MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 2,4,5-Trichlorophenol (CAS # 95-95-4)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: 2,4,5-Trichlorophenol ITSL change in the averaging time from 24 hrs to annual

DATE: December 28, 2016

The current ITSL for 2,4,5-Trichlorophenol is 350 ug/m^3, with annual averaging time (AT).

Previously, the ITSL was established on March 25, 1996 at 350 ug/m^3 with 24 hr averaging time (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 ITSL was based on an EPA (1987) Reference Dose (RfD) of 0.1 mg/kg-d, which EPA derived from a subchronic (98 day) rat oral bioassay. EPA (1987) applied a total uncertainty factor (UF) = 1000 to the NOEL to derive the RfD; the total UF consisted of a UF = 10 for each interspecies extrapolation and intraspecies variability, and UF = 10 for subchronic-to-chronic conversion. 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).

References:

EPA. 1989. Integrated Risk Information System (IRIS database). Chemical file for 2,4,5-Trichlorophenol. Oral RfD assessment last revised 1/31/87. Retrieved on 12/28/16.

March 25, 1996

TO: File for 2,4,5-trichlorophenol (CAS# 95-95-4)

FROM: Robert Sills

SUBJECT: Screening Level development for 2,4,5-trichlorophenol

A review of the available literature indicates that the appropriate screening level for 2,4,5-trichlorophenol is an ITSL of 350 ug/m^3 with a 24-hour averaging time. This is based on an EPA RfD of 0.1 mg/kg-day. Details of the literature review and ITSL development follow.

Literature Review

In addition to reviews of standard references (IRIS, HEAST, NTP, IARC, OEL sources, etc.) the CAS, NLM, and NTIS abstracting services were searched on-line through 4/28/95. EPA (1996; IRIS) states that there is insufficient data for RfC development, and that the assessment of carcinogenic potential is pending further EPA review. The RfD is 0.1 mg/kg-d, based on a subchronic oral rat study (McCollister et al., 1961), a NOEL of 100 mg/kg-d, and a total UF of 1000. The UF reflects 10X for each interspecies and intraspecies variability, and 10X for subchronicity of the study. The confidence in the RfD is stated as low, due to the paucity of supporting data. Further details of the key study are provided below.

Review of ACGIH (1991) and NIOSH (1994) indicates that occupational exposure limits are not available. EPA (1994a) states that the agency has classified this chemical as "Group D, not classifiable as to human carcinogenicity due to inadequate human and animal data". EPA (1994b) states that "A draft preliminary assessment indicates that the weight-of-evidence classification is such that this chemical may be considered a "nonthreshold" hazardous air pollutant." However, personal communication (Sills, 1995) with one of the two authors of this document revealed that the basis for the above statement was as follows: 1) lack of chronic bioassays; 2) an unpublished 1986 bioassay in mice injected subcutaneously with a singe exposure, followed by observation for 18 months, with no tumor induction seen; and 3) a 1959 study (Boutwell and Bosch authors; full citation not known) involving 2,4,5-trichlorophenol injected subcutaneously to mice over 16 weeks as a promoter in an initiation-promotion assay, resulting in increased papilloma induction. This information does not indicate the need for risk-based screening level development.

The IARC (1979) reported that the available data did not permit an evaluation of the carcinogenicity of this chemical to be made. Available short-term assays indicated that 2,4,5-trichlorophenol was not mutagenic to bacteria, and did not induce sister chromatid exchange or chromosomal aberrations in exposed workers. The WHO (1989) reports that there is suggestive evidence that absorption into the blood is rapid with exposure via inhalation or ingestion. Excretion is primarily via urine, with fecal elimination as a secondary route. The major metabolic transformation is conjugation with sulfate or glucuronate, prior to clearance via the urine (Ch. 6; pp. 94-99). The major mode of action of chlorophenols appears to be the uncoupling of oxidative phosphorylation (Ch. 8; p. 132).

