MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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February 9, 2017

TO: File for Diisobutyl Ketone (CAS No. 108-83-8)

FROM: Michael Depa, Air Quality Division, Toxics Unit

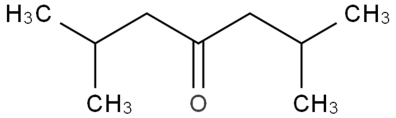
SUBJECT: Initial Threshold Screening Level Derivation

The Initial Threshold Screening Level (ITSL) for diisobutyl ketone (DIBK; also known as 2,6-dimethyl-4-heptanone) is 1500 µg/m³ with 8-hr averaging time.

The ITSL for DIBK was originally established July 14, 1992 at 1500 µg/m³, with 8-hr averaging time, based on the occupational exposure limit (OEL) of 25 ppm (150 mg/m³). The ITSL of 1500 µg/m³ is being retained because the OEL remains the best health protective exposure level; it is based on human data, and the use of 100-fold uncertainty/adjustment factor (see equation in Rule 232(1)(c) below) provides an adequate margin of safety for protecting the general public, especially sensitive individuals.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), the California Office of Environmental Health Hazard Assessment (Cal OEHHA), National Library of Medicine's TOXNET and TOXLINE, Toxic Substance Control Act (TSCA) Test Submissions (TSCATS), EPA's Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV), European Chemicals Agency (ECHA) Risk Assessment (REACH) database, Chemical Abstract Service (CAS) SciFinder database and US EPA (epa.gov). The molecular weight of DIBK is 142.27g. The molecular structure is shown in Figure 1.

Figure 1. Diisobutyl ketone (108-83-8)



Both ACGIH and NIOSH have occupational exposure levels (OELs) of 25 ppm (150 mg/m^3[1]). ACGIH (2001) stated:

> In human response studies on three volunteers, a 3-hour exposure at 50 and 100 ppm diisobutyl ketone caused slight irritation to the eyes, nose, and throat. Concentrations above 50 ppm were considered unsatisfactory; 50 ppm was considered satisfactory. Using 12 subjects, Silverman et al found the majority had some degree of eye irritation and complained of unpleasant odor at concentrations above 25 ppm.

Animal Toxicity Information

A well conducted inhalation animal study was performed in groups of 10 male and female Fischer rats; exposure concentrations of 0, 98,300 or 905 ppm DIBK were for 6 hours per day for 9 days (Dodd et al., 1987). Additional groups of 10 male and female rats were exposed to 0 and 905 ppm and observed for two weeks (recovery period). Measurements included: food and water intake, organ weights, histopathology, hematology, and urine analysis. RESULTS: Classic male nephropathy was exhibited in male rats; including hyaline droplet formation and α2μ-globulin buildup in the renal proximal tubules. Liver weights were statistically increased ($p<0.05$) in male and female rats at 300 and 905 ppm, but without histopathologic changes. After two weeks recovery the liver weights were back to normal at the 905 ppm dose (there was no 300 ppm dose group for the two week recovery assessment, as designed by the authors). Other changes observed at 905 ppm included statistically increased platelet count, which returned to normal during the recovery period. Statistically increased platelet count was also observed at 300 ppm in males only. Signs of ocular irritation were observed at 905 ppm after 9 days of exposure, but without any histopathological indication of effect under light microscopy. A Lowest-Observed-Adverse-Effect-Level (LOAEL) could be considered to be 300 ppm, based on increased liver weight and platelet count; however, these observations were not observed after a two week recovery. Given that increased liver weights were not observed under histopathological examination, and that after the recovery period the weights returned to normal, it was concluded that this effect (i.e., hypertrophy) was a mild-effect or possibly not an "adverse effect".

Derivation of the Screening Level

The screening level was based on the OEL of 25 ppm because the occupational exposure limit was based on human data, which showed only slight irritation effects at levels at 50 ppm. ACGIH (2001) stated that, "No reports of worker illness from exposure to diisobutyl ketone have been reported." The animal study (Dodd et al., 1987) corroborates that the OEL for DIBK is health protective, as mild and reversible adverse effects were only observed at higher concentrations of 300-905 ppm in animals.

Pursuant to Rule 232(1)(c), the ITSL for DIBK is calculated as follows:

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[1] mg/m^3 = (ppm x molecular weight)/24.45;
mg/m^3 = (25 ppm x 142.27g)/24.45 = 145.47mg/m^3, ~ 150 mg/m^3

ITSL = OEL/100
ITSL = 150 mg/m³/100 x unit conversion factor
ITSL = 1.5 mg/m³ x 1000µg/mg
ITSL = 1500 µg/m³

Pursuant to Rule 232(2)(a), the averaging time is 8-hr.

References

ACGIH. (2001) Diisobutyl Ketone Documentation of the threshold limit values and biological exposure indices Vol: 7th Ed. 2 pages

Dodd DE, Losco PE, Troup CM, Pritts IM, Tyle TR (1987) Hyalin droplet nephrosis in male Fischer-344 rats following inhalation of diisobutyl ketone. Toxicol Ind Health. Dec;3(4):443-57. http://journals.sagepub.com/doi/pdf/10.1177/074823378700300401