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Styrene

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Chapter 1 Summary Table

Table 1 provides a summary of health- and welfare-based values from an acute and chronic evaluation of styrene. Table 2 provides summary information on styrene's physical/chemical data.

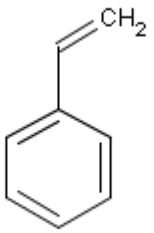
Table 1 Health- and Welfare-Based Values

Short-Term Values	**Concentration**	**Notes**
^{acute}ESL [1 h] (HQ = 0.3)	6,500 μg/m^3 (1,500 ppb)	Critical Effect(s): eye, nose and throat irritation, nausea, discomfort, and impairment of coordination and balance in male volunteers
Acute ReV (HQ = 1)	22,000 μg/m^3 (5,100 ppb) *	Critical Effect(s): Same as above
^{acute}ESL$_{odor}$	110 μg/m^3 (25 ppb)* **Short-Term ESL for Air Permit Reviews**	50% odor detection, sharp, sweet odor
^{acute}ESL$_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{nonlinear(nc)}$ (HQ = 0.3)	140 μg/m^3 (33 ppb) **Long-Term ESL for Air Permit Reviews**	Critical Effect(s): memory and sensory/motor function; abnormal responses to the neuropsychological tests in male workers
Chronic ReV (HQ = 1)	470 μg/m^3 (110 ppb)*	Critical Effect(s): Same as above
^{chronic}ESL$_{linear(c)}$ ^{chronic}ESL$_{nonlinear(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
^{chronic}ESL$_{veg}$	---	No data found

* Values that may be used for evaluation of air monitoring data

Abbreviations: **HQ**, hazard quotient; **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Levels; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **^{acute}ESL$_{odor}$**, acute odor-based ESL; **^{acute}ESL$_{veg}$**, acute vegetation-based ESL; **^{chronic}ESL$_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effect; **^{chronic}ESL$_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; and **^{chronic}ESL$_{veg}$**, chronic vegetation-based ESL

Table 2 Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	C_8H_8	ACGIH 2001
Chemical Structure		ChemIDplus
Molecular Weight	104.16	ACGIH 2001
Physical State	Oily liquid	ACGIH 2001
Color	Colorless to yellowish	ACGIH 2001
Odor	Sweet/Sharp	ACGIH 2001
CAS Registry Number	100-42-5	ACGIH 2001
Synonyms	Ethenylbenzene; Phenylethylene; Vinylbenzene	ACGIH 2001
Solubility in water	Slightly soluble, 310 at 25ºC	ChemIDplus
Log P_{ow}	2.95	ChemIDplus
Vapor Pressure	6.4 mmHg at 25ºC	ChemIDplus
Relative Vapor Density (air = 1) Relative	NA	
Density (water = 1)	0.863 at 25ºC	ACGIH 2001
Melting Point	-30.6ºC	ACGIH 2001
Boiling Point	145.2ºC	ACGIH 2001
Conversion Factors	1 μg/m^3 = 0.23 ppb @ 25ºC 1 ppb = 4.26 μg/m^3	Toxicology Section

Chapter 2 Major Uses and Sources

Styrene is widely used for the manufacture of polystyrene, copolymers of styrene with acrylonitrile and/or butadiene, plastics, rubber resins, and insulators. It is a common cross-linking agent in glass fiber-reinforced and unsaturated polyester resins. Styrene-butadiene rubber has been the most widely employed type of synthetic rubber (ACGIH 2001).

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Studies

Styrene is a colorless to slightly yellowish oily liquid with a slightly sweetish, sharp odor (refer to Section 3.2.1). It is soluble in ethanol, benzene, and ether and slightly soluble in water. The main chemical and physical properties of styrene are summarized in Table 2.

Irritation of the eyes and mucous membranes, as well as central nervous system (CNS) effects, are observed in animals and humans following acute exposure to styrene. High occupational exposures (> 100 ppm in air) to styrene have been shown to cause pre-narcotic CNS depression with symptoms including drowsiness, headaches, and disturbance of balance. Toxicological studies have identified other neurotoxic effects of styrene, including disruption of dopaminergic functions of the brain, as well as changes in nerve conduction and neurobehavioral test performance. Styrene is a respiratory tract toxicant in rodents but is unlikely to have same effect in humans (ATSDR 2007, NAC 2004, OEHHA 1999, Cohen et al. 2002; see Section 3.1.2).

3.1.1.1 Human Studies

3.1.1.1.1 Stewart et al. (1968)

Local irritation and CNS effects were studied by Stewart et al. (1968). The inhalation exposure study was conducted with a group of 9 male volunteers. Three subjects were exposed to 51 ppm for 1 h, 6 were exposed to 99 ppm for 7 h with a 30-minute (min) break at half-time, 1 was exposed to 117 ppm for 2 h, 3 were exposed to 216 ppm for 1 h, and 5 were exposed to 376 ppm for 1 h. No symptoms were reported in any of the 3 subjects after exposure to 51 ppm for 1 h. Eye and throat irritation were observed in 3 out of 6 volunteers exposed to 99 ppm for 20 min. Nasal irritation was first noted in one subject after 20 min of exposure to 216 ppm. Nasal irritation was observed in all 5 volunteers after exposure to 376 ppm for 1 h. In addition, after 25 min of exposure to 376 ppm, all 5 subjects exhibited nausea, significant discomfort, and an abnormal Romberg test (balancing on one foot with eyes closed and both arms at a side), which is indicative of cerebellar dysfunction. No signs of CNS effects (impairment of coordination and balance) were observed during the 1 h exposure to 216 ppm or less. A no-observed-adverse-

effect-level (NOAEL) of 51 ppm for local irritation and a NOAEL of 216 ppm for CNS effects were identified from this study.

