

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 19, 2016

TO: File for o-Xylene (CAS # 95-47-6), p-Xylene (CAS # 106-42-3), m-Xylene (CAS # 108-38-3), and Xylenes (CAS # 1330-20-7)

FROM: Mike Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level for o-Xylene (CAS # 95-47-6), p-Xylene (CAS # 106-42-3), m-Xylene (CAS # 108-38-3), and Xylenes (CAS # 1330-20-7)

The Initial Threshold Screening Level (ITSL) for o-xylene (CAS # 95-47-6), p-xylene (CAS # 106-42-3), m-xylene (CAS # 108-38-3), and xylenes (CAS # 1330-20-7) is 390 µg/m³ with annual averaging time.

Previously, the averaging time (AT) assigned to xylenes was 24 hours, as per the default methodology (see attached memo from Doreen Lehner dated May 12, 2014). The current file review concludes that the AT 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). Therefore, the AT is set to annual.

Additionally, the value of the ITSL is changing from a value of 100 µg/m³ (Lehner, 2014), to 390 µg/m³. The database uncertainty factor (UF) of 3 was removed because there was no chemical-specific or toxicity-specific reason that a database uncertainty factor (UF) was justified and appropriate.

A total uncertainty factor (UF) of 100 was used to derive the new ITSL as follows:

$$\text{ITSL} = \text{No-observed-adverse-effect-level}(\text{NOAEL}^1) / \text{UF}_1 \times \text{UF}_2 \times \text{UF}_3$$

Where,

UF1 = 3 ($\sqrt{10}$) for animal to human

UF2 = 10 intraspecies

UF3 = 3 ($\sqrt{10}$) for subchronic to chronic

ITSL = 39 mg/m³ / 100 x 1000 µg/mg

ITSL = 390 µg/m³, with annual averaging time.

As previously mentioned, the ITSL has an annual averaging time pursuant to Rule 229(2)(b).

¹ This is the human equivalent concentration (see attached memo for more information)

Attachment

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TO: File for *o*-Xylene (CAS # 95-47-6), *p*-Xylene (CAS # 106-42-3), *m*-Xylene (CAS # 108-38-3), and Xylenes (CAS # 1330-20-7)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Screening Level for *o*-Xylene (CAS # 95-47-6), *p*-Xylene (CAS # 106-42-3), *m*-Xylene (CAS # 108-38-3), and Xylenes (CAS # 1330-20-7)

DATE: May 12, 2014

The Initial Threshold Screening Level (ITSL) for *o*-xylene (CAS # 95-47-6), *p*-xylene (CAS # 106-42-3), *m*-xylene (CAS # 108-38-3), and xylenes (CAS # 1330-20-7) is 100 µg/m³ based on a 24-hour averaging time. This ITSL is based on an EPA Reference Concentration for Chronic Inhalation Exposure (RfC) for xylenes (CAS # 1330-20-7) of 0.1 mg/m³. The EPA derived the RfC from rat behavioral changes in a sub-chronic inhalation study by Korsak et al. (1994). EPA (2003) stated:

Korsak et al. (1994) exposed groups of 12 male Wistar rats by inhalation to 0, 50, or 100 ppm *m*-xylene or *n*-butyl alcohol or a 1:1 mixture (purity of chemicals not provided) for 6 hours per day, 5 days per week, for 3 months and evaluated...[by] rotarod performance and spontaneous motor activity were assayed 24 hours after termination of the exposure periods. The rotarod test was used as a measure of motor coordination disturbances from exposure to *m*-xylene. The rotarod test involves placing the subject animals on a rotating rod and evaluating their ability to remain on the rod for a period of 2 minutes. The animals were trained to perform the task, exposed to chemical or control gas, and evaluated at defined intervals. By the time interval after exposure, considerable proportions of absorbed xylenes are expected to have been eliminated from the body. Blood for clinical biochemistry and hematologic analysis was collected 24 hours after termination of exposure. (EPA, 2003)

