III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Xylene, $C_6H_4(CH_3)_2$, (formula weight 106.16), also called dimethylbenzene or xylol, exists in 3 isomeric forms: 1,2 (ortho); 1,3 (meta); and 1,4 (para). The more important physical properties of these isomers are presented in Table X-1. [1]

Commercial xylene is produced both from petroleum and from coal tar. A typical petroleum product contains approximately 20% o-xylene, 44% m-xylene, 20% p-xylene, and 15% ethylbenzene. Xylene from coal tar generally consists of 10-15% ortho-, 45-70% meta-, about 23% para-, and 6-10% ethylbenzene. Commercial xylenes may also contain small amounts of toluene, trimethylbenzene, phenol, thiophene, pyridine, and nonaromatic hydrocarbons. [2,3] The possibility that commercial xylene may also contain benzene should not be ignored.

Total US xylene production in 1971 was 612,325,000 gallons, an increase of 13.9% over 1970. [4] Of this total, 609,419,000 gallons were from petroleum. Production from coke ovens has decreased rapidly in recent years (35.4% from 1970-1971) and totaled only 2,906,000 gallons in 1971. The US Tariff Commission report [4] did not include data reported by tar distillers because publication would have disclosed operations of individual companies.

Xylene can be easily chlorinated, sulfonated, or nitrated. [5] It is used as a solvent for some gums and resins, castor and linseed oils, rubber, and dibenzyl cellulose. [6] It is a constituent of paint, lacquers and varnishes, [5,6] inks, dyes, adhesives and cements, and cleaning fluids

[7]; it is also an additive in gasoline. [5-7] In the chemical industry it is used as a starting material for xylidines [5] and in the production of phthalic and terephthalic acids. [2,6] Other uses are in the manufacture of quartz crystal oscillators, hydrogen peroxide, perfumes, and insect repellents, [8] in the leather industry, in coating and impregnation of fabric and paper, and as a carrier in the production of epoxy resins. [2]

NIOSH estimates that approximately 140,000 workers are potentially exposed to xylene in the United States.

Historical Reports

Many early reports of xylene exposures involved exposure not to pure xylene but to mixed aromatic hydrocarbons. For example, in 1929 Stocke [9] reported that, although the term "xylene" was used in the occupational medical literature of the time, he found that the solvent called "xylene" in the intaglio printing industry might be pure xylene, pure toluene, a mixture of these, or a mixture containing benzene and paraffin hydrocarbons. Stocke examined approximately 40 workers exposed to these mixed solvents and observed symptoms of overexposure: headaches, nausea, feelings of drunkenness, and reduced alcohol tolerance. In 10 of these, selected because they were the most severely affected, there was no anemia, but Stocke did report a relative lymphocytosis. To explain the reduced alcohol tolerance, he hypothesized that alcohol facilitated the diffusion of xylene (and toluene) in the body, and in particular expedited their entry into the lipids of the central nervous system.

In 1931 Nelken [10] examined 399 intaglio printers and 276 other printers not exposed to xylene. Relative lymphocytosis was observed in 29%

of the intaglio printers and in 23.7% of the nonintaglio printers. An apparently significant difference in the incidence of leukopenia was observed, with 18.55% of the intaglio printers having a leukocyte count below 5,800, 15.03% below 5,500, and 9.29% below 5,000 compared to 13.64%, 8.18%, and 3.63%, respectively, among the nonintaglio printers. Nelken considered this evidence of poisoning caused by "xylene (or toluene and benzene)."

In the same year Rosenthal-Deussen [11] described the experience of 20 workers who were exposed to unknown concentrations of vapor of a commercial solvent, consisting of 35% benzene and its homologs, principally xylene. The major constituent(s) was not identified. Workers were exposed for 1-6 days while painting the inside of a tank that was not ventilated properly. Of the 20 workers exposed, 15 were reported as manifesting urinary abnormalities, among other signs and symptoms. There were 2 cases of anuria, 1 of which was fatal. In 13 cases the urine was described as "coffee-brown" in color. These included the 2 cases of anuria. In 2 other cases the urine was described as being red. With the limited environmental data available, it is impossible to say what role, if any, xylene may have played in the etiology of these disorders.