3.1.1.1.2 Seeber et al. (2002)

Seeber et al. (2002) investigated psychological reactions related to chemosensory irritation during exposure of young healthy male volunteers to a number of chemicals, including styrene. The concentrations of styrene were 0 ppm for 4 h (16 subjects), 20 ppm for 3 h (16 subjects), or 0.5 ppm for 50 minutes followed by 40 ppm peaks for 30 min during a total of 4 h exposure duration (24 subjects). Self-reported ratings for irritation, odor, and annoyance were assessed. The results show that for odor and annoyance, ratings increased similarly with increasing styrene concentration. In contrast, there was no statistical significance for eye irritation at 20 ppm. A NOAEL of 20 ppm for 3 h for irritation effects was identified from this study.

3.1.1.1.3 Ödkvist et al (1982)

In a study by Ödkvist et al. (1982), 10 healthy non-smoking volunteers (5 men, 5 women, ages 20 – 30 years) inhaled styrene via a mouth-tube at concentrations between 87 and 139 ppm for 1 h. During styrene inhalation, the test subjects performed slight physical work on a bicycle ergometer. Vestibulo-oculomotor tests (swing test, optovestibular test, visual suppression test, optokinetic test, saccade test, slow pursuit moving test) were performed before, during, and 1 h after exposure. Each individual served as their own control. A significant inhibition of the vestibulo-oculomotor system was observed in subjects exposed to 87 ppm for 1 h. The authors concluded that the results suggest that styrene affects the vestibulo-ocular system by blocking inhibitory mechanisms in the CNS. A lowest-observed-adverse-effect-level (LOAEL) of 87 ppm for vestibular effects was identified from this study.

3.1.1.1.4 Edling and Ekberg (1985)

Acute behavioral effects and symptoms of exposure to low levels of styrene were investigated in a cross-sectional study (Edling and Ekberg 1985). Twelve men occupationally exposed to styrene were studied and compared with a control group of 10 unexposed men. Neuropsychiatric symptoms (questionaire) and a reaction time test were conducted before and after work. Active and passive sampling of airborne styrene was carried out and urinary mandelic acid concentrations were measured. The mean 8-h time-weighted average (TWA) of breathing zone personal samples was 43 ± 28 mg/m³ (10 ± 6.5 ppm) in the morning shift and 54 ± 37 mg/m³ (13 ± 9 ppm) in the afternoon shift. No significant differences in neuropsychiatric symptoms or reaction time were observed between pre- and post-shift evaluations or between exposed and control groups. A NOAEL of 13 ppm for neuropsychiatric symptoms was identified from this study.

3.1.1.1.5 Ska et al. (2003)

In another study by Ska et al. (2003), 42 healthy men were exposed to 5 exposure scenarios during 6 h exposure sessions: 1) exposure to 106 mg/m³ (25 ppm); 2) variable exposure with a

mean concentration of 25 ppm and four 15 minutes peak exposures up to 213 mg/m³ (50 ppm); 3) exposure to 50 ppm; 4) mean exposure to 50 ppm with four peaks of 426 mg/m³ (100 ppm); and 5) exposure to 1 ppm (control). Before and after exposure, the volunteers were subjected to a battery of sensory tests (visual and olfactory), neuropsychological tests (reaction time, attention, memory, psychomotor function), and self-evaluation questionaires (mood and symptoms). The different exposure scenarios did not show any impairment of the sensory tests. Olfaction, color vision, and contrast sensitivity were not altered by exposure. A NOAEL of 100 ppm for CNS effects was identified from this study.

3.1.1.1.6 Seeber et al. (2004)

In a study by Seeber et al. (2004), groups of 16 volunteers (8 in the morning, 8 in the afternoon) were exposed to either 0.5 (odor threshold) or 20 ppm styrene at a constant level for 3 h. The subjects were tested for simple reaction time, choice reaction time, and attention prior to exposure initiation during the third hour of expsoure and 1.5 h after exposure. A symptom questionaire was completed before, during, and after exposure, and the blood styrene level in each subject was measured after exposure. The mean concentrations of styrene in blood were 2.2 and 80 µg/L, respectively, for the 0.5 and 20 ppm exposure groups. The blood levels of styrene were correlated with styrene exposure levels in air ($r = 0.98$). Only an increase in reported breathing problems was found; however, it was not statistically significant, and the ranking of the severity of the breathing problem was very low (0.5 on a scale of 5). No significant alterations in performance on neurobehavioral tests were found. A free-standing NOAEL of 20 ppm for CNS effects was identified from this study.

3.1.1.2 Animal Studies

Inhalation studies in rats and mice have reported irritation, CNS effects, and damage to the nasal epithelium in rats and mice (ATSDR 2007). In mice, RD_{50} (50% irritation dose) values for sensory irritation of 156 ppm - 980 ppm were reported (Alarie 1973, de Ceaurriz et al. 1981, and Bos et al. 1992 in NAC 2004). CNS depression in rats and mice was observed at higher concentrations. Rats lost consciousness at 2000 ppm after a 5 h exposure and showed reduced attention following a 6 h exposure to 1,500 ppm (Withey and Collins 1979, and Jary et al. 2002 in NAC 2004). In mice, signs of CNS depression during a 4 h exposure were staggered: gait at 1,420 ppm and apathy followed by narcosis at higher concentrations of 2,983 and 3,766 ppm (BASF 1979b in NAC 2004).

3.1.1.2.1 Green et al. (2001)

The most sensitive target of styrene toxicity in mice appears to be the nasal olfactory epithelium. In a study by Green et al. (2001), groups of male CD-1 mice (20 per dose group) were exposed to 0, 40, or 160 ppm styrene 6 h/day for 3 days. Mice were sacrificed 17 h after the last exposure. At 160 ppm, degenerative, mostly focal changes, were observed in the olfactory tissue in all mice. At 40 ppm, animals were largely unaffected, and only one mouse showed minimal atrophy

of the olfactory mucosa. A NOAEL of 40 ppm for nasal olfactory epithelium toxicity was identified from this study.

