May 14, 2013

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
State of California
1001 I Street
Sacramento, CA 95814

Re: Request for Relevant Information on Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Methyl Isobutyl Ketone, March 15, 2013

Dear Ms. Oshita:

The Ketones Panel of the American Chemistry Council submits the following information in response to the Office of Environmental Health Hazard Assessment's (OEHHA) request for information related to its consideration of listing of methyl isobutyl ketone (MIBK) as a reproductive toxicant under Proposition 65. The Ketones Panel represents US manufacturers of MIBK and other ketones.

The March 15, 2013 notice indicates that listing of MIBK is being considered under the authoritative bodies mechanism (Health and Safety Code Section 25306), based on the 2003 update of the US Environmental Protection Agency's (USEPA) Integrated Risk Information System (IRIS) assessment for MIBK. As part of this update, USEPA calculated a reference dose (RfD) for developmental effects in rats and mice exposed to a massive dose of MIBK in a study by Tyl *et al.,* 1987. Effects were only noted in the study by Tyl *et al.* at a dose level that exceeds USEPA's own guidance for conducting developmental toxicity studies. The IRIS assessment also indicates that maternal toxicity in the study exceeded the levels specified in USEPA's test guidance.

Available Reproductive and Developmental Studies

The 2003 IRIS assessment indicates that there is no epidemiological evidence related to the potential for MIBK to cause reproductive or developmental effects. Consequently, USEPA's assessment focused on the results from the following two studies[1] in laboratory animals –

[1] Copies of these studies are included on the enclosed CD. The disk includes the raw data and analysis from the two studies.

- Inhalation two-generation reproductive toxicity study of methyl isobutyl ketone in Crl:CD®(SD)BR rats, and

- Developmental toxicity evaluation of inhaled methyl isobutyl ketone in Fischer 344 rats and CD-1 mice.

The Ketones Panel is not aware of any human or animal evidence on reproductive and developmental toxicity that has become available subsequent to USEPA's analysis.

Two-Generation Reproductive Toxicity Study (Nemec, 2000)

Nemec (2000) evaluated the reproductive toxicity of MIBK in a two-generation inhalation study in Crl:CD®(SD)BR rats. Groups of 30 male and 30 female F0 rats were exposed whole-body to MIBK vapors at mean measured concentrations of 0, 491 or 506, 999 or 1002, and 1996 or 2006 parts per million (ppm) – equal to 0, 2012 or 2073, 4093 or 4105, and 8178 or 8219 milligrams per m^3 or mg/m^3 – for 6 hrs/day for 70 consecutive days prior to mating, throughout mating, and for two generations. F0 and F1 parental rats were evaluated for reproductive endpoints, survival, clinical signs, startle response, food consumption, body weight, organ weights, comprehensive gross pathology, and histopathology of major organ systems and all gross lesions. F1 and F2 pups were evaluated for developmental endpoints, including postnatal survival, clinical signs, body weight, and external anatomical integrity. F1 pups were also evaluated for balanopreputial separation in males and vaginal perforation in females. Complete gross pathology evaluations were performed in F1 pups that were not selected for mating and in all F2 pups.

Nemec reported no reproductive or neonatal developmental effects in either generation of rats exposed to air concentrations of MIBK up to 8219 mg/m^3. The evaluation included the number of offspring with gross external malformations at birth, number of stillbirths, number of live births, body weight on postnatal day 1, and survival to postnatal day 4.

Developmental Toxicity Study (Tyl et al., 1987)

Developmental and maternal toxicity were evaluated by Tyl *et al.* (1987) in groups of 30 pregnant CD-1 mice and 35 pregnant Fischer 344 rats exposed by inhalation to 0, 300, 1000, or 3000 ppm (0, 1229, 4106, 12292 mg/m^3) MIBK for 6 hrs/day on gestation days 6 through 15. Animals were sacrificed on gestation day 18 (mice) or 21 (rats). Dams were evaluated for exposure-related changes in clinical signs, body weight, food consumption, organ weights (kidney, liver, and gravid uterus), and reproductive parameters. Fetuses were evaluated for exposure-related changes in body weight and viability, and for external, skeletal, and thoracic and peritoneal visceral alterations.

