MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 12, 2016

TO: Methyl Chloride File (CAS# 74-87-3)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: ITSL Derivation

Previously, the averaging time (AT) assigned to methyl chloride was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from Doreen Lehner dated September 3, 2013. The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Methyl Chloride (CAS # 74-87-3)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Screening Level for Methyl Chloride (CAS # 74-87-3)

DATE: September 3, 2013

The initial threshold screening level (ITSL) for methyl chloride (CAS # 74-87-3) is $90 \ \mu g/m^3$ based on a 24-hour averaging time. The Initial Risk Screening Level (IRSL) for methyl chloride of 1.6 $\mu g/m^3$ based on an annual averaging time that was developed in 1985 will be rescinded as there is insufficient carcinogenicity data to support an IRSL on this chemical.

Methyl chloride (CAS# 74-87-3) also known as chloromethane, R-40, or HCC 40 is a haloalkane with a molecular weight of 50.49 g/mol. It is a colorless, extremely flammable gas that can be compressed into a colorless liquid, with a mildly sweet odor with an odor threshold of 250 ppm (520,000 µg/m³), which is detected at possibly toxic levels. It is moderately soluble in water, in which it decomposes to methanol and hydrogen chloride. Methyl chloride was once widely used as a refrigerant and as a local anesthetic, but due to concerns about its toxicity, it is no longer present in consumer products. Methyl chloride is used industrially as a methylating and chlorinating agent, as an extractant for greases, oils, and resins, as a propellant and blowing agent in polystyrene foam production, as an intermediate in drug manufacturing, as catalyst carrier in low-temperature polymerization, as a fluid for thermometric and thermostatic equipment, and as an herbicide (EPA, 2001; Wikipedia, 2013). Methyl chloride is produced by algal marine micro-organisms during cellular metabolism (Wikipedia, 2013). The structure of methyl chloride is shown below.



Figure 1. Structure of methyl chloride.

A literature review was conducted to determine an initial threshold screening level (ITSL) for methyl chloride and also to determine if there was enough data to support the current initial risk screening level (IRSL). The following references and databases were searched to derive the above screening level: Chemical Criteria Database (CCD), United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2010

guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 6/6/2013), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, US EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

Determination of the ITSL

There are many studies on the effects of methyl chloride. The principle route of human exposure to methyl chloride is inhalation, with a minor route being dermal absorption. Methyl chloride is readily absorbed into the lungs and rapidly reaches a steady-state concentration in the blood, where it is distributed to most organs and tissues (EPA, 2001a). Methyl chloride is metabolized by glutathione (GSH) and that depletion of GSH levels in target tissues could lead to toxicity. Methyl chloride acts as a CNS depressant, whose effects include drunkenness, vomiting, painful neck, loss of appetite, diarrhea, dizziness, giddiness, blurred vision, ataxia, confusion, slurred speech, double vision, tremors of the hands and lips, drooping eyelids and eye twitch, muscle spasms, convulsions and body spasms, cold and clammy skin, loss of memory, hallucinations, respiratory depression, unconsciousness, coma, and death (EPA, 2001a). "Reported cardiovascular effects include tachycardia, increased pulse rate, low blood pressure and electrocardiogram abnormalities; reported hepatic effects include clinical jaundice, cirrhosis of the liver, and impaired performance on the levulose tolerance test; and reported renal effects include albuminuria, increased serum creatinine and blood urea nitrogen, proteinuria, anuria, and hematuria" (EPA, 2001a).