3.1.1.2.2 Cruzan et al. (2001)

In a repeated dose, subchronic study by Cruzan et al. (2001 in NAC 2004), groups of 55 male CD-1 mice were exposed to 0, 40, or 80 ppm styrene 6 h/day, 5 days/week for up to 13 weeks. A subgroup of 5 mice from each exposure group was terminated after one exposure and other subgroups were terminated after subsequent exposures. In the nasal olfactory epithelium, single cell necrosis was found after a single exposure to 80 ppm, but not to 40 ppm. No changes were observed in the lung at 40 or 80 ppm up to the end of the 13th week. A NOAEL of 40 ppm for nasal olfactory epithelium toxicity was also identified from this study.

3.1.2 Mode of Action (MOA) Analysis and Dose Metric

Styrene is known to be toxic to the nasal olfactory epithelium of both mice and rats. Although nasal irritation has been observed in humans exposed to 376 ppm for 1 h (Stewart et al. 1968) and lesions in the nasal olfactory epithelium were observed in rats exposed to 500, 1,000, and 1,500 ppm for 13 weeks (Cruzan et al. 1997 in ATSDR 2007), mice appear to be unusually susceptible to this effect. The observed species differences may be due to differences in styrene metabolism in the nasal cavity.

An MOA analysis was conducted in a study by Green et al. (2001). The authors concluded that the primary reactive metabolite of styrene, styrene oxide, was responsible for the observed nasal toxicity. Mice appear to have a greater capacity than humans to generate styrene oxide in the nasal cavity and a lower capacity to detoxify styrene oxide. The findings of Green et al. (2001) were further confirmed by the results of in vitro assays of human nasal tissue. Styrene oxide has not been detected and high levels of epoxide hydrolases (to detoxify styrene oxide) have been found in these in vitro assays. Thus, humans are not likely sensitive to the nasal toxicity of styrene. Accordingly, nasal lesions in mice are not suitable for derivation of an acute Reference Value (ReV) (NAC 2004, ATSDR 2007).

Styrene also acts as an acute CNS depressant. The effect is likely related to the physico-chemical properties of styrene and the amount of styrene in the brain. Therefore, it is not dependent on styrene metabolism or the reactive metabolite of styrene, styrene oxide (NAC 2004). The results of a study by Ödkvist et al. (1982) suggested that styrene blocks inhibition of the vestibulo-oculomotor system. Thus, exposure concentration of the parent chemical (styrene) will be used as the dose metric.

3.1.3 Point of Departure (POD) for the Key Study and Critical Effect

While data suggest that the CNS is the most sensitive target of styrene toxicity in humans (ATSDR 2007), the NOAEL and LOAEL values identified from several human studies are varied (see Section 3.1.1.1 above). A NOAEL of 20 ppm for both local irritation and CNS effects

from Seeber et al. (2002, 2004) is the lowest reported value; however, it is a freestanding NOAEL, and the exposure duration is 3 h. The next higher NOAEL for CNS effects is 100 ppm (Ska et al. 2003); however, a LOAEL of 87 ppm was identified from another study (Ödkvist et al. 1982 in NAC 2004). Thus, a higher NOAEL for CNS effects, if further elucidated, could be between 20 and 87 ppm. For this reason, a NOAEL of 51 ppm for local irritation identified from the Stewart et al. (1968) study was used as the human equivalent concentration POD (POD_{HEC}). In addition, this study was chosen because there were dose-related responses for eye, throat, and nasal irritation in subjects who were exposed for 1 h.

3.1.4 Adjustments of POD_{HEC} to Health-Based Acute ReV and ^{acute}ESL

The acute ReV of 5.1 ppm (22 mg/m^3 or 22,000 μg/m^3) was derived by applying an uncertainty factor (UF_H) of 10 for human variability and a UF_D of 1 for database uncertainty, as the overall quality and number of the studies are high. Other UFs are not applicable (i.e., extrapolation from a LOAEL to NOAEL or extrapolation from animals to humans). The ^{acute}ESL of 1.5 ppm (6.5 mg/m^3 or 6,500 μg/m^3) was set according to the ESL guidance (TCEQ 2006) based on the acute ReV of 5.1 ppm (5,100 ppb) multiplied by a hazard quotient (HQ) of 0.3 (Table 3).

Table 3 Derivation of the Acute ReV and ^{acute}ESL

Parameter	**Summary**
Study	Stewart et al. 1968
Study Population	9 healthy male volunteers
Study Quality	Medium to high
Exposure Method	exposure via inhalation at 51, 216 and 375 ppm for 1 h, at 116 ppm for 2 h, and at 99 ppm for 7 h
Critical Effects	Eye and nasal irritation
POD_{HEC}	51 ppm ($NOAEL_{[HEC]}$)
Exposure Duration	1 h
Extrapolation to 1 h	N/A
Total uncertainty factors (UFs)	10
Interspecies UF	N/A
Intraspecies UF	10
LOAEL-to-NOAEL UF	N/A
Incomplete Database UF	1
Database Quality	High
Acute ReV [1 h] (HQ = 1)	**22,000 μg/m^3 (5,100 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**6,500 μg/m^3 (1,500 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

Styrene has a sweet and sharp odor. There have been several published odor threshold values which meet the criteria accepted by American Industrial Hygiene Association (AIHA) and USEPA (AIHA 1989 and USEPA 1992) (discussed from the oldest study to the most current studies).

3.2.1.1 Stalker (1963)

In a community odor study conducted from 1956 to 1957 in Louisville, Kentucky, a minimal olfactory perception threshold of 17 ppb for styrene was reported by Stalker (1963). Individual odor threshold was measured on each member of a panel of 23 persons by a dynamic-stream, dilution-type olfactometer. The test panel (ages ranged 18 to 71 years) was deemed a reasonably representative cross section of the community, excepting that anosmic (i.e., lack of olfactory sensitivity) and extremely hyposmic (i.e., lowered olfactory sensitivity) subjects were excluded. A geometric mean odor detection threshold of 17 ppb was obtained by computing the individual minimal threshold for the panel. Since the panel represented the community, the measured odor perception threshold was considered a population threshold.

