IV. EFFECTS OF EXPOSURE

EFFECTS ON HUMANS

Historical Reports

As mentioned in the Scope of the Document, the first published reference to styrene was by Bonastre in 1831 who wrote: "Its odor is sharp, penetrating....Its taste is bitter, burning and caustic; an unpleasant sensation remains after tasting [16]." In a literature review published in the United States in 1940, Von Oettingen [51] reported that the toxicity of styrene had not been studied. However, according to a 1960 report [52], data on the acute animal toxicity of styrene had been published in Russia in 1936 by Larionov indicating changes in the lungs and bronchi, fat accumulation in the liver, and slight degenerative changes in the kidneys, as well as decomposition of leukocytes in the spleen, lymph nodes, and blood.

The first U.S. report of the effects of styrene was written by Spencer et al. [53] in 1942 who, based on animal studies, estimated that repeated exposure of workers to styrene at 650 ppm would produce no serious disturbances. However, it was noted that this concentration was definitely irritating to the eyes and nose and, therefore, the investigators [53] suggested 400 ppm as a tentative permissible limit for occupational exposure to styrene, a level producing a disagreeable odor but only slightly irritating.

Based on his experiences in the synthetic rubber industry, in 1943, Mallette [54] described styrene as a lung and skin irritant that produced light narcosis and possible liver and kidney injury. He noted that in a series of several hundred periodic examinations of the blood of workers in the rubber industry who were exposed to styrene, no traces of the "blood damage so characteristic of benzol" were found. Mallette [54] suggested that a styrene limit of 400 ppm was too high to prevent skin irritation among workers in synthetic rubber producing factories, and he stated that 200 ppm, which was not irritating to the eyes or nose, was preferable.

Case Studies and Miscellaneous Reports

Few cases of styrene intoxication as such have come to the attention of physicians because of obscure etiologies associated with styrene exposure, and there have been no reports of fatalities.

In 1946, McLaughlin [55] reported that among 458 chemical burns of the human cornea treated by him over a three-year period, thirty cases were caused by styrene. In the styrene cases there were only superficial transient disturbances of the eye, with return to normal within 48 hours in all but one case in which healing took three to ten days.

In 1952, Barsotti et al. [56] studied seven workers from a polystyrene manufacturing facility in Italy. The styrene concentration in the work area where styrene was loaded into the polymerization tower was reported as 188 ppm. Traces of styrene were found in the pumproom air, but no styrene was detected in any other area of the factory. Methods of sampling and analysis were not given. The workers had been employed in this factory for 18 months, and most had conjunctival and pharyngeal congestion. Two workers had an erythematopapular dermatitis localized on the back of the arms, with increasingly intense itching. Another had suffered for 3 months with a pruriginous dermatitis. Three workers had hyperactive deep reflexes. Complete blood counts and urinary hippuric acid concentrations were normal. None of 20 workers who handled the polymerized product had disturbances of any consequence. Atmospheric concentrations of polystyrene dust were not reported [56].

In 1964, Pratt-Johnson [57] described a case of retrobulbar neuritis in a 48-year-old self-employed Canadian who had worked for five years making reinforced plastics. The individual admitted that he had handled styrene carelessly, and had frequently come into contact with it with his bare hands. Initially, painless deterioration of vision to 20/400 and centrocecal scotomata were noted in each eye. Upon treatment with vitamin B compound and nicotinic acid for six months, visual acuity and visual fields improved slowly, recovery being complete within a year. The author [57] noted that circumstantial evidence alone incriminated styrene as the toxic agent. Kohn [58], in reviewing this study, stated "the likelihood of nutritional amblyopia could not be excluded."

In 1968, Matsushita et al. [59] described the case of a 35-year-old Japanese worker who developed symptoms of both central and peripheral nervous system poisoning while employed in a resin coating operation for 3.5 years. As a result of falling at work, he was examined by a physician who diagnosed his condition as organic solvent poisoning on the basis of progressive symptoms of peripheral numbness, fatigue, and dizziness, and work conditions. During a subsequent neurologic examination, a slight decrease in the muscular strength of the legs and arms, and the grasping strength of the right hand were found. Most reflexes were normal except for muscular reflexes of the upper limbs. Decreased sensation in the forearms and lower limbs was indicated by objective pain and vibration tests. Abnormal electromyograms (EMGs) of the arm and leg muscles were recorded and interpreted as indicating peripheral neuromyogenic nervous disorders. However, findings of normal motor nerve conduction velocities for ulnar, median, peroneal, and tibial nerves may not support this hypothesis. A slight contraction of the visual fields and a slight expansion of Mariott's dark point without eye fundus changes were found during ophthalmologic examination. No electroencephalographic abnormalities, indications of impaired liver function, or blood dyscrasias were found. The man was removed from work, treated as an outpatient, and slowly began to recover; however, about 22 months after treatment had begun, he was still hypersensitive to cold in his arms and legs. As a result of this case, the investigators [59] subsequently studied other workers in the factory and

determined that exposures were due primarily to styrene (up to 600 ppm) and occasionally to traces of toluene, ethyl acetate, and methanol. The results of this subsequent study are discussed in the Clinical Studies Section.

In 1971, a case of accidental exposure was reported by Schwarzmann and Kutscha [60]. In this incident a student inhaled some styrene vapor and spilled a "small" amount on his hand. Thirty minutes later the student noticed central blind spots in both eyes, and, 30 minutes after this, a headache developed. The blind spots had almost disappeared 1.5 hours after the initial contact, but the headache persisted and he was visibly shaking. He experienced hot and cold spells, had periodic sensations of numbness on the hand where styrene was spilled, and was extremely restless. For 7 hours following the accident, he felt very weak. After eating dinner he noticed the headache was gone. Other reports of this type of reaction to styrene have not been found, and many of the symptoms described could also be explained as hysteria or anxiety on the part of the student.

In 1971, Araki et al. [61] provided information of an 11-year history of lacrimation, nasal irritation, muscle soreness, headache, insomnia, general malaise, and anxiety, which led to the hospitalization of a 55-year-old man. The man had worked for 14 years in a Japanese factory where polyester resin tubs were manufactured. Although no information about airborne concentrations of styrene was given, the authors reported that the man typically handled styrene with his bare hands. As a result of this work practice, the skin on the man's hands was generally thin and atrophic. Biopsy revealed thinning of the prickle cell layer, flattening of the papillary layer, and marked edema with mild perivascular infiltration of the round cells throughout the dermis.

This case also had signs of neuropathy. Although pathologic reflexes were not found, he did have generally exaggerated deep tendon reflexes, paresthesia (tingling sensation) of the extremities, and bilaterally decreased cold sensation of the legs and feet. An electromyogram indicated a reduced number of motor units during maximal voluntary effort, and larger polyphasic action potentials of long duration. Biopsy of the biceps humeri and the gastrocnemius muscles revealed degeneration of the fibers with an increase of the sarcolemmal nuclei in some places. Biopsy of a peripheral nerve, n. suralis, showed no remarkable changes. The man's visual field and acuity were intact and an electroencephalogram (EEG) was normal. Since Raynaud's syndrome was absent and the man's symptoms were not consistent with scleroderma, Araki et al. [61] thought that the skin, muscle, and nerve changes were the result of the direct action of styrene and suggested, without explanation, that effects on the autonomic and central nervous systems were due to the action of styrene on the man's brain stem.

A chest roentgenogram of the man revealed pulmonary emphysema, but it was noted that the man smoked about 20 cigarettes a day. Hippuric acid excretion and results of tests of liver competence and blood counts were all normal, but creatinuria (0.187 g/24 hours) was noted. Araki et al. [61] also reported that about the time of the onset of symptoms (11 years prior

to hospitalization) the man was admitted to a hospital because of jaundice, but its cause was not established.