EPA has an RfC of 9E-2 mg/m³ based on a NOAEL of 50 ppm (103.2 mg/m³) from Landry et al., (1983, 1985) an 11-day continuous exposure inhalation study on C57BL/6 mice. In the Landry et al., (1985) study, groups of "female C57BL/6 mice (12/dose) were exposed 'continuously' (22-22.5 hours/day) to 0, 15, 50, 100, 150, or 400 ppm (0, 31, 103, 206, 309, 412, or 824 mg/m³) or 'intermittently' (5.5 hours/day) to 0, 150, 400, 800, 1600, or 2400 ppm (0, 309, 824, 1648, 3296, or 4956 mg/m³) of methyl chloride for 11 days. Continuous exposure was interrupted once in the morning and once in the afternoon to move intermittently exposed mice in and out of the exposure chambers, observe all animals, train or test animals, etc. Neurofunctional testing was conducted during the course of the study, which consisted of monitoring mice (previously trained for 2 weeks on the apparatus) for their abilities to stay on an accelerating rod (acceleration = 1 rpm/sec, from 10 rpm up to 70 rpm) 2 to 2.5 hours post-exposure after 4, 8, and 11 days of exposure. Upon termination, the non-fasted mice were subjected to gross and histopathological examination (to include brain, thymus, liver, and kidneys). Body and organ weights were obtained, as were samples of most major organs and tissues (including spinal cord). Tissue samples from the cerebella of three preselected mice were examined by electron microscopy from each of the 0 and 150 ppm continuously exposed groups after 1, 2, 4, 6, 8, or 10.5 days of exposure" (EPA, 2001a).

"No exposure-related mortality was observed in mice exposed continuously to the lower concentrations of methyl chloride (15 and 50 ppm), whereas exposure to 400 or 200 ppm was lethal after 4 or 5 days, respectively after leading to loss of appetite and ataxia with frequent falling. Mice exposed to 150 to 400 ppm developed poor motor coordination and deteriorated to a moribund condition with accompanying inanition (i.e., marked weakness) at a rate that was dose-dependent. Mice in the 200-ppm group were sacrificed on day 5 because one mouse had died prior to scheduled necropsy and most of those remaining were moribund. Mean body weights were significantly diminished in the 200 and 150 ppm groups and somewhat diminished

File For Methyl Chloride File (CAS# 74-87-3)

Attachment, Page 3: Memo from Doreen Lehner (September 3, 2013)

at 100 ppm, but were not affected at 50 ppm. Body weights were not obtained for 400-ppm mice. No significant decrements in rotating rod performance were noted for the control and 15 to 100 ppm groups, while substantially diminished performance was seen in the 150 ppm group after 4 and 8 days, with animals moribund or dead by day 11." (EPA, 2001a). "Exposure to 100 or more ppm resulted in concentration and duration dependent degenerative changes to the cerebellum, principally in the granule cells, that were characterized by nuclear pyknosis and karyorrhexis, the latter referring to the rupture of the cell nucleus in which chromatin disintegrates. These effects were observed most frequently in the dorso-medial cerebellar folia. At 150 ppm, there was a marked loss of granule cells, a decrease in Purkinje cells, and an increase in macrophages. Lesions were more severe in [the] 200 and 400 ppm groups. Transient intra- and extracellular vacuolation in the Purkinje and /or molecular cell layer and in the white matter were also noted. Electron microscope observations were consistent with those obtained through light microscopy. Decreased glycogen content in 100 to 200 ppm mice was the principal significant change observed in the liver, although focal periportal hepatocellular degeneration and/or necrosis was noted in the 400 ppm group. No exposure related histopathological effects were observed in the 15 and 50 ppm groups" (EPA, 2001a).

For intermittently exposed mice, "inanition was apparent in the 2400 [ppm] group (also slow movement and roughened haircoats), as was thin, watery blood from the heart, a finding supported by low blood PCV values. The spleens of this group were considerably enlarged, suggestive of extramedullary hematopoiesis, which was microscopically confirmed. The in-life observation of red urine in the 2400 ppm group was determined to result from hemoglobinuria consistent with intravascular hemolysis (hemoglobinemia), rather than from hematuria. These animals deteriorated (e.g., hind limb extensor rigidity) and were sacrificed moribund on days 8-9." (EPA, 2001a). "Mice exposed to 1600 ppm displayed less severe effects, including slightly rigid hind limbs and some tendency to rear on hind legs (2/12) and be more excitable than controls; these effects tended to mitigate during overnight periods of nonexposure. Mean body weights were significantly diminished in the 2400 ppm group, but were not affected at 1600 ppm. No significant decrements in rotating rod performance were noted for the control, 150 and 400 ppm groups" (EPA, 2001a). "Microscopically, evidence of kidney toxicity was found only in the 2400 ppm group and consisted of slight multifocal tubular degeneration and regeneration and eosinophilic-staining tubular casts...Decreased hepatocyte size, without degeneration or necrosis, were variably seen in mice from the 400 through 2400 groups. Decreases in mean absolute and relative thymus weight were statistically significant and considered exposurerelated (reflecting decreased body weights and stress) for the 2400 and 1600 ppm groups; the latter group evidenced a decrease in the size of the thymus. No gross exposure-related effects were noted in the 400 ppm or 800 ppm groups." (EPA, 2001a).

