MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Styrene Chemical File (CAS No. 100-42-5)

FROM: Michael Depa, Air Quality Division, Toxics Unit

DATE: May 12, 2014

SUBJECT: Update Screening Levels

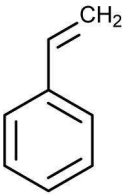
The Initial Threshold Screening Level (ITSL) is 1000 µg/m³ with an annual averaging time. The Initial Risk Screening Level (IRSL) is 2 µg/m³, and the Secondary Risk Screening Level (SRSL) is 20 µg/m³, both with annual averaging times.

This memo documents the following two changes to the screening levels for styrene:

1) The ITSL averaging time is changing from 24-hrs to annual, recognizing that the derivation method explicitly adjusts the ITSL value to account for long-term (chronic) exposures, which are best approximated with an annual average, and
2) The IRSL value is changing from 1.7 to 2 µg/m³ in order to round to 1 significant figure.

The following information sources were searched in order to update the screening levels for styrene: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS, 2012), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) Online (1993- October 2012), National Library of Medicine (limited to 2009 through October, 2012), Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has established a reference concentration (RfC) of 1 mg/m³ for styrene. California Office of Environmental Health Hazard Assessment (Cal-OEHHA) established a chronic reference exposure level (REL) at 0.2 ppm (900 µg/m³). The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) established chronic minimal risk level (MRL) at 0.2 ppm (900 µg/m³). The ACGIH Threshold Limit Value (TLV) and Short Term Exposure Limit (STEL) for styrene are 85 mg/m³ (20 ppm) and 170 mg/m³ (40 ppm), respectively. The NIOSH Recommended Exposure Level (REL) is 215 mg/m^3 (50 ppm). The molecular formula for styrene is shown in figure 1. The molecular weight of styrene is 104.2g.

Figure 1. Molecular Formula for Styrene



Derivation of the EPA RfC

The EPA (2012) established the RfC in 1993 from an occupational exposure study by Mutti et al. (1984). The no-observed-adverse-effect-level (NOAEL) was 94 mg/m³ (25 ppm = 150 mmole urinary styrene metabolites/mole creatinine adjusted to lower 95% confidence limit = 22 ppm). The human equivalent concentration (HEC) was calculated by using the 8-hour time weighted average occupational exposure.

NOAEL(HEC) = 94 mg/m³ x MVho/MVh x 5 days/7 days
NOAEL(HEC) = 34 mg/m³

Where,
MVho[1] = 10 m³/day, breathing volume for an 8 hour occupational exposure (10 m^3)
MVh[2] = 20 m³/day, breathing volume for an 24 hour non-occupational exposure (20 m^3)

EPA (2012) describes the study used to derive the RfC for styrene in their online database called Integrated Risk Information System (IRIS):

> In a cross-sectional study, Mutti et al. (1984) examined the neuro- psychological function in 50 workers whose mean duration of styrene exposure was 8.6 (SD of 4.5) years. Styrene exposure was assessed by the authors to correspond to air concentrations ranging from 10-300 ppm as a mean daily exposure. These concentrations were estimated from the summation of the principal urinary metabolites of styrene, mandelic acid (MA) and phenylglyoxylic acid (PGA). Urinary metabolite levels are considered as reliable biological indicators of styrene exposure (ACGIH, 1986; WHO, 1983), and several laboratories have determined collectively that the specific method used in this study, the summation of the principal metabolites collected in next-morning urine, is the most reliable and representative of actual air exposure concentrations (Guillemin et al., 1978, 1982; Ikeda et al., 1982; Franchini et al., 1983). Workers with absence of metabolic and neurologic disorders, smoking habits of <20 cigarettes/day, and an alcohol intake of <80 mL of ethanol/day were chosen. These same eligibility criteria were used to select a control group of 50 workers that was matched for age, sex, and educational level. The exposed workers were further segregated into four subgroups (n = 9-14) according to increasing levels of urinary styrene metabolites. A battery of neuropsychological tests was conducted on the same day as the urine collection and included exams evaluating visuo-motor speed, memory, and intellectual function. No other endpoints were considered. Correlation analysis of the test results and urinary metabolite levels showed a clear concentration response in at least three of eight tests, including block design (intellectual function), digit-symbol (memory), and reaction times (visuo-motor speed). Evidence of a concentration-response relationship was also present for short- and long-term logical memory and embedded figures (impaired visual perception). When the results were analyzed using duration of exposure as a covariate, increases in reaction times and a decrease in digit symbol (memory, concentration) were apparent. The only test showing results in the lowest exposure group, short-term verbal memory loss, exhibited no concentration-response relationship. The neuropsychological results from this study are from established tests for CNS dysfunction, are present when compared against a stringently matched control population, and show concentration-response relationships…
>
> The concentration-response relationship between urinary metabolite concentration (mandelic acid and phenylglyoxylic acid levels normalized to creatinine in "morning-after" urine) and test results indicated a significant effect level in the subgroup whose urine

