Styrene; CASRN 100-42-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Styrene

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	01/31/1987
Inhalation RfC (I.B.)	yes	11/01/1992
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Styrene
CASRN — 100-42-5
Last Revised — 01/31/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an

elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: The Oral RfD for styrene may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Red blood cell and liver effects **Dog Subtronic Oral Study** **Quast et al., 1979**	NOAEL: 200 mg/kg-day LOAEL: 400 mg/kg-day	1000	1	2E-1 mg/kg-day

* Conversion Factors: none

I.A.2. Principal and Supporting Studies (Oral RfD)

Quast, J.F., C.G. Humiston, R.Y. Kalnins, et al. 1979. Results of a toxicity study of monomeric styrene administered to beagle dogs by oral intubation for 19 months. Toxicology Research Laboratory, Health and Environmental Sciences, DOW Chemical Co., Midland, MI. Final Report.

Four beagle dogs/sex were gavaged with doses of 0, 200, 400, or 600 mg styrene/kg bw/day in peanut oil for 560 days. No adverse effects were observed for dogs administered styrene at 200 mg/kg-day. In the higher dose groups, increased numbers of Heinz bodies in the RBCs, decreased packed cell volume, and sporadic decreases in hemoglobin and RBC counts were observed. In addition, increased iron deposits and elevated numbers of Heinz bodies were found in the livers. Marked individual variations in blood cell parameters were noted for animals at the same dose level. Other parameters examined were body weight, organ weights, urinalyses, and clinical chemistry. The NOAEL in this study is 200 mg/kg-day and the LOAEL is 400 mg/kg-day.

Long-term studies (120 weeks) in rats and mice (Ponomarkov and Tomatis, 1978) showed liver, kidney, and stomach lesions for rats (dosed weekly with styrene at 500 mg/kg) and no significant effects for mice (dosed weekly with 300 mg/kg). Rats receiving an average daily oral dose of 95 mg styrene/kg bw for 185 days showed no adverse effects, while those receiving 285 or 475 mg/kg-day showed reduced growth and increased liver and kidney weights (Wolf et al., 1956). Other subchronic rat feeding studies found LOAELs in the 350-500 mg/kg-day range and NOAELs in the range of 100-400 mg/kg-day.

The lifetime studies in rats and mice (Ponomarkov and Tomatis, 1978) are not appropriate for risk assessment of chronic toxicity because of the dosing schedule employed. The Wolf et al. (1956) study is of insufficient duration (185 days) to be considered chronic.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 1000 reflects 10 for both intraspecies and interspecies variability to the toxicity of this chemical in lieu of specific data, and 10 for extrapolation of subchronic effects to chronic effects.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

None.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The principal study is well done and the effect levels seem reasonable, but the small number of animals/sex/dose prevents a higher confidence than medium at this time. The database offers strong support, but lacks a bona fide full-term chronic study; thus, it is also considered to have medium confidence. Medium confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

U.S. EPA. 1984. Health and Environmental Effects Profile for Styrene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Styrene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

The ADI in the 1984 Health and Environmental Effects Profile document has received an Agency Review with the help of two external scientists.

Agency Work Group Review — 10/09/1985, 11/06/1985, 10/09/1985

Verification Date — 10/09/1985

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Styrene
CASRN — 100-42-5
Last Revised — 11/01/1992

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this

substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
CNS effects **Occupational Study** **Mutti et al. (1984)**	NOAEL: 94 mg/cu.m (25 ppm = 150 mmole urinary styrene metabolites/mole creatinine adjusted to lower 95% confidence limit = 22 ppm) NOAEL(HEC): 34 mg/cu.m LOAEL: >94 mg/cu.m (>22 ppm derived as in NOAEL listing)	30	1	1E+0 mg/cu.m

*Conversion Factors: MW = 104.15. Assuming 25 C and 760 mmHg, NOAEL (mg/cu.m) = NOAEL (ppm) x MW/24.45 = 94 mg/cu.m. The NOAEL exposure level is based on a back extrapolation from worker urinary concentration of styrene metabolites reported in the principal study and adjusted to the lower 95% confidence limit listed in Guillemin et al. (1982), which was 88%, 25 ppm x 0.88 = 22 ppm. The NOAEL(HEC) is calculated using an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. NOAEL(HEC) = 94 mg/cu.m x MVho/MVh x 5 days/7 days = 34 mg/cu.m. The feasibility of applying the exposure model of Perbellini et al. (1988) for extrapolation of the values in the principal study is currently being investigated. Application of this model may result in changes in the NOAEL(HEC) value and, therefore, the RfC.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Mutti, A., A. Mazzucchi, P. Rusticelli, G. Frigeri, G. Arfini, and I. Franchini. 1984. Exposure-effect and exposure-response relationships between occupational exposure to styrene and neuropsychological functions. Am. J. Ind. Med. 5: 275-286.