In 1973, Stepien [62] described the case of a 33-year-old female who suffered from thrombosis of the central retinal vein. She had worked over a year in a Polish experimental chemical laboratory and had been exposed mainly to styrene and solvents (not specified) in testing polyester laminates and epoxide films. Stepien [62] concluded that the interview, type of work, increased red blood cell count (RBC), toxic changes in the bone marrow, increased mandelic acid levels to 980 mg% ten days after last workplace exposure, and a lack of other reasons pointed to a toxic background for the disease, caused mainly by styrene.

In 1975, Hruba et al. [63] reported a study of two groups of workers from four Czechoslovakian plants; the styrene exposures were unspecified. The first group consisted of 101 workers who had been exposed to styrene for 2 months to 6 years; the other group, called a "control" group, included 21 workers just beginning employment. The most common subjective complaints of the 122 workers (95 women, 27 men, average age 35) were drowsiness (34%), headaches (28%), fatigue (25%), and increased irritability (14%). Examinations revealed signs of vegetative imbalance (64%), lowered tendon and periostal reflexes (19%), and slight signs of cerebellar nerve disturbances (14%). Normal EEGs were found in 13 of the exposed workers, borderline EEGs (including flat graph and conspicuous sleep activity) were found in 42, and mildly abnormal EEGs (including synchronous rhythms and centralized predominance of dispersed changes) were found in 46 of the 101 workers. Of the 21 workers in the "control" group just starting employment, 7 had normal EEGs, 7 had borderline readings (including mildly disturbed rhythm, increased beta, or flat graph), and 7 had slightly abnormal EEGs because of increased slow activity. After 3 years of employment, only 1 of the 21 "controls" had an EEG that the investigators [63] considered normal, 12 had borderline EEGs (including flat graphs and mildly increased sleep rhythms), and 8 workers had abnormal EEGs (not defined).

In 1974, Axelson et al. [64] described two men who were engaged in plastic boat production and had chronic emotional insufficiency with symptoms suggesting cerebral lesions around the time they started to work with styrene. TWA styrene concentrations measured at some worksites at one of the plants about a year after the men became ill were 200-292 ppm; instantaneous styrene peaks were sometimes higher than 1,500 ppm. There were some complicating factors, such as alcohol and drug abuse by one man, but these did not seem to the authors [64] to be of sufficient degree to have been likely causes. Axelson et al. [64] thought styrene might have contributed to the conditions, but believed the evidence was inadequate for a definite conclusion.

In 1976, Dowty et al. [65] reported qualitative analyses by gas chromatography and mass spectrometry of 11 paired maternal blood and umbilical cord blood samples obtained at birth. Styrene was identified in blood from both sources. The mothers were all healthy and 10 of the babies

normal. One infant with a lumbosacral meningomyelocele had numerous volatile organic compounds (apparently including styrene, acetone, and butylated hydroxytoluene) identified in the cord blood. The concentrations in these blood samples were not reported and are apparently not known. There were no known occupational exposures to styrene, and its sources were not determined.

In 1977, Holmberg [66] described CNS birth defects in children born to two women who were employed in factories in Finland where reinforced plastics were made. These two women were in a group of 43 women who responded to questionnaires sent to all women, without regard to their occupation, who had borne children with CNS defects in the previous year.

In the first case, the mother was a 19-year-old woman (first pregnancy, first birth). She and her 26-year-old husband, a carpenter, worked in a factory where reinforced plastics were made; her regular job was grinding, polishing, and mending reinforced plastic products. She was potentially exposed to styrene, polyester resin, organic peroxides, acetone, and polishes. At one point in her pregnancy (about the 4th month), she was "heavily exposed" to styrene for 3 days when she cleaned a mold. Her pregnancy was generally unremarkable, except for bronchitis during the 3rd month. The mother worked until 2 weeks before delivery. The baby, born in the 9th month, was 54 cm long and weighed 3,900 g. It had congenital hydrocephalus, anomaly of the right ear, and bilateral malformations of the thoracic vertebral column and ribs [66].

The other case involved a 24-year-old woman (first pregnancy, first birth) who also worked in the reinforced plastics industry. She was married to a 24-year-old welder-plater and gave birth to a 47-cm, 2,200-g girl. The child died during delivery and was anencephalic. The 7-month pregnancy was essentially uncomplicated although contractions that occurred in the 2nd month were controlled with 10 mg of isoxsuprine three times daily for 1 week. In the 7th month, the mother was treated for slight edema with 500 mg of chlorothiazide once daily for 1 week [66]. In the 3rd month, the woman was exposed to styrene, acetone, organic peroxides, and polyester resin while performing a hand-rolling operation for about 3 weeks with no respiratory protection. Afterwards, she was assigned to needlework in the same shop with occasional assignments in the hand-rolling operation.

Holmberg [66] reported still another case, not involving occupational exposure; it involved a 20-year-old woman (first pregnancy) who gave birth in the 7th month to a stillborn, anencephalic child. The mother was exposed to styrene on six occasions when her husband did repair work with reinforced plastics at home. The materials used were styrene, polyester resin, and organic peroxides. This case was complicated by a history of juvenile diabetes in the mother.

Based on information from the Finnish Register of Congenital Malformations, Holmberg [66] reported that the combined incidence of hydrocephaly and anencephaly among Finnish women of child-bearing age was

0.5/1,000 live births. He predicted 12 live births among women in the reinforced plastics industry during the 9-month study period, based on estimates of the number of women of child-bearing age employed in the Finnish reinforced plastics industry in 1974 (i.e., 250) and on Finnish fertility data. Thus, the normal combined rate of anencephaly and hydrocephaly (0.5/1,000 live births) was exceeded more than 300-fold.

Melgaard et al. [67] described chronic CNS changes in seven Danish workers, all males aged 42-65 years with a mean time of exposure to styrene of 15 years, ranging from 6 to 28 years. Exposure concentrations were not known, but the workers were all employed in small workshops with what were described as poor hygienic conditions. Details of the examinations were not provided except that neuroradiologic examinations were performed either with pneumoencephalography or computerized tomography.

The men had often experienced acute CNS effects (symptoms of acute intoxication with headache, dizziness, and a sense of drunkenness toward the end of the workday). At the time of examination in the hospital, they had complaints of fatigue, memory loss, difficulty in concentrating, unstated emotional complaints, and headache. In one man who had for several years imbibed alcohol excessively, there was biochemical evidence of liver damage and signs of polyneuropathy. Based on undescribed neuropsychological examinations, there was intellectual impairment in 6 men, 5 showed a moderate degree, and 1 was severe. Cerebral atrophy was found in 4 men by computerized tomography scan and in 1 man by pneumoencephalography.

Experimental Exposures

In 1944, Carpenter et al. [68] reported the results of an experimental study of two men exposed to styrene in a chamber at 800 ppm for 4 hours. The two men experienced eye and throat irritation immediately after entering the chamber. Increased nasal mucous secretion, a pronounced and persistent metallic taste, listlessness, drowsiness, and impairment of balance also occurred during this exposure. After exposure, symptoms of weakness, unsteadiness, inertia, and depression were reported. Urine collected over a 24-hour period from both subjects was analyzed for hippuric acid and neutral sulfur. In one subject, hippuric acid excretion was considerably increased. Neutral sulfur in the two subjects was increased by 17% and 48%, respectively.

In 1968, the effects of inhalation of styrene vapor at 51-376 ppm on human subjects were reported by Stewart et al. [69] . Nine healthy men were studied, some several times, in five experiments according to the design in Table IV-1.

