MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Dipropyl ketone [CAS# 123-19-3]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: February 7, 2017

SUBJECT: Dipropyl ketone [CAS# 123-19-3] ITSL change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for dipropyl ketone is 250 µg/m^3 based on an annual averaging time. The ITSL was originally established on 11/2/2009 and was based on a 83 day gavage study in male rats (NTIS, 1980). The critical effects included significantly decreased average body weight, changes in organ weights, and significantly decreased blood glucose levels. As the key study used to derive the ITSL is a 83 day gavage study, the averaging time is appropriately set at annual. Therefore, the averaging time is being changed from 24 hours to annual.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

NTIS. 1980. EPA/OTS 86-95-0000344 (microfiche). Eastman Kodak. 90-day repeated oral administration of five ketones and n-heptane to rats. Authors John L. O'Donoghue and Walter J. Krasavage. January 21, 1980. EPA, Office of Toxic Substances.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

November 2, 2009

To: File for Dipropyl Ketone (CAS# 123-19-3)

From: Michael Depa, Toxics Unit

Subject: Screening Level Determination

The initial threshold screening level (ITSL) for dipropyl ketone (4-heptanone) is 250 µg/m³ (based on a 24-hour averaging time).

The following references or databases were searched to identify data to determine the screening level: Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967- October 26, 2009), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established an reference concentration (RfC) or reference dose (RfD). Both the NIOSH REL and the ACGIH TLV are 50 ppm (233 mg/m³). The molecular weight is 114.18 g and the vapor pressure is 5.5 mmHg at 20°C.

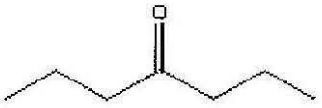

Figure 1. Molecular Formula of Dipropyl Ketone

Animal Toxicity

A summary of a French publication (Muller and Greff, 1984) reported a mouse RD50 (a 50% decrease in respiratory frequency) of 1100 ppm (5129 mg/m³) (Bos et al., 1992). The exposure time was not given.

Carpenter et al. (1974) reported that there was no mortality after a 4-hour exposure to 2000 ppm (9325 mg/m³) but that 4000 ppm killed 6 out of 6 rats. The authors also reported that the rat oral LD50 was 3.73 ml/kg. Since the specific gravity of dipropyl ketone is 0.817 the LD50 was calculated to be 3.04 g/kg.

A group of 5 male CD rats were gavaged with 1000 mg/kg for 5 days per week for 83 days (Eastman Kodak, 1980). The total duration of the study was actually 90 days: 7 days of dosing at 2000 mg/kg and 83 days of dosing at 1000 mg/kg. The original dose was reduced from 2000 mg/kg to 1000 mg/kg due to 3 deaths, one due to chemically induced pneumonia following direct contact of the compound with pulmonary tissues and two due to severe central nervous system depression and subsequent cardiorespiratory failure. There were 8 rats in the original group. All 5 remaining rats that were dosed at 1000 mg/kg for 83 days survived until sacrifice. The average body weight was significantly decreased compared to control rats at week 4 and thereafter. There were no differences from control

rats in hemoglobin, %PCV, white blood cell count, % polymorphonuclear leukocytes and % lymphocytes. Blood glucose levels were significantly decreased compared to controls. The following relative organ weights were significantly different from controls: liver, kidney, adrenal gland, and testes. The following absolute organ weights were significantly different from controls: brain and heart. The 1000 mg/kg dose group was determined to be a lowest-observed-adverse-effect-level (LOAEL) based on organ weight changes and blood glucose concentrations.

In an inhalation study, groups of 5 male Sprague-Dawley rats were exposed via whole-body inhalation to 0 or 1200 ppm dipropyl ketone for 6 hours/day, 5 days/week for a total of 10 exposures (Eastman Kodak, 1999). Clinical signs following treatment consisted of reduced activity. Weight gain was similar in treated and control groups. The following clinical chemistry and hematology parameters were considered statistically similar to control values using the Student's t test at the 5% level: glutamic oxalacetic transaminase, glutamic pyruvic transaminase, lactic acid hydrogenase, alkaline phosphatase, urea nitrogen, glucose, hemoglobin concentration, hematocrit, white blood cell count, and differential white blood cell count. The ream relative liver weight was marginally elevated statistically in the treated group as compared to the control this was not considered biologically significant. Mean absolute liver weight and mean absolute and relative kidney weights were similar between treated and control groups. No compound-related gross or histopathologic changes were identified.