[1] mechanical ventilation occupational (MVho)
[2] mechanical ventilation (MVh)

contained 150-299 mmole urinary metabolites/mole creatinine. Workers with metabolite concentrations of up to 150 mmoles/mole appeared to have no significant effects, and this level is therefore designated as the NOAEL in this study. The authors state that this level of urinary metabolites corresponds to a mean daily 8-hour exposure to air styrene of 25 ppm (106 mg/m^3). Derivation of this air level is from the creatinine-normalized, combined concentration of the styrene metabolites, MA and PGA, in urine collected from the workers on Saturday mornings. Guillemin et al. (1982) demonstrated a logarithmic relationship (r = 0.871) between the summation of urinary metabolites (MA + PGA, next morning) and air concentrations of styrene (ppm x hours). Guillemin calculated the mean combined urinary metabolite concentration (next morning) for an 8-hour exposure to 100 ppm. This relationship was used by both Mutti et al. (1984) and Guillemin and Berode (1988) in a proportional manner to obtain styrene air levels at lower urinary metabolite concentrations. The 95% confidence interval was also calculated for an 8-hour exposure at 100 ppm, the lower limit of the confidence calculation being 88% of the mean styrene exposure. This factor was applied directly to the NOAEL of 25 ppm [25 ppm x 0.88 = 22 ppm (94 mg/m^3)]. Due to the construction of the subgroups, designation of a LOAEL was the lower limit of the subgroup in which adverse effects were observed [i.e., greater than the NOAEL of 22 ppm (94 mg/m^3)].

The EPA used Uncertainty Factors (UFs) to calculate the RfC (see Table 1.).

Table 1. Uncertainty Factors Used by EPA for the RfC for Styrene

UF	Description	
3	Database inadequacy	UF_1
3	Intraspecies variability	UF_2
3	Subchronic to chronic	UF_3
30	Total	

EPA (2012) explains the justification for the UFs:

A partial UF of 3 was used for database inadequacy, including the lack of concentration-response information on respiratory tract effects. A partial UF of 3 instead of 10 was used for intraspecies variability since the lower 95% confidence limit of the exposure extrapolation was used and because Perbellini et al. (1988) demonstrated that this biological exposure index (i.e., urinary metabolites) accounts for differences in pharmacokinetic/ physiologic parameters such as alveolar ventilation rate. A partial UF of 3 instead of 10 was also used for lack of information on chronic studies as the average exposure duration of the principal study of Mutti et al. (1984) was not long enough (8.6 years) to be considered chronic. The total uncertainty is therefore 30 (three times the one-half logarithm of 10).

The RfC was calculated as follows:

$RfC = NOAEL(HEC)/(UF_1 \times UF_2 \times UF_3)$

$RfC = 34 \text{ mg/m}^3/(3 \times 3 \times 3)$

$RfC = 1 \text{ mg/m}^3$

Typically the ITSL is equal to the RfC, pursuant to Rule 232(1)(a).

Rule 232 Methodology for determining initial threshold screening level.

Rule 232 continued…

(1) The initial threshold screening level (ITSL) for each toxic air contaminant shall be determined as follows:

(a) If an inhalation reference concentration (RfC) can be determined from best available information sources, then the initial threshold screening level equals the inhalation RfC.

Alternatively, an ITSL can be derived according to Rule 229:

(2) The initial threshold screening level shall be determined by either of the following:

(a) The methodology for determining the initial threshold screening level contained in R 336.1232.

(b) Any alternative methodology to assess noncarcinogenic health effects that can be demonstrated to the department to be more appropriate based on toxicological grounds and that is supported by the scientific data.

If an ITSL is derived according to Rule 232, then the averaging time for an RfC derived ITSL is 24-hrs, see Rule 232(2)(b). However, if an ITSL is derived pursuant to Rule 229(2)(b), the averaging time associated with the ITSL is not designated. Because EPA used a subchronic-to-chronic uncertainty factor of 3, it was determined that the RfC specifically protects for long-term effects, and therefore an annual averaging time will be used for the ITSL.