TABLE IV-1

STYRENE EXPOSURE SCHEDULE

Experiment	No. of Subjects	Exposure Duration (h)	Styrene Concentration (ppm) Mean	Range
1	1	2	117	112-121
2	6	7*	99	95-107
3	3	1	51	50-55
4	3	1	216	203-236
5	5	1	376	368-403

*Two 3.5-hour sessions with an intervening 30-minute lunch period
Taken from Stewart et al. [69]

The styrene was 99.6% pure as determined by infrared (IR) analysis and contained 2 ppm of p-tert-butylcatechol to inhibit polymerization [69]. Styrene concentrations in the 12.5.xl.8x2.3-m (52.2-cu m) chamber were measured continuously with an IR spectrometer. The minimum detectable styrene concentration in the chamber using this method was about 11 ppm. Breathing zone samples, collected in 50-ml glass pipets every 10 minutes in experiments 1, 3, 4, and 5, and every hour in experiment 2, were analyzed by gas chromatography with a hydrogen flame detector. The minimum detectable styrene concentration by their method of sampling and analysis was 0.05 ppm. Total expired air samples were collected every 15 minutes and similarly analyzed during experiments 1, 3, 4, and 5 and every hour during experiment 2 by having the subjects breathe through a tube connected to a bag outside of the chamber. Urine samples were collected for 24 hours before the exposures and up to 2 days after the exposures for hippuric acid determination; urine samples from nine laboratory workers were used for comparison. Venous blood was collected in experiments 1, 2, and 3 during the final 10 minutes of exposure, and, in experiment 1, after 1 hour of exposure. Tests administered during exposure included a modified Romberg test (balancing on one foot with eyes closed and hands at side), heel and toe, finger to nose, the Crawford manual dexterity collar and pin test, and the Flanagan coordination test. Subjective and objective responses were recorded every 15 minutes during the exposures [69].

Two of five subjects exposed to styrene for 1 hour at 376 ppm reported eye irritation within 3 minutes; two more reported eye irritation within 15 minutes. All five subjects noted nasal irritation at this concentration. After 20 minutes, a burning sensation of the face was reported by one subject. After 25 minutes of exposure, one subject was unable to perform

the modified Romberg test normally. After 50 minutes of exposure to 376 ppm, two subjects exhibited decrements of 20% and 33%, respectively, in the Crawford manual dexterity collar and pin test, and three subjects dropped to a 10 percentile below their pre-exposure performance on the Flanagan coordination test. Nausea that occurred in one subject after 45 minutes of exposure persisted for 1 hour after the exposure. At the end of the exposure, two subjects reported feeling slightly inebriated; one of these subjects and one other individual who complained of headache performed the Romberg test abnormally [69].

After 20 minutes of a 1-hour exposure at 216 ppm, nasal irritation was noted by one of three subjects. Coordination and balance were not affected by this exposure [69].

During the 7-hour exposure at 99 ppm, two of six subjects noted mild eye irritation, and one noted mild throat irritation within 20 minutes after the exposure began. Eye irritation persisted for 30 minutes before subsiding, and the throat irritation subsided after drinking coffee. The Romberg test was performed eight times by each of the six subjects during this experiment. Two subjects perceived themselves as having difficulty performing the test on one occasion, and one subject perceived having difficulty on two occasions. The perceived difficulty was not reflected in the actual performance of the Romberg test, however, since Stewart et al. [69] stated there were no objective signs of impairment of balance during the seven hours. Performances on the Crawford dexterity and Flanagan coordination tests were also unaffected. Two subjects noted that the odor of styrene was faint, while the other four barely perceived it at the end of the experiment [69].

Although the odor of styrene was reported to be moderately strong by the subject in the 2-hour exposure at 117 ppm and by the three subjects in the 1-hour exposure at 51 ppm, no untoward subjective symptoms or objective signs of illness were reported [69].

Clinical laboratory test results that remained normal following each of the exposure sessions included complete blood count (CBC), sedimentation rate, reticulocyte count, serum glutamic-pyruvic transaminase (SGPT), lactic dehydrogenase, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and blood glucose. Urinary hippuric acid excretion was not significantly altered by the styrene exposures; pre-exposure values were 0.8-3.0 g/24 hours and the postexposure values were 1.0-2.9 g/24 hours. Styrene concentrations in exhaled breath samples during the exposures were 25% of the concentration present in the exposure chamber, which indicated about 75% retention. Concentrations of styrene found in the blood and postexposure alveolar air at the end of various periods are presented in Table IV-2. Percentages of absorbed styrene exhaled during various periods after removal from exposure are also given. After the exposure, only small amounts of styrene were eliminated in the breath; for example, 1.2% of the absorbed styrene was eliminated during the 4 hours after the end of exposure at 117 ppm [69].

TABLE IV-2

CONCENTRATIONS OF STYRENE IN CHAMBER AIR, POSTEXPOSURE VENOUS BLOOD, AND ALVEOLAR AIR

Exposure (h)	Styrene Concentration			Absorbed Styrene Exhaled in Postexposure Periods
	Chamber air (ppm	Blood (mg/liter)	Alveolar Air (ppm)	
1	51	0.2-0.7	1.0	0.7% in 7 h
7	99	0.9-1.4	1.3	0.7% in 2 h
1	117	1.7	-	-
2	117	2.7	1.8	1.2% in 4 h

Taken from Stewart et al. [69]

Hake et al. [70] exposed 10 men in groups of 2-4 for 1, 3, or 7.5 hours a day to 0, 20, 100, or 125 ppm styrene vapor. Eight women in groups of 1-4 were exposed at 0 or 100 ppm. Each subject was part of more then one group, but nonexposure weekends or control exposures (i.e., 0 ppm) were interspersed with the styrene exposures. For the men there were 3 days of exposure at 20 ppm, 4 days at 100 ppm, 4 days at 100 ppm with the concentration fluctuating between 75 and 125 to simulate workroom exposures, 5 days at 125 ppm, and 7 days at 0 ppm. The women were exposed to 100 ppm on 4 days and to 0 ppm on 2 days. The exposure chamber for control exposures was initially odorized by the introduction of styrene vapor at 10 ppm upon entry of the subjects, then reduced within 10 minutes to 0 ppm.

Daily check of the temperature and blood pressure, urinalysis, and continual medical surveillance during the study by a physician revealed no unusual abnormalities that could be attributed to exposures to styrene vapor; neither did the weekly battery of clinical chemistry tests. The weekly CBC did reveal that eight of the ten male subjects, after three consecutive days of exposure to 125 ppm, had elevated basophils in the differential analysis of blood samples drawn on the morning of the fourth day. The abnormal values ranged from 3 to 5%, the normal laboratory value being 0 to 1% [70].

No deleterious effect on equilibrium was found as measured by modified Romberg and heel-to-toe tests. There were some changes in 3 of 6 subjects in both visual evoked response and EEG amplitude over the course of the study deemed by the investigators [70] as consistent with CNS depression. However, the changes were neither uniform in all subjects identically exposed to styrene, nor were they consistent in magnitude within subjects.

Pulmonary ventilation (VE) values, forced vital capacity (FVC), fraction of FVC exhaled in one second (FEV_1/FVC), peak expiratory flow-rate (PEFR), and maximal mid-expiratory flow-rate (MMEF) in general showed no effects of styrene exposure. The investigators [70] stated that decrements in maximal expiration values, found in subjects repeatedly exposed for 7 1/2 hours to 100 ppm styrene, indicated a potential effect on pulmonary mechanics that needed further study.