Derivation of Initial Threshold Screening Level

Both the NIOSH recommended exposure limit (REL) and the ACGIH threshold limit value (TLV) are 50 ppm (233 mg/m^3). The TLV for dipropyl ketone was based on the TLV for methyl isobutyl ketone (MIBK; CAS No. 108-10-1). The ACGIH (1992) stated that MIBK and dipropyl ketone have similar acute toxicity, however, no support for this statement was cited. In the TLV documentation for MIBK, ACGIH stated that during a 24-hour exposure of 100 ppm MIBK rats developed toxic nephrosis of the proximal tubules. The TLV for MIBK is 50 ppm. The margin of safety is 2 fold between the "safe" occupational level (50 ppm) and that which produces kidney injury (100 ppm). An OEL derived ITSL for dipropyl ketone would be 2330 µg/m^3 with a 8-hour averaging time. However, given that dipropyl ketone is a systemic toxicant, and is not expected to have respiratory tract effects specific to the inhalation route of exposure it was deemed appropriate to use the 90 day oral toxicity study (Eastman Kodak, 1980) in order to derive the ITSL.

As mentioned above the 1000 mg/kg dose was determined to be a lowest-observed-adverse-effect-level (LOAEL) based on 90 day oral study, 5 days per week, where organ weight changes and blood glucose changes were observed. The RfD was determined from this as follows:

LOAEL(Adjusted) = LOAEL x 5days/7days
LOAEL(Adj) = 1000 mg/kg x 5/7
LOAEL(Adj) = 714 mg/kg

RfD = LOAEL(Adj)/(UF_1 x UF_2 x UF_3 x UF_4)
Where UF_1 is an uncertainty factor of 10 used to extrapolate for interspecies (animal to human) effects,
UF_2 is 10 to extrapolate intraspecies (sensitive individual) effects,
UF_3 is 10 to extrapolate subchronic to chronic duration, and
UF_4 is 10 to extrapolate LOAEL to no-observed-adverse-effect-level (NOAEL).
RfD = 714/(10 x 10 x 10 x 10)
RfD = 0.0714 mg/kg

The ITSL was calculated pursuant to Rule 232(1)(b) hierarchy as follows:

ITSL = RfD x 70kg/20m^3
ITSL = (0.0714 mg/kg) x 70kg/20m^3
ITSL = 0.250 mg/m^3
ITSL = 250 µg/m^3 (based on a 24-hour averaging time)

References

ACGIH. 1992. Threshold limit values (TLVs) and biological exposure indices (BEI) documentation. American Conference of Governmental Industrial Hygienists. Cincinnati, OH, 45240-1634.

Bos P, Zwart A, Reuzel P, Bragt P. 1992. Evaluation of the sensory irritation test for the assessment of occupational health risk. Critical Reviews in Toxicology. Volume 21(6) 423-450.

Carpenter CP, AWeil CS, Smyth HF. 1974. Range-finding Toxicdiy Data: List VIII. Toxicology and Applied Pharmacology. Volume 28, 313-319.

Eastman Kodak. 1980. 90-day repeated oral administration of five ketones and n-heptane to rats. authors John L. O"Donoghue and Walter J. Krasavage. January 21, 1980. Obtained from EPA, Office of Toxic Substances, EPA/OTS 86-95-0000344 (microfiche).

Eastman Kodak. 1999. Personal communication from Deborah Rice Gordon, Applied and Regulatory Toxicology, Health and Environment Laboratories, Eastman Kodak Company, Building 320 , Kodak Park, Rochester, NY 14652-6253. October 20, 1999.

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

EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. United State Environmental Protection Agency, Office of Research and Development. Washington D.C. 20460. EPA/600/8-90/066F

Muller J, Greff G. 1984. Recherche de relations entre toxicite de molecules d'interet industriel et proprietes physico-chemiques: test de'irritation des voies aeriennes superieurs applique a quatre familles chimiques. Food Chemical Toxicology. Volume 22, Number 8, pages 661-664.

NIOSH. 1997. Pocket guide to chemical hazards. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. NIOSH publication number 97-140.