MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Isopropyl Alcohol (CAS # 67-63-0)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Isopropyl Alcohol ITSL change in the averaging time from 24 hrs to annual

DATE: December 1, 2016

The current ITSL for isopropyl alcohol (220 ug/m^3) was established on August 19, 1993, consistent with the recommendation of the AQD's Scientific Advisory Panel (see attached). The averaging time (AT) assigned to the ITSL at that time was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The key study was a 13 week inhalation bioassay, and the ITSL derivation (see attached) included a 10X uncertainty factor to adjust to chronic exposure. The current file review concludes that the AT 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). Therefore, the AT is being changed from 24 hours to annual at this time.

10/28/93

Recommendations of the Scientific Advisory Panel

ISOPROPYL ALCOHOL

CAS Number 67-63-0

August 19, 1993

After consideration of all the available research data on isopropyl alcohol toxicity, the Panel has agreed to revise the screening level for this compound. During the course of the Panel's review of IPA, a number of other studies were brought forward for consideration. Some of these studies provided NOAEL's instead of LOAEL's, which are more appropriate for screening level derivation. The panel based its recommendations on a consideration of the totality of the available toxicological information on isopropyl alcohol, including:

A teratogenicity study on inhaled isopropyl alcohol in rats (Nelson, et al., 1988).

Japanese research which looked at general toxicity and irritant effects (Nakaseko, 1990; Ohashi, Y. 1987)

Several unpublished studies and supporting data presented by the Chemical Manufacturer's Association (CMA), Isopropanol Panel. These studies measured mutagenicity; two generation oral dose reproductive toxicity in rats; developmental toxicity via gavage in rats and rabbits; developmental neurotoxicity via oral administration in rats; acute and subchronic inhalation neurotoxicity in rats; and pharmacokinetics. Two year chronic bioassays in rats and mice are currently in process.

Pharmacokinetic and biotransformation data presented by the IPA Panel of CMA indicate that the distribution and excretion of isopropanol and its metabolite, acetone, are similar regardless of the route of administration. High doses appear to exceed the metabolic threshold (threshold probably <5000 ppm).

A comparison of NOAEL's from the various sensitive endpoints examined (i.e., reproductive/developmental toxicity; neurotoxicity; or irritant effects) determined that the majority of the no effect levels were in a similar range, regardless of endpoint. The best data for calculation of a screening level at this time is provided by the subchronic inhalation neurotoxicity study in rats presented by the IPA panel of the CMA. The NOAEL from this study was 500 ppm. Data from the other studies are supportive of this NOAEL.

Then new Initial Threshold Screening (ITSL) for IPA =

$$500\ ppm\ x\ 2.5\ \frac{mg/m^3}{ppm} = 1250\ \frac{mg}{m^3}$$

$$\frac{1250\frac{mg}{m^3}\ x\ \frac{6}{24}\ \frac{hr}{day}\ x\ \frac{5}{7}\ \frac{days}{week}}{10\ x\ 10\ x\ 10} = 0.223\ \frac{mg}{m^3}$$

$$ITSL = 220\ \frac{ug}{m^3}\ with\ 24\ hr\ averaging$$

The safety factors include 10 for animal to human, 10 for individual variation and 10 for duration of study.

The panel noted that a chronic toxicity study for IPA was in its final stages. Preliminary data indicate that the ITSL for IPA may increase upon review of the final draft of the long-term study.

References:

1. Nelson, B.K., et al. 1988. "Teratogenicity of n-Propanol and Isopropanol Administered at High Inhalation Concentrations to Rats". Fd. Chem. Toxic. v. 26(3). p. 247-254.

2. Nakaseko, H., 1990. "Experimental studies on the toxicity of isopropyl alcohol". Osaka-shi Igakkai Zasshi. v. 39(2). p. 213-31.

3. Ohashi, Y., et al. 1987. "Recovery process of tracheal mucosa of guinea pigs exposed to isopropyl alcohol". Arch.Toxicol. v.61 p.2-20.

4. Ohashi, Y, et al. 1987. "An Experimental Study on the Respiratory Toxicity of Isopropyl Alcohol". J. of Appl. Tox. v. 8(1), p.67-71.

5. Unpublished Reports and Data presented by BIOTOX for the CMA, IPA panel:
   a) "*In vitro* and *In vivo* Assays of Isopropanol for Mutagenicity"
   b) "Two-generation Reproduction Toxicity Study with Isopropanol in Rats"
   c) "Developmental Toxicity Evaluation of Isopropanol by Gavage in Rats and Rabbits"
   d) "Developmental Neurotoxicity Evaluation of Orally Administered Isopropanol in Rats"
   e) "Isopropanol: Acute Vapor Inhalation Neurotoxicity Study in Rats"
   f) "Isopropanol Thirteen-Week Vapor Inhalation Study in Rats and Mice with Neurotoxicity Evaluation in Rats"
   g) "Disposition and Pharmacokinetics in F-344 Rats and B6C3F1 Mice"