Hirsch [12] in 1932 investigated conditions in a print shop after 2 of its workers died of valvular heart disease. Suspecting benzene poisoning because 1 of the deceased workers was anemic and the other had aplastic anemia, Hirsch examined 34 workers. Despite the fact that some thinners contained up to 29% benzene and toluene, Hirsch concluded that xylene was responsible for the anemia observed because xylene predominated (up to 87%) in the solvents and thinners used. Overall, he observed a

moderate degree of anemia and relative lymphocytosis, but the latter was thought not to be necessarily occupationally related. Increases in urinary urobilin and urobilinogen were seen in 18 of 34 workers, with a very marked increase in 3 of them. Such an increase (ie, in the last 3 cases) may be regarded as an indication of liver damage. A majority of the workers were hypotensive. Radiography revealed pathological alterations of cardiac outline and size in 50% of the subjects, with dilatation of the aorta present in the majority of the abnormals. Hirsch attributed these phenomena to the "vasodilatory effect of xylene." Nineteen of the 34 subjects were also anemic with hemoglobin levels of below 95% Autenreith in 5 subjects, and a red cell count below 5 million/cu mm in 15 subjects. The observed hypotension might have been partly secondary to this anemia. Two years later in 1934, Verhoogen [13] also reported a fatal case of aplastic anemia and extreme leukopenia in a printer. Although he gave no details as to exposure, Verhoogen stated that the anemia was due to xylene exposure in a print shop. De Oliveira [14] in 1936 described a similar fatality due to aplastic anemia, but like Veerhoogen, [13] he failed to give any details concerning exposure except to state that the individual was exposed to xylene in the printing industry.

In 1935 Glibert [15] published 6 case reports involving pseudopernicious anemia and aplastic anemia which he ascribed to xylene exposure in the printing industry. The very imprecise meaning of the term "xylene" at that time was demonstrated by Glibert when he stated that the "commercial xylenes" used in the printing industry showed a variable composition, with "yellow or light xylene" being pure benzene with no trace of xylene, "green or dark xylene" being pure xylene, and some other xylenes actually being

toluene with 15% benzene. Obviously, the term xylene was applied to a variety of solvents, and even what was considered to be pure xylene must have been contaminated if it was green or dark in color, since pure xylene is colorless.

A detailed study of occupational disease associated with exposure to solvents in the printing industry was conducted in this country by Greenburg et al [16] in 1939. In this report toxicity was attributed to benzene, but the report provides an insight into the mixed nature of solvents in use at that time. In this study, benzene in the ink solvents and thinners ranged from 10-80% and other volatile solvents present included toluene, xylene, methylethyl ketone, petroleum naphtha, ethyl, butyl, and amyl acetate, and butyl and amyl alcohol. Thus, one must question the accuracy of those papers which reported "xylene" exposure in the printing industry through the 1940's. In most cases the thinners used probably consisted of a mixture of volatile solvents. Xylene probably was one of these, but benzene was almost certainly present as well.

Effects on Humans

In 1943 Nelson et al [17] investigated sensory response to 16 industrial solvent vapors by exposing "an average number of ten persons, of mixed sexes," to metered concentrations of solvent vapors for a period of 3-5 minutes. Based on the subjective responses of test subjects, xylene at 200 ppm was reported to cause irritation of the eyes, nose, and throat in a majority of those exposed. A majority also estimated that 100 ppm would be a satisfactory 8-hour exposure level. The authors did not report the lowest concentration which was irritating to any subject, or which any

subject estimated to be satisfactory for 8 hours. In comparison, toluene caused irritation of the eyes and throat in the majority at 300 ppm and most estimated 200 ppm as satisfactory for an 8-hour exposure.

In 1966 May [18] estimated the odor thresholds of 37 organic solvents, one of which was xylene. After measured volumes of solvent were vaporized in an evacuated 10-liter bottle, air was introduced and volunteers smelled the air at the mouth of the bottle. For xylene the odor threshold was reported as 20 ppm, with the odor of 40 ppm reported as distinctly noticeable. The odor threshold for toluene was reported as 40 ppm, with 70 ppm distinctly noticeable.

Carpenter et al [19] exposed 6 human volunteers for 10 seconds to xylene in the following sequence: 60.0, 0.0, 6.0, 0.6, 0.6, 6.0, 60.0, and 0.0 mg/cu m (these concentrations were estimated from the metered concentrations, based on previous analytical measurement data; 0.0 represents controls). This resulted in a total of 12 exposures at each level. Xylene was detected 12 times at 60.0 mg/cu m (about 14 ppm) and 8 times at 6.0 mg/cu m (1.4 ppm), but was not detected at the 2 lower concentrations. Based on these results, the most probable odor threshold was estimated to be 4.5 mg/cu m, or about 1.0 ppm.