In the key study selected by EPA(1996) for RfD development, McCollister et al. (1961) exposed groups of 10/sex Wistar rats to 0, 0.01, 0.03, 0.1, 0.3 or 1% 2,4,5-trichlorophenol in the diet for 98 days. During the study, animals were monitored for body weight, appearance and behavior. At termination, blood samples were taken for urea nitrogen determination. The lungs, heart, liver, kidneys, spleen, testes, and brain were weighed and examined histologically. No effects were observed at exposures up to 0.1% or 1000 ppm, which the authors (and EPA(1995)) estimated as 100 mg/kg-d. At exposures of 0.3% or higher, a diuretic effect was noted, and histological changes were found in the liver and kidneys. The authors described these pathological changes as slight, and probably reversible and of minor significance. The LOAEL is therefore 0.3% or 3,000 ppm, which the authors and EPA (1996) estimated as 300 mg/kg-d.

Neubert and Dillman (1972) reported that 2,4,5-*trichlorophenoxyacetic acid* caused an increase in resorptions in NMRI mice administered 9 mg/kg (but not 0.9 mg/kg) via gavage on gestation days 6-15. However, similar studies of 2,4,5 trichlorophenol have not found developmental effects at doses this low. Chernoff and Kavlock (1982, 1983) evaluated 2,4,5-trichlorophenol in an in vivo teratology screen. A group of 30 CD-1 mice were administered 800 mg/kg-d via gavage in corn oil for 5 consecutive days (gd 8-12). An apparent increase in maternal death (4/30 vs. 0/40) in controls) was not statistically tested, but was noted as "increased" in a subsequent review by Gray and Kavlock (1984). Compared to a vehicle control group, treatment resulted in a significant ($p < 0.05$) reduction in the number of live pups at postnatal day 1. However, the reduction was not significant at postnatal day 3. Therefore, a questionable LOAEL for reduced litter size was 800 mg/kg-d. No effects were seen on pup weights, which were evaluated on days 1 & 3 postpartum. In an extension of this study, Gray and Kavlock (1984) randomly selected 8 dams from the treatment group and randomly gave each of them six treated pups (3/sex) at postnatal day 6. At 30 days of age the pups were weaned, and females were checked for patent vaginas. At 35 days of age a single male was housed with a single nonlittermate female for breeding. Males were necropsied at 150 days of age. The results of this study showed no significant effect on the day 30 body weights, organ weights at necropsy, viability to day 30, percent pregnant, and age at parturition. There was a reduction in the F_1 litter size (11.4 vs. 13.9), which was significant in a t-test ($p < 0.05$) but not significant by MANOVA or ANOVA tests. The authors noted that the control value was unusually high, and recommended that the study should be replicated.

In another bioassay for developmental effects, Chernoff et al. (1990) administered 2,4,5-trichlorophenol to groups of female Sprague-Dawlwy rats via gavage in corn oil, on days 6-15 of gestation . The dose level was set at 650 mg/kg-d based on a finding of significant weight loss or mortality in female adult rats at this dose level in a range-finding study. Treatment resulted in a reported increase in maternal mortality during pregnancy (88.4% survival, versus 100% in vehicle-treated controls; statistical significance not reported). Significant effects were not seen in maternal organ weights, litter size, fetal weight, fetal death, or fetal anomalies.

Screening Level Derivation

The above studies and reviews support ITSL development based on the EPA RfD, per rule 232 (1)(b). Supporting studies indicate that this approach is protective of potential developmental effects, and suggest that the inhalation screening level will be appropriately protective of the critical systemic effects observed via oral exposure. Derivation of the ITSL is as follows:

$$\text{ITSL} = \text{Oral RfD} \times \frac{70\ \text{kg}}{20\ \text{m}^3}$$

$$= 0.1\ \text{mg/kg-d} \times \frac{70\ \text{kg}}{20\ \text{m}^3} = 0.35\ \text{mg/m}^3 = 350\ \text{ug/m}^3\ \text{(24 hour averaging)}$$

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