began an initiative to update health-based screening levels, with a priority focus on those screening levels that differed from values used by the U.S. Environmental Protection Agency (USEPA) in recent risk assessment reports. Methanol was identified as one of these chemicals. As part of this initiative to update screening levels, complete literature reviews are not being done, rather the focus is on reviewing relevant summary documents prepared by appropriate governmental or scientific agencies.

Update of the ITSL

The most complete, updated review of the scientific literature detailing the toxicological effects of methanol is the USEPA's *Toxicological Review of Methanol (Noncancer)* (EPA, 2013a), published in support of the most recent oral reference dose (RfD) and inhalation reference concentration (RfC) for methanol. The updated oral RfD and new inhalation RfC were listed on the USEPA's Integrated Risk Information System (IRIS) database on September 30, 2013. The inhalation RfC for methanol is 20 mg/m^3 (EPA, 2013b).

Animal toxicity studies and human epidemiological data indicate that exposure to methanol by inhalation may result in irritation of the eyes and mucous membranes, central nervous system

effects, reproductive and developmental effects, as well as adverse effects to the lungs, liver, and kidney. The USEPA identified developmental effects as the critical effect for establishing the inhalation RfC. Two studies (Rogers et al, 1993; NEDO, 1987) were chosen as key studies to evaluate for dose response relationships for the purpose of developing an inhalation RfC.

In the study by Rogers et al (1993), pregnant CD-1 mice were exposed to 0, 1000, 2000, 5000, 7500, 10,000, or 15,000 ppm methanol vapors for 7 hours per day on gestation days (GD) 6-15. Fetuses in all exposure groups were evaluated for external malformations, but only those in the control, 1000, 2000, 5000, and 15,000 ppm dose groups were examined for skeletal and visceral effects. The incidence of cleft palate/litter was significantly increased at all dose levels ≥ 5000 ppm. The incidence of exencephaly/litter was significantly increased in the 5000, 10,000 and 15,000 ppm dose groups. The incidence of cervical ribs/litter was significantly increased at concentrations of 2000, 5000, and 15,000 ppm (dose levels of 7500 and 10,000 ppm not evaluated for this effect). The most sensitive indicator of developmental toxicity from this study was an increase in the number of fetuses per litter with cervical rib abnormalities, with a NOAEL of 1000 ppm and LOAEL of 2000 ppm.

The NEDO (1987) study involved three different studies using Sprague-Dawley rats. The first was a teratology study in which 36 pregnant females were exposed to 0, 200, 1000, or 5000 ppm methanol vapor. Animals were exposed on GD7 - GD17 for 22.7 hours/day. On GD20, 19-24 dams/group were sacrificed and fetuses examined for adverse effects. The remaining 12 dams/group were allowed to deliver and nurse their litters to evaluate postnatal effects of methanol exposure. The authors reported statistically significant effects occurred only in the 5000 ppm dose group, and consisted of increased late-term resorptions, decreased live fetuses, reduced fetal weight, and increased frequency of litters with fetal malformations, variations, and delayed ossifications (NEDO, 1987). The USEPA's further dose-response analyses showed statistically significant linear trends for pre-implantation resorptions, pre-implantation resorption rate and bifurcated vertebral center (EPA, 2013a).

The second study by NEDO (1987) was a two generation study in which male and female Sprague-Dawley rats were exposed to 0, 10, 100, or 1000 ppm methanol vapor for 20 hours/day. Effects reported by the authors included decreased brain, pituitary, and thymus weight, and testicular descent in offspring of the F_0 and F_1 rats exposed to 1000 ppm methanol. The third study by NEDO (1987) was a follow up study to confirm the effects of methanol on brain weight. In this study, Sprague-Dawley rats were exposed from the first day of gestation through the F_1 generation. Animals were exposed to 0, 500, 1000 or 2000 ppm methanol for 20 hours/day. Statistically significant decreased brain weight was observed in F_1 male rats exposed to ≥1000 ppm at 3, 6, and 8 weeks of age. In F_1 female rats, brain weight was significantly decreased in animals exposed to ≥ 1000 ppm at 3 weeks, and only in the 2000 ppm dose group at 6 and 8 weeks.