Developmental effects were limited to the highest dose group in both rats and mice and included a decrease in fetal body weight in both species (5.9 to 6.9% in rats; 10.2 to 13.9% in mice) and an increase in skeletal variations. The observed fetal toxicity is indicative of a developmental delay secondary to maternal toxicity and is consistent with external publications (Carney and Kimmel, 2007; Collins *et al.*, 1987; Marr *et al.*, 1992). In mice, the significant maternal toxicity in the 12292 mg/m^3 group was manifested by the death of 3 dams (12% of the group) on the first day of exposure. In the rats, evidence of excessive maternal toxicity include clinical signs in the majority of animals (coordination loss, piloerection), body weight loss (GD 6-9), and 85% lower body weight gain (GD 6-12).[2] Also, the dams had a 5% lower body weight at termination relative to the control group.

Sufficiency of Evidence Presented in the IRIS Assessment

Section 25306(g) of the Health and Safety Code states that the criteria for reproductive toxicity shall be met if there exists a causal relationship between the chemical and reproductive toxicity "taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity." Section 25306(h) further notes that "a chemical does not satisfy the definition of 'as causing reproductive toxicity' if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria."

OEHHA's November 1993 criteria for recommending listing as a reproductive toxicant[3] specify that the high dose level used in experimental animal tests "should elicit maternal toxicity," but do not provide guidance on what can be considered an appropriately high dose. USEPA's test guidelines for developmental toxicity studies,[4] on the other hand, do provide such guidance which appears to have been ignored in the 2003 IRIS assessment. According to the USEPA guidelines, the highest dose should be chosen to induce some maternal toxicity but not "death or severe suffering." The guidelines elaborate further that maternal mortality "should not be more than approximately 10 percent." USEPA's developmental toxicity guidelines also indicate that the highest dose "need not exceed . . . 2 mg/L by inhalation, unless potential human exposure data indicate the need for higher doses."

---

[2] Based upon high-dose selection for current regulatory guideline prenatal developmental toxicity studies targeting a 5-10% reduction in body weight gains, this dose level would clearly be considered excessively maternally toxic and unsuitable. [need citation]

[3] Available at http://www.oehha.ca.gov/prop65/policy_procedure/pdf_zip/dartCriteriaNov1993.pdf.

[4] USEPA. Health Effects Test Guidelines OPPTS 870.3700 Prenatal Developmental Toxicity Study. Office of Prevention, Pesticides and Toxic Substances. EPA 712-C-98-207 (August 1998). Available at http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm.

The highest dose employed in the study by Tyl *et al.* (1987) clearly exceeds both of the provisions of the USEPA guidelines. As indicated, 3 of the 36 mice dams (12%) in the study died after just one day of exposure to the highest dose and the rat dams exhibited excessively low weight gain during GD 6 through 12. The IRIS assessment briefly discusses the deaths among the mouse dams, in response to public comments, but fails to address the low weight gain in the rat study. The assessment also fails to discuss the appropriateness of the highest dose used in the studies, which is more than 6 times greater than the highest dose level recommended in USEPA guidance (2 mg/L) and well above potential human exposures.

The highest tested MIBK dose concentration (12292 mg/m^3) in the teratogenicity study was excessively high and should not be considered as a basis for Proposition 65 regulation. The study by Tyl *et al.* was conducted prior to the implementation of USEPA's test guideline. Had the study been performed after 1998, the researchers likely would have selected a much different dose range.[5] The test guidance was in place when the IRIS assessment was conducted, however, and it is not clear why the guidance is not referenced. Instead the IRIS assessment cites 1991 guidance for developmental toxicity risk assessment.[6] This 1991 guidance suggests that excessive toxicity among the dams should not affect the dose-response methodology, but indicates that "when maternal toxicity is significantly greater than the minimal maternally toxic dose, developmental effects at that dose may be difficult to interpret." The 2003 IRIS assessment makes little attempt to explain this interpretation.

USEPA's test guidance for developmental toxicity studies clearly represent scientifically valid data, as specified in Section 25306(h) of the Health and Safety Code. The Agency's failure to reference this guidance in the IRIS assessment, and the assessment's failure to address the highest-dose criteria outlined in the guidance, provides clear evidence that the 1998 guidance were not considered in the IRIS assessment. As a consequence, USEPA's 2003 assessment does not satisfy the criteria of 'as causing reproductive toxicity' and should not be used as a basis for consideration of listing of MIBK.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

Enclosure

---

[5] Even the middle dose of 4106 mg/m^3 in the study by Tyl *et al.* is above the inhalation limit concentration of 2 mg/L outlined by the relevant developmental toxicity guidelines (OPPTS 870.3700).

[6] Available at http://www.epa.gov/raf/publications/pdfs/DEVTOX.PDF.