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. Also, the deficiencies noted in the reaction-times corroborate the results presented by Moller et al. (1990) and others discussed below.

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 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/cu.m). 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/cu.m)]. 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/cu.m)].

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — 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 evoked 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).

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Central nervous system effects caused by exposure to styrene have been reported by several investigators in studies since the early 1970s. Gotell et al. (1972) noted significantly increased reaction times in a group of six polyester plant workers exposed to >150 ppm styrene as compared with unexposed controls and another group exposed to <150 ppm. Gamberle et al. (1975) noted longer and more irregular reaction times in 106 exposed workers (estimated at 13-101 ppm styrene for an average of 2.7 years) as compared with a control population. Cherry et al. (1980) found no alteration in reaction times among 27 workers exposed to a mean of 92 ppm styrene (duration unspecified) and no difference in performance on four behavioral tests of memory and vigilance. However, a follow-up study conducted 21 months later by these authors on 8 of the same 27 individuals (Cherry et al., 1981) found that the three men with the highest urinary mandelic acid concentrations all improved reaction times significantly ($p < 0.05$) as compared with their earlier values. These alterations were correlated with those individuals having slow clearance of mandelic acid. Among 98 male laminating workers (mean styrene exposure of 5.1 years), Lindstrom et al. (1976) reported weak correlations of CNS-behavioral testing (poor psychomotor performance and visuomotor inaccuracy) with levels of styrene exposure estimated to be between 25 and 75 ppm based on urinary mandelic acid levels. The study of Mutti et al. (1984) is one of few in which extensive CNS-behavioral testing was carried out. The recent studies of Moller et al. (1990) and Flodin et al. (1989) couple functional

decrements with adverse behavioral effects in a chronically exposed worker population. The effect of styrene on peripheral nerves has also been reported, although not to the extent of central effects. These studies are briefly described in the recent study of Murata et al. (1991) in which data on a small number of workers suggest that styrene may differentially affect sensory nerves.

The studies of Moller et al. (1990) and Flodin et al. (1989) both examined central effects of styrene in the same worker population. The Flodin et al. (1989) study on neuropsychiatric effects of styrene exposure provides documentation of the styrene levels to which these workers were exposed.

In a cross-sectional occupational study, Moller et al. (1990) studied 18 male Swedish boatbuilders exposed to styrene for an average of 10.8 years (range of 6-15 years). Personal sampling (8-hour TWA concentrations) available for 7/10 years showed that the workers had been exposed to 50-140 mg/cu.m styrene. The exposure data is discussed at length in the text of the Flodin et al. (1989) study below. These workers were not further subgrouped into high-and low-exposure groups as in the Flodin et al. (1989) study. Two reference groups were used for evaluation of the tests; both were unexposed to industrial solvents and matched to the exposure group with respect to smoking and alcohol consumption. These workers were subsequently given a thorough otoneurological examination, evaluating auditory, visual, and vestibular systems, as well as coordination of vestibular sensations with compensatory eye movements manifest in the vestibuloocular reflex (VOR). The test showing the greatest and most consistent deviation in performance between the exposed workers and the reference population was the visual suppression of the VOR. Execution of this test required the subjects to fixate on a target that moved with movement of the subjects' chair. The normal VOR functions to maintain steady gaze of the eyes despite movements of the head. However, when the target moves with the subject, this reflex must be suppressed in order to follow the target. Quantitation of a subject's capacity to suppress VOR is measured as the ratio between eye and target velocity (gain) and in the temporal relationship between eye and target velocity (phase). Abnormal functioning would be manifest by an increase in gain and a decrease in phase, if the values exceeded the mean +/- 2 SD units of the corresponding measurement in a reference population. Abnormal phase shifts were recorded for 4/18 workers; in each of the four cases, the gain was also abnormal. These differences were reflected in the group values that showed a higher mean gain ($p < 0.001$) and a decrease in angle of phase lead ($p < 0.001$) in examinations carried out with predictable (sinusoidal frequency sweep) and unpredictable (pseudorandomized) conditions. The deficits shown in these tests suggest lesions in the brainstem or cerebellar regions, because these findings are in accordance with findings in patients with known brainstem or cerebellar disorders (Odkvist et al., 1982, 1987). Other tests reported in this study also gave indications of neurological deficits. The posturography test demonstrated increases in sway area of subjects with their eyes closed, which are consistent with vestibular deficits. The overall results of this test are, however, internally inconsistent as more of these workers showed abnormal scores with their eyes open than with

their eyes closed. Although examination of saccadic eye movements (brief, fast movements occurring with change in fixation point) did reveal abnormal scores in latency for 7/18 subjects, none of the 18 were found to have abnormal velocity. This also is an internal inconsistency within the exam, making these results equivocal. A similar internal inconsistency was noted in the results of the smooth-pursuit eye movement during which the subject is asked to visually track a slowly moving stimulus. Seven of the 18 subjects had abnormal results in lag time (phase), whereas none of the 18 tested abnormal for gain. Disturbances were found in the central auditory pathways of seven workers but the significance of these effects were not evaluated (see discussion of Pryor et al., 1987). This study provides credible toxicological information on the possible long- term consequences of human exposure to styrene. No effect levels are assigned based on these data as the number of subjects is small and no indication is given of a dose-response relationship among these chronically exposed workers.