The USEPA used a benchmark dose (BMD) approach to deriving the inhalation RfC. The overall approach involved using physiologically based pharmacokinetic (PBPK) modeling to estimate an internal dose metric from the applied dose, BMD modeling to determine the BMDL (lower limit on the 95% confidence interval on the BMD) based on the selected internal dose metric, application of appropriate uncertainty factors to the BMDL to determine an internal RfC, and finally converting the internal RfC to a human equivalent concentration (HEC) RfC using the PBPK model parameterized for humans (EPA, 2013a).

The two critical effects the USEPA considered for derivation of the inhalation RfC included the incidence of extra cervical ribs in CD-1 mice from Rogers et al (1993), and decreased brain

weight at six weeks of age in male Sprague-Dawley rats exposed throughout gestation and continuing into the F_1 generation from NEDO (1987). These endpoints were chosen because they were the most sensitive, resulting in the lowest BMDs and BMDLs for these two studies.

For the cervical rib data in mice, the USEPA determined that the peak (Cmax) internal methanol blood concentration in dams was the appropriate dose metric to use in the BMD modeling because the magnitude of exposure was believed to be more important for this effect. This effect has been shown to have a very short gestational window of susceptibility, thought to be between GD6 and GD7. For the BMD analysis of the decreased brain weight in rats, PBPK estimates of the daily area under the curve (AUC) methanol in blood for the dams was determined to be the appropriate dose metric because both magnitude and duration of exposure was considered important for this effect (EPA, 2013a).

The USEPA modeled both a 10% and 5% benchmark response (BMR) for the mouse cervical rib data. Following the criteria provided in their Benchmark Dose Technical Guidance (EPA, 2012), the USEPA determined that the nested logistic model provided the best fit to the data. For the brain weight data in rats, the USEPA modeled a one standard deviation (SD) change from the control mean, and a 5% change relative to the control mean for the BMR. The Hill model was selected for RfC derivation using the rat brain weight data because it gave the lowest BMDL and provided the best fit in the low dose region of the dose response curve.

A total uncertainty factor (UF) of 100 was applied to the BMDLs determined from both the cervical rib and brain weight data to derive internal RfCs. The uncertainty factor of 100 consisted of an UF of 3 to account for extrapolating from rodents to humans ($UF_A = 3$), an UF of 10 to account for variation in sensitivity within the human population ($UF_H = 10$), a database UF of 3 to account for deficiencies in the database ($UF_D = 3$), and an UF of 1 for less than chronic exposure since the critical effect was based on developmental endpoints ($UF_S = 1$). The internal RfCs were then converted to an inhalation RfC_{HEC} using the PBPK model parameterized for humans. Table 1 lists the four candidate RfCs considered for derivation of the final RfC.

Table 1. Candidate inhalation RfCs derived by the USEPA (2013a) from Rogers et al (1993) and NEDO (1987)

	Mouse Cervical Rib (Rogers et al, 1993)		Rat Brain Weight (NEDO,1987)	
	10% BMR	5% BMR	5% BMR	1 SD BMR
RfC_{HEC} (mg/m^3)	41.8	20.0	24.5	17.8

From the four candidate RfCs in Table 1, the USEPA selected the RfC of 17.8 mg/m^3 based on a one standard deviation decrease in brain weight in male rats to derive the final RfC. This value was selected because it was the lowest candidate RfC, and would therefore be protective against other effects of methanol exposure. The selected candidate RfC was then rounded to one significant figure to give a final inhalation RfC of 20 mg/m^3. It should also be noted that the candidate RfCs based on a 5% BMR using both the mouse cervical rib data and the rat brain weight data would also result in a final RfC of 20 mg/m^3 when rounded to one significant figure.