The Landry et al., (1985) study identifies a NOAEL of 50 ppm and a LOAEL of 100 ppm, based on cerebellar damage in the continuous exposure group; for the intermittent exposure group the NOAEL of 150 ppm and the LOAEL was 400 ppm. Cerebellar lesions were observed in the 150 ppm continuously exposed mice as well as impaired performance on the rotorod. Evidence of pyknosis and karyorrhexis was observed in the 100 ppm continuously exposed mice which did not affect the mice's performance on the rotorod.

The EPA RfC used the Landry et al. (1983, 1985) study NOAEL of 50 ppm (103.2 mg/m³) and adjusted this value to a continuous exposure by using the following equation:

NOAEL (ADJ) = 103.2
$$mg/m^3 \times \frac{22 hrs}{24 hrs} \times \frac{7 days}{7 days} = 94.6 mg/m^3$$

The EPA also used a total uncertainty factor of 1,000 (UF of 3 for interspecies [no male mice used]; UF of 10 for subchronic to chronic; UF of 10 for intraspecies [known differences in metabolism rates due to genetic polymorphisms]; and an UF of 3 for data gap [no studies on histopathology of cerebellar lesions for offspring of affected mice]). After application of these uncertainty factors, the EPA RfC is 9E-2 mg/m³.

According to Rule 232(1)(a), the EPA RfC can be used as an ITSL. Therefore, 9E-2 mg/m³ is the same as 90 μ g/m³. According to Rule 232(2)(b) the default averaging time is 24 hours. This is an appropriate averaging time for this ITSL as this RfC is based on an 11-day inhalation study and it would be inappropriate for such a study to have an annual averaging time, notwithstanding the application of an UF of 10 for subchronic to chronic.

The initial threshold screening level (ITSL) for methyl chloride (CAS # 74-87-3) is 90 μ g/m³ based on a 24-hour averaging time.

Determination of an IRSL

The updated literature search for methyl chloride provided insufficient data to maintain the current IRSL. EPA IRIS database (EPA, 2001b) has no inhalation unit risk (IUR) for methyl chloride; EPA (2001b) lists "inadequate information to determine carcinogenicity". EPA (2001b) does suggest that methyl chloride may be a weak mutagen due to an increased incidence of tumor formation (benign and malignant) in male mouse kidneys, which was not seen in female mice or rats tested in the same study (CIIT, 1981). In humans the primary path in metabolizing methyl chloride involves glutathione which produces S-methylgluta-thione and Smethylcysteine. This reaction has been observed in human erythrocytes and may also occur in the liver. When glutathione levels are depleted, a secondary metabolic pathway in the body using cytochrome P450 CYP2E1 is available, which leads to the production of formaldehyde. In the CIIT (1981) study, it was postulated that the tumor formation in male mouse kidneys was associated with the metabolism of methyl chloride by CYP2E1 in the kidney. Male mice have high levels of CYP2E1 protein in their kidneys, much higher than female mice and rats. Humans do have cytochrome P450s in their kidneys, but CYP2E1 is not found in human kidneys. The cytochrome P450s found in human kidneys are CYP3A isoforms which unknown activity to environmental chemicals and CYP4 isoforms, which have no known activity to environmental chemicals. Therefore, the formation of kidney tumors associated with CYP2E1 would not be likely to affect humans. As there are no other studies on methyl chloride with carcinogenic findings it is not appropriate to determine an IRSL on this compound. The IRIS review of methyl chloride was last updated in 2003. A CAS search performed on June 6, 2013 found no recent carcinogenicity studies for this compound. As this chemical is a weak mutagen it is possible that it may be a carcinogen, but there is inadequate data available for an IRSL determination. The ITSL provides adequate protection against potential cancer effects.

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