3.2.1.2 Hellman and Small (1973, 1974)

Hellman and Small (1973, 1974) reported that an absolute odor threshold and a 50% odor recognition threshold were 52 and 150 ppb, respectively. These odor values were measured by a selected odor panel coupled with an odor presentation device - “odor fountain”.

3.2.1.3 Dravnieks (1974)

AIHA (1989) and USEPA (1992) reported an acceptable odor detection value of 1.8 ppm measured by Dravnieks (1974). However, the TS reviewed the Dravnieks (1974) article and failed to verify the reported values from this article. Therefore, the odor detection value has not been included in Table 4 and was not considered in this DSD.

3.2.1.4 Hoshika et al. (1993)

Hoshika et al. (1993) reported an odor detection level of 33 ppb for styrene. The odor threshold value was determined in an odor-free room (4 to 10 m^3) by a trained panel (20 male perfumers, age 30-45 years) who sniffed the odors directly. The actual concentrations of styrene in the odor test room air were measured by gas chromatography.

3.2.1.5 Nagata (2003)

Nagata (2003) reported an odor detection threshold of 35 ppb for styrene, which was measured by the triangle odor bag method. The threshold was obtained by detecting the difference from odor-free background by an odor panel consisting of 6 trained panelists (4 women and 2 men,

age range 20-50 years). The primary styrene sample was measured by gas chromatography. The author indicated that results from an inter-laboratory comparison study demonstrated good reproducibility and accuracy of the measurement of odor threshold by the triangle odor bag method.

3.2.1.6 van Doorn et al. (2002)

van Doorn et al. (2002) reported an odor detection threshold of 49 ppb for styrene, which was measured by a standardized dynamic olfactometry method (European Committee for Standardization, CEN 13725). The CEN standard method, which uses a reference value of 40 ppb of n-butanol in air as an internal reference, is considered a reliable method by the authors.

An odor detection threshold for styrene was measured by the Organisation for Applied Scientific Research (TNO), Netherlands in 1988. The Netherlands method uses a precursor of the CEN 13725 method with a mean n-butanol reference value of 25 ppb instead of the reference value corresponding to a n-butanol concentration of 40 ppb used in the CEN13725 standard. A standardized odor detection threshold of 25 ppb for styrene was calculated by applying a ratio of the mean n-butanol threshold of 25 ppb measured in the test panel and the CEN13725 reference value of 40 ppb (40/25 = 1.6) to the odor threshold measured by TNO (van Doom et al. 2002). The author also noted that a n-butanol threshold of 38 ppb was measured by a test panel following the Japanese traingle method in Japan. The detection thresholds obtained using the Japanese triangle method appear to be in close agreement with those obtained using the European or Dutch standard methods. All three methods are considered compatible and preferred methods for measuring odor (van Doom et al. 2002 and van Harreveld 2003).

3.2.2 Comparison of Various Odor Threshold Values

Table 4 is a comparison of the reported styrene odor threshold values, arranged in chronological order, which meet the criteria accepted by AIHA and USEPA.

Table 4 Comparison of Styrene Odor Threshold Values

Odor Study	50% Odor Detection Value	50% Odor Recognition Value
Stalker (1963)	73 $\mu g/m^3$ (17 ppb) [a]	
Hellman and Small (1973, 1974)	220 $\mu g/m^3$ (52 ppb)	640 $\mu g/m^3$ (150 ppb)
Hoshika et al. (1993)	140 $\mu g/m^3$ (33 ppb) [b]	
van Doorn et al. (2002)	107 $\mu g/m^3$ (25 ppb) [c]	
van Doorn et al. (2002)	210 $\mu g/m^3$ (49 ppb) [d]	
Nagata (2003)	150 $\mu g/m^3$ (35 ppb) [b]	

[a] Minimal olfactory perception threshold (Population Threshold)

[b] Measured by the Japanese triangle odor bag method

[c] Measured by Dutch Standardized Method (NVN2820) in the Netherlands, 1988

[d] Measured by the European Committee for Standardization Method (CEN13725)

3.2.3 Selection of Odor-Based ESL

As noted by van Doorn et al. (2002), modern performance tests, such as using forced choice dynamic olfactometry or the Japanese triangle bag method, has greatly improved the sensitivity, repeatability, and reproducibility of odor threshold determinations. Odor thresholds reported more than several decades ago probably were not obtained under the same conditions of methodological precision taken by today's olfactometer methods. van Harreveld et al. (1999 in van Doorn et al. 2002) indicated that since the early 1990s, the introduction of improved instrument calibration, improved panel screening procedures and the adoption of n-butanol as a reference material, have enabled more objective odor measurements. For these reasons, the odor thresholds reported by Stalker (1963) and Hellman and Small (1973, 1974) were not used to set the odor-based ESL.

The standardized odor detection threshold of 25 ppb calculated by van Doorn et al. (2002) was considered reliable and therefore was used to set the odor-based ESL. The level is not only compatible with that measured by the CEN standard method (49 ppb) and the Japanese triangle bag method (33 ppb by Hoshika et al. 1993 and 35 ppb by Nagata 2003) but is also the lowest reported odor threshold from among the more recent studies that meet AIHA and USEPA acceptability criteria (TCEQ 2006) of the most recent odor detection studies. Thus, the odor-based ESL for styrene was set at 25 ppb or 107 $\mu g/m^3$. Rounding to two significant figures yields an odor-based ESL of 25 ppb or 110 $\mu g/m^3$.