Rule 232(1)(a) of the Michigan Air Pollution Control Rules specifies than when an inhalation RfC is available, the ITSL equals the RfC. Inhalation RfCs that include a database uncertainty factor are examined on a case-by-case basis to determine the appropriateness of including this uncertainty factor in derivation of the ITSL. The USEPA's rationale for including the database uncertainty factor relies heavily on the concern for developmental effects observed in a monkey

study by Burbacher (1999). This study was considered inadequate for the quantitative analysis necessary for deriving an inhalation RfC, but identified uncertainties related to the potency and importance and relevance of the observed effects. With regards to potency, the USEPA states that "uncertainty is warranted given evidence that these effects have been observed in monkeys with average blood levels that are close to, and in one case as little as 0.5 mg/L higher than, the range of uncontaminated background levels in humans" (EPA, 2013a, p. 5-21). The USEPA's further rationale is "metabolic similarities that suggest monkeys should most closely represent the potential for effects in humans" (EPA, 2013a, p. 5-22). Lastly, the USEPA's analysis of the monkey and rodent data indicates that the "rodent LOAEL blood level is 12-fold higher than the monkey LOEL blood level" (EPA, 2013a, p. 5-23). The USEPA then goes on to conclude the following:

> Some of this 12-fold difference may be due to differences in species sensitivity, for which the UF_A of 3-fold is intended to account, but some of the difference may be due to other factors, including whether appropriate and comparable endpoints were examined and whether appropriate study designs and quality control measures were used. To account for these additional factors, a 3-fold UF_D is applied (EPA, 2013a, p.5-23).

While not highly compelling, the rationale provided by the USEPA does provide sufficient justification for the use of the database uncertainty factor of three for inclusion in the derivation of the ITSL from the inhalation RfC. Rule 232(2)(b) of the Michigan Air Pollution Control Rules specifies that the averaging time for an ITSL derived from an inhalation RfC is 24 hours. Therefore, the updated ITSL for methanol is 20 mg/m^3 or 20,000 $\mu g/m^3$ based on a 24-hour averaging time. It should be noted that a 24-hour averaging time is especially appropriate for this ITSL considering the following: the critical effect is developmental and the short gestational window of susceptibility that may exist for such effects; for the mice cervical rib data the peak (Cmax) internal methanol blood concentration was considered the appropriate dose metric; for the rat brain weight effect a daily AUC dose metric was appropriate; both the mouse (BMR=5%) and rat data resulted in the same inhalation RfC when rounded to one significant figure; and an uncertainty factor of one for less than chronic exposure (UF_S=1) was used in derivation of the inhalation RfC.

A search for health benchmark values for methanol, applicable to the general public and derived by other governmental agencies, was made to compare to the USEPA inhalation RfC and to identify potential ITSLs with alternative averaging times. No minimal risk levels (MRLs) for methanol were available from the Agency for Toxic Substance and Disease Registry. Two state agencies, the Texas Commission on Environmental Quality (CEQ) and the California EPA, were identified that had derived inhalation health benchmark values for methanol, that included a clearly defined process for developing the criteria, review of the scientific literature, a review process, and adequate documentation of the information. It should be noted that the TCEQ inhalation health benchmark values are only proposed values and have not yet been finalized (TCEQ, 2013). Table 2 lists these health benchmark values derived by the Texas CEQ and California EPA.

Table 2: Inhalation health-based benchmark values derived by the Texas CEQ (2013) and California EPA (2008a; 2008b).

Agency	Acute Value		Chronic Value	
	Concentration ($\mu g/m^3$)	Averaging Time	Concentration ($\mu g/m^3$)	Averaging Time
California EPA	28,000	1-hour	4,000	Annual
Texas CEQ	7,000 (proposed)	1-hour	2,200 (proposed)	Annual

