MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Update to File for Methylene chloride (CAS # 75-09-2)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

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SUBJECT: Update of Screening Levels for Methylene chloride (CAS # 75-09-2)

The initial risk screening level (IRSL) for methylene chloride (CAS # 75-09-2) is 60 µg/m^3 annual averaging time. The secondary risk screening level (SRSL) for methylene chloride is 600 µg/m^3 annual averaging time. The initial threshold screening level (ITSL) for methylene chloride is 2,000 µg/m^3 annual averaging time and an acute ITSL is 14,000 µg/m^3 based on a 1-hour averaging time.

The Environmental Protection Agency Integrated Risk Information System (IRIS) released a final assessment for methylene chloride (CAS# 75-09-2) also known as dichloromethane (DCM). A review of the IRIS assessment found that the studies used in the assessments for the quantitative estimate of carcinogenic risk from inhalation exposure – inhalation unit risk (IUR) of 1 x 10^{-8} per µg/m^3 and the reference concentration for chronic inhalation exposure (RfC) of 6 x 10^{-1} mg/m^3 were derived from well performed and the results were statistically significant. The Agency for Toxic Substances and Disease Registry (ATSDR) has an acute inhalation minimal risk level (MRL) of 0.6 ppm.

According to Rule 231(1) the IRSL is determined using the equation below:

$$IRSL = \frac{1 \times 10^{-6}}{unitrisk}$$

The EPA determined the IUR of 1 x 10^{-8} per µg/m^3 using the benchmark dose software multistage model with linear extrapolation from the point of departure ($BMDL_{10}$). "EPA has concluded, by a weight of evidence evaluation, that dichloromethane is carcinogenic by a mutagenic mode of action. As a result, increased early-life susceptibility is assumed and the age-dependent adjustment factors (ADAFs) should be used when estimating age-specific cancer risks." (EPA, 2011). The IUR was based on Mennear et al., (1988) and NTP (1986) study on male $B6C3F_1$ mice, which developed hepatocellular carcinomas or adenomas and bronchalveolar carcinomas or adenomas after exposure of groups of 50 mice/sex/group to either 0, 2000, or 4000 ppm methylene chloride for two years.

ADAFs should be used since methylene chloride is carcinogenic by a mutagenic mode of action. The EPA states that a 10-fold adjustment should be used for ages 0 to <2 years of age for increased early life susceptibility. The EPA also states that a 3-fold adjustment should be used for ages 2 to <16 years of age. Over a 70 year lifespan, the ADAF TWA = 1.6571.

$$IRSL = \frac{1 \times 10^{-6}}{(1 \times 10^{-8})(1.65714)} = 60 \, {}^{\mu g}/_{m^3}$$

According to Rule 231(4) the averaging time is annual. Therefore, the IRSL for methylene chloride is 60 µg/m^3 based on an annual averaging time and the SRSL is 600 µg/m^3 based on an annual averaging time.

The EPA also determined a chronic inhalation RfC of 6 x 10^{-1} mg/m^3, based of a 2-year rat inhalation bioassay by Nitschke et al. (1988a). Groups of 90 male and 90 female Sprague-Dawley rats were evaluated following inhalation of methylene chloride concentrations of 0, 50, 200, 500 ppm methylene chloride for 6 hr/day, 5 days/week for 2 years. Five rats/sex were sacrificed at 6, 12, 15, and 18 months. All animals were examined histopathologically. No adverse effects on mortality rates, body weights, organ weights, clinical chemistry values, or plasma hormone levels were noted in animals exposed to methylene chloride in any of the exposure groups. Statistically significant increased incidences of nonneoplastic liver lesions (hepatic lipid vacuolation and multinucleated hepatocytes) occurred only in females in the 500 ppm group. Incidence of hepatocyte vacuolation was elevated at 500 ppm in male rats, but was not statistically significant. "In female rats exposed for only 12 months to 500 ppm, significantly increased incidences of nonneoplastic lesions compared with controls were restricted to liver cytoplasmic vacuolization (16/25 = 64%) and multinucleated hepatocytes (9/25 = 36%) in rats exposed during the first 12 months of the study; rats exposed only during the last 12 months of the study showed no elevated incidences of the liver lesions….Data from a similar two-year inhalation bioassay in Sprague-Dawley rats by Burek et al. (1984) provide additional support for the Nitschke et al. (1988a) observations; an increased incidence of hepatic vacuolation, correlated with fatty changes, was seen at exposures between 500 and 3,000 ppm. Because Nitschke et al (1988a) examined a lower range of exposures than was included in the Burek et al. (1984) study, the former study was selected as the principal study for derivation of a chronic inhalation RfC." (EPA, 2011).

A study by Aranyi et al. (1986) "…demonstrated evidence of immunosuppression following a single 100 ppm dichloromethane exposure for 3 hours in CD-1 mice. This exposure is lower than the POD for the liver effects that serve as the critical effect for the RfC. This study used a functional immune assay that is directly relevant to humans (i.e., increased risk of Streptococcal pneumonia-related mortality and decreased clearance of Klebsiella bacteria). (EPA, 2011). This study and others "suggest a localized portal-of-entry effect within the lung rather than a systemic immunosuppression. Because the Aranyi et al. (1985) study involved a single acute inhalation exposure, interpretation of the findings from this study in the context of chronic inhalation exposure is unclear." (EPA, 2011).