3.2.4 Vegetation Effects

No information was found to indicate that special consideration should be given to possible vegetation effects from styrene.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

This acute evaluation resulted in the derivation of the following acute values:

- acute ReV = 22,000 $\mu g/m^3$ (5,100 ppb)
- $^{acute}ESL$ = 6,500 $\mu g/m^3$ (1,500 ppb)
- $^{acute}ESL_{odor}$ = 110 $\mu g/m^3$ (25 ppb)

The short-term ESL for air permit evaluations is the $^{acute}ESL_{odor}$ of 110 $\mu g/m^3$ (25 ppb) (Table 1). Both the $^{acute}ESL_{odor}$ of 110 $\mu g/m^3$ (25 ppb) and the acute ReV of 22,000 $\mu g/m^3$ (5,100 ppb) may be used for evaluation of air monitoring data (Table 1). The $^{acute}ESL$ is only applicable to air permit reviews and is not used for the evaluation of ambient air monitoring data.

Chapter 4 Chronic Evaluation

4.1 NonCarcinogenic Potential

A large number of occupational exposure studies have examined the chronic noncarcinogenic toxicity of styrene. The most widely examined and sensitive endpoint is neurotoxicity. A variety of neurological effects have been observed, including decreased color discrimination, slowed reaction time, altered performance on neurobehavioral tests of memory and learning, altered vestibular function, altered hearing, reduced nerve conduction velocity, and increased clinical symptoms such as dizziness, tiredness, memory loss, and feeling drunk (ATSDR 2007).

4.1.1 Key Studies

4.1.1.1 Mutti et al. (1984)

An occupational study on the CNS effects of styrene by Mutti et al. (1984) was selected to derive a noncancinogenic chronic ESL. This cross-sectional study compared memory and sensory/motor function in a group of 50 male workers exposed to styrene for an average of 8.6 ± 4.5 (standard deviation, SD) years to a control group of 50 manual workers. Styrene exposure was assessed from urinary metabolite levels of mandelic acid (MA) and phenylglyoxylic acid (PGA). The exposed workers were separated into four subgroups (n = 9-14) according to increasing levels of urinary styrene metabolites: < 150 [75 (mean) ± 33 (SD), n = 14], 150-299 [216 (mean) ± 45 (SD), n = 9], 300-450 [367 (mean) ± 49 (SD), n = 14], and > 450 [571 (mean) ± 108 (SD), n = 13] millimoles (mmoles) (MA + PGA)/mole creatinine. 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. The results were expressed as continuous and quantal data as the percent of tested workers who responded abnormally to ≥ 1, ≥ 2, or ≥ 3 out of a battery of 8 tests.

The study results showed that positive dose-response relationships existed between intensity of styrene exposure (mmoles MA + PGA/mole creatinine) and abnormal scores. The concentration-

response relationship between urinary metabolite concentrations and test results indicated a significant effect level in the subgroup whose urine contained 150-299 mmole urinary metabolites (MA + PGA)/mole creatinine. Workers with metabolite concentrations of < 150 mmoles/mole appeared to have no significant effects. The cut-off of 150 mmoles/mole creatinine is therefore designated as the NOAEL for neuropsychological effects in this study. The authors stated that the cut-off of level of urinary metabolite (< 150 mmoles/mole) corresponds to a mean daily 8 h exposure to 25 ppm styrene in air.

4.1.1.2 Benignus et al. (2005)

Benignus et al. (2005) performed a meta-analysis using data from 9 occupational exposure studies examining delays in choice reaction time (CRT) and color vision impairment. Data were pooled into a single database for each endpoint and were transformed to a common metric of effects magnitude (percentage of baseline). Styrene concentrations were estimated from biomarkers of exposure (styrene or mandelic acid in urine) using standardized conversion methods. The dose levels were expressed as inhalation-air styrene concentrations by work-years of exposure and then fitted to a dose-effect regression equation.

The results of the meta-analysis showed that cumulative styrene exposure was associated with increased CRT as well as an increased color confusion index (CCI) score in a dose-related manner. For an exposure of 8 work-years to 150 ppm, the estimated increases in CRT and CCI score were approximately 50 and 17%, respectively. For an exposure of 8 work-years to 20 ppm, there were an estimated 6.5 and 2.23% increase in CRT and CCI scores, respectively. Based on this analysis, 20 ppm is considered a LOAEL for neurological effects. However, the authors acknowledge that the effects of styrene on CRT and CCI may have been overestimated due to underestimates of past exposure and bias from experimenter knowledge of subject exposure status while testing.

4.1.2 Additional Chronic Toxicity Data that Support the $^{chronic}ESL_{nonlinear(nc)}$

4.1.2.1 Human Supporting Studies

A large number of occupational exposure studies have examined the neurotoxicity of styrene in reinforced plastic workers (ATSDR 2005). Fallas et al. (1992) studied 60 male workers (average air styrene concentration = 24.3 ppm). The results from a standardized test battery showed decrements in the aiming response, acquired color vision loss (dyschromatopsia), and increases in reaction times in the styrene-exposed workers compared to controls. In another study by Gobba and Cavalleri (1993), workers (n = 36) exposed to a time-weighted average of 30.2 ppm styrene exhibited significantly greater dyschromatopsia than controls. The results from these studies were consistent with the Mutti et al. (1984) study.

4.1.2.2 Animal Supporting Studies

In a subchronic inhalation study (NTP 1992), mice were exposed to 0, 62.5, 125, 250, or 500 ppm and rats were exposed to 0, 125, 250, 500, 1,000, or 1,500 ppm styrene (6 h/d, 5 d/wk, 13 wks). The results showed a LOAEL of 62.5 ppm (olfactory epithelial, forestomach, and respiratory lesions) for mice; and a LOAEL of 125 ppm (respiratory tract lesions) for rats.

