

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,2,4-Trichlorobenzene (CAS # 120-82-1)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: 1,2,4-Trichlorobenzene ITSL change in the averaging time from 24 hours to annual

DATE: December 7, 2016

The current Initial Threshold Screening Level (ITSL) for 1,2,4-trichlorobenzene ($4 \mu\text{g}/\text{m}^3$) has a justification (attached) dated January 9, 2006. The averaging time (AT) assigned at that time was 24 hours, as per the default methodology (Rule 232(2)(b)). The current file review concludes that the AT may appropriately be set at annual as the ITSL was originally derived from a sub-chronic rat inhalation study by Watanabe et al (1977), where rats were exposed to either 0, 2.8, or 10.2 ppm (0, 21, or $76 \text{ mg}/\text{m}^3$) 1,2,4-trichlorobenzene for 6 hours a day, 5 days a week for 3 months. Three 10-fold uncertainty factors were used in the calculations for each of the following factors: sensitive individuals in the population, animal to human; and sub-chronic to chronic duration adjustment. As allowed under Rule 229(2)(b), since the evaluation included a sub-chronic to chronic duration adjustment, it is appropriate to change the AT from 24 hours to annual averaging time.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

Watanabe, P. G., Kociba, R. J., Heffner, R. E., Yakel, H. O. and Leong, B. K. J. (1978). Subchronic toxicity studies of 1,2,4-trichlorobenzene in experimental animals. *Toxicol. app. Pharmacol.* 45:332-333 (abst. 265).

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Attachment

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: 1,2,4-Trichlorobenzene file (CAS # 120-82-1)

FROM: Gary Butterfield

SUBJECT: Screening level for 1,2,4-trichlorobenzene

DATE: January 9, 2006

1,2,4-Trichlorobenzene is a colorless liquid at ambient temperatures. It has an aromatic odor, with an odor threshold of 3 ppm. The molecular weight is 181.46 g/mol. The melting point of 1,2,4-trichlorobenzene is 17C. The boiling point is 213C. The vapor pressure has been reported to be 0.27 mmHg at 20C, and 0.29 mmHg at 25c. This material has been classified as one of the 188 hazardous air pollutants by the EPA.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Environmental Quality (DEQ) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1968 - Nov 2003), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line literature searches were conducted on November 17, 2003 to evaluate recent published literature. There were no recently published toxicity articles on 1,2,4-trichlorobenzene. The December 2005 EPA IRIS file contains an RfD, but not an RfC. There exists an ACGIH ceiling TLV value and NIOSH ceiling REL of 5 ppm (or 37 mg/m³) for 1,2,4-trichlorobenzene. There is an EPA (2002) Provisional RfC of 4 ug/m³.

Kociba et al (1981) exposed groups of 20 male Sprague-Dawley rats, 4 male New Zealand rabbits and 2 male beagle dogs by inhalation to 0, 30 or 100 ppm (0, 223 or 742 mg/m³) for 7 hours a day, 5 days per week for a total of 30 exposures over 44 days. There was no exposure related effect on body weights. Exposure to 100 ppm caused increased liver weight in rats and dogs, increased kidney weight in rats, and increased testes weight in rabbits. Urinary porphyrins and coporphyrin levels were increased in the rats at both exposure levels. There were no gross or microscopic alterations in tissues or organs. The authors considered increased porphyrins to be a physiological effect (a result of induced hepatic enzymes) rather than being a toxicological effect (interference with heme synthesis).

In Coate et al (1977), groups of 30 male Sprague-Dawley rats, 16 male New Zealand rabbits and 9 male cynomolgus monkeys were exposed to 0, 25.3, 49.2 or 92.8 ppm (0, 188, 365, or 689 mg/m³) for 7 hours a day, five days a week for a total of 26 weeks. There were transient changes in the liver and kidneys observed at all doses during the interim sacrifices at 4 and 13 weeks. The liver changes observed in rats at with a dose related increase included enlarged hepatocytes (hepatomegaly) that were more noticeable at the 4 week sacrifice than at 13 weeks. The livers also had increased vacuolation, which may be an indication of liver damage. The kidney changes observed in all dose levels at the 4 week sacrifice, but only at 92.8 ppm at 13 weeks, included hyaline degeneration of the inner cortex. This change is consistent with alpha-2u-globulin nephropathy, but too few details are in the report to make the alpha-2u-globulin nephropathy conclusion. However, there were no adverse effects in either liver or kidney organs observed at the study's termination at 26 weeks. The rat liver changes (enlarged hepatocytes with increased vacuolation) observed during interim sacrifices identifies 25.3 ppm as being a LOAEL.

