MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Tergitol 15-S-3 (CAS # 68131-40-8)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Tergitol 15-S-3 ITSL change in the averaging time from 24 hrs to annual

DATE: January 17, 2017

The current ITSL for Tergitol 15-S-3 is 290 ug/m^3, with annual averaging time (AT).

Previously, the ITSL was established on June 23, 2000 at 290 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, and UF = 3 for LOAEL-to-NOAEL extrapolation. 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).

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

June 23, 2000

TO: File for Tergitol 15-S-3 (68131-40-8)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for Tergitol, or alkyloxypolyethylene-oxyethanol is 290 $\mu g/m^3$ based on a 24 hour 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.

Tergitol 15-S-3, is an anionic surfactant that is mainly used in the textile dyeing and finishing industries. A complete reference search was conducted for Tergitol, but information was limited to proprietary toxicity studies by Union Carbide. These studies included a variety of short-term tests along with a subchronic dietary investigation. A summary of these studies is presented below.

In an oral LD_{50} study, Tergitol was slightly toxic to rats, causing several delayed deaths. Signs of toxicity included sluggishness, diarrhea, red discharge around eyes and nose, unkempt appearance, periurogenital wetness, lacrimation and instances of unsteady gait or prostration. Deaths occurred at one to 4 days. Survivors recovered at 3 to 8 days. At necropsy, there were mottled and red lungs as well as distended and liquid-filled stomachs and intestines. The LD_{50} was determined to be 11.7 ml/kg or 10,764 mg/kg (Sp.Gr. 0.92 @20/20C) for males and 5.6 ml/kg or 5152 mg/kg for females (Sp.Gr. 0.92 @20/20C).

By the percutaneous route, the LD_{50} for male and female rabbits was 4.8 ml/kg and 4.9 ml/kg, respectively. Local dermal effects included erythema, edema, ecchymosis, desquamation, fissuring, scabs and alopecia. There were also instances of necrosis and ulceration. Time of death ranged from 2 to 5 days. Most survivors recovered at 2 to 9 days. Gross pathologic findings included mottled and red lungs, red tracheas, red staining on perinasal fur and fluid-filled stomach and intestines.

In an 8 hr. single exposure inhalation study, 6 rats were exposed to a "substantially saturated vapor" (*concentration estimated to be ~178mg/m^3). No deaths were reported, nor were any clinical signs or gross pathology observed.

In a subchronic dietary study, Tergitol was tested on both Beagle dogs at 3 dogs/sex/group and Harlin-Wistar rats at 10 rats/sex/group. During a 3-month (12-week) interval, the Tergitol incorporated feed produced nominal dosage levels of 0, 0.315, 0.688 and 0.955 gm/kg, and 0, 0.25, 0.50, 1.0, and 2.0 gm/kg for dogs and rats, respectively.

After the first 5-weeks of the study, there was a consistent weight loss in dogs at the highest dose level of 0.955 gm/kg. This dose group consumed about one-third less diet than the controls. Subsequently, these animals were fed only the control diet, which resulted in normal food consumption and body weight by the end of the study. Significantly depressed body weight changes were also noted in the mid-dose group (0.688 gm/kg) during the first 5-weeks, but was statistically equivalent to those of controls for the remainder of the study. No effects were found in any of the biochemical or hematological parameters after 12-weeks except for a statistically lower hemoglobin content of the blood in the high-dose dogs. Other parameters that were measured and showed to be within normal ranges were blood urea nitrogen, alkaline phosphatase, bromsulfalein retention, hematocrit, and a total red and white blood cell count and differentiation. Cranial, pleural and abdominal organs were examined grossly and stained sections were studied microscopically. Results from these examinations indicated no organ damage in dogs fed 0.315, 0.688 gm/kg for 3 months, and liver weight increase as a percentage of body weight did not differ from controls. According to the investigators, the no-adverse-effect-level (NOAEL) for the dog study was 0.315 gm/kg.

Comparatively, results from the rat study included decreased food consumption and body weight gain in males and females receiving 1.0 or 2.0 gm/kg. While actual liver weight was statistically increased only at the 2.0 gm/kg dose group in the females, the mean weights expressed as percentages of body weight were statistically significantly higher at all 4 dose levels in the females and in the highest 3 dose levels in the males. Kidney weight, as percentage of body weight was not significantly altered in males and females for all dose groups. No effects were found in gross or histopathology in either male or female rats, even in sections of the liver where the weight of this organ relative to body weight was increased in a dose-related manner. According to the investigators, since there was no histopathological effect on livers at 2 gm/kg, the liver weight increase in rats fed 0.25 gm/kg does not constitute an adverse effect. Therefore, they concluded that the NOAEL was 0.25 gm/kg.

The investigators alluded in the conclusion of the rat study that relative liver weights increased for each of the dose groups because body weights decreased. However, data

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* $\frac{\text{vapor pressure of Tergitol}}{760 \text{ mm Hg}} \times 1\text{x}10^6 = \text{ppm}$

$\frac{\text{ppm x Mole. Wt.}}{24.45} = \text{mg/m}^3$

from the study revealed that absolute liver weight in female rats was elevated at all dose levels. This suggests that the relative increase in liver weight was not solely dependent on a decrease in body weight. In fact, body weight gain, absolute liver weight, and relative liver weight all increased for females at the 0.25 gm/kg dose level. Absolute liver weight increased at this dose level by 15%, while relative liver weight increased by 8%. This compares to an increase in body weight of only 6%. The investigators didn't consider the change in absolute liver weight at 0.25 gm/kg to be significant because liver histopathology revealed no adverse effects at any of the dose levels for the duration of the study. However, when absolute liver weight changes progress from 12-20%, and relative liver weight increases from 8-33% in a dose-response fashion as it did in female rats, it is uncertain whether a change this great would not cause adverse liver effects if the study was conducted for the life span of the animal. Therefore, it seems judicious to account for this uncertainty by considering 0.25 gm/kg a LOAEL and applying a 3-fold uncertainty factor. This 3-fold uncertainty factor accounts for differences in extrapolating a LOAEL to a NOAEL, but acknowledges the lack of histopathologic effects of the liver by not using a full 10-fold uncertainty factor. The LOAEL of 0.25 gm/kg will be used to determine the ITSL by Rule 232(1)(b).

The ITSL was derived as follows:

LOAEL = 250 mg/kg actual dosage level from diet

Uncertainty Factors

10 - specie to specie
10 - sensitive sub-populations
10 - subchronic to chronic
3 - LOAEL to NOAEL

$$\frac{250 \text{ mg/kg}}{10 \times 10 \times 10 \times 3} = 0.083 \text{ mg/kg}$$

Conversion from mg/kg to *ug/kg*

$$0.083 \text{ mg/kg} \times \frac{1000 \text{ ug}}{1 \text{ mg}} = 83 \text{ ug/kg}$$

Conversion from ug/kg to *ug/m^3*

$$83 \text{ ug/kg} \times \frac{70 \text{ kg}}{20 \text{ m}^3} = 290.5 \text{ ug/m}^3$$

The ITSL for Tergitol 15-S-3 = 290 ug/m^3 based on a 24 hr averaging.

References:

1. Union Carbide proprietary report. 1967. *Tergitol 15-S-3 results of three-month feeding to rats and dogs.* Union Carbide Corporation, Chemicals and Plastics Operations Division. Mellon Institute - Industrial Fellowship 274-30; special report #30-41.