Twenty-one male Swedish workers were exposed to styrene for an average of 11.6 years (range of 6-21 years) as a consequence of their occupation, boatbuilding (Flodin et al., 1989). Personal sampling (8-hour average concentrations) had been carried out in 9 of the last 12 years, with the number of sampling days for each year ranging from 3 to 27; the data presented indicate an exposure range of around 40-140 mg/cu.m during this time. In one year, 30-minute sampling times were performed on most tasks and showed that peak exposures were exceptional, with only about 1% of all measurements of styrene >300 mg/cu.m; about 44% of the samples were <25 mg/cu.m, and about 65% were <50 mg/cu.m. Based on these sampling data, the workers were classified into two groups: those exposed to about 50 mg/cu.m styrene for the past 7 years and those exposed to about 25 mg/cu.m. The higher exposed workers were primarily involved in lamination processes. Workers were examined by a clinical interview that included a detailed inquiry about neuropsychiatric symptoms; psychometrical tests and some clinical chemistry were also included. The workers were examined twice, the first time (21 workers examined) occurring when they had not been exposed for 1 week. The second examination (17 workers examined; nine in the higher exposure group and eight in the lower exposure group) occurred after the workers had not been exposed for a minimum of 3 months because the factory had gone bankrupt. Two of the remaining four workers refused participation in the second interview, and results from two others were disallowed as one was diagnosed as having pulmonary thrombosis and the other psycho-organic syndrome (POS) (see discussion of Moller et al., 1989). No concurrent control group was used. According to the questionnaire, the symptoms at the first examination were distributed in a exposure-related manner, with the higher exposure group having an average of 10.4 symptoms/worker and the lower exposure group having an average of 5.3 symptoms/worker. On the second examination, the average symptoms/worker decreased to 1.9 in both exposure groups. The claim that the higher exposure group performed significantly worse in one psychometrical test (manual dexterity) is not interpretable due to lack of specifics in the text. Internal inconsistencies of the results and the lack of a concurrent matched control group cause the results from this study to be equivocal. No effect levels were designated in this

study.

The levels of styrene reported in the study of Mutti et al. (1984) were estimated from levels of urinary styrene metabolites. As already discussed, this method is considered as a biological indicator of exposure and has been shown to reliably reflect the total concentration of styrene to which individuals have been exposed. The relationships between styrene exposure and urinary metabolite concentrations have been established by a number of studies including those of Guillemin et al. (1982) and Ikeda et al. (1982) and reviewed by the WHO (1983). The work of Perbellini et al. (1988) has shown that the variability of urinary metabolite levels observed in styrene-exposed worker populations may reflect physiologic and metabolic variability inherent in humans. These characteristics are not shared by the extensive studies on styrene levels reported by Lemasters et al. (1985a) and of Jensen et al. (1990), both of which are historical and are based on area and personal sampling procedures.

A diagnosis of psycho-organic syndrome has been used to describe the symptomatology observed in workers heavily exposed to a variety of organic solvents. Examples of specific effects include neurasthenia, personality alterations, unsteadiness, dizziness, and vertigo. Moller et al. (1989) examined nine men who had been diagnosed as having POS, subjecting them to a battery of audiological and vestibular-oculomotor tests, the latter of which measure the capacity to transform signals from the inner ear to compensatory eye movements for purposes such as maintenance of equilibrium. The men were described as having been exposed to various mixtures of alcoholic, aromatic, and aliphatic industrial solvents during their working careers of 8-30 years (mean = 21 years). Seven of them had been granted disability pensions at the time of the examinations. Abnormal static posture was noted in 4/9 members of the POS group ($p < 0.001$). Voluntary saccades (rapid intermittent movements of the eye) were abnormal (both prolonged latency and decreased maximum speed) in 5/9 of the POS group, but in only 2/9 matched controls. As these functions are considered to be controlled centrally in the area of the cerebellum, these findings indicate that cerebellar lesions may occur from chronic exposures to a variety of organic solvents. The results presented by Moller et al. (1990) for these tests in workers exposed to styrene indicate this chemical to be capable of eliciting this toxicity.