A PBPK model for the rat was used to estimate rat internal doses from the Nitschke et al. (1988a) study. The EPA used an uncertainty factor of 30 (3 [$10^{0.5}$] for extrapolation from rat to human, 3 [$10^{0.5}$] for variations to protect sensitive populations, and 3 for uncertainty reflecting database deficiencies). The EPA's justification for the database gap uncertainty factor involves a limitation in the design of the available developmental studies and lack of neurodevelopmental endpoints. The EPA cites several developmental studies including a two-generation inhalation reproductive study in rats (Nitschke et al., 1988b) that used 30 male and female F344 rats/group exposed to 0, 500, 1200, or 1500 ppm. It is hard to justify the uncertainty factor of 3 for database deficiencies as methylene chloride has been well studied, with repeated dose inhalation studies, two-year inhalation studies on rats, as well as reproductive and developmental studies. Therefore, the final uncertainty factor of 3 for database deficiencies will not be used to develop an ITSL for methylene chloride. The EPA derived PBPK point of departure (POD), 1st percentile human equivalent

concentration was calculated to be 17.2 mg/m^3 for hepatic effects (hepatic vacuolation). Using this value along with the uncertainty factor of 10 (3 [$10^{0.5}$] x 3 [$10^{0.5}$]) gives the following result:

$$ITSL = inhalationRfC = \frac{POD}{UF} = \frac{17.2\,{}^{mg}/_{m^3}}{10} = 1.72\,{}^{mg}/_{m^3} = 1{,}720\,{}^{\mu g}/_{m^3} = 2{,}000\,{}^{\mu g}/_{m^3}$$

According to rule 232(2)(a) the averaging time is 24 hours, but as this ITSL is based on a two-year inhalation study and as there is also be an acute ITSL, the averaging time for this ITSL will be annual. Therefore, the ITSL for methylene chloride is 2,000 µg/m^3 based on an annual averaging time.

There are several acute benchmarks for methylene chloride which are summarized in the following table.

Table 1. Methylene chloride acute toxicity benchmarks and candidate acute ITSLs.

Available Benchmark type	Value (µg/m^3)	Candidate acute ITSL (in descending order)	Candidate ITSL averaging time
ERPG-1	1,000,000	1,000,000	1 hour
AEGL-1	700,000	700,000	1 hour
Cal EPA acute REL	14,000	14,000	1 hour
OSHA PEL-STEL	400,000	PEL/100 = 4,000	1 hour
ACGIH TLV-TWA	200,000	TLV/100 = 2,000	8 hour
ATSDR acute MRL	2,000	2,000	24 hour
OSHA PEL-TWA	90,000	PEL/100 = 900	8 hour

AIHA set an ERPG-1 value for methylene chloride at 300 ppm (1.0 x 10^6 µg/m^3). An ERPG "is the maximum concentration in the air below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor." (http://www.atlintl.com/DOE/teels/teel/teeldef.html) ERPG values are not meant to be used in evaluations to fully protect public health from potentially repeated exposures and are only used with caution to derive an acute ITSL on a case-by-case basis.

The EPA set an interim AEGL-1 value for methylene chloride at 200 ppm (7 x 10^5 µg/m^3) for a 1-hour exposure duration based on Stewart et al. (1972) which studied humans that were exposed to concentrations of 868 and 986 ppm (n=3) could lead to light-headedness and speech difficulties. "These effects were absent at a 1-h exposure to 514 (n=3) or 515 ppn (n=8). The concentration of 514 ppm is used as point of departure for AEGL-1. These effects could be attributed to the DCM concentration in the brain rather than to CO. The human brain concentration of DCM following a 1-h exposure to 514 ppm was calculated to be 0.063 mM, using the human PBPK-model. Since susceptibility for gross CNS-depressing effects do not vary by more than a factor 2-3, an intraspecies uncertainty factor of 3 is considered sufficient, resulting in a maximum target concentration of DCM in the human brain of 0.021 mM" (NAS/COT, 2009) which was used in the PBPK-model calculation to determine the AEGL-1 of 200 ppm for a 1-hour exposure duration.

Cal EPA has set an acute inhalation REL at 14,000 µg/m^3 for a 1-hour exposure based on a study by Putz, et. al., (1976) showing impaired performance on dual-task and auditory vigilance tests on 12 human volunteers (6 non-smoker male and 6 non-smoker, non-pregnant females between 18-40 yrs of age) after a 4-hour consecutive exposure with to 195 ppm methylene chloride (to produce ~ 5% carboxyhemoglobin [COHb]). Each subject was his or her own control and were tested before methylene chloride exposure and after 90 minutes exposure to 195 ppm, on a visual-manual, dual task, and an auditory vigilance task of varying degrees of difficulty followed by taking samples of blood and expired air. No subjective symptoms, such as headache, nausea, or irritation of the nose and throat were reported. Performance measures decreased after exposure to methylene chloride levels that result in a 5.1% blood carboxyhemoglobin level (from 1.35% pre-exposure carboxyhemoglobin level), which is believed to be an indication of a temporary decrease in the level of central nervous system activation. Therefore, methylene chloride levels in the atmosphere could detrimentally impact job performance (Putz, 1976). Cal EPA gave a total uncertainty factor of 60 (uncertainty factor of 6 for a LOAEL and an uncertainty factor of 10 for individual variability in response). Cal EPA determined an equivalent 60 minute exposure from the 90 minute exposure using the Haber equation ($C^n * T = K$) where n=2. Using the above data, Cal EPA derived an acute REL of 14,000 µg/m^3 for a 1 hour averaging time (Cal EPA, 2008). As Cal EPAs RELs are peer reviewed, this value will be adopted as the acute ITSL for methylene chloride.

Based on the above information, the initial risk screening level (IRSL) for methylene chloride (CAS # 75-09-2) is 60 µg/m^3 annual averaging time. The secondary risk screening level (SRSL) for methylene chloride is 600 µg/m^3 annual averaging time. The initial threshold screening level (ITSL) for methylene chloride is 2,000 µg/m^3 annual averaging time and an acute ITSL is 14,000 µg/m^3 based on a 1 hour averaging time.

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