There was no significant variance in cognitive testing scores because of styrene exposures. Electrically evoked electromyogram (EMG) configuration and latency between stimulus and response were found to be consistent throughout the period of study. The subjects were also asked to note on a checklist subjective symptoms during the experiment. The overall data indicated a dose-response relationship between two subjective symptoms, eye, nose, and throat (EyNT) irritation and headache. For the men, the incidence of EyNT irritation was 13% at 0 ppm, 17% at 20 ppm, 20% at 100 ppm, 33% at exposures fluctuating between 75 and 125 ppm that averaged 100 ppm, and 45% at 125 ppm; the incidence of headache was 3% at 0 and 10 ppm, 0% at 100 ppm, 13% at 100 ppm (fluctuating exposures), and 12% at 125 ppm [70]. There was no specific indication as to which exposure time (i.e., 1, 3, or 7 1/2 hours) the various subjective responses were elicited at a given exposure concentration. For the women, the incidence of EyNT irritation was 8% at 0 ppm and 32% at 100 ppm; the incidence of headache was 0% at 0 ppm and 35% at 100 ppm.

In 1974, changes in psychomotor function during styrene exposure were examined by Gamberale and Hultengren [71]. Twelve healthy men, 21-31 years old, were assigned to either of two groups of six. Each group was sequentially exposed to styrene vapor for four consecutive 30-minute periods at 50, 150, 250, and 350 ppm. The subjects, while at rest, inhaled styrene-air mixtures through a mouthpiece with very little breathing resistance. During the final 20 minutes of each 30-minute exposure period, tests of perceptual speed (numerical recognition and numerical sequence), simple reaction time, choice reaction time, and manual dexterity were given. At some point during each of the five tests, each subject's heart rate was recorded.

These same tasks were also performed under control conditions. To disguise the introduction of styrene into the exposure chamber and the changing concentrations of styrene, the authors [71] began the control experiments with a strong smell of styrene still in the mouthpiece, and ended with a 3-minute exposure to styrene. Upon completion of each 2-hour session, the volunteers evaluated their own conditions. Six pairs of contrasting condition descriptions were used: calm/hurried, active/passive, relaxed/tense, well disposed/ill disposed, unaffected/affected, and spry/tired. These were evaluated on 7-point scales in which point 4 described normal feelings and points 1 and 7 the extremes. At the end of the exposure, the subjects felt generally more tense and affected than under control conditions. None of the subjects believed that his performance on any test during exposure had been impaired [71].

There were no significant changes from control values in the manual dexterity or perceptual tests. However, there were changes in results of the reaction time tests. The differences between experimental and control values for simple reaction time increased throughout the exposure and with the increasing of the styrene concentrations. These differences were statistically significant only during exposure at 350 ppm styrene after consecutive 30 minute exposures each to 50, 150, and 250 ppm. The investigators did not employ an experimental design that allowed them to distinguish the effects of both exposure time and concentration [71].

In 1974, Oltramare et al. [72] reported their study of the toxicity of styrene in man. The study included experiments with six volunteers, three of whom had previous occupational exposure to styrene. None of the occupationally exposed group had worked with styrene during the 15 days prior to experimental exposure. Comprehensive physical examinations were given before the studies began.

The results of these examinations were within normal limits except for one case of slight anemia. The exposures were conducted in a chamber that was 2.6x2x3 m (15.6 cu m); styrene was introduced by blowing air from outside the chamber across a styrene vaporizer. The chamber was designed with an air intake vent in the ceiling that provided a slight air change in the chamber during exposure [72].

Forty-three exposure sessions (1-3 hours each) were held, using one to two subjects at a time. Two subjects were exposed to styrene once at 300 ppm, all six subjects were exposed one or two times at concentrations of 100 and 200 ppm, and most were exposed at 3-5 ppm and 50 ppm. For comparison, five of the six participants were exposed to toluene at 200 ppm, and two were each exposed to 1,1,2-trichloro-1,2,2-trifluoroethane at 300 and 600 ppm.

Psychomotor functions of the three subjects who had been occupationally exposed were studied with simple visual, audiovisual, and multiple stimuli reaction time tests. The subjects were individually exposed in sessions that lasted 90 minutes. All subjects were first exposed at 3-5 ppm of styrene to obtain control data. In other exposure sessions at least 1 week apart, the subjects were exposed in random order to styrene at 50, 100, and 200 ppm, and to toluene at 200 ppm. A final exposure session at 3-5 ppm styrene was conducted to obtain additional control data. One subject was not exposed to styrene at 50 ppm, and data from another subject were not obtained for toluene or the final 3-5 ppm session. At each session reaction times were determined before, 1 hour after start, and then 30 minutes after the exposures [72].

Simple visual reaction times measured during, and 30 minutes after exposure at 3-5 ppm were about the same as pre-exposure values. At 50, 100, and 200 ppm of styrene, reaction times lengthened by 12-37% during exposure as compared with pre-exposure values; half an hour after removal from exposure, reaction times in subjects exposed at 200 ppm were still increased 11-35% compared with pre-exposure values [72].

The audiovisual reaction time test required the subjects to push a button in response to either a green light or a sound. Results obtained during exposure were similar to those of the simple visual reaction time test, i.e., a drop in performance at exposures to styrene at 50, 100, and 200 ppm.

The multiple stimulus reaction time test consisted of three visual and two auditory stimuli. The 50 ppm styrene concentration had no effect on performance. The ability of the subjects to perform this diffuse attention test improved with repeated trials, both during each session and from the first session to the last. Thus, as the authors [72] commented, an effect of styrene at 50 ppm, if present, might have been masked by learning effects. However, decrements of about 2% were found during and after exposure to styrene at 100 ppm and of about 10% during and after exposures to styrene at 200 ppm. The functional significance of the decreases in performance found in any of the three tests was not discussed [72].

The authors [72] concluded that measurement of reaction time was a more sensitive method than vigilance tests for revealing slight effects of styrene on higher nervous system functions, and that styrene inhalation leads to narcosis. It is not evident whether the same conclusions on the relative merits of the two types of tests would have been reached had the investigators [72] controlled for the effect of learning rate or the order of presentation of tasks.

Equilibrium disorders (loss of balance) during styrene exposure were also investigated by Oltramare et al. [72] in three of the six subjects using a special platform for quantitative assessment of each subject's movements during performance of a modified Romberg test. In each 4-minute period, the number of movements was recorded. Statistically significant differences between results obtained from 1-hour exposures at 3-5 and 200 ppm and between 100 and 200 ppm were found, but no differences were found between results obtained at 3-5 ppm and those obtained at 100 ppm, suggesting a threshold between 100 ppm and 200 ppm at which performance of this test was impaired. However, due to the small sample size and the large dispersion of data, the authors [72] stated that the results should be confirmed with other experiments before drawing any definite conclusions.

Styrene in exhaled and alveolar air was measured in a series of experiments with a hydrogen flame ionization hydrocarbon analyzer, and the percentage of retained styrene was calculated. Usually two subjects were exposed together. To determine alveolar styrene concentrations, the subjects were asked to exhale normally into a plastic bag and then make a forced exhalation into a tube connected to a hydrocarbon analyzer. The average retention was about 64% of the inhaled styrene. A correlation coefficient of 0.88 was found between the styrene concentration in alveolar air during exposure and that in inspired air. Alveolar air concentrations were monitored for several hours after the exposures. At a given exposure concentration, the removal of styrene from alveolar air depended on duration of exposure. The fat content of the subjects was estimated from

anthropometric measurements; persons with the greatest estimated amount of fat had lower styrene concentrations in alveolar air and longer retention of styrene [72].

