MICHIGAN DEPARTMENT OF NATURAL RESOURCES AND ENVIRONMENT

INTEROFFICE COMMUNICATION

TO: Methycyclopentane File (CAS # 96-37-7)

FROM: Gary Butterfield

SUBJECT: Screening level for Methycyclopentane

DATE: October 4, 2010

Methylcyclopentane is a colorless liquid with a boiling point of 71.8C, with a melting point of -142C, and a vapor pressure of 138 mmHg at 25C. The molecular formula is C_6H_{12} and the molecular weight is 84.2 grams/mol.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Environmental Quality (DEQ) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1968 - August 2010), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The NLM toxline and CAS on-line searches were conducted on September 2, 2010. There is little toxicity information on this particular chemical. This can mostly be attributed to methylcyclopentane normally being found as a component of a mixture, commercial grade hexane solvent, rather than as a pure unique chemical. The commercial hexane consists of approximately 50% n-hexane, and smaller amounts of many other C_5 and C_6 materials including methylcyclopentane.

A few studies actually tested methylcyclopentane for toxic effects. Ono et al (1981) gavaged, average dose of 897 mg/kg, groups of 6 male Wistar rats over an eight week period while measuring nerve conduction velocity in the tail nerves. They found decreased velocity – an indication of neurotoxicity – near the end of the study. However, no other endpoints (pathology, organ weights, etc.) were evaluated by the authors making this article of questionable use for setting a screening level. In the study by Halder et al (1985), groups of 10 male F344 rats were gavaged 5 days a week for four weeks at doses of 0, 500 or 2000 mg/kg to look for which of the gasoline components caused nephrotoxicity (the alpha-u2-globulin accumulation). Mortality occurred at the high dose, some of it due to gavage errors. As this study only looked at kidney changes and was too short of duration to fully evaluate neurotoxicity effects;

again, it is considered questionable for use for setting a screening level for methylcyclopentane.

There are several toxicity studies available on mixtures of C6 hydrocarbons, commonly referred to as commercial hexane. Methylcyclopentane is a component of these mixtures, making up to as much as 25% of the total mixture, although the neurotoxic n-hexane often is 50% of these commercial mixtures.

In the study by Egan et al (1980), they compare n-hexane free C6 mixture to see if neurotoxic changes happen - similar to what occurred with n-hexane exposure - with exposure to a commercial hexane solvent (free of n-hexane). This study only looked for neurotoxic endpoints; no other clinical signs, or pathology of other tissues were evaluated. The potential neurotoxic effects were evaluated in a group of 6 male Sprague-Dawley rats who were exposed to only one dose level of 1750 mg/m^3 of an n-hexane free C6 mixture (which was identified as being 24% methylcyclopentane, 35% 2-methylpentane, and 30% 3-methylpentane, 6% cyclohexane) for 22 hours a day, 7 days a week for 6 months. Two rats, of the total 6, were sacrificed following 2, 4 or 6 months of exposure to evaluate neuropathology changes. Tissues microscopically examined included: cerebellar vermis; cervicomedullary junctions; lumbar cord; sinal roots and ganglia; sciatic notch; and tibia nerve. The authors found the n-hexane free C6 mixture to not cause neurotoxic effects at the exposure level of 1750 mg/m^3. This study only looked for neurotoxic effects, no histopathology of other tissues was conducted, and there were only two rats examined each of the three sacrifice points – making this study of questionable use for setting a screening level.

In Biodynamic (1995), groups of 50/sex/dose F344 rats and B6C3F1 mice were exposed to 0, 900, 3000 or 9018 ppm 6 hours a day, 5 days a week for 2 years to commercial hexane (which was 51% n-hexane). Female mice had statistically significant increased hepatocellular neoplasms (combined incidence of adenomas and carcinomas) 7/50, 8/50, 9/50 and 16/50 for control to high dose, respectively. Male mice and rats of both sexes did not have statistically significant increased neoplasms different than controls. The ATSDR did not report any other pathology changes or development of neurotoxicity, therefore this summary can not be used to derive an ITSL for methylcyclopentane. It is also not possible to claim the increased neoplasm occurrence is due to methylcyclopentane due to the presence of many other substances in the mixture.