The chronic health benchmark value derived by the California EPA was based upon the Rogers et al (1993) teratogenicity mouse study. A benchmark dose modeling approach was used for the most sensitive endpoint of the increase in cervical ribs. PBPK modeling was not used in determining the dose metric for dose-response modeling, as with the derivation of the USEPA inhalation RfC; instead a human equivalent concentration was determined using the regional gas dose ratio (RGDR) approach. A total UF of 30 (UF_A = 3; UF_H = 10) was used to derive the final chronic value. One of the uncertainties identified by the California EPA for their chronic health benchmark value was "the difficulty in addressing reproductive short-term effects within the chronic REL framework" (Cal/EPA, 2008a). In contrast, the Texas CEQ chronic health benchmark value was derived from the NEDO (1987) study, utilizing the data from male rats in which an increased incidence of nodes in the lungs was observed in male rats (TCEQ, 2013). In deriving their proposed chronic health benchmark value, the Texas CEQ used a BMD modeling approach, dose equivalency based on the RGDR methodology for determining a human equivalent concentration, and a total UF of 30 (UF_A = 3; UF_H = 10).

The acute health benchmark value derived by the California EPA was based upon a study by Cook et al (1991) in which twelve young, paid male volunteers were exposed to filtered air or 192 ppm (250 mg/^{3}) methanol vapor for 75 minutes. The subjects were administered a series of 20 tests that evaluated sensory, behavioral, and reasoning performance before, during, and after exposure. Although statistically significant effects were observed in a couple of tests, the authors stated that the changes were "subtle and within the normal range for healthy young men" (Cook, 1991, p.28). The authors suggested that additional studies were needed to better address the potential for acute neurological effects of methanol. The California EPA identified the dose level of 192 ppm as a NOAEL. This value was adjusted to a one hour concentration of 214 ppm methanol using Haber's Rule with modification by ten Berge (1986) as follows:

$$C_1^2 \times T_1 = C_2^2 \times T_2$$
$$(192 \text{ ppm})^2 \times 1.25 \text{ hour} = (214 \text{ ppm})^2 \times 1 \text{ hour}$$

A total uncertainty factor of 10 (UF_H = 10) was applied to this dose, resulting in an acute health benchmark value of 21 ppm, equivalent to 28 mg/m^3 or 28,000 $\mu g/m^3$ (Cal/EPA, 2008b).

The Texas CEQ utilized a study by Mann et al (2002) to derive their proposed acute health benchmark value for methanol. In this study, twelve healthy, nonsmoking individuals were exposed to 20 and 200 ppm methanol vapor for four hours. Subclinical irritating effects were evaluated by measuring the levels of various inflammatory markers in the nasal respiratory mucosa. The median levels of interleukin-8 and interleukin-1beta were significantly increased after exposure to 200 ppm methanol. The Texas CEQ identified a LOAEL of 200 ppm for this study. The LOAEL was adjusted to a one hour concentration of 323 ppm using Haber's Rule modified by ten Berge, followed by application of a total uncertainty factor of 60 (UF_H = 10; UF_L = 2; UF_D = 3), giving a proposed acute health benchmark value of 5.4 ppm, equivalent to

7 mg/m^3 or 7,000 µg/m^3 (TCEQ, 2013). If the default UF for database deficiencies was not used for the TCEQ proposed acute health benchmark value, the resulting value would be 21,000 µg/m^3, closer to the California acute health benchmark value of 28,000 µg/m^3.

The chronic inhalation health benchmark values (annual averaging time) derived by the California EPA (2008a) and TCEQ (2013) were not selected for use as ITSLs. The studies that were used to derive these values (Rogers et al, 1993; NEDO, 1987) have been reviewed by the USEPA (2013a) and gone through the extensive IRIS review process in developing the methanol inhalation RfC. Use of the inhalation RfC to derive the ITSL is also consistent with the hierarchy of methodologies specified in Rule 232 of the Michigan Air Pollution Control Rules.

The California EPA acute inhalation health benchmark value of 28,000 µg/m^3 was selected to use as an acute based ITSL with a one hour averaging time. This benchmark value was selected over the Texas CEQ value, because it is a final value, the actual exposure time in the study and the selected averaging time are very similar, it utilizes a NOAEL instead of LOAEL, and it addresses concern for neurological effects of methanol due to short term exposures. The acute based ITSL of 28,000 µg/m^3 (one hour averaging time) is derived pursuant to Rule 229(2)(b) of the Michigan Air Pollution Control Rules.

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