Urinary mandelate/creatinine ratios were elevated by statistically significant amounts ($p<0.05$) over control values in the two subjects studied after 90-minute styrene exposures. However, exposures for 90 minutes at 100, 200, and 300 ppm did not produce differences in mandelic acid concentrations that were large enough to distinguish between the exposures [72]. The six subjects were asked to note the occurrence of 12 symptoms during and after the exposures. From all of the experimental exposure sessions, a total of 55 reports of individual responses were available for analysis (Table IV-3). For each of the 12 symptoms in the table, the number of positive responses is presented as the numerator of a ratio. The denominator is the total number of individual reports for the exposure concentration. A given subject could have been tested more than once at a given concentration. For example, at 100 ppm there were 13 subject-exposures(denominator), gastralgia was experienced 3 times (numerator). It was not evident from the report whether one subject experienced gastralgia on three occasions or whether three different subjects experienced gastralgia [72].

TABLE IV-3

NUMBER OF TIMES SYMPTOMS REPORTED/NUMBER OF SUBJECT-EXPOSURES

Symptom		Styrene ppm 3-5	50	100	200	300
Irritation						
Lips	D	0/10	0/6	1/13	2/12	0/2
	P	0/10	0/6	0/13	1/12	0/2
Eyes	D	1/10	4/6	4/13	7/12	2/2
	P	0/10	0/6	1/13	2/12	0/2
Nose	D	4/10	3/6	7/13	5/12	1/2
	P	2/10	1/6	3/13	2/12	0/2
Gastralgia	D	0/10	0/6	3/13	5/12	1/2
	P	0/10	0/10	1/13	2/12	0/2
Nausea	D	0/10	0/6	5/13	4/12	2/2
	P	0/10	0/6	1/13	2/12	0/2
Dizziness	D	1/10	1/6	0/13	3/12	0/2
	P	0/10	1/6	0/13	2/12	0/2
Headaches	D	1/10	3/6	10/13	10/12	2/2
	P	0/10	2/6	8/13	9/12	0/2
Sleepiness	D	3/10	2/6	12/13	12/12	2/2
	P	1/10	1/6	4/13	11/12	2/2
Poor concentration	D	1/10	4/6	9/13	11/12	2/2
	P	0/10	2/6	4/13	9/12	2/2
Intoxication	D	0/10	1/6	2/13	6/12	1/2
	P	0/10	1/6	1/13	3/12	0/2
Fatigue	D	2/10	4/6	10/13	9/12	2/2
	P	2/10	4/6	9/13	9/12	2/2
Malaise	D	0/10	1/6	7/13	7/12	2/2
	P	0/10	0/6	1/13	0/12	0/2

D = occurrences during exposure
P = persistence after exposure

Taken from Oltramare et al. [72]

Symptoms indicative of narcosis and those referable to the digestive tract increased with increasing styrene concentrations. At 50 ppm, the investigators [72] reported that about half of the subjects experienced what was described as prenarcotic discomfort. The frequency of eye irritation generally increased with styrene concentration, but the other symptoms of irritation did not.

When subjects who had worked with styrene were compared with those without occupational exposure, it appeared that the styrene workers had become accustomed to some styrene effects. With the exception of symptoms of irritation, the symptoms noted were consistently fewer for the subjects with previous styrene exposures than for the other subjects. The workers previously exposed to styrene reported irritation at 3-5 ppm, and Oltramare et al. [72] considered that the greater degree of discomfort of the eyes, nose, and mouth may have been due to chronic inflammation from working with styrene. Oltramare et al. [72] also concluded that the nervous systems of the subjects with previous styrene exposure were either less sensitive than those of other subjects or that the subjects occupationally exposed to styrene in the past had become accustomed to the effects of styrene.

Subjects who had not been previously exposed to styrene complained of eye irritation, headaches, sleepiness, difficulty in concentrating, and fatigue when exposed at 50 ppm. When exposed at 100 ppm, they also complained of gastralgia, nausea, and malaise. The authors [72] cautioned that their studies were preliminary and based on an insufficient number of subjects.

In 1979, Odkvist et al. [73] reported the experimental study of five men, 22-34 years old, exposed to styrene at 300 ppm for 1 hour. The volunteers had no history that indicated disease of the nervous system, eyes, or ears. The exposure took place via a breathing valve during light exercise (50 Watts) on a bicycle ergometer with no significant electrocardiogram (ECG) changes recorded. The ability of the eyes to follow a stripe pattern (passing at a rate of 40 angular degrees per second) in an optokinetic test, immediately after styrene exposure, deteriorated in all five test subjects, although not significantly more so than in controlled experiments with no styrene exposure. No positional nystagmus, fixation nystagmus, or balance disturbance (standing on one leg with eyes closed and walking on a line with eyes closed) was observed in any of the test subjects. The mean concentration of styrene in the blood after 1 hour of exposure was 8.7 mg/kg. The authors [73] interpreted the deterioration of the eye's capability to follow an object as a styrene effect that decreased the inhibitory effect of the cerebellum on the motor function of the eyes.

Clinical Studies

Clinical studies of workers exposed to styrene can be classified by the relative extent to which effects are likely to be due to styrene. In the

production of polystyrene, occupational exposures are almost entirely to styrene. In plants that produce styrene monomer, there may also be exposure to benzene and ethylbenzene. In plastics applications such as reinforced plastics/composites (RP/C) where styrene is a solvent-reactant for copolymerization, styrene is the major air contaminant; however, there are concomitant exposures to fibrous glass, catalysts, accelerators, cleaning solvents, and other chemicals. In many of the RP/C applications, the operations involve potential contact of the skin with liquid styrene. During SBR production, workers are exposed to numerous ingredients and emissions (during vulcanization and curing) besides low levels of styrene. Thus, the likelihood that observed toxic effects are due to styrene exposure alone is greatest in the production of polystyrene, less in the production of styrene and reinforced plastics, and even less in SBR production.

(a) The Production of Styrene and Polystyrene

In 1963, an industry-wide retrospective study of morbidity with temporary loss of work among 1,240 workers from five Russian factories was conducted by Troshina [74]. Styrene, styrene-containing latex, polystyrene, and synthetic rubber were produced in four of the factories; styrene concentrations were not reported. In the fifth factory, products were made from polystyrene, which resulted in exposures to only "traces" of styrene. A comparison group consisted of workers with no styrene exposure from auxiliary shops in one factory. Only data from workers employed for at least a year were considered.

In general, liver and gall bladder illness were the main diseases recorded; Troshina [74] found that the morbidity rate among women was about twice that of the men. Details are presented in Table IV-4. Morbidity due to liver and gall bladder illness increased with increasing length of employment. However, due to the lack of exposure data, the cause of the reported effects is unknown.

TABLE IV-4

MORBIDITY DUE TO LIVER AND GALL BLADDER ILLNESS
IN WORKERS WITH EXPOSURE TO STYRENE

Factory	Percentage of Workers with Illness		
	Men	Women	Total
Styrene production	3.0	5.7	4.7
Production of styrene-containing latex	3.2	6.7	4.8
Polystyrene production	5.4	11.9	10.5
Fabrication of polystyrene products	0.0	0.7	0.5
Rubber production	2.6	4.0	3.3
Auxiliary shops (control)	1.3	2.0	1.5

Taken from Troshina [74]

In 1978, several clinical studies of workers in a styrene and polystyrene production plant in the Federal Republic of Germany were published by Theiss and Friedheim [75], Fleig and Theiss [76], and Theiss and Fleig [77]; Frentzel-Beyme et al. [78] also reported in 1978 on a retrospective cohort mortality study (which will be discussed in the Epidemiological Studies Section) at this same facility. Operations in the plant began in 1931, but what were described as considerable improvements in equipment and safety precautions were made about 1960. Only closed systems were in use at the time of the report. It is assumed that these changes led to a significant decrease in the styrene concentration, but comparative data were not given. Concentrations of styrene as high as about 50 ppm were found around some equipment. However, workers were seldom present in these areas. In areas where workers were frequently present, styrene concentrations in excess of 1 ppm were seldom found and were always less than 10 ppm. Styrene concentrations were determined in 1975 and 1976 by gas chromatography, and the techniques used had a lower limit of detection of 0.01 ppm styrene.

