MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

November 17, 2015

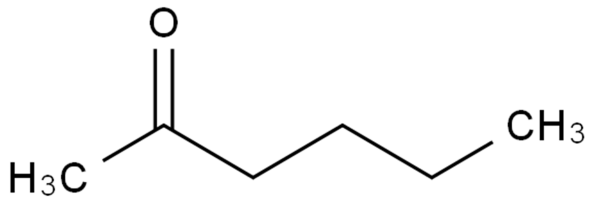
To: File for Methyl-n-butyl Ketone File (CAS No. 591-78-6)

From: Mike Depa, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for methyl-n-butyl ketone is 30 µg/m^3 with annual averaging time.

Methyl butyl ketone (2-hexanone) has the chemical formula $C_6H_{12}O$ and a molecular weight of 100.16g. It is a clear, volatile, flammable fluid with a pungent, acetone-like odor. 2-Hexanone is most commonly used as a paint or printing ink thinner, as a solvent for oils, waxes, and resins, or as a cleaning agent. It is currently not produced commercially in the U.S.



The ITSL was derived from a U.S. Environmental Protection Agency (EPA) reference concentration (RfC)(EPA, 2009).

> Critical Effect: Motor conduction velocity of the sciatic-tibial nerve
> Point of Departure: BMCL05[1] (HEC[2]): 90 mg/m^3
> UF[3]: 3000
> RfC: 3x10^{-2} mg/m^3

The principal study used to derive the RfC is summarized in EPA (2009) as follows:

> Johnson et al. (1977) exposed male monkeys (Macaca fascicularis) (8/group) to 0, 100, or 1000 ppm[4] (0, 410, or 4100 mg/m^3) commercial grade 2-hexanone (purity not stated) for 6 hours per day, 5 days per week for up to 10 months. Monkeys in the 1000-ppm group progressively lost body weight beginning at 8 weeks. No significant effect of 2-hexanone on body weight was found in the low-dose exposure groups.

[1] Benchmark concentration lower 5% confidence limit
[2] Human equivalent concentration
[3] Uncertainty factor
[4] Parts per million

> Four neurological tests were conducted on monkeys: MCV[5] of right sciatic-tibial nerves, MCV of the right ulnar nerve, absolute refractory period of these nerves, and MAP[6] recorded in response to both sciatic and ulnar stimulation. In addition, electroencephalograms and visual evoked potentials were recorded from monkeys. All animals were administered an anesthetic prior to neurological testing: rats received an i.p. injection of 35 mg/kg of sodium pentobarbital, and monkeys were given 15 mg/kg of ketamine hydrochloride intramuscularly.
>
> After 25 weeks, all monkeys in the high-dose exposure group were removed from further exposure because neuropathy (hind-limb drag) apparently had developed. All eight monkeys in the 100 ppm group were exposed for a total of 41 weeks. Beginning at 3 months of exposure, monkeys in the 1000 ppm group showed a progressive decrease in the MCV of the sciatic-tibial nerves. After 6 months, the mean MCV of this group was 63% of the mean of control animals. Commencing at 9 months, the MCV for the sciatic-tibial nerves in monkeys in the 100 ppm group was significantly different from control values ($p = 0.05$). At the termination of the study, the MCV of monkeys from the 100 ppm group was 12% less than in the corresponding controls ($p < 0.05$).

The Benchmark Response (BMR) of 5% was used instead of the default 10% BMR. EPA (2009) based the use of 5% BMR as follows:

> A BMR of 5% extra risk was selected based on the following considerations: (1) this effect level is considered to be a minimal biologically significant change; (2) the potential for nerve fiber damage (i.e., axonal degeneration) with little to no change in MCV; and (3) the BMDL05 falls within the low end of the range of the observable data.

The $BMCL_{ADJ}$[7] was calculated as 116 ppm x 6/24 x 5/7 = 21 ppm; converted to 86.1 mg/m^3 (rounded to 90 mg/m^3). For systemic effect of a category 3 gas, the HEC was calculated using the ratio of the blood gas partition coefficients between animals and humans. The blood:gas partition coefficient $(H_{b/g})_H$ for 2-hexanone in humans is 127 (Sato and Nakajima, 1979); however, no value has been reported for monkeys. According to EPA's RfC methodology (U.S. EPA, 1994), when the ratio of animal to human blood:gas partition coefficients $[(H_{b/g})_A/(H_{b/g})_H]$ is greater than one or the values are unknown, a value of one is used for the ratio by default. Thus, $BMCL05_{HEC} = 90 \times [(H_{b/g})_A/(H_{b/g})_H] = 90$ mg/m^3.