In a sub-chronic Sprague-Dawley rat inhalation study by Watanabe et al (1977), rats were exposed to 0, 2.8, or 10.2 ppm (0, 21 or 76 mg/m³) for 6 hours a day, five days per week for 3 months. The NOAEL of 21 mg/m³ was identified for increased in urinary porphyrins observed at the 76 mg/m³ dose level. The urinary porphyrins are assumed to be related to the liver changes observed in other studies with higher dose levels, Coate et al and Kociba et al.

Calculation of a screening level is possible using the EPA's RfC methodology and the NOAEL (21 mg/m³) from Watanabe et al. The Watanabe et al NOAEL is selected as the most appropriate point of departure for RfC calculation because a NOAEL was identified, and the lowest reported LOAEL (76 mg/m³) among available studies was also from this study. In this calculation, 1,2,4-TCB can be considered to be a category 3 gas - with little to no water solubility, and remote or non-respiratory tract effects (i.e., urinary porphyrins) being observed. The NOAEL_[HEC] can be calculated below using the default ratio of animal to human blood:gas partitioning factor of one, as no blood:gas partition factors are known to be available for either humans or animals.

$$\begin{aligned} \text{NOAEL} &= 21 \text{ mg/m}^3 \\ \text{NOAEL}_{[\text{ADJ}]} &= (21 \text{ mg/m}^3) \times 6/24 \times 5/7 = 3.8 \text{ mg/m}^3 \\ \text{NOAEL}_{[\text{HEC}]} &= 3.8 \times 1 = 3.8 \text{ mg/m}^3 \\ \text{RfC} &= (3.8 \text{ mg/m}^3)/(10 \times 10 \times 10) = 4 \text{ ug/m}^3 \end{aligned}$$

The 10 fold uncertainty factors were used in the above calculation for each of the following three factors - sensitive individuals in the population, animal to human, and sub-chronic to chronic duration adjustment.

The initial threshold screening level for 1,2,4-trichlorobenzene can be set to the above calculated draft RfC of 4 ug/m³ with 24 hour averaging, under R232(1)(a).

The above ITSL is consistent with EPA's 2002 provisional RfC, in terms of the key study, toxicity endpoints, UF, and the final RfC value. There is a 1997 HEAST RfC value for 1,2,4-TCB of 200 ug/m³. However, this value is based on NOAEL of 223 mg/m³ (30 ppm) for increased liver and kidney organ weights at 100 ppm from Kociba et al 1981. The HEAST value does not consider the more sensitive increase in urinary porphyrins found in the Watanabe et al study.

References:

Coate et al. 1977. Chronic inhalation exposure of rats, rabbits, and monkeys to 1,2,4-trichlorobenzene. Arch Environ Health 30:249-255.

EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F.

EPA. 2002. PPRTV Derivation support document for 1,2,4-trichlorobenzene (120-82-1): Derivation of the provisional RfC. EPA doc # SRC SF 01-015a/10-16-02.

EPA. 2005. IRIS found at www.epa.gov/iris.

Kociba et al. 1981. Subchronic toxicity study of 1,2,4-trichlorobenzene in the rat, rabbit and beagle dog. Drug Chem Toxicol 4:229-249.

Watanabe et al. 1977. Subchronic toxicity studies of 1,2,4-trichlorobenzene in experimental animals. Unpublished submission to EPA's ToSCA program. EPA OTS # 0215163.

Watanabe et al. 1978. Subchronic toxicity studies of 1,2,4-trichlorobenzene in experimental animals. Toxicol Appl Pharmacol 45:332-3 (abstract only).