Mandelic acid concentrations in urine of the styrene-exposed workers were determined by the gas chromatographic method of Engstrom and Rantanen [79], as described by Schaller et al. [80]. Concentrations of mandelic acid in urine were less than 50 mg/l in 61 of 67 styrene and polystyrene production workers, and greater than 100 mg/l in 3 of the remaining 6. The data were presented only in bar graph form, and the maximum value was not reported. However, as will be discussed in a later section (see Figure V-1, p. 141), mandelic acid concentrations of 200 mg/l correspond to 8-hour TWA exposures of about 10 ppm.

In the morbidity study at this plant [75] there were 84 workers who had been engaged in styrene production for 1-36 years, 93 workers who had been engaged in polystyrene production for 1-38 years, and 62 control subjects with similar ages. In 1975-1976, the numbers of days lost through sickness were no greater for styrene and polystyrene workers than for all workers at the factory, and accident rates were no greater than for all production workers. There were no significant findings from examination of medical records or from physical examinations that included chest roentgenograms and measurements of vital capacity. Laboratory tests included CBC, thrombocyte count, measurement of activities of serum glutamic-oxaloacetic transaminase (SGOT), gamma-glutamyltranspeptidase (GGTP) (also known as gamma-glutamyltransferase), lactic dehydrogenase, SGPT, and alkaline phosphatase, measurement of total bilirubin, albumin, erythrocyte sedimentation rate, thymol turbidity, and creatinine and urea concentrations. Although unusual values were occasionally found among the test results, there were no statistically significant differences in the frequencies of their occurrence between the exposed workers and the unexposed controls.

Studies of chromosomes from lymphocytes of workers exposed to styrene at this German plant were reported in 1978 by Fleig and Thiess [76] and Theiss and Fleig [77]. A reference group of 20 men from the same factory, but not exposed to styrene, was used for comparison with each group of workers studied. Five workers engaged in the production of styrene had a slightly lower frequency of aberrant cells than the reference group (1.6% vs. 2.1%). Twelve workers who had spent 19-39 years in the production of polystyrene also had a lower rate of aberrations than the reference group (1.9% vs. 2.1%).

There have been a number of reports [58,81,82,83,84,85,86,87] on studies of workers in one U.S. plant that manufactured styrene and polystyrene. Sixty-five personal charcoal tube samples for organic vapors were collected during surveys in 1973 by Maier et al. [84]. All but 10 of the styrene concentrations were less than 5 ppm, and all but one were less than 20 ppm. Six benzene samples were in the range of 10-50 ppm, two were between 5 and 10 ppm, and 43 were less than 1 ppm with 34 of those being below the limit of detection. The highest concentration of ethylbenzene was 4 ppm. Except for 3 of 65 toluene samples being 212-262 ppm, toluene was present at less than 10 ppm. Acetone was present in 8 samples at 3-10 ppm. There were traces of pentane (used as a blowing agent) in 15 samples. The highest concentrations of styrene, benzene, and toluene resulted from spills and leaks. Of 34 detector tube samples, one indicated a high benzene concentration (30-60 ppm) and one indicated a high toluene concentration (300-400 ppm) after a spill of a benzene-toluene solution in the benzene building; the benzene concentration determined by a detector tube sample in this building the next day was 15 ppm [84].

One of the five samples of respirable dust (7.6 mg/cu m) measured in the polystyrene screening area was above the OSHA limit of 5 mg/cu m. Tricalcium phosphate personal respirable dust samples taken in the

polystyrene screening area contained 8.3 and 4.5 mg/cu m, respectively. Coal dust concentrations in the power house were 1.2, 1.8, 5.0, and 11.9 mg/cu m. The highest dust concentration occurred when fly ash was loaded into a truck. The sample of cadmium sulfide dust collected from the breathing zone of a worker who weighed cadmium sulfide pigments was 0.023 mg/cu m [84].

When the workers in this factory were studied in 1975 [58,81,82,83,85,86,87], environmental measurements were not made. However, environmental samples collected in early 1976 by the company and reported by Wolff et al. [85] indicated that exposures of styrene polymerization workers were similar to those found in 1973 by Maier et al. [84], and that exposures to styrene during copolymer production and styrene purification may have increased.

Styrene was not detected by spectrophotofluorometry (lower detection limit of 2 ng/l) in the blood of 244 of the 364 workers; the highest concentration found was 90 ng/ml [86]. By comparison, Stewart et al. [69] found 910 ng styrene/ml of blood in test subjects exposed for 7 hours at 99 ppm styrene, and Astrand et al. [88] found 300 ng styrene/ml of blood in test subjects exposed to styrene for 30 minutes at 50 ppm.

Various hydrocarbons in fat samples taken by needle aspiration were determined by gas-liquid chromatography and gas-liquid chromatography/mass spectrophotometry [87]. Styrene concentrations of 0.1-1.2 µg/g of fat were found in 13 of 25 workers, all 13 whose last exposure to styrene was 3 days or less before the fat samples were taken. No styrene was found in fat samples taken from the remaining workers whose exposure to styrene was either low or had occurred more than 3 days before the fat sampling.

Urinary mandelic acid was determined by the gas chromatographic method of Buchet et al. [89]. Mandelic acid concentrations were below the limit of detection (10 mg/g of creatinine) in 341 of 477 urine samples [86]. The highest mandelic acid concentration was 140 mg/g of creatinine. By comparison, Philippe et al. [90], using the same method, found mandelic acid at about 250 mg/g of creatinine in urine collected at the end of the workshift from workers exposed at 7-26 ppm. Other investigators [91,92] using other gas chromatographic methods found that a mandelic acid concentration of 140 mg/g of creatinine was associated with TWA exposures of workers to styrene at 7.5-15 ppm. In summary, the mandelic acid, and blood and fat styrene data [85,86,87] indicated that TWA exposures to styrene were probably less than 10 ppm.

Toluene was detected in 16 of 25 workers, but in measurable amounts of 0.2-0.3 µg/g of fat in only 3. Benzene was detected in three workers, but not in measurable amounts. Ethylbenzene was found in fat samples from 21 of 25 workers at concentrations of 0.1-0.7 µg/g. Although the workers were never exposed to ethylbenzene at airborne concentrations greater than 4 ppm, ethylbenzene was found in 84% of the fat samples, and traces were found as long as 90 days after exposure. A gas-liquid chromatographic peak that had

a retention time identical to that of 1-phenylethanol, a possible metabolite of both styrene and ethylbenzene, was found in the analysis of fat from all seven polymerization workers. However, the presence of 1-phenylethanol was not confirmed by other methods [87].

According to Maier et al. [84], company policy required that white blood cell counts (WBC) and hemoglobin and hematocrit determinations be made every 6 months for each worker in areas where benzene exposure was possible. Reports from the previous year were examined, and on eight occasions abnormal results consistent with benzene poisoning were found. However, when the individuals were retested, either these results were not confirmed or a cause other than benzene exposure was found. Based on their evaluation of the available medical information, Maier et al. [84] concluded that there was no evidence of chronic benzene effects among the workers.

