

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

November 23, 2015

To: File for Methylstyrene (CAS No. 25013-15-4)
From: Michael Depa, Air Quality Division, Toxics Unit
Subject: Screening Level Update

The Initial Threshold Screening Level (ITSL) for methylstyrene (also known as vinyl toluene) is 5 µg/m³ with annual averaging time.

Gary Butterfield authored a memo to the file for methylstyrene dated May 25, 1993 (see attached) in which he describes the derivation of the ITSL. The dose in mice was converted to a human equivalent concentration using a dosimetric adjustment factor, specifically the regional gas dose ratio. An uncertainty factor (UF) of 10 was used for interspecies extrapolation (i.e., to extrapolate from animals to humans). However, U.S. Environmental Protection Agency (EPA) reference concentration (RfC) guidance (U.S. EPA, 1994) states that:

The RfC methods use 3 for the UF for interspecies extrapolation due to the incorporation of default dosimetric adjustments.

The ITSL was recalculated as follows:

Lowest-observed-adverse-effect-level (LOAEL) = 10 parts per million (ppm) (NTP, 1990)

Unit conversion of ppm to mg/m³:

$$\text{mg/m}^3 = (\text{ppm} \times \text{molecular weight})/24.45$$

$$\text{mg/m}^3 = (10 \text{ ppm} \times 118.19\text{g})/24.45$$

$$\text{mg/m}^3 = 48.3 \text{ mg/m}^3$$

The duration adjusted LOAEL (LOAEL_{adj}) is adjusted for continuous exposure as follows:

$$\text{LOAEL}_{\text{adj}} = 48.3 \text{ mg/m}^3 \times 6\text{hrs}/24\text{hr} \times 5\text{days}/7\text{days}$$

$$\text{LOAEL}_{\text{adj}} = 8.63 \text{ mg/m}^3$$

The Human Equivalent Concentration (HEC) of the LOAEL (LOAEL_{HEC}) was calculated as follows:

$$\text{LOAEL}_{\text{HEC}} = \text{LOAEL}_{\text{adj}} \times \text{RGDR}$$

Where the RGRD is the regional gas dose ratio, and is calculated as:

$$\text{RGDR} = (\text{MV}_a/\text{S}_a)/(\text{MV}_h/\text{S}_h)$$

Where,

MV_a (minute volume of animal) = 0.05 m³/day,

MV_h (minute volume of human) = 20 m³/day,

S_a (surface area animal) = 2.9 cm², and

S_h (surface area human) = 177 cm².

$$RGDR = (0.06 \text{ m}^3/\text{day}) / (2.9 \text{ cm}^2) / (20 \text{ m}^3/\text{day}) / (177 \text{ cm}^2)$$

$$RGDR = 0.183$$

The $LOAEL_{HEC}$ is calculated as

$$LOAEL_{HEC} = LOAEL_{adj} \times RGDR$$

$$LOAEL_{HEC} = 8.62 \text{ mg/m}^3 \times 0.183$$

$$LOAEL_{HEC} = 1.58 \text{ mg/m}^3$$

The RfC can be recalculated using EPA guidance as follows:

$$RfC = LOAEL_{adj} / (UF1 \times UF2 \times UF3)$$

Where,

UF1 = 10 to account for variation in sensitivity among members of the human population (i.e., interindividual variability).

UF2 = 3 for interspecies extrapolation to account for extrapolating from laboratory animals to humans

UF3 = 10 to account for uncertainty when extrapolating from a LOAEL to a no-observed-adverse-effect level (NOAEL).

$$RfC = LOAEL_{HEC} / (10 \times 3 \times 10)$$

$$RfC = (1.58 \text{ mg/m}^3) / 300 \times 1000 \mu\text{g/mg}$$

$$RfC = 5.3 \mu\text{g/m}^3 ; \text{ rounding to 1 significant figure yields } \sim 5 \mu\text{g/m}^3.$$

Pursuant to Rule 232(1)(a) the ITSL is equal to the RfC. The current file review also concludes that the averaging time for the chronic RfC derived 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

ACGIH. 2010. American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. "TLV Booklet" Cincinnati, OH ISBN: 978-1-607260-19-6

U.S. EPA (Environmental Protection Agency). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC, EPA/600/8-90/066F.

