MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Tripropylene glycol n-butyl ether (CAS # 55934-93-5)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Tripropylene glycol n-butyl ether ITSL

DATE: January 17, 2017

The current ITSL for Tripropylene glycol n-butyl ether is 346 ug/m^3, with annual averaging time (AT).

Previously, the ITSL was established on December 12, 2000 at 116 ug/m^3 with 24 hr averaging time (see attached justification memo). The averaging time (AT) assigned to the ITSL previously was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The ITSL derivation applied a total uncertainty factor (UF) = 3000, which consisted of a UF = 10 for each interspecies extrapolation, intraspecies variability, and subchronic-to-chronic conversion (the key study was a rat 13-week drinking water study), and a database UF = 3. The current file review concludes that the AT for the 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). Additionally, the current file review does not find that the previous use of a database UF = 3 was justified based on chemical-specific data or concerns, and therefore it is being removed. The previous ITSL was 115.5 ug/m^3, which was rounded to an ITSL = 116 ug/m^3. The current removal of the database UF results in an ITSL = 346.5, which is rounded to 346 ug/m^3.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

December 12, 2000

TO: File for Tripropylene Glycol N-Butyl Ether (55934-93-5)

FROM: Marco Bianchi, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for tripropylene glycol n-butyl ether (TPnB) is 116 $\mu g/m^3$ based on a 24 hr averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, HEAST, NTP Management Status Report, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC, NIOSH Pocket Guide, and ACGIH Guide, and Patty's Industrial Hygiene and Toxicology.

A detailed database search was conducted for tripropylene glycol n-butyl ether, but only limited information was available. An acute toxicological summary from Dow revealed an LD_{50} of 3100 mg/kg in male rats and 2600 mg/kg in female rats, while a dermal LD_{50} of >2000 mg/kg was observed for rats and rabbits. TPnB was not significantly irritating to the skin of rabbits, was not a sensitizer in guinea pigs, and caused slight to moderate ocular effects in rabbits which resolved within 14 days.

A 13-week unpublished drinking water study was provided by Dow Chemical Company on Fischer 344 rats. In this study, TPnB was administered in the drinking water to groups of 10 male and 10 female rats at dose levels of 0, 100, 350, or 1000 mg/kg/day. Two additional groups of 10 rats/sex were given TPnB in the drinking water at dose levels of 0 and 1000 mg/kg/day for 13-weeks, and then tap water during a four-week recovery period. Parameters evaluated included general appearance and demeanor, functional observational battery, body weights, feed and water consumption, hematology, clinical chemistry, urinalysis, organ weights, gross pathology and histopathology.

According to the report, dose-related decreases in water consumption, attributed to reduced water palatability, occurred in males and females at all dose levels. Decreased water consumption in high-dose males and females was associated with decreased feed consumption and body weight gain. Feed consumption and body weight gain was not affected at 100 or 350 mg/kg/day. Histopathologic and organ weight alterations involving the liver and kidneys occurred in male rats given 1000 mg/kg/day and in the livers and kidneys of female rats given 350 and 1000 mg/kg /day. The hepatic effects were interpreted to be an adaptive change associated with the metabolism of TPnB. The renal changes were characterized as slight tubular degeneration/regeneration and represented a minimal difference in severity as compared to the controls. All other apparent alterations (e.g., clinical chemistry and hematological effects), observed on various study parameters were considered of no toxicological significance as they were within normal physiologic limits or within historical control values, and were not associated with histopathologic alterations. Body weight, organ weight and histopathologic effects (renal tubule degeneration) were considered reversible as the changes observed in the 13-week study were either no longer present following the four-week recovery period or had recovered significantly.

From the study results, Dow interpreted changes in liver and kidney weights lacking histopathologic effects or histopathologic effects resolving after the 4-week recovery period as adaptive. Since renal tubule degeneration was still present at 1000 mg/kg/day after the recovery period, Dow considered this dose a LOAEL (lowest-observable-effect-level) and 350 mg/kg/day a NOAEL (no-observable-adverse-effect-level).

Presently, uncertainty exits in the scientific community as to whether a change in organ weights, especially the liver is a clear indication of potential adverse effects. U.S. Environmental Protection Agency (USEPA) does not have a policy on this issue, but some staff considers compound related changes in liver weights as adaptive in nature provided no other adverse effects have been observed. Other citings in the literature seem to concur that adverse effects based on liver weights alone should not be utilized for risk assessments. However, others in the scientific community state that "an increase in liver weight...is a clear harbinger of potential cancerous effects." (Gary Foureman, USEPA; personal communication 9/18/97).

Although there has been much scientific debate on interpretation of liver weight changes, statistically significant weight changes in other organs such as in the kidney is still considered an adverse effect by Air Quality Division (AQD). This decision is in concurrence with National Toxicology Program staff, who stated that increases in liver weights may provide equivocal results, but for other organ weights this is not true.

Based on information presented above, the weight of evidence suggests changes in liver weights could be interpreted as adaptive under certain histopathologic conditions. These conditions exist in the 13-week study to appropriately use the data in this manner. Alterations in liver weight suggest an adaptive effect due to no morphologic changes and organ weight resolving to control group levels during the recovery period. However, USEPA guidance differs in opinion for changes in kidney weight. Increases in kidney weights with associated degenerative effects in the renal tubule are considered an adverse effect from TPnB toxicity. The lowest dose that increased kidney weights with degenerative effects was at 350 mg/kg/day. Therefore, NOAEL for this study is 100 mg/kg/day.

Data from this 13-week drinking water study was sufficient to justify developing an ITSL using the oral reference dose (RfD) methodology according to Rule 232(1)(b). This justification was based on the use of four dose groups, plus an additional two dose groups that were used in a 4-week recovery period. Parameters for all dose groups were evaluated for general appearance and demeanor, functional observational battery, body weights, feed and water consumption, hematology, clinical chemistry, urinalysis, organ weights, gross pathology and histopathology. In addition to the customary use of uncertainty factors, an additional uncertainty factor (UF) of 3 will be used to account for the inability of any single animal study to adequately address all potential endpoints at various critical life stages of the animal. According to USEPA, assuming the range of the UF is distributed log-normally, reduction of a standard 10-fold uncertainty factor by half results in a UF of approximately 3.

The ITSL was determined as follows:

NOAEL = 100 mg/kg/day.

Uncertainty Factors

10 - specie to specie
10 - sensitive sub-populations
10 - subchronic to chronic
3 - uncertainty factor to account for database gaps

$$\frac{100 \text{ mg/kg}}{10 \times 10 \times 10 \times 3} \times 0.033 \text{ mg/kg}$$

Conversion from mg/kg to μg/kg

$$0.033 \text{ mg/kg} \times \frac{1000 \text{ μg}}{1 \text{ mg}} = 33 \text{ μg/kg}$$

Conversion from μg/kg to μg/m^3

$$33 \text{ μg/kg} \times \frac{70 \text{ kg}}{20 \text{ m}^3} = 115.5 \text{ μg/m}^3$$

The ITSL for tripropylene glycol n-butyl ether = 116 μg/m^3 based on a 24 hr averaging.

References:

1. Kirk HD et al., 1992. Tripropylene glycol n-butyl ether: 13-week drinking water toxicity study in Fischer 344 rats. Unpublished Report - The Dow Chemical Company.

MB:ST
cc: Cathy Simon, AQD
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