Other investigators [81,82] conducted clinical studies on 494 workers from this plant. Styrene exposures were classified as high or low on the basis of job information and environmental data obtained from the employer [85] and environmental data reported by Maier et al. [84]. Hemoglobin concentrations in 14% of the workers were below 14 g/100 ml of blood; 3% had a WBC below 4,800 [82]. The low values were randomly distributed with respect to duration and extent of exposure. Activities of serum alkaline phosphatase, SGPT, GGTP, and SGOT, and the concentrations of serum bilirubin were determined. Only GGTP activity demonstrated a significant relationship to styrene exposure with about 3% of the values greater than 45 international units in low exposure workers and 7% in high exposure workers.

Lilis et al. [81] and Lorimer et al. [82] also studied effects on the nervous system. Prenarcotic symptoms had been experienced by about 10% of the workers in the low styrene exposure group and 19% of those in the high exposure group. Prenarcotic symptoms were reported most frequently by workers exposed more than 7 years. Among 412 workers who had no history of diabetes, back injury, or significant alcohol consumption, distal hypoesthesia (decreased sensitivity to touch) of the lower extremities and hypoactive deep tendon reflexes were found more frequently as duration of exposure increased. Distal hypoesthesia of the lower extremities was found in 4.1% of those who had worked 0.1-7.0 years, in 5.4% of those who had worked 7-20 years, and in 8.5% of those who had worked more than 20 years. Lilis et al. [81] did not differentiate between high and low exposure groups and did not say whether an effect of the workers' ages was considered. Because duration of exposure probably correlated with age, the effect might have been age-related rather than exposure-related.

Radial nerve conduction velocities were studied in 80 of the workers, and peroneal nerve conduction in 73 workers; workers with a history of diabetes, back injury, or significant alcohol consumption were excluded. Radial nerve conduction velocities of less than 55 meters per second (m/s) were found in 15 workers, but there was no relation to the duration or intensity of exposure to styrene. Peroneal nerve conduction velocities were

less than 40 m/s in 12 of 63 workers with more than 7 years of exposure and in none of 10 workers with less than 7 years. The mean peroneal nerve conduction velocities decreased with duration of exposure, but the decreases were not statistically significant and were not related to the intensity of exposure. Lilis et al. [81] did not give data concerning normal nerve conduction velocities, although it appears that neither 55 m/s for the radial nerve nor 40 m/s for the peroneal nerve is an abnormally low value, at least without making adjustment for age. The mean age of those with slower nerve conduction velocities was greater than that of those with velocities described as normal, but the age difference was not statistically significant.

Kohn [58] reported the results of a screening ophthalmological examination of 345 of the styrene-exposed workers. Styrene exposures averaged approximately 5 ppm. No evidence of optic neuritis or retrobulbar neuritis was found. Several workers gave a history of having had styrene beads embedded in their corneas, and one worker complained of beads embedded in the eyelid after a valve had burst. Conjunctival irritation related to styrene exposure occurred in 22% of the workers. The irritation was noted commonly at styrene concentrations above 50 ppm.

In respiratory system studies of these workers by Lorimer et al. [82], it was found that 19% of the high exposure group had experienced wheezing or tightness of the chest, compared with 7% of those in the low exposure group. These symptoms occurred weekly or monthly in about 12% of the high exposure group compared with symptoms occurring in about 5% of the low exposure group. However, spirometric studies of airway effects did not suggest significant changes, nor was there any radiologic evidence of significant lung change observed.

In 1971, Ponomareva and Zlobina [93] reported on workers in a Russian factory engaged in the production of block and emulsion polystyrene and styrene-acrylonitrile (SAN). The investigators examined 236 workers; 120 were engaged in the production of block polystyrene, 56 in emulsion polystyrene production, and 60 in copolymer production. Eighty percent of the workers were women, and most workers were 30-49 years of age.

The 120 block polystyrene production workers were divided into three groups: (I) those involved with the polymerization of styrene, where concentrations of styrene were occasionally as high as 5 ppm; (II) workers involved with polystyrene film and filament production, where they were exposed to styrene only 25-50% of the time at concentrations below 1 ppm, but at temperatures of 30°to 40°C; and (III) auxiliary and technical workers who had short, intermittent exposures to styrene (concentrations were not specified) [93].

The 56 workers involved in the emulsion production of polystyrene were also divided into three groups. Because styrene concentrations were usually below 1 ppm but polystyrene dust concentrations of 8-12 mg/cu m were frequent in the drying and packaging rooms, the groupings were based on

concentrations of polystyrene dust. The groups were: (I) workers engaged in polymerization, sedimentation, and centrifugation; (II) drying and packaging workers; and (III) a group of miscellaneous workers who experienced only brief contact with styrene vapor and polystyrene dust. Workers in Group I (polymerization) were occasionally exposed to styrene concentrations above 1 ppm. For the other groups, styrene concentrations were generally less than 1 ppm [93].

The 60 workers engaged in SAN manufacture were exposed to styrene at concentrations below 1 ppm. In certain operations the concentration of acrylonitrile exceeded 0.2 ppm [93].

In each case within the individual production units, it was those workers in the groups engaged in the polymerization process, i.e., groups designated I, who were exposed at the highest styrene concentrations. No additional information was presented about exposures, such as sampling and analytical methods, frequency of sampling, number of samples taken, or the number of workers in each subgroup.

Upon examination of the workers who complained of frequent sore throats, Ponomareva and Zlobina [93] found that most workers had a history of sore throats before employment at the facility. However, the frequency of this complaint increased after employment. About 29% of the workers from Groups I and II of the block polystyrene production unit and 21% of the workers from Group I of the emulsion polystyrene unit had tonsillitis with a high fever 4-8 times a year.

Workers involved in block polystyrene production had a significantly higher incidence of upper respiratory tract complaints than those workers who had only intermittent contact with either styrene vapor or polystyrene dust. Those workers with only occasional exposure to styrene vapor and polystyrene dust had a frequency of respiratory complaints no different from that of the population of the adjacent town. However, the incidence of respiratory complaints among the residents of the adjacent town was not reported, nor was the time of year when the study was conducted [93].

In the workers engaged in block polystyrene production for more than 5 years, there was a high frequency of dry, pale mucosa in the nose, the pharynx, and occasionally the larynx, which the investigators [93] thought might make these workers more susceptible to respiratory infection. These mucosal changes were found in 78% of those workers who had been exposed to styrene at 5 ppm periodically during their workshift (Group I), and among those workers exposed at less than 1 ppm for 25-50% of their workshift for more than 5 years (Group II). Ponomareva and Zlobina [93] speculated that high temperatures (30°to 40°C) contributed to the effects observed in the Group II workers. In some cases the mucosa was covered with a viscous muco-purulent secretion, and nosebleeds were reported. Ponomareva and Zlobina [93] diagnosed chronic inflammation of the nasal mucosa with atrophy of the mucous membranes in about 68% and chronic tonsillitis in about 39% of these workers.

Dystrophic upper respiratory changes similar to those found in the block polystyrene workers were found in about 45% of the workers in Group II of the emulsion polystyrene unit workers. Workers in the emulsion polystyrene production unit were found to have the mucosa of their noses and throats covered with polystyrene dust. However, there were fewer complaints in the emulsion polystyrene department, and fewer diagnoses of upper respiratory disease. The exception were workers of Group I where styrene concentrations were occasionally above 1 ppm [93].

High concentrations of polystyrene dust and elevated environmental temperatures may have been responsible for some of the health effects noted in the workers. In addition, the absence of any description of how the investigators assessed the working environment makes impossible an evaluation of this report in terms of the effect of styrene at various concentrations. The investigators [93] concluded that the workers who had the lowest exposure to styrene, heat, and polystyrene dust had a lower incidence of upper respiratory complaints.