A duration-response between length of exposure to solvents and incidence of altered cerebellar functioning (as evidenced by effects on hearing and the vestibular-oculomotor system) is indicated in the study of Odkvist et al. (1987). This study examined 23 workers, all of whom had been extensively exposed to aliphatic and aromatic solvents. Sixteen of the 23 workers were diagnosed with POS. The average length of exposure of these 16 workers was 27 years (range 9-40 years), considerably more than the average of 21 years (range 5-30 years) for the remaining seven individuals. In the battery of 11 vestibular-oculomotor tests, five (including saccade, visual-suppression, Romberg's test, and electronystagmography) showed a dose-response relationship with the percentage incidences being higher in the group diagnosed with POS; the

other six tests either were not conducted in one or the other group or exhibited no change. Thus, both the number of workers diagnosed with POS and incidence of cerebellar dysfunctioning were correlated with duration of exposure to organic solvents.

The specific capacity of styrene to cause alterations in cerebellar function in humans under short-term acute exposure conditions was experimentally shown by Odkvist et al. (1982). Ten people (5/sex) were exposed to 370-591 mg/cu.m styrene for 80 minutes. A battery of six vestibular-oculomotor tests was administered before, during, and after the exposure. Visual suppression and saccade tests both showed statistically significant alterations in 8/10 subjects. Results between exposed subjects and controls did not differ for the optovestibular, optokinetic, and slow pursuit movement test or the sinusoidal swing test. These results indicate that acute exposures to high concentrations of styrene may affect processes within the cerebellum. It should be noted, however, that the results obtained by Moller et al. (1990) and Flodin et al. (1989) were obtained in workers that had not been exposed to styrene for a minimum of 3 months.

Larsby et al. (1978) investigated the relationship between vestibulo- oculomotor function and styrene levels in arterial blood and cerebrospinal fluid. Rabbits (n = 16) were cannulated and infused with a 10% solution of styrene introduced at 3.1-12.6 mg/minute. Vestibular function was evaluated using electronystagmography in response to rotary acceleration. Styrene concentration was monitored in both arterial (ear) and cerebrospinal fluid. During the exposure, positional nystagmus (i.e., involuntary eye movement response to rotary movement evident only when the animal is lying on one side or the other, not prone) was observed in 10/11 rabbits tested. In addition, a paradoxical rotary response was observed in 6/16 rabbits. This phenomenon is described as involuntary eye movement opposite to the direction of rotation (left-beating eye movements when rotated clockwise and vice versa). Both observations indicate that vestibular function was affected. Results also showed that, at an infusion rate of 4.9 mg/minute, arterial blood levels reached a constant level only after about 2 hours. Styrene concentrations in cerebrospinal fluid had the same shape as the arterial curve and was constantly 5-10% of the corresponding arterial concentration.

A number of other occupational studies investigating the effects of styrene on workers are available in the literature. Most of these reports examine either central or peripheral nervous function, although blood effects (Stengel et al., 1990), nephrotoxicity (Viau et al., 1987), and liver effects (Hotz et al., 1980) have also been examined. Nearly all of these reports suffer from one or more deficiencies, the most common being lack of exposure information. Almost all, however, indicate that styrene affects central processes in humans. An overview of several of these studies follows.

In addition to the auditory data listed in the Moller et al. (1990) study, two other studies have reported hearing loss, one in humans and the other in laboratory animals. Muijser et al. (1988) evaluated hearing thresholds up to 16 kHz in 59 workers exposed to airborne styrene. Air samples (4-hour mean averages, 6-16 samples/group work area) were taken in the breathing zone during 3 consecutive days in work areas where 31 workers were directly exposed to styrene (mean = 138 mg/cu.m) and 28 workers were indirectly exposed to styrene (mean = 61 mg/cu.m). The duration of employment for the combined group was 8.6 +/- 6.5 years. The control population consisted of 88 individuals not exposed to styrene or other chemicals but who were comparable in age and socio-economic status to the exposed workers. Audiometric analyses were corrected for age. Comparison of hearing thresholds between the controls and both exposed groups revealed no differences in hearing thresholds at frequencies up to and including 16 kHz. Comparison between the experimental groups, however, did reveal that the directly exposed workers had higher thresholds for frequencies at 8-16 kHz than did the indirectly exposed workers (p value from multivariate analysis of covariance = 0.012). Quantitative and qualitative differences in the background noise between the control and study plants may have compromised the control population in this study. Although difficulties with the control population prevent definite assignment of effect levels, human exposure to 138 mg/cu.m styrene appears to have resulted in high-frequency hearing loss [LOAEL(HEC) = 69 mg/cu.m]. Pryor et al. (1987) exposed male Fisher 344/N rats (12/group) to 0 (clean air), 800, 1000, or 1200 ppm (0, 3408, 4260, or 5112 mg/cu.m, respectively) styrene for 14 hours/day, 7 days/week for 3 weeks. The duration-adjusted values are 0, 1988, 2485, or 2982 mg/cu.m, respectively. Auditory response thresholds were determined by both behavioral and electrophysiologic methods, apparently some weeks after the last exposure. Increases in auditory thresholds were recorded at 8-20 kHz with both methods at the lowest concentration used [LOAEL(HEC) = 1988 mg/cu.m].