Derivation of ATSDR Chronic MRL (for informational purposes only)

The following text was taken from the Toxicological Profile for Styrene (ATSDR, 2010):

Benignus et al. (2005) used data from occupational exposure studies examining color vision impairment (Campagna et al. 1996: Eguchi etal. 1995: Gobba et al. 1991: Gong et al. 2002; Kishi et al., 2001) and delays in choice reaction time (Jegaden et al. 1993: Mutti et al. 1984: Triebig et al. 1989: Tsai and Chen 1996). Average styrene exposure concentrations for each study were estimated from individual data reported in the papers: for studies reporting individual data as urinary mandelic acid levels, standardized methods for converting to styrene exposure levels were used. Cumulative styrene exposure was estimated by multiplying exposure level by length of employment. A common metric of effect magnitude (percentage of baseline) was calculated for the different neurological effects.

Effect noted in study and corresponding doses: A significant linear relationship between choice reaction time and cumulative styrene exposure was found: cumulative exposure accounted for 91% of the variance in reaction time. Similarly, a significant relationship between CCI[3] and cumulative styrene exposure was found with cumulative exposure accounting for 35% of the variance in CCI. Using the regression equations for these two effects, the investigators estimated that exposure to 150 ppm for 8 work-years would result in a 50% increase in choice reaction time and a 17% increase in CCI score: exposure to 20 ppm for 8 work-years would result in a 6.5% increase in choice reaction time and a 2.23% increase in CCI score. As discussed in Benignus et al. (2005), a 7% decrease in reaction time would prevent 58,000-70.000 injuries per year from automobile accidents. The investigators also noted that CCI increases with age and the rate of increase is about 10% per 13 years of age; thus, a 2.23% decrease in color perception would be roughly equivalent to 2.9 additional years of age. Based on this analysis, 20 ppm is considered a LOAEL for neurological effects.

A minimal LOAEL of 20 ppm in the Benignus et al. (2005) meta-analysis was selected as the point of departure for the chronic-duration inhalation MRL. The LOAEL

[3] color confusion index (CCI). Alterations in color discrimination and reaction time are two neurological effects consistently found in styrene workers.

was classified as a minimal LOAEL based on the findings of Triebig et al. (2001) that alterations in color vision were reversible and the workers were not aware of any changes in color vision.

UF_1 = 3 for minimal LOAEL (LOAEL-to-NOAEL)
UF_2 = 10 for human variability (sensitive individuals)

$LOAEL_{ADJ}$= 20 ppm x 8 hrs/24hrs x 5days/7days
$LOAEL_{ADJ}$= 4.8 ppm

The Chronic Minimal Risk Level (MRL) was calculated from the $LOAEL_{ADJ}$ as follows:

MRL = $LOAEL_{ADJ}$/30
MRL = 4.8 ppm/30
MRL = 0.16 ppm
MRL = 0.2 ppm (rounded to 1 significant figure)(900 µg/m³)

California Reference Exposure Level (for informational purposes only)
California Office of Environmental Health Hazard and Assessment (Cal-OEHHA, 2000) derived a Reference Exposure Level (REL) for styrene based on Mutti et al. (1984). Cal-OEHHA employed the EPA Benchmark Dose Software program to find the benchmark concentration (BMC) at a 5% response rate (BMC_{05}) of 1.7 ppm. Cal-OEHHA adjusted the duration for continuous exposure using the same method used by EPA and ATSDR (see above), i.e., 10 m³/day = breathing volume for an 8 hour occupational exposure (10 m^3); 20 m³/day = breathing volume for an 24 hour non-occupational exposure (20 m^3); and 5 days exposure per week (7 days). The HEC dose was calculated as 0.61 ppm. Cal-OEHHA used a total uncertainty factor of 3 for intraspecies uncertainty (no adjustment for LOAEL-to-NOAEL, Subchronic-to-Chronic, and Interspecies). The REL was calculated as:

REL = BMC_{05HEC}/3
REL = 0.61 ppm/3
REL = 0.2 ppm (852 µg/m³; rounded to 1 significant figure yields 900 µg/m³)

Cancer Risk Assessment
EPA (1989) derived an Inhalation Unit Risk (IUR), which was subsequently used to derive an IRSL. The following excerpt summarizes the data and quantitative assessment used to calculate the IUR for styrene (p. 38):