In a chronic study conducted by Cruzan et al. (1998), groups of 70 male and 70 female CD rats were exposed whole body to styrene vapor at 0, 50, 200, 500, or 1,000 ppm for 6 h/day for 104 weeks. There were no changes of toxicologic significance in hematology, clinical chemistry, urinalysis, or organ weight. However, decreases in body weight and changes in the olfactory epithelium were found in male and female rats. A NOAEL of 200 ppm for body weight changes was indentified. Styrene-related, non-neoplastic histopathologic changes were seen at all exposure concentrations but were confined to the olfactory epithelium of the nasal passages. However, the lung and olfactory tissue have not been found to be the targets of styrene toxicity in humans (Cruzan et al. 2002).

In a developmental neurotoxicity study of styrene conducted by Cruzan et al. (2005), four groups of male and female Crl:CD rats (25/sex/group) were exposed to 0, 50, 150, or 500 ppm styrene for 6 h/day for at least 70 consecutive days prior to mating for the F_0 and F_1 generations. Inhalation exposure continued for the F_0 and F_1 females throughout mating and throughout gestation day 20. Potential adverse functional and/or morphological effects of styrene on the neurological system in the F_2 were assessed. A NOAEL of 50 ppm for F_2 growth and a NOAEL of 500 ppm for F_2 developmental neurotoxicity were indentified from this study.

4.1.3 MOA Analysis and Dose Metric

The most relevant chronic non-cancer effects for styrene are CNS effects. One postulated mechanism is the binding of the highly reactive styrene oxide to components of nervous tissue. Another postulated mechanism is an alteration in the levels of circulating catecholamines (e.g., dopamine and norepinephrine) due to their binding with PGA, a major end product of styrene metabolism in human, and the subsequent changes in physiological functions that are under biogenic amine control (Mutti 1993, Mutti et al. 1984a, Checkoway 1994 in OEHHA 2005). The Mutti et al. (1984) study results showed that positive dose-response relationships existed between intensity of styrene exposure (mmoles MA + PGA/mole creatinine) and abnormal scores (see Section 4.1.1). Thus, the measured levels of urinary metabolites corresponding to the mean daily 8-hour exposure concentrations of styrene in air will be used as the dose metric.

4.1.4 POD for the Key Study and Critical Effect

The cross-sectional occupational study on CNS effects of styrene by Mutti et al. (1984) (see Section 4.1.1) has been used to perform dosimetric analysis and dose response assessment by USEPA, California EPA, Agency for Toxic Substances and Disease Registry (ATSDR), and Rabovsky et al. (2001). The Toxicology Section (TS) used the benchmark dose-response analysis

by Rabovsky et al. (2001) as the occupational POD (POD_{OC}). Please refer to Section 4.1.6 for a discussion of the dose-response analysis conducted by USEPA, Cal EPA, and ATSDR.

Rabovsky et al. (2001) used the neuropsychological test quantal data reported by Mutti et al. (1984) (see Section 4.1.1.1) to conduct a benchmark dose (BMD) analysis (Tox-Risk software, Version 3.5). The mean urinary metabolite levels from each of four exposure groups reported by Mutti et al. (1984) were used in the BMD analysis. The mean metabolite levels were converted to air styrene concentrations by applying a conversion factor of 4.97. The resulting mean air styrene exposure levels associated with those four groups were calculated to be 15, 44, 74, and 115 ppm, respectively. The authors used the Mutti et al. (1984) quantal data to determine if the subjects in Group 1 responded abnormally to the neurobehavioral tests. The results from the analysis by the Fisher's exact tests showed that an air styrene level of 15 ppm represented a LOAEL, and that a NOAEL was not available from the data. Furthermore, maximum-likelihood estimates (MLEs) and BMDs at 5 and 10% response levels of the exposed population were obtained from log-normal analysis of the quantal data. The terminology used by Rabovsky et al. (2001) is different than the terminology used in the ESL Guidelines (TCEQ 2006). The MLE, which is the central estimate, is analogous to the term benchmark concentration or BMC. The BMDs at the 5 and 10% response are analogous to the statistical 95% confidence limit on the concentration ($BMCL_{05}$ or $BMCL_{10}$, respectively). The following MLEs and BMDs were calculated:

- The MLE was 4 ppm (BMD = 1.7 ppm) styrene for the abnormal responses to ≥ 3 tests by 5 % of the exposed population.
- The MLE was 3.2 ppm (BMD = 0.8 ppm) styrene for the abnormal responses to ≥ 2 tests by 5 % of the exposed population.
- The most health protective MLE of 2 ppm (BMD = 0.3 ppm) represented abnormal responses to ≥ 1 test by 5 % of the exposed population.

Thus, the TS conservatively selected the BMD of 0.3 ppm as the POD_{OC} for chronic ReV calculations.

4.1.5 Dosimetric Adjustments

The POD_{OC} of 0.3 ppm was then adjusted from discontinuous exposure (8 h/d for 5d/wk) to continuous exposure applicable to the general population (POD_{HEC}) using the following dosimetric adjustments:

$POD_{HEC} = POD_{OC} \times (VE_{ho}/VE_h) \times (\text{days per week}_{oc}/\text{days per week}_{res})$

where: VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/day)

VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/day)

$\text{days per week}_{oc}$ = occupational weekly exposure frequency (study specific)

$\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per week)

POD_{HEC} = 0.3 ppm x (10/20) x (5/7) = 0.107 ppm

4.1.6 Adjustments of the POD_{HEC}

The MOA by which styrene produces urinary metabolites MA and PGA level is considered a threshold, nonlinear MOA. Therefore, UFs were applied to the POD_{HEC} of 0.107 ppm to derive a chronic ReV. The TS selected a UF of 1 for human variability (UF_H), because the selected POD_{HEC} of 0.107 ppm, which is based on the lowest BMD (0.3 ppm) estimated by Rabovsky et al. (2001), is considered very conservative (see Section 4.1.4.). The TS usually does not use a LOAEL to NOAEL UF (UF_L) if the $BMCL_{05}$ modeling value is used (TCEQ 2006). Since the average exposure duration of 8.6 years in the Mutti et al. (1984) study is more than 10% of the expected life span in humans, the study would be considered a chronic study (USEPA 2002), so a subchronic to chronic UF (UF_{Sub}) was not used. A database UF of 1 (UF_D) was used, because the chronic database for styrene is considered adequate. Confidence is considered medium to high on the ReV derived from the BMD method.