NTP. 1990. Toxicology and carcinogenicity studies of vinyl toluene (mixed isomers) in F344/N rats and B6C3F1 mice. NTP TR# 375

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

May 25, 1993

To: Methylstyrene File (CAS No. 25013-15-4)
From: Gary Butterfield, Air Quality Division, Toxics Unit
Subject: ITSL for Methylstyrene

Methylstyrene is also known as vinyltoluene. The ACGIH has a TLV of 50 ppm (or 242 mg/m³) for vinyltoluene. The OSHA PEL and NIOSH REL are 100 ppm (or 480 mg/m³). EPA's IRIS database indicates that the RfC for methylstyrene is under review. There apparently are no plans by EPA to complete the RfC review in the near future. A CAS on-line search was conducted for all available articles. Only a few studies have used mice as the experimental species. However, in the few studies available, mice seem to be more sensitive to methyl styrene toxicity than rats. The reason for the species difference has not been well studied. The difference in sensitivity is illuminated in the bioassay by NTP (1990), in which mice were exposed to 10 or 25 ppm, while rats were exposed to 100 or 300 ppm.

A reduction of liver tissue non-protein sulfhydryl groups occurred in rats at exposures of 50 ppm (Heinonen et al 1982). The reduction of liver tissue non-on that the exposure level is close to one where adverse effects may occur. A NOAEL of 50 ppm was identified for effects on nerve conduction in rats by Seppalainen and Savolainen (1982).

A LOAEL of 10 ppm was identified by changes in mouse respiratory tract epithelium and inflammation (NTP 1990). Those changes included respiratory epithelium hyperplasia and chronic active inflammation of the lungs. Other rat studies (Heinonen et al (1982), Seppalainen and Savolainen (1982)), although conducted by the inhalation route of exposure, did not comment on pathological findings of the respiratory tract. It can be assumed that respiratory tract pathology was not evaluated in those studies. Mice are a sensitive species and respiratory tract effects are a sensitive endpoint. The respiratory tract effects observed in the mice at 10 ppm by NTP (1990) is the lowest LOAEL available, with no NOAEL for mice being available. It would not be appropriate to base the ITSL on the TLV when adverse effects are observed at lower concentrations in mice. There is no data available to indicate if humans are as sensitive to methyl styrene vapors as mice. Thus the ITSL can be derived from the LOAEL of 10 ppm identified in mice by NTP (1990). The ITSL can be calculated by methods described for calculation of RfCs in EPA (1990) as follows.

LOAEL to NOAEL adjustment: $(10 \text{ ppm} \times 4.9 \text{ mg/m}^3/\text{ppm}) \times 1/10 = 4.9 \text{ mg/m}^3$
NOAEL(adj) = $4.9 \text{ mg/m}^3 \times (6/24 \times 5/7) = 0.875 \text{ mg/m}^3$

$$\text{NOAEL(hec)} = \text{NOAEL(adj)} \times \text{RDGR} = 0.875 \text{ mg/m}^3 \times 0.183 = 0.16 \text{ mg/m}^3$$

$$\text{RfC} = \text{NOAEL(hec)} \times \text{UF} = 0.16 \text{ mg/m}^3 \times 1/100 = 1.6 \text{ } \mu\text{g/m}^3$$

ITSL = RfC 2 $\mu\text{g/m}^3$ with a 24 hour average time.

The RDGR (regional gas dose ratio) is described in EPA (1990) as the method to account for respiratory tract effects in humans based on animal data, and is determined as follows.

where

$$\text{RDGR} = \frac{[(\text{inhalation rate})/(\text{ET surface area})]_{\text{mouse}}}{[(\text{inhalation rate})/(\text{ET surface area})]_{\text{human}}}$$

$$\text{RDGR} = [(0.06 \text{ m}^3/\text{day})/(2.90 \text{ cm}^2)]/[(20 \text{ m}^3/\text{day})/(177 \text{ cm}^2)]$$

$$\text{RDGR} = 0.183$$

and the uncertainty factor (UF) of 100 is based on 10 for animal to human, and 10 for sensitive individuals.

The calculation of the ITSL by this method is consistent with EPA methods, EPA (1990). Although draft RfC's are not generally available for public review, a copy of the draft RfC for methylstyrene was obtained and found to be in agreement with these calculations.

References:

ACGIH. 1986. Documentation of the TLV's and BEI's.

EPA. 1993. IRIS2 database.

EPA. 1990. Interim methods for development of inhalation reference concentrations - review draft. EPA/600/8—90/066A.

Heinonen et al. 1982. Subacute toxicity of vinyltoluene vapor: effects on the hepatic and renal drug biotransformation and the urinary excretion of thioethers. *Acta Pharmacol Toxicol* 51:69-75.

NIOSH. 1990. Pocket guide to hazardous chemicals.

NTP. 1990. Toxicology and carcinogenicity studies of vinyl toluene (mixed isomers) in P344/N rats and B6C3F1 mice. NTP TR 1 375.

OSHA. 1989. 54 FR 2604.

Seppalainen and Savolainen. 1982. Impaired nerve function in rats after prolonged exposure to vinyltoluene. *Arch Toxicol (Suppl)* 5) 100-102.

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