In 1963, Zlobina [94] reported a study of 40 workers selected at random from two departments of a Russian polystyrene production facility. Styrene was the only contaminant present in significant amounts. In the block polystyrene production department, the styrene concentration (measured in the winter and summer of 1962) ranged from 0.5-2 ppm. The second department, emulsion polystyrene production, had styrene concentrations of 1-2 ppm; during the cleaning of process equipment, styrene concentrations frequently exceeded 12 ppm.

The morbidity rates, based on illnesses with absence from work, showed an increase in conditions ascribed to the liver and bile duct among workers in the two departments responsible for polystyrene production, compared with the rate for the entire factory (see Table IV-5). The lack of the diagnostic criteria used for determining liver and bile duct morbidity or information concerning the workers' personal habits, such as alcohol consumption, makes it difficult to interpret these results.

TABLE IV-5

MORBIDITY OF POLYSTYRENE PRODUCTION WORKERS
COMPARED WITH REST OF FACTORY

	Morbidity* (per 100 Workers) 1959	1960	1961
Total factory	1.7	2.7	2.1
Block polystyrene production	6.7	9.7	7.5
Emulsion polystyrene production	2.9	6.4	5.5

*Based on indicators of liver and bile duct disease
Taken from Zlobina [94]

The average blood pressure of twenty workers in the block polystyrene department was found to drop continually during the workweek from 105/65.7 to 93/57.5 mm Hg, while workers from the emulsion polystyrene production department exhibited a blood pressure decrease from 104.4/64.4 mm Hg to 92.8/57.2 mm Hg. Such changes were not seen in an undefined comparison group of workers similarly observed. When the workers returned to work after a day off, their blood pressures had returned to the initial values. However, the initial values were not reported, and it is not known why the systolic and diastolic pressures were so low. In addition, Zlobina [94] reported that 38% of the 40 workers had frequent headaches and subcostal (below a rib) pain on the right side, 44% expressed symptoms of irritation of the mucous membranes of the upper respiratory tract, and about 20% had pains in the epigastric and heart regions.

In 1975, Zlobina et al. [95] reported the results of a study of 110 women workers at a Russian polystyrene plant where the concentrations of styrene were about 1 ppm. Other volatile components were present in only trace amounts. The sampling and analytical methods used were not given. The investigation included a questionnaire, in-depth gynecological examinations, and inspection of individual clinic cards and birth histories. The control group was composed of 231 female workers in the plant management and children's group who had no previous industrial contact with chemical substances. To ascertain group comparability, the social-domestic factor was investigated by means of a questionnaire which included education, income, length of holidays, number of children, use of pre-school nurseries, time spent on housework, and time spent traveling to work. There were no significant differences between the groups of workers and controls on the criteria selected. Both groups were divided according to work experience and age.

An analysis of extragenital disease revealed a high incidence of gastrointestinal diseases (not specified) in the workers as compared to the control group. Gynecological examinations were given and there were no significant differences with respect to inflammatory diseases of the cervix or vagina, infertility, benign tumors, or deviation of internal sex organs. The styrene workers' incidence of inflammatory diseases of the uterus and appendages (12.7% vs. 4.7%) and the incidence of disorders in menstrual function (29.1% vs. 9.1%) significantly differed from the controls. Ten women complaining of disorders in menstrual function were examined by the colpocytological method which showed moderate estrogen insufficiency in five and pronounced insufficiency in two of them. No disorders in estrogen saturation were found in the other three women examined, although a hypermenstrual syndrome was observed in one of them [95].

The reproductive function of 67 female workers and 70 women in the control group was evaluated. There were no significant differences between the groups in the number of pregnancies, births, or induced or spontaneous abortions. Toxemias were more frequent in the first half of pregnancy in the experimental group (49.2% vs. 18.5%). Of the toxemias, nephropathy was observed significantly more often in the second half of pregnancy in the experimental group (10.4% vs. 1.4%).

In 1978, Veretinskaya et al. [96] examined hepatic function in 370 workers in three Russian polystyrene production plants. Industrial hygiene surveys at one of these plants 3 years after work began there showed that styrene concentrations varied considerably, but on the average did not exceed 1 ppm. Other workroom air contaminants were isopentane, benzaldehyde, benzene peroxide, and formaldehyde; all were within recommended concentration limits. The second plant had airborne concentrations of styrene stated as "not significantly exceeding 1 ppm." There were 20 workers examined from a third plant. This plant, since closed, had work conditions stated to be "unfavorable."

In the first plant, 22% of the workers had elevated bilirubin, caused in 50% of the cases by the free bilirubin fraction, in 30% by the conjugated fraction, and in 20% by an increase in both fractions. In a few cases (8%), beta-lipoprotein concentrations in blood serum were elevated. Studies of SGPT activities were unrevealing. Workers known to have hepatobiliary disease or to be alcoholic were excluded from testing. In the second plant, there were increases in beta-lipoprotein and SGPT, but not in bilirubin. However, while these changes were significant in terms of comparison with the control group, they did not exceed the physiological limits of variability [96].

In one shop in the third plant, 29% of the workers had bilirubin levels above normal limits and there was a slight and apparently insignificant number of workers with elevated levels of beta-lipoproteins. Enlarged livers were found in 6 workers, and pain in the area of the gall bladder was noted in 20% of those examined. In another shop in this plant, styrene concentrations had at one time exceeded the maximum permissible

concentration (MPC) of 1 ppm several hundredfold, but more recently styrene concentrations had been reduced in most places to less than the MPC. In this shop, there were elevated serum bilirubin concentrations in 20% of the examinees, elevated beta-lipoproteins in an unstated number (but not beyond physiologic limits), and an increase in SGPT in 13%. Leukopenia, stated to be a characteristic effect of styrene exposure, was found in 30% of these workers and in 18% of the controls; almost identical incidences of moderate leukopenia had been found in workers in the first plant and in their controls.

There were various effects attributed to functional changes in the liver. These changes did not reach pathological proportions in the majority of the cases; however, the changes suggested to Veretinskaya et al. [96] definite metabolic disturbances in the liver cells. The relationship of styrene to these effects is difficult to evaluate in this study because of the similarity in responses in areas with airborne styrene exposures believed almost always to be below the MPC (1 ppm) and in other areas with styrene exposures exceeding the MPC several hundredfold.

(b) Plastics Applications (Mainly Production of RP/C)

A clinical study of two factories in Czechoslovakia where reinforced plastics were made was reported in 1960 by Bardodej et al. [97]. In both facilities the styrene polyester resin was applied to wooden molds by hand; in one factory, however, the resin was sometimes sprayed on. Regular medical examinations (not specified) were given to the workers for a 3-year period.

Apparently, area rather than breathing zone air samples for the determination of styrene were collected on numerous occasions during an entire workshift in various work areas and analyzed by UV spectrophotometry [98], spectrophotometry after nitration [98], and polarography after formation of alpha-nitroso-beta-nitroethylbenzene [99]. The method of collection was not specified. The styrene concentrations found averaged about 50 ppm.

The investigators [97] measured benzoic acid and phenol in urine collected at the end of the workshifts from 58 workers and 23 controls. Elevated concentrations of substances measured as benzoic acid were demonstrated (800 vs. 400 mg/l). In a later publication, Bardodej and Bardodejova [100] stated that, with the analysis method used, both hippuric acid and mandelic acid were oxidized to benzoic acid. No increases in urinary phenols were found. There were no major medical findings in the RP/C workers except for four cases of dermatitis that were attributed to other agents. All but five of the workers reported developing increased fatigue and drowsiness toward the end of the workshift.

In 1972, Dzyuba [101] published the results of an investigation of a Russian reinforced plastics plant. Three groups of workers were evaluated over a 3-year period for neurological dysfunctions. Group I consisted of 70