Several occupational studies have reported adverse health effects on workers whose exposure was at or near 25 ppm (110 mg/cu.m) styrene. Lindstrom et al. (1976) reported that the visuomotor accuracy of styrene-exposed workers (n = 98, average exposure 4.9 years, range 0.5-14 years) was significantly poorer ($p < 0.05$) than that of the nonexposed workers. Moreover, this deficit was shown to be related to concentration in two subgroups whose exposures (estimated from urinary mandelic acid) were 25 and 75 ppm. Seppalainen and Harkonen (1976) conducted a cross-sectional study on 96 styrene workers, all of whom received EEG examinations 24 hours after termination of exposure. Mean exposure to styrene was estimated from urinary mandelic acid to be 808 mg/L, approximately 36 ppm in air. Twenty-three of 96 (24%) EEG's were abnormal in the exposed group as compared with a normal population (indicated as about 10% in the text), a difference that is statistically significant ($p < 0.05$).

Human irritation from styrene exposure has been characterized in a limited study by Stewart et al. (1968). Nine male volunteers were exposed to air concentrations of styrene of 50-375 ppm (213-1597 mg/cu.m) for periods of 1-7 hours. Urinalysis, hematology, and blood chemistry studies were conducted prior to exposure and at 16 and 72 hours postexposure; subjective

symptoms were also recorded. Within 15 minutes following a 60-minute exposure to 375 ppm styrene, 4/5 volunteers complained of mild eye and nasal irritation. (Throughout the remainder of the exposure, all subjects noted a progressive loss of their ability to perceive the odor of styrene.) It is not clear from the text whether or not the irritation remained throughout the exposure. After 45 minutes of exposure, one of the subjects reported being nauseated and two others complained of feeling slightly inebriated. At 216 ppm styrene, 1/3 subjects noted nasal irritation 20 minutes into a 60-minute exposure. No adverse symptoms were reported by the three subjects exposed to 52 ppm styrene for 1 hour. Six subjects were then exposed to 99 ppm styrene for a total of 7 hours. Three of the six subjects complained of mild eye and throat irritation 20 minutes after the start of the exposure; in two of these subjects, the eye irritation persisted for 30 minutes before subsiding. At the end of the exposure, none of the subjects reported nausea, headache, or eye, nose, or throat irritation. The clinical studies were all normal. None of the six individuals exposed to 99 ppm (422 mg/cu.m) styrene for 7 hours or 216 ppm for 1 hour experienced any subjective symptoms of significant consequence. Although these results suggest no symptoms of consequence in humans exposed to styrene concentrations as high as 216 ppm (920 mg/cu.m), the population tested was small (only three subjects), and the duration was minimal.

Considerable success has been attained in modeling levels of inhaled styrene in biological systems. The physiologically based pharmacokinetic model for styrene of Ramsey and Andersen (1984) allows simulation over a wide range of concentrations on the time course of styrene distributed to four main tissue groups: (1) highly perfused organs, (2) moderately perfused organs (predominately muscle), (3) slowly perfused tissue (predominately fat), and (4) liver. When applied to actual rat data, this model accurately predicted blood styrene levels of 80-1200 ppm (340-5112 mg/cu.m). Then the behavior of inhaled styrene in humans was simulated successfully by substitution of human physiological parameters. These authors were able to demonstrate that blood concentrations of inhaled styrene in rats, mice, and humans were nearly identical at air concentrations of less than or equal to 200 ppm (852 mg/cu.m) but differed widely at higher concentrations. Perbellini et al. (1988) developed a physiologically based mathematical model for human exposure to airborne styrene that accounts for metabolism, subsequent synthesis, transfer, and urinary excretion of the principal metabolites MA and PGA. The model comprises eight compartments: (1) lung; (2) the richly perfused tissues of heart, brain, and kidney; (3) muscle; (4) fat; (5) liver tissue for catabolism of styrene; (6) liver tissue for transfer of metabolites; (7) body water in which the metabolites are distributed; and (8) urine in which the metabolites are excreted. Simulation results using this model were in agreement with reported urinary metabolite concentrations measured in various studies of worker populations, including that of Guillemin et al. (1982). Further simulations demonstrated that the use of urinary metabolites as a biological exposure index can accurately account for variability in pharmacokinetic/ physiologic parameters such as the alveolar ventilation rate. Simulations using an alveolar ventilation rate of 6-12 L/minute resulted in less than a three-fold range in model output (urinary metabolite concentration).

