MICHIGAN DEPARTMENT OF NATURAL RESOURCES AND ENVIRONMENT

INTEROFFICE COMMUNICATION

To: File for Isoprene (CAS No. 78-79-5)

From: Michael Depa

Date: August 28, 2012

Subject: Correction of Unit Risk Estimate Units

The interoffice communication memo by Gary Butterfield dated February 12, 1997 for the Initial Risk Screening Level (IRSL) for Isoprene states that the "potency factor" is 0.0538 $(\mu g/m^3)^{-1}$. However, the correct potency factor (i.e., inhalation unit risk estimate; inhalation URE) should be 5.38E-5 per $\mu g/m^3$ (or 0.0538 per mg/m^3).

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 12, 1997

TO: Isoprene file (CAS #78-79-5)

FROM: Gary Butterfield, Toxics Unit, Air Quality Division

SUBJECT: Initial Risk Screening Level (IRSL) for Isoprene

Isoprene is formed and emitted to ambient air by plants and animals, in addition to emissons from industrial processing of tires and hoses, generating polymers, and from terpene processing. In animals isporene is formed durning the cholesterol biosynthesis process. A January 9, 1997 CAS and NLM on-line search found several short term studies evaluating the pharmacokinetics and cytogenics of isoprene. Isoprene has not been found to be mutagenic in in vitro bacterial assays. In vivo tests have found increased numbers of micronuclei and sister chromatid exchanges in bone marrow, and increases in micronucleus frequency in peripheral blood cells. The monoepoxide metabolite of isoprene are not alkylating (ie. not mutagenic), however the diepoxide metabolite has been found to be an active bacterial mutagen.

The structural similarity of isoprene to the well know carcinogen, 1,3-butadiene, has been noted in many of the studies evaluating isoprene. However, there are only two long term exposure, carcinogenicity studies that have been conducted with isoprene, NTP (1995) and Placke et al (1996). In the NTP 1995 study, groups of male rats and male mice were exposed to isoprene for 6 months, followed by a 6 month recovery period. This study found increased incidences of lung, liver, Harderian gland and forestomach tumors in the mice, while rats had an increased incidence of tumors of the testis. This is the study that led IARC (1994) to classify isoprene as a group 2B carcinogen.

The second carcinogenicity study, groups of male B6C3F1 mice were exposed to isoprene for 20, 40 or 80 weeks and then held for a recovery period until the study ended at 104 weeks, Placke et al (1996) - which is also know as the Battelle study. For the purposes of calculating a screening level, the groups that were exposed for 80 weeks for 8 hours a day were used (groups 1, 2, 4, 7, 8 and 12), because this majority of animals received an essentially lifetime (80 weeks) exposure. It was not known how to appropriately compare the 80 week exposed animals to the 20 and 40 week exposed animals. It should be noted however, that the authors do note that the concentration and duration of exposure did not affect tumor incidence symmetrically. For example, increased isoprene concentrations by a factor of 4 (70 to 280 ppm) with a reduction in duration (from 80 to 20 weeks) resulted in a significant increase in lung tumors from 12% to 38%, and the liver tumor incidence inciences increased 25%, despite the equivalent cummulative exposure values. Further, exposure to

common concentration (2200 ppm) for 4 hr/d for 80 weeks compared to 8 hr/d for 40 weeks resulted in significantly different tumor incidences - lung tumor incidences in 8 hr/d for 40 weeks was nearly double but the histocytic sarcoma incidence was lower.

In the 8 hr/d 80 week exposed groups, the exposure concentrations were 0, 10, 70, 280, 700 and 2200 ppm. Adjusting for 8 hr/d exposures on 5 days a week during 80 of 104 weeks of the study results in study adjusted doses of 0, 5.11, 35.8, 143, 358 and 1120 mg/m3. Because this study has been reported in a journal article of 12 pages, some of the details are missing when compared to the detail report from the NTP study document. However, this study also found increased incidences of lung, liver, Harderian gland, and forestomach tumors, as well as, increased incidences of histocyctic sarcomas. After running all of these possible tumor incidences through Gloabl82, the incidence of liver tumors (20/50, 18/50, 24/50, 40/50, 44/48, 46/50 from control to high dose, respectively) resulted in the highest potency, 0.0538 (ug/m3)-1.

Use of this potency factor, 0.0538 (ug/m3)-1, results in a calculated IRSL of 0.02 ug/m3 and an SRSL of 0.2 ug/m3 with annual averaging.

References:

IARC. 1994. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 60, pg 215-232.

NTP. 1995. NTP Technical report on the toxicity studies of isoprene (CAS # 78-79-5) administered by inhalation to F344 rats and B6C3F1 mice. Tox report series # 31.

Placke et al. 1996. Chronic inhalation oncogenicity study of isoprene in B6C3F1 mice. Toxicology 113:253-262.

GB:slb