In the IRDC (1981) study, a group of 16 or 17 rats (strain unspecified) were exposed to 494 ppm vapors of mixed hexane (that contained less than 1% n-hexane) for 22 hours a day for 6 months. There was a control group of 8 rats. There were no signs of neurotoxicity, signs of clinical effects, or any histopathology in the mixed hexane group. The use of only one dose group with exposure to mixed hexane vapors (not able to identify when adverse effects will begin to occur), and the relatively small dose groups are limitations of this study.

In Neeper-Bradley et al (1989), a Sprague-Dawley rat and CD-1 mice inhalation develop-mental toxicity study was reported. Groups of 25 pregnant rats and 30 pregnant mice were exposed to 0, 914, 3026, or 9017 ppm (converts to 0, 3140, 10400, or 31000 mg/m^3) commercial hexane (that was 53% n-hexane) 6 hours a day on gestation days 6-15. The 3026 and 9017 ppm dose level was maternally toxic – decreased body weight – in both rats and mice. The maternal NOAEL is 914 ppm or 3140 mg/m^3. The developmental toxic dose to mice was 9017 ppm due to the increased incidence of variations (reduced bone ossification), NOAEL 3026 ppm. The highest dose tested was not developmental toxic to rats. The relatively short exposure duration for a developmental study could be considered a limitation for utilizing this study for setting a screening level.

Although study limitations are considered significant, possible screening levels for C6 mixtures could be calculated from the above studies as in the following table. The R232 full uncertainty factors were used in the following calculations, even though most were longer than 7 days and could have the 35-fold, 7-day to chronic duration adjustment factor reduced.

Study	NOAEL (mg/m^3)	calc basis	potential ITSL (ug/m^3)
Ono	897 mg/kg	R232(1)(e)	285
Egan at al	1750	R232(1)(d)	460
IRDC	494 ppm or 1660	R232(1)(d)	440
Neeper-Bradley	3140	R232(1)(d)	220

The AQD has established ITSLs for several other C6 compounds at fairly high concentrations; see the following table.

CAS #	chemical	ITSL (ug/m^3)
107-83-5	2-methylpentane	17600 8-hour
96-14-0	3-methylpentane	3500 8-hour
110-82-7	cyclohexane	6000 24-hour
110-54-3	n-hexane	700 24-hour

At this time, it is concluded that the ITSL for methylcyclopentane should be set at the lowest of the above ITSLs for C6 compounds: 700 ug/m^3, 24-hour average. From the above information, the ITSL for methylcyclopentane could be greater than 700 ug/m^3 if adequate toxicity data was available for methylcyclopentane. This ITSL is still considered to be health protective for methylcyclopentane, and more appropriate than using the overly restrictive default, 0.1 ug/m^3 annual, for a lack of adequate toxicity data.

References:

ATSDR. 1999. Toxicological profile for hexane.

Biodynamics. 1995. An inhalation oncogenicity study of commercial hexane in rats and mice: Part I (rats) and part II (mice). As summarized in ATSDR

Egan et al. 1980. n-Hexane free hexane mixture fails to produce nervous system damage. Neurotoxicology 1:515-524.

Halder et al. 1985. Hydrocarbon nephropathy in male rats: identification of the nephrotoxic components of unleaded gasoline. Toxicol Ind Health 1(3):67-87.

IRDC. 1981. Six month continuous inhalation exposures of rats to hexane mixtures. As summarized in ATSDR

Neeper-Bradley. 1989. Developmental toxicity studies of commercial hexane vapor in CD (Sprague-Dawley) rats and CD-1 mice. As summarized in ATSDR

Ono et al. 1981. A comparative study on the toxicity of n-hexane and its isomers on the peripheral nerve. Int Arch Occup Environ Health 48:289-294.

GB:lh