The RfC for 2-hexanone based on peripheral neuropathy as the critical effect is derived from the $BMCL_{HEC}$ by application of UFs as follows:

$RfC = BMCL_{HEC} \div UF$
$RfC = 90 \div 3000 = 0.03$ mg/m^3 x 1000µg/mg
$RfC = 30$ $\mu g/m^3$

[5] mean sciatic motor conduction velocity
[6] muscle action potential
[7] Adjusted for continuous exposure from 6-hrs/day and 5 days/week to 24-hrs/day and 7 days/week

This composite UF of 3000 is composed of the following:

- A default intraspecies UF (UF_H) of 10 was applied to adjust for potentially sensitive human subpopulations (intraspecies variability). A 10-fold UF is warranted because insufficient information is currently available to assess human-to-human variability in 2-hexanone toxicokinetics or toxicodynamics.
- A default subchronic-to-chronic UF (UF_S) of 10 was applied to account for use of data following 6 months of exposure to 2-hexanone for the derivation of an RfC.
- An UF of 3 was applied to account for uncertainties in extrapolating from monkeys to humans (UF_A). This value is adopted by convention where an adjustment from an animal-specific $BMCL_{ADJ}$ to a $BMCL_{HEC}$ has been incorporated. Application of an UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic). In this assessment, the toxicokinetic component is mostly addressed by the determination of an HEC as described in the RfC methodology (U.S. EPA, 1994). The toxicodynamic uncertainty is also accounted for to a certain degree by the use of the applied dosimetry method, and a UF of 3 is retained to address this component.
- An UF of 10 was applied to account for database deficiencies (UF_D). The database includes a human occupational exposure study (with co-exposure to MEK[8]), subchronic animal studies in rats and hens, and a chronic study in cats. One postnatal development and behavior study (Peters et al., 1981) on 2-hexanone in F344 rats exists, identifying a LOAEL[9] of 1,000 ppm (no NOAEL[10] reported). The database does not include a multigenerational reproductive study or developmental studies. The database also lacks information regarding axonal degeneration at concentrations similar to those inducing minimal reductions in nerve MCV. Additionally, Katz et al. (1980) observed a reduction in total white blood cell counts to 60% of control values in rats exposed to 2-hexanone in a subchronic inhalation study, suggesting that further study of immunotoxicity may be warranted. Because of the absence of a two-generation reproductive study and studies evaluating the developmental toxicity and possible immunotoxicity of 2-hexanone following exposure via inhalation, an UF_D of 10 is warranted.

Since there was chemical specific reasons to use an uncertainty factor for database deficiencies, it was retained for the purposes of ITSL derivation.

Pursuant to Rule 232(1)(a) the ITSL is equal to the RfC. The current file review also concludes that the averaging time for the chronic RfC derived ITSL 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).

[8] Methyl ethyl ketone
[9] Lowest-observed-adverse-effect-level
[10] No-observed-adverse-effect-level

References

Johnson, BL; Setzer, JV; Lewis, TR; et al. (1977) Effects of methyl n-butyl ketone behavior and the nervous system. Am Ind Hyg Assoc J 38(11):567–579.

Katz, GV; O'Donoghue, JL; DiVincenzo, GD; et al. (1980) Comparative neurotoxicity and metabolism of ethyl n-butyl ketone and methyl n-butyl ketone in rats. Toxicol Appl Pharmacol 52(1):153–158.

Peters, MA; Hudson, PM; Dixon, RL. (1981) The effect totigestational exposure to methyl n-butyl ketone has on postnatal development and behavior. Ecotoxicol Environ Saf 5(3):291–306.

Sato, A; Nakajima, T. (1979) Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br J Ind Med 36(3):231–234.

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH; EPA/600/8-90/066F. Available from the National Technical Information Service, Springfield, VA, PB2000-500023, and online at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=71993.

U.S. EPA (2009) Toxicological Review Of 2-Hexanone (CAS No. 591-78-6) In Support of Summary Information on the Integrated Risk Information System (IRIS). September 2009. EPA/635/R-09/008F. www.epa.gov/iris. U.S. Environmental Protection Agency. Washington, DC.
http://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1019tr.pdf