No statistically significant exposure-related changes were noted in body weight gain, absolute or relative organ weights, hepatic activities of microsomal monooxygenases, lipid peroxidation, or levels of triglycerides in the liver. Statistically significant decreases in erythrocyte number were seen in animals exposed to 50 ppm (93% of controls) or 100 ppm (80.5% of controls) of *m*-xylene alone. Similarly, decreased levels of hemoglobin were reported in both groups (92% of controls for both groups). At 100 ppm, a statistically significant increase in leukocyte number (35% increase over controls) was reported. Exposure to 50 or 100 ppm *m*-xylene alone also resulted in decreased rotarod performance starting at 1 month of exposure, which remained at the same level until the end of the 3-month exposure. Decreases were statistically significant in the 100 ppm group when compared with the controls. (EPA, 2003)

Sensitivity to pain was assessed using the hot plate behavior test, in which the animals are placed on a hot (54°C) surface and the time interval between being placed on the plate and licking of the paws is measured. Rats exposed to 50 or 100 ppm *m*-xylene alone had statistically increased sensitivity to pain at the end of the 3-month exposure (latency of the paw-lick response was 8.7 and 8.6 seconds, respectively, vs. 12.2 seconds for the controls). The LOAEL is 100 ppm, based on decreased rotarod

Attachment

performance and decreased latency in the paw-lick response in the hot-plate test, and the NOAEL is 50 ppm. (EPA, 2003)

The EPA (2003) determined that the critical effect was impaired motor coordination (decreased rotorod performance) with a NOAEL of 50 ppm (NOAEL[HEC] of 39 mg/m³) (Korsak et al., 1994). The first calculation was used to convert ppm to mg/m³ by using the molecular weight of xylene which is 106.17 g/mol and multiplying that by the NOAEL of 50 ppm and dividing by 24.45 to get 217 mg/m³.

The NOAEL[adj] = 217 mg/m was then adjusted by 6/24 hours day and by 5 days/7 day = 39 mg/m³.

The NOAEL[HEC] was calculated for extrarespiratory effects of a Category 3 gas (EPA, 1994).

Blood/gas coefficients: H(b/g)rat = 46.0; H(b/g)human = 26.4 (Tardiff et al, 1995).

(Hb/g)rat/(Hb/g)human = 1.7; value of 1 is used when the ratio is >1 (EPA, 1994).

NOAEL[HEC] = NOAEL[ADJ] x (Hb/g)rat/(Hb/g)human = 39 mg/m³.

An uncertainty factor of 300 (3 animal to human, 10 intraspecies, 3 subchronic to chronic, and 3 database uncertainty factor) was applied to the NOAEL[HEC] to obtain the RfC of 0.1 mg/m³.

According to Rule 232(1)(a) an ITSL can be determined to be equal to an EPA inhalation RfC. Therefore the ITSL for o-xylene, p-xylene, m-xylene, and xylenes is 100 µg/m³ based on a 24- hour averaging time. Also a footnote needs to be added that states, "the combined ambient impact of all forms of xylene with Note #2 cannot exceed the initial threshold screening level (ITSL) of 100 µg/m³ (24-hour average)."

References

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

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

EPA. 2003. Integrated Risk Information System. Xylenes (CASRN 1330-20-7). Retrieved data on 4/14/2014. Available online at: <http://www.epa.gov/iris/subst/0270.htm>

Korsak Z, Wisniewska-Knypl J, and Swiercz R. 1994. Toxic effects of subchronic combined exposure to n-butyl alcohol and m-xylene in rats. Int J Occup Med Environ Health 7:155-166.

Tardif R, Larare' S, Charest-Tardif G, Brodeur J, and Krishnan K. 1995. Physiologically-based pharmacokinetic modeling of a mixture of toluene and xylene in humans. Risk Anal 15:335-342.

DL:lh