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February 12, 2014

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

RE: Reconsideration of the listing of Methyl Isopropyl Ketone (MIPK, CAS # 563-80-4) on PROP 65 as known to cause reproductive toxicity

Dear Madam,

Eastman Chemical Company, a major producer of methyl isopropyl ketone (MIPK), is pleased to provide comments to the Office of Environmental Health Hazard Assessment (OEHHA) of the State of California regarding the Developmental and Reproductive Toxicity Identification Committee (DARTIC) reconsideration to retain a reproductive listing of MIPK on Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). We request that OEHHA provide this letter and the attached summary table along with the study report (Edwards, T.L. An Inhalation Prenatal Developmental Toxicity Study of Methyl Isopropyl Ketone in Rats. WIL Research, Project ID: WIL-387019, 2012) be provided to the DARTIC for their review and consideration.

MIPK was initially listed on Proposition 65 under the Labor Code section 6382(d) using the federal Hazard Communication Standard identification of reproductive toxicants. As such, MIPK was listed due to the latest edition of the American Conference of Governmental Industrial Hygienists (ACGIH) "Threshold Limit Values (TLVs)." The TLV for MIPK was assigned on the basis of ACGIH's findings of reproductive effects (developmental toxicity endpoint) from an OECD 421 Reproductive Developmental Toxicity Screening Study.

This letter is to inform OEHHA and the DARTIC of the entire database on the reproductive and developmental toxicity of MIPK and specifically to provide information from an MIPK prenatal developmental toxicity study. The current OEHHA MIPK data summary table and the prior ACGIH documentation for MIPK did not include results from a prenatal developmental toxicity

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study (OECD 414) conducted at WIL Research Laboratory in 2012. A copy of the study report from the MIPK OECD 414 developmental toxicity study is included in this submission.

DISCUSSION OF THE RESULTS FROM THE MIPK DEVELOPMENTAL TOXICITY STUDY

Pregnant female rats (23-25/group) were exposed to MIPK by inhalation from gestation day 0 through 19 in a guideline (OECD TG-414 and US EPA OPPTS 870.3700) prenatal developmental toxicity study (Edwards, 2012). The measured exposure concentrations were 0, 304, 757 and 1529 ppm and the animals were exposed for 6 hours each day. The exposure concentrations selected were based upon replicating the previous OECD 421 screening study. In this study, reduced reactivity to noise stimulus, lower mean body weights and body weight gains, and corresponding reduced mean food consumption were noted for females in the 304, 757, and 1529 ppm groups. The LOEL for maternal toxicity was therefore 300 ppm, confirming the OECD 421 screening study data collected in the Bernard, 2001 study. Gross external observations of the fetuses were followed with a detailed examination of the visceral organs and skeletal development. There was no evidence of developmental toxicity at any of the exposure concentrations tested, up to and including 1529 ppm. The NOAEL for developmental toxicity in this definitive study was therefore 1529 ppm.

DISCUSSION OF THE OECD 421 STUDY RESULTS

The OECD 421 reproductive/developmental toxicity screening study conducted with 0, 284, 710 and 1420 ppm (Bernard, 2001) reported the lowest-observed-adverse-effect level (LOAEL) for maternal and paternal toxicity was 284 ppm (1.0 mg/L) based upon the increased incidence of "reduced activity" (defined as less movement, decreased alertness and slower response to an external stimuli (tapping on the chamber wall with a metal object)) during the inhalation exposure periods. In addition, an increased incidence of salivation, unkempt hair coat, partially closed eyes and porphyrin discharges from eyes and nose were noted at varying incidences in the MIPK-exposed animals, including animals from the 284 ppm exposure group. These clinical signs are indicative of sedation and nasal and oral irritation and possibly an acute parasympathomimetic response. The postnatal endpoints noted were a decrease in live litter size on PND 0 (1420 ppm; 5 mg/L group), increased number of dead pups on PND 0 (710 ppm; 2.5 mg/L group), and increased lethality of pups between PND 0 and 4 (1420 ppm; 5 mg/L group).

DISCUSSION OF DATABASE FOR MIPK REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The data from the definitive developmental toxicity study (Edwards, 2012) concludes that MIPK is not a developmental toxicant, even with exposures 5-fold higher than the maternal toxicity LOAEL value. The reproductive and developmental toxicity screening study found reproductive toxicity (postnatal deaths and decreased litter size) at exposure concentrations greater than those reported to cause parental toxicity (either male or female). An attempt must be made to try and reconcile these results.

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First, the ability of the OECD 414 prenatal developmental toxicity study to detect maternal toxicity was considerably enhanced with the increased size of the exposed groups. Close examination of the OECD 421 screening study data suggested effects on body weight and feed consumption but the difference was not large enough to achieve statistical significance (with an n = 12/group). Adverse findings that are not sensitive to group size (e.g. group observations during exposures within the chambers) yielded similar results (e.g. reduced activity/response to external stimuli) at similar exposure concentrations. The ability of the OECD 414 study design to detect developmental effects is far greater than the OECD 421 screening assay, as the examination of the fetal internal organs and skeleton is far more detailed and precise.

Second, the increase in postnatal death and decreased live litter size in the screening study are rare events and therefore less dependent on group size. While severe developmental toxicity can cause an increase in postnatal death, the lack of developmental toxicity in the definitive OECD 414 prenatal developmental toxicity study suggests that this was not the case with MIPK. Another cause of an increase in postnatal deaths and/or decreased live litter size is maternal toxicity as newborn rat pups are altricial when born and require constant maintenance from the dam to regulate body temperature, nurse and urinate. The maternal toxicity occurring in the OECD 421 screening study has been dismissed by some (e.g. ACGIH) as a possible cause for the increase in postnatal deaths, primarily because the maternal effects observed (reduced activity during exposure) were transient in nature. However, the more robust OECD 414 prenatal developmental toxicity study clearly demonstrates maternal toxicity (e.g. decreased feed consumption, decreased body weights and rates of weight gain) that were prolonged and significant. Whether similar effects were noted during the lactation period of the OECD 421 screening study is impossible to determine given the limited observations collected. Since the OECD 414 prenatal developmental toxicity study did not include a postnatal component (by necessity), it is not possible to describe specifically what caused the postnatal deaths in the OECD 421 screening study.

While the developmental and reproductive outcomes of the two studies cannot be reconciled due to differences in study design, both of the studies describe evidence of maternal toxicity that occurred at exposure concentrations well below those causing postnatal effects.

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CONCLUSION

MIPK should not be considered a developmental toxicant for the purposes of listing on Proposition 65 based upon the results from the definitive OECD 414 prenatal developmental toxicity study. MIPK did cause an increase in postnatal deaths in the OECD 421 reproductive screening study but it is highly likely that there was a significant maternal toxicity component to those adverse postnatal outcomes.

We appreciate your consideration of this letter and the enclosed information. If you have any questions, I can be reached at (423) 229-2466 or by email at sgreen@eastman.com.

Sincerely,

Steve Green, Ph.D., DABT
Eastman Chemical Company

Reference cited:

Bernard, L.G. Methyl Isopropyl Ketone: Reproduction/Developmental Toxicity Screening Test in the Rat. Eastman Kodak Company, Toxicological Sciences Laboratory, Project ID: 2001250I1, 2001.

Edwards, T.L. An Inhalation Prenatal Developmental Toxicity Study of Methyl Isopropyl Ketone in Rats. WIL Research, Project ID: WIL-387019, 2012

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