Jersey et al. (1978) exposed Sprague-Dawley rats (96/sex/group) to 0, 600, or 1200 ppm (0, 2556, or 5112 mg/cu.m, respectively) of 99.5% styrene for 6 hours/day, 5 days/week for up to 20 months. The exposure concentration of the 1200 ppm exposure group was reduced to 1000 ppm (4260 mg/cu.m) after 2 months because the males showed signs of toxicity (narcosis leading to anesthesia and excessive weight loss) with death coming to three animals. Exposures were terminated when mortality reached 50% for one exposure group of each sex; this was at 18.3 months for males and 20.7 months for females. All surviving rats were euthanized at the end of 2 years with interim group samplings at 6 and 12 months. Hematology, clinical chemistry, body weights, gross anatomical and histopathological analysis, and cage-side observations were performed for evaluation of toxicity. The respiratory tract (including the lungs, trachea, and nasal turbinates) was not examined in all animals; the nasal turbinates, for example, were examined only in a portion of the controls and high-exposure animals (14/28 animals, sexes combined). The number of sections examined in the nasal turbinates, trachea, or lungs is not indicated in the text. No exposure-related increase in mortality was noted in either sex. An inverse relationship between mortality and exposure was noted in male rats. A high incidence of murine pneumonia was associated with an increased mortality, but only in the control and high-exposure animals; no dose-response relationship was apparent from the data. Average body weights of both females and males were decreased at both dose levels at various times throughout the experiment. However, only the body weights of the males exposed to the highest concentration were decreased more than 10% (14% maximum), consistently only during treatment days 82-263. The only concentration-dependent alteration in organ weights observed was in absolute and relative liver weights in females sacrificed at 6 months. At the terminal sacrifice, an increase in absolute liver weights was observed only in the females exposed to the highest concentration; no histopathology accompanied this alteration. The only histological result considered to be concentration-dependent was an increase in incidence of alveolar histiocytosis (areas containing lipid-laden alveolar macrophages) that corresponded to grossly visible subpleural pale foci in the lungs of the females exposed to the highest concentration. No concentration- related effects were reported in any groups for hematology, clinical chemistry, or urinalysis. Deficiencies in this study preclude assigning effect levels.

Conti et al. (1988) exposed Sprague-Dawley rats (30/sex/dose) to 0, 25, 50, 100, 200, or 300 ppm (0, 106, 213, 426, 852, or 1278 mg/cu.m, respectively) styrene for 4 hours/day, 5 days/week for 52 weeks. The animals were kept under observation until spontaneous death. Histopathologic examinations were performed on each animal; tissues examined included brain, liver, kidneys, gonads, spleen, and pancreas. The lungs were apparently the only portion of the respiratory tract examined in this study. No noncancer results were reported or discussed in this study. No effect levels could be assigned in this study.

Effects of styrene on the respiratory tract have been addressed in mouse subchronic studies by the NTP (NTP, 1991a). B6C3F1 mice (10/sex/group) were exposed to 0, 62.5, 125, 250, or 500 ppm (0, 266, 532, 1065, or 2130 mg/cu.m, respectively) styrene for 6 hours/day, 5 days/week for

13 weeks. The duration-adjusted values for this exposure regime are 0, 47.5, 95, 190, or 380 mg/cu.m. Body weight changes, hematology, serum chemistry, sperm morphology, vaginal cytology, gross pathology, and histopathology (including the entire respiratory tract) were monitored for toxicity. Death occurred in the first week of exposure but only in the males exposed to 250 ppm; no deaths at the highest concentration were noted. Histopathology of these animals showed evidence of thymic and renal cortical necrosis. In exposed female mice, the average liver to body weight ratio was increased in the animals at the two highest concentrations. Histopathology revealed concentration-related increases in centrilobular liver cytomegaly, karyomegaly, and necrosis at these same concentrations with no effects being recorded at 125 ppm styrene or below. The lung to body weight ratios were increased at all levels relative to the control values. Histopathology of the respiratory tract revealed that the incidence of metaplasia and degeneration of the olfactory epithelium of the nasal cavity were already total (10/10 mice) in females at the lowest concentration, with necrosis being observed at higher concentrations. Likewise, bronchiolar regeneration was present in all female animals at all concentrations. The incidence of epithelial hyperplasia of the forestomach was also maximal at the lowest concentration. Similar results were noted for the males. No NOAEL for either respiratory or extrarespiratory effects was achieved in this study. The LOAEL(ADJ) for this study would be 47.5 mg/cu.m. The effects described occurred in both the nasal cavity [extrathoracic (ET)] and bronchiolar region [tracheobronchiolar (TB)]. The LOAEL(HEC) would therefore be based on effects in these regions with an RGDR of 1.55 = 74 mg.cu.m.