$$\text{Chronic ReV} = POD_{ADJ} / (UF_H \times UF_D)$$
$$= 0.107 \text{ ppm} / (1 \times 1)$$
$$= 0.107 \text{ ppm}$$
$$= 107 \text{ ppb}$$

Accordingly, by applying a cumulative UF of 1 to the aforementioned POD_{HEC}, the ReV is 107 ppb.

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Rounding to two significant figures at the end of all calculations yields a chronic ReV of 110 ppb (470 $\mu g/m^3$). The $^{chronic}ESL_{nonlinear(nc)}$ of 33 ppb (140 $\mu g/m^3$) was set according to the ESL guidance (TCEQ 2006), based on the chronic ReV multiplied by a HQ of 0.3 (Table 5).

Table 5 Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Summary**
Study	Rabovsky et al. 2001 BMD analysis based on CNS test quantal data reported by Mutti et al. 1992
Study Population	50 male styrene-exposed workers for an average exposure of 8.6 years and a control group of 50 manual workers
Study Quality	Medium
Exposure Method	Occupational exposure to styrene in the reinforced-plastics industry at mean concentrations of 15, 44, 74, or 115 ppm for an average of 8.6 years
Critical Effects	Memory and sensory/motor function; abnormal responses to neuropsychological tests
POD_{OC}	0.3 ppm [($BMCL_{05}$), abnormal responses to ≥ 1 test in 5 % of the exposed population, BMC analysis by Rabovsky et al. (2001)]
Exposure Duration	8 h/day, 5 days/week, for an average of 8.6 years
Extrapolation to continuous exposure (POD_{HEC})	0.3 ppm x (10/20) x (5/7) = 0.107 ppm (107 ppb)
Total UFs	1
Interspecies UF	1
Intraspecies UF	N/A
LOAEL-to-NOAEL UF	N/A
Subchronic to chronic UF	N/A
Incomplete Database UF	1
Data Quality	High
Chronic ReV (HQ = 1)	**110 ppb (470 µg/m^3)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**33 ppb (140 µg/m^3)**

4.1.7 Comparison of Various Chronic Toxicity Values

Table 6 is a comparison of the toxicity values derived by other federal and state agencies.

Table 6 Comparison of Styrene Chronic Toxicity Values

Parameter	Chronic Toxicity Value	POD[HEC]	Key Study
ReV	470 µg/m^3 (110 ppb)	0.107 ppm ($BMCL_{05}$)[b]	Rabovsky et al. 2001[a]
RfC (USEPA 1993)	1,000 µg/m^3 (300 ppb)	34 mg/m^3 ($NOAEL_{[HEC]}$)[c]	Mutti et al. 1992
REL (OEHHA 2005)	900 µg/m^3 (200 ppb)	1.7 ppm ($BMCL_{05}$)[d]	Rabovsky et al. 2001[a]
MRL (ATSDR 1992)	260 µg/m^3 (60 ppb)	25 ppm (LOAEL)[e]	Mutti et al. 1992
MRL (ATSDR 2007)	900 µg/m^3 (200 ppb)	20 ppm (LOAEL)	Benignus et al. 2005

[a] BMD analysis based on CNS test quantal data reported by Mutti et al. (1992)

[b] Based on the MLE of 2 ppm styrene for the abnormal responses to ≥ 1 test by 5 % of the exposed population

[c] The NOAEL of 25 ppm identified by Mutti et al. (1992) was adjusted to the lower 95% confidence limit

[d] Based on the MLE of 4 ppm styrene for the abnormal responses to ≥ 3 tests by 5 % of the exposed population

[e] ATSDR identified the lowest exposure group (< 150 MA + PGA mmole/mole creatinine; equivalent to < 25 ppm styrene concentration) of the Mutti et al. (1992) study as a LOAEL

4.1.7.1 USEPA (1993)

The USEPA Integrated Risk Information System (IRIS) (USEPA, 1993) derived an inhalation reference concentration (RfC) of 1 mg/m^3 (0.3 ppm) for styrene. The RfC is based on the findings of Mutti et al. (1984) utilizing the continuous data and standard NOAEL methodology. USEPA established the lowest exposure concentration (< 150 MA + PGA mmole/mole creatinine; equivalent to < 25 ppm styrene concentration) as a NOAEL for neuropsychological effects. The NOAEL of 25 ppm was adjusted to the lower 95% confidence limit listed in Guillemin et al. (1982) study, which was 88% (25 ppm x 0.88 = 22 ppm or 94 mg/m^3). The human equivalent concentration NOAEL ($NOAEL_{[HEC]}$) of 34 mg/m^3 was calculated by adjusting an 8-h TWA occupational exposure of 10 m^3/day for 5 d/wk to a continuous exposure of 20 m^3/d for 7 d/wk ($NOAEL_{[HEC]}$ = 94 mg/m^3 (22 ppm) x (10 m^3/d) /(20 m^3/d) x (5 d/7 d) = 34 mg/m^3). The RfC was calculated by applying a total uncertainty factor (UF) of 30 (a UF of 3 for intraspecies variability, a UF 3 for lack of information on chronic studies, and a UF of 3 for database inadequacy) to the $NOAEL_{[HEC]}$ of 34 mg/m^3.

