MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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February 6, 2017

TO: Ethyl Amyl Ketone (CAS# 541-85-5)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: Derivation of Initial Threshold Screening Level

The initial threshold screening level (ITSL) for ethyl amyl keton is 220 µg/m^3, with annual averaging time.

Previously, the averaging time (AT) assigned to the ethyl amyl ketone ITSL was 24 hours, pursuant to Rule 232(2)(b) of the Air Pollution Control Rules promulgated at that time (October 22, 1997; see attached memo). The recently promulgated (December 22, 2016) Air Pollution Control Rule 232(2)(b) states that ITSLs based on Rule 232(1)(a) are assigned an annual averaging time. An updated literature review was not performed at this time.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

OCTOBER 22, 1997FEBRUARY 6, 2017

TO: File for Ethyl Amyl Ketone (CAS# 541-85-5)

FROM: Michael Depa, Toxics Unit

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for ethyl amyl ketone (EAK; also called 5-methyl-3-heptanone) is 220 µg/m³ based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, RTECS, ACGIH Threshold Limit Values, NIOSH Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, IARC Monographs, CAS Online (1967 - September 19, 1997), National Library of Medicine, Health Effects Assessment Summary Tables, and NTP Status Report. Review of these sources found that EPA has not established an RfC or RfD for EAK. The ACGIH and NIOSH have established occupational exposure limits (OELs) for EAK at 131 mg/m³. The molecular weight of EAK is 128.21 g. The subchronic toxicity of EAK was examined in an oral toxicity study available from Toxic Substance Control Act Documents under the 8(e) program. This study is described below.

Groups of 5 adult male CD rats were gavaged daily with 0, 82, 410, or 820 mg/kg/day EAK 5 days/week for 13 weeks (IBM, 1989a). A Functional Observational Battery (FOB) was also conducted to assess functional impairment of the nervous system prior to the first dose and on days 7, 14, 30, 60, 63, and on 91 of exposure. Forelimb and hindlimb grip strength were quantified as well. Dose related reductions in feed consumption and weight gain were observed at both the 410 and 820 mg/kg dose levels. No differences in absolute testes weights were apparent at any dose. The results of the FOB clearly indicated peripheral neuropathy in animals exposed to the highest dose. The authors stated that similar functional differences were detected in the mid-dose group, but were less severe. The authors also stated that there were no functional deficits apparent in the 82 mg/kg dose group. Microscopic examination of the sciatic and tibial nerves from the 820 mg/kg group revealed neuropathy predicted by gamma-ketones. These changes included axonal swellings, reduction of myelin thickness, and Wallerian degeneration. Nerves from the 410 mg/kg group generally had one or two fragmented and degeneration axons undergoing Wallerian degeneration and several axons with small focal swellings. Myelin infolding was also observed more frequently than in control nerves. Nerves in the 82 mg/kg dose group did not show any evidence of pathology attributable to EAK exposure. A LOAEL of 410 mg/kg was identified from this study based on

neuropathy and functional decrements in the FOB. A NOAEL was identified from this study at 82 mg/kg.

The ACGIH Documentation of Threshold limit Values (ACGIH, 1991) was reviewed in order to determine the appropriateness of the TLV. The ACGIH recommended that the TLV be set at 25 ppm (131 mg/m³), "as a comfort level for unconditioned workers." ACGIH described a study of humans exposed at 25 ppm where they experienced irritation of the eyes and respiratory tract and detected a strong odor. At 100 ppm, irritation of mucous membranes, headache, and nausea were too severe to tolerate for more than a few minutes. ACGIH stated that, "Workers may complain of odor and transient eye irritation when the concentrations exceeds 25 ppm, but experience shows that transient responses did not lead to significant systemic effects."

Other than respiratory irritation no data was found to indicate that the effects of oral and inhalation exposure are different. Furthermore, no data was found to indicate that it would be inappropriate to develop an inhalation screening level based on an oral study especially if that screening level protects against the respiratory irritation effects cited by ACGIH (1991). Therefore, the subchronic gavage rat study (IBM, 1989a) was deemed appropriate to use to derive an ITSL.

An RfD was first developed using the NOAEL of 82 mg/kg from the subchronic gavage study (IBM, 1989a); then an ITSL was calculated from the RfD based on Rule 230(1)(b) hierarchy.

$RfD = NOAEL/(UF_1 \times UF_2 \times UF_3) \times (\text{days dosed per week})/(7 \text{ days}) \times W_a/I_a$

Where, UF_1 = uncertainty factor of 10 for extrapolating animal data to human,
UF_2 = 10 to account for sensitive individuals,
UF_3 = 10 for converting a subchronic study to a chronic study,
W_a = weight of the male rat (EPA, 1988), and
I_a = inhalation rate of the rat (EPA, 1988).

$RfD = (82 \text{ mg/kg})/(10 \times 10 \times 10) \times 5/7 \times (0.47 \text{ g})/(0.43 \text{ m}^3)$

RfD = 0.064 mg/kg

The ITSL was calculated as follows:

$ITSL = RfD \times (70 \text{ kg})/(20 \text{ m}^3)$

$ITSL = 0.22 \text{ mg/m}^3$

$ITSL = 220 \text{ µg/m}^3$ (based on a 24-hour averaging time)

The ITSL for ethyl amyl ketone is 220 µg/m³ based on a 24-hour averaging time.

REFERENCES

ACGIH. 1991. Threshold limit values (TLVs) and biological exposure indices (BEI) documentation. American Conference of Governmental Industrial Hygienists. Cincinnati, OH, 45240-1634.

EPA. 1988. Recommendation for and documentation of biological values for use in risk assessment. PB 88-179874.

IBM. 1989. A subchronic oral toxicity study of 5-methyl-3-heptanone in the rat utilizing a functional observational battery and neuropathology to detect neurotoxicity with cover letter 121589. Obtained from TSCA 8(e) documents (202-260-7099) EPA/OTS Doc# 89-900000074