In a rat subchronic study (NTP, 1991b), F344/N rats (10/sex/group) were exposed to 0, 125, 250, 500, 1000, or 1500 ppm (0, 532, 1065, 2130, 4260, or 6390 mg/cu.m, respectively) styrene for 6 hours/day, 5 days/week for 13 weeks. The duration-adjusted values for this exposure regime are 0, 95, 190, 380, 761, or 1141 mg/cu.m. The same toxicological endpoints as in the mouse study were monitored. No deaths were recorded. Liver to body weight ratios were elevated at the three highest exposure levels in males and the two highest exposure levels in females, although no histopathology accompanied this alteration. Concentration-related goblet-cell hypertrophy was noted in the nasopharyngeal duct starting at 125 ppm styrene in males and at 250 ppm in females. Concentration-related degeneration of the olfactory epithelium (described as minimal to mild) was noted starting at 1000 ppm styrene in females and at 1500 ppm in males. Degeneration of the olfactory epithelium was noted also at the two highest exposure levels in both sexes. A NOAEL of 500 ppm is designated for extrathoracic effects [NOAEL(ADJ) = 380 mg/cu.m x RGDR of 0.107 = NOAEL(HEC) = 41 mg/cu.m].

The effect of styrene on the trachea of rats was addressed in two studies conducted by Ohashi et al. (1985, 1986). Both ciliary activity and histopathology were evaluated. Male Sprague-Dawley rats (10/exposure group and 10 controls) were exposed to styrene at 30 or 800 ppm for 8 consecutive weeks or at 150 or 1000 ppm for 3 consecutive weeks. Nasal and tracheal mucosa were examined by electron microscopy, immediately and several weeks after cessation of exposure. The 8-week study (Ohashi et al., 1985) found that there was a strong increase in mucus

secretion, with an increase in number of dense bodies in the nasal, but not tracheal, mucosal cells after exposure to 30 ppm styrene. There was an increase in secretory granules in goblet cells at 3-weeks postexposure. At the higher concentration in the 8- week exposure, there was a marked increase in mucus secretion, vacuolation, and sloughing of epithelial cells in both the nasal and tracheal epithelium. Compound cilia were observed, together with nuclear pyknosis, vacuolization of epithelial cells, and changes in electron density in goblet cells, which also exhibited cores with high electron density. Sloughing of epithelial cells from the basement membrane also persisted at 3-weeks postexposure. Severe ciliary denudation was observed in the high-exposure group (1000 ppm styrene) in the 3-week exposure, with ciliary activity in the nose disabled and decreased to 18% of control values in the trachea. No effect levels were designated from these studies as the quantitative relationship between ciliary activity and mucus transport is not clear. In his review of mucociliary transport, Wanner (1977) suggests considerable functional reserve of this system; in chicken trachea 30-50% of particle transport activity was present at a time when only 10% of the epithelium was ciliated.

In two studies, Lemasters et al. (1985b, 1989) examined the reproductive outcomes of female workers involved in plastics manufacturing. In the 1985 study, data from a total of 174 styrene-exposed and 449 unexposed women were collected and analyzed. No increased prevalence in menstrual disorders was observed in subgroups of the workers exposed to either 13 or 52 ppm styrene. In the 1989 study, the authors examined the relationship between styrene exposure and lowered birth weights. During the study, the authors collected and analyzed data from 819 no-, 154 low- (2-29 ppm), and 75 high- (30-82 ppm) exposed pregnancies. There was not a statistically significant concentration- response relationship in decreasing average birth weights. In women who worked at the most highly exposed jobs (estimated at 82 ppm), however, a 4% reduction in average birth weight that approached statistical significance ($p = 0.08$), despite the small sample size ($n = 50$), was detected.

Murray et al. (1978) exposed pregnant Sprague-Dawley rats and New Zealand rabbits to inhaled styrene at concentrations of 0, 300, or 600 ppm (0, 1278, or 2556 mg/cu.m., respectively) for 7 hours/day from gestation days 6-15 (rats) and 6-18 (rabbits). No concentration-related developmental toxicity was evident in either species by either route. Adverse maternal effects (decreased food consumption and a $p < 0.05$ decrease in weight gain only during the first 3 days of exposure) were noted. This study identifies a freestanding NOAEL for developmental effects of 2556 mg/cu.m.

Beliles et al. (1985) conducted a three-generation reproductive study concomitantly with a 2-year chronic study of exposure of rats to styrene in their drinking water. Sprague-Dawley rats were treated with monomeric styrene in their drinking water at 0, 125, or 250 ppm. These doses corresponded to 8- 14 mg/kg/day for males and 12-21 mg/kg/day for females. After animals were dosed for 90 days, 20 females and 10 males from the styrene groups and 30 females and 15 males from the controls were used for the F0 generation and then returned to the chronic study.