4.1.7.2 ATSDR (1992, 2007)

ATSDR (1992) also calculated a chronic inhalation minimal risk level (MRL) of 0.06 ppm for styrene based on the same Mutti et al. (1984) study. ATSDR identified the lowest exposure level (< 150 MA + PGA mmole/mole creatinine; equivalent to < 25 ppm styrene concentration) as a LOAEL for neuropsychological effects. ATSDR adjusted from discontinuous exposure (8 h/d for 5 d/wk) to continuous exposure and applied an UF of 10 for the use of LOAEL and an UF of 10

for intraspecies variability. However, in a draft toxicological profile for styrene, ATSDR (2007) proposes a new chronic inhalation MRL based on a LOAEL of 20 ppm for neurobehavioral effects (reaction time and color vision) estimated from a meta-analysis using data by Benignus et al. (2005) (see Section 4.1.1.2). A cumulative UF of 100 (10 for use of LOAEL and 10 for human variability) was applied to the 20 ppm LOAEL to derive the new draft chronic MRL of 0.2 ppm.

4.1.7.3 OEHHA (2005)

California EPA's Office of Environmental Health Hazard Assessment (OEHHA, 2005) (CalEPA) derived a chronic reference exposure level (REL) based on the Rabovsky et al. (2001) BMC approach (see Section 4.1.4.4 below). A BMC_{05} of 1.7 ppm was chosen based on the MLE of 4 ppm styrene for the abnormal responses to ≥ 3 tests by 5 % of the exposed population. Following dosimetric adjustment for exposure continuity (10 m^3/20 m^3/d and 5/7d/wk) and application of an UF of 3 to account for human intraspecies variability, a REL of 0.2 ppm (0.9 mg/m^3) was calculated.

4.2 Carcinogenic Potential

ATSDR (2007) provides a detailed description of animal and human epidemiology studies that have investigated the carcinogenic potential of styrene. The following sections are summaries of the carcinogenic MOA and weight of evidence for styrene based on a review of ATSDR (2007).

4.2.1 Carcinogenic MOA

Based on animal studies, styrene induces lung tumors in mice, lung Clara cell toxicity, and nasal olfactory lesions. Styrene does not induce tumors in rats, but it does induce olfactory lesions (Cruzan et al. 1998, 2000). However, the lungs and olfactory tissue have not been found to be the targets of styrene toxicity in humans.

The differences in toxicity among rats, mice, and humans were further studied by Cruzan et al (2002). The study indicates that styrene-induced respiratory tract toxicity in mice and rats, including mouse lung tumors, is mediated by CYP2F-generated metabolites (7,8-styrene oxide, predominantly R-styrene oxide). The authors concluded that tissues, i.e., mouse lung Clara cells and nasal olfactory epithelium, that are high in CYP2F and produce R-styrene oxide, are most susceptible to styrene-induced toxicity. Lung tumors in mice most likely result from a nongenotoxic MOA as a result of cytotoxicty leading to hyperplasia.

An MOA-based physiologically based pharmacokinetic (PBPK) model, developed by Sarangapani et al. (2002), predicted a 10-fold lower R-styrene oxide concentration in the terminal bronchioles in rats compared to mice, which is consistent with the observed species sensitivity to the development of respiratory-tract neoplasms. The PBPK model also suggests that humans would be expected to be 100-fold less sensitive to styrene-induced lung tumors than

mice. The postulated MOA for these effects indicates that respiratory tract effects in rodents are not relevant for human risk assessment (Cruzan et al. 2002).

4.2.2 Carcinogenic Weight of Evidence

In its latest evaluation in 2002, The International Agency for Research on Cancer (IARC) concluded there is *"limited evidence* in humans for the carcinogenicity of styrene*"* and, taking into account the results from animal carcinogenicity studies, that styrene is *"possibly carcinogenic to humans (Group 2B)".* OSHA chose not to classify styrene as a carcinogen in the 1989 Air Contaminant Rulemaking, concluding that "current evidence on styrene's carcinogenicity does not support its classification as a carcinogen." USEPA states that data is not available to evaluate styrene's carcinogenic potential. As stated previously, chronic styrene inhalation studies in rodents have demonstrated species specificity in the resulting pulmonary toxicity and carcinogenicity. Increased incidences of pulmonary bronchioloalveolar tumors have been observed in mice, but not in rats (Cruzan et al. 1998, Cruzan et al. 2002) (see Section 4.2.1).

No epidemiologic evidence has been published to date to conclude that styrene exposure presents an excessive carcinogenic risk to humans. Studies of styrene-exposed worker cohorts, conducted in both Europe and the United States, have been reviewed recently by Cohen et al. (2002). The study found no evidence for an excess risk of lymphatic and hematopoietic cancer associated with exposure to styrene in the reinforced plastic boat building facilities studied. Ruder et al. (2004) updated their 1985 mortality study for 5,204 workers exposed to styrene between 1959 and 1978 at two reinforced plastic boatbuilding plants. The study also found no excess leukemia or lymphoma mortality. Since the postulated MOA suggests that respiratory tract effects in rodents are not relevant for human risk assessment and no epidemiologic evidence exists to indicate styrene presents an excessive carcinogenic risk to humans, a unit risk factor was not developed for styrene. Using the weight-of-evidence narrative recommended in the 2005 cancer guidelines (USEPA 2005), the TCEQ has determined that "Data are inadequate for an Assessment of Human Carcinogenic Potential" of styrene (TCEQ 2006).

4.3 Welfare-Based Chronic ESL

No information was found to indicate that special consideration should be given to possible vegetation effects from styrene.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

This chronic evaluation resulted in the derivation of the following chronic values:

- chronic ReV = 470 µg/m^3 (110 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 140 µg/m^3 (33 ppb)

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{nonlinear(nc)}$ of 140 µg/m^3 (33 ppb) (Table 1). For the evaluation of air monitoring data, the chronic ReV of 470 µg/m^3 (110 ppb) is used (Table 1).

Chapter 5 References

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