> The Incidence in either treated group is not statistically significant when compared with concurrent controls. When compared with historic controls (incidence 11/808, 1.3%), however, the incidences in the treated groups are statistically significant by the Fisher Exact test (p=0.0033). This significance reflects the greater statistical power of the larger number of historic than concurrent controls, rather than a lower incidence in historic controls. Because the incidence in treated rats compared with historic controls is significant, it is appropriate to compute a q_1* from data in the Jersey et al. (1978) study. The data used in computation are presented in Tables 6-3 and 6-4. Using the multistage model developed by Howe and Crump (1982), a q_1* of $2x10^{-3}$ $(mg/kg/day)^{-1}$ is calculated. This corresponds to a unit risk for air of $6x10^{-7}$ $(\mu g/m^3)^{-1}$ by assuming a human ventilatory volume of 20 m³/day, a body weight of 70 kg and complete absorption. This study (Jersey et al., 1978) may not be appropriate for low dose extrapolation because of pharmacokinetic constraints (U.S. EPA, 1987). This issue is being evaluated. In the interim, the slope estimate of $2x10^{-3}$ $(mg/kg/day)^{-1}$ and the unit risk for air of $6x10^{-7}$ $(\mu g/m^3)^{-1}$ appear on IRIS (U.S. EPA, 1987).

TABLE 6-3. Female Rats (Jersey et al., 1978)(excerpt of EPA, 1989)

Experimental Doses or Exposure[a]	Transformed Animal Dose[b] (mg/kg/day)	Human Equivalent Dose[e] (mg/kg/day)	Incidence No. Responding/ No. Tested
0	0	0	1/85
600 ppm[c]	265.1	46.75	6/85
1000 ppm[d]	441.8	77.92	6/85

Human $q_1^* = 2 \times 10^{-3}$ $(mg/kg/day)^{-1}$

[a]Exposures were for 6 hours/day, 5 days/week over a 621-day period: 437/621 days.

[b]Transformed doses calculated by expanding to continous exposure, estimating a breathing rate for 0.384 kg rats from the expression [0.105 (body weight/0.113)$^{2/3}$] and expanding exposure to the full experimental period (30 hours/week/168 hours/week; 20.7 months/24 months).

[c]Mean measured concentration = 592 ppm (2522 mg/m^3)

[d]Mean TWA concentration 1007 ppm (4290 mg/m^3) based on 38 days at 1197 ppm and 399 days at 989 ppm.

[e]Transformed using a surface area adjustment $(W_A/W_H)^{1/3}$

Table 6-4. Male Rats (Jersey et al., 1978) (excerpt of EPA, 1989)

Experimental Doses or Exposure[a] (ppm)	Transformed Animal Dose[b] (mg/kg/day)	Human Equivalent Dose[c] (mg/kg/day)	Incidence No. Responding/ No. Tested
0	0	0	1/62
600	180.2	36.14	5/78
1000	300.3	60.23	1/78

Human $q_1^* = 1 \times 10^{-3}$ $(mg/kg/day)^{-1}$

[a]Exposures were for 6 hours/day, 5 days/week over 549 days out of a 24-month expermental duration.

[b]Breathing rate estimated as [0.105 (0.565 kg/0.113)$^{2/3}$] and expanding for continuous exposure by multiplying by 30 hours/week/168 hours/week; 18.3 months/24 months.

[c]Transformed using a surface area adjustment $(W_A/W_H)^{1/3}$

After a thorough review of the literature, it was determined that the EPA (1989) quantitative risk assessment for cancer risk provides the best basis with which to evaluate styrene air emissions. A recent review by the National Toxicology Program (2011) provides support for the carcinogenic potential from styrene exposure:

> Styrene is reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and supporting data on mechanisms of carcinogenesis

Concerning the mechanism of carcinogenesis, NTP (2011) states:

> Detection of styrene-7,8-oxide-DNA adducts at base-pairing sites and chromosomal aberrations in lymphocytes of styrene-exposed workers supports the potential human cancer hazard from styrene through a genotoxic mode of action.

It should be noted that the IUR derived by EPA (1989) was listed as $6x10^{-7}$ $(\mu g/m^3)^{-1}$. Using 1 significant figure to derive the Initial Risk Screening Level (IRSL) results in an IRSL of 2, as follows:

$IRSL = 1x10^{-6}/(6x10^{-7}$ per $\mu g/m^3)$
$IRSL = 1.667\ \mu g/m^3$
$IRSL = 2\ \mu g/m^3$(rounded to 1 significant figure).

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