Representatives of these pups, the F1 generation, were then exposed until they were 110 days of age, at which time they were mated to produce the F2 generation. The F3 generation was produced in the same manner. Each generation was evaluated for fertility (male and female), litter size, pup viability, pup survival, sex ratio, pup body weight, weanling liver and kidney weight, physical and behavioral abnormalities on each day of lactation, and marrow cytogenetics. Reduction in the gestation and 1-, 7-, and 14-day survival indices of the high dose F2 pups was observed. A reduction in survival was also noted among the high dose F1 pups, but only at 21 days. No other evidences of fetotoxicity were noted. Although the authors claim these effects to be due to extensive losses in only 1 or 2 litters, only data on individual fetuses is presented. The high-dose level is designated as a NOAEL for reproductive effects.

Kankaanpaa et al. (1980) exposed pregnant BMR/T6T6 mice (15 controls and 13 exposed) to 250 ppm (1065 mg/cu.m) >99% pure styrene on gestation days 6-16 for 6 hours/day. Parameters monitored included number of litters and fetuses (total, live, dead, and malformed). No description of maternal toxicity is given, although narrative is provided on two preliminary experiments, one conducted at 500 ppm (2130 mg/cu.m) in which 2/6 pregnant mice and the surviving females had a fetal death rate of 47%. The other experiment was conducted at 700 ppm (2982 mg/cu.m) in which 3/5 pregnant animals died, with the surviving dams having a 95% fetal death rate. No dams died during the 250 ppm experiment, and the difference in the fetal death rate between controls and exposed dams was not statistically significant (27% vs. 18% in the controls; $p < 0.10$). The number of malformed fetuses was also increased in the exposed vs. the control mice (2.9% vs. 0.9%), but no statistical analysis was performed. A steep concentration response is indicated by this study: 500 ppm bringing death to both dams and fetuses, whereas 250 ppm appears to be without effect [NOAEL(HEC) = 1065 mg/cu.m]. These authors also exposed pregnant Chinese hamsters (2-7/treatment group and 15 controls) to 0, 300, 500, 750, or 1000 ppm (1278, 2130, 3195, or 4260 mg/cu.m, respectively) styrene for 6 hours/day on gestation days 6-18. Although the small number of animals limits the interpretation of this study, the highest concentration appears to be an effect level [LOAEL(HEC) = 4260 mg/cu.m], as the number of dead or resorbed fetuses was 66% as compared with 26% in the controls. There were no incidences of malformed fetuses in any treatment group or in the controls.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

The study of Mutti et al. (1984) documents concentration-response relationships of CNS effects in a relatively small worker population. However, the results of this study are consistent with a number of other studies showing central effects in chronically exposed worker populations, most notably that of Moller et al. (1990). The urinary metabolites, MA and PGA, are direct biological

indicators of exposure to styrene. Numerous studies have demonstrated the relationship between urinary metabolites and air levels of styrene to be reliable and quantitative. Physiologically based pharmacological modeling of this exposure methodology demonstrates that it reflects and incorporates at least a portion of intrahuman variability related to pharmacokinetics. The study is therefore assigned a medium confidence level. The database can be considered medium to high as chronic laboratory animal studies addressing noncancer endpoints are not yet available, but a number of human exposure studies support the choice of critical effect. Preliminary information in mice indicate that styrene is a respiratory tract irritant in mice at concentrations lower than 47.5 mg/cu.m. The RfC is assigned an overall confidence rating of medium.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — The assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA 1984a,b, 1985, 1989, 1991

Agency Work Group Review — 09/20/1989, 03/26/1992

Verification Date — 03/26/1992

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Styrene
CASRN — 100-42-5

Not available at this time.

VI. Bibliography

Substance Name — Styrene
CASRN — 100-42-5

VI.A. Oral RfD References

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VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Styrene
CASRN — 100-42-5

Date	Section	Description
11/01/1992	I.B.	Inhalation RfC summary on-line

VIII. Synonyms

Substance Name — Styrene
CASRN — 100-42-5
Last Revised — 01/31/1987

- 100-42-5
- BENZENE, VINYL-
- CINNAMENE
- CINNAMENOL
- CINNAMOL
- DIAREX HF 77
- ETHENYLBENZENE
- ETHYLENE, PHENYL-
- NCI-C02200
- PHENETHYLENE
- PHENYLETHENE
- PHENYLETHYLENE
- STIROLO
- STYREEN
- STYREN
- Styrene
- STYRENE, MONOMER
- STYROL
- STYROLE
- STYROLENE
- STYROPOL
- STYROPOR
- UN 2055