Volunteers were also exposed [19] to measured xylene concentrations of 460, 1,000, and 2,000 mg/cu m (about 105, 230, and 460 ppm). The 15-minute exposures were limited to 1 a day to prevent buildup of symptoms. The odor of xylene was detected at each concentration by all subjects, and olfactory fatigue was reported by 3 subjects at each concentration but all reported full recovery within 10 minutes after the exposure ended. These and other effects are summarized in Table X-2. According to Carpenter et

al, [19] all of these effects were minor. The "tears" were described as increased wetness of the eyes rather than actual tearing, the dizziness was characterized as slight lightheadedness without loss of equilibrium or coordination, and the subject reporting throat irritation was not positive of the sensation. The authors concluded that 1.0 mg/liter (230 ppm) should not be objectionable to most people.

Dutkiewicz and Tyras [20] described experiments with 10 volunteers in which a known quantity of xylene was kept in contact with the skin for a measured length of time, and the residual xylene was then calculated. In this way the absorption of liquid xylene through the skin was estimated to be at the rate of 4.5-9.6 mg/sq cm/hr.

In 1965 Gusev [21] studied the effects on human volunteers of low concentrations of xylene (also benzene and toluene). In 18 subjects, the odor threshold increased in the sequence xylene, toluene, benzene. For xylene, the minimal perceptible concentration was 0.6-1.9 mg/cu m (about 0.14-0.44 ppm), and the maximal imperceptible concentration was 0.4-1.4 mg/cu m (about 0.09-0.32 ppm). To investigate the effects of each solvent on the electrical activity of the cerebral cortex, Gusev exposed 4 subjects at concentrations of solvent that were imperceptible by odor. The 4 subjects chosen were those with the lowest olfactory threshold for each solvent. Benzene and toluene were found to increase the electric potentials of the cerebral cortex, while xylene caused a marked inhibition of electrical activity. The threshold for these cortical effects by xylene was 0.32 mg/cu m (0.07 ppm), and 0.21 mg/cu m (0.05 ppm) was subliminal. Therefore 0.2 mg/cu m was recommended by this author as the "maximum permissible one-time" atmospheric concentration. Further investigations

are necessary to validate these findings.

While painting the inside of a tower with a paint containing 80% xylene and 20% methylglycolacetate, 8 workmen experienced headache, vertigo, gastric discomfort, dryness of the throat, and feelings of slight drunkenness. [22] Forced ventilation could not be used, so the painters were instructed to go outside for 10 minutes every half-hour. While cycling home from work, an 18-year-old who had been "working with paints" for 2 months suddenly felt weak and dizzy. After reaching home he had an epileptiform seizure lasting about 20 minutes. He was sent to the hospital where he suffered another seizure of much shorter duration. When examined, all reflexes were normal as was an electroencephalogram. Because there had been an instance of possibly epileptic aura in the patient at age 14, Goldie [22] suggested that organic solvents might provoke seizures in patients with latent epilepsy. No follow-up information on this patient was given.

Glass [23] described the symptoms of a man who was intermittently exposed to solvent vapors over a period of 2 months. He was examined after an acute episode of vomiting and giddiness at the end of a day's work. His appetite was poor for the following week. The solvent was 75% xylene with 25% ethylbenzene, methylethylbenzenes, and trimethylbenzenes. Concentrations of xylene in air were measured and found to be as high as 270-350 ppm at head level. However, the worker probably was intermittently exposed to much higher concentrations for 12- to 15-minute periods while he was bending over into the paint vessels he cleaned with a solvent-soaked rag.

Morley et al [24] in 1970 reported an incident in which 3 painters in a shipbuilding yard were exposed to xylene vapor in a confined space. The

concentration of xylene was later estimated to have been 10,000 ppm. After an unknown time interval, 2 of the 3 men became unconscious and therefore remained in the xylene atmosphere until they were discovered 18.5 hours later. The third man had left the tank for a period of 3 hours and then returned and also became unconscious. One of the men died shortly after discovery. At autopsy, apart from severe lung congestion with focal intra-alveolar hemorrhage and acute pulmonary edema, the victim was found to have petechial hemorrhages in the brain and evidence of anoxic neuronal damage. The other 2 men were mentally confused for some time after recovering consciousness, and both had retrograde amnesia for events preceding their loss of consciousness. There was evidence of severe impairment of renal function (a temporary severe rise in blood urea, and fall in endogenous creatinine clearance) in 1 case, but the kidneys had largely recovered by the 15th day after exposure. Both nonfatal cases showed what was interpreted as evidence of hepatic impairment (elevation of serum transaminase levels after 48 hours in 1 case to over 50 and in the other to over 100 international units, but enzyme levels then fell to within normal limits).

In 1957 Ghislandi and Fabiani [25] reported an incident of accidental ingestion of a "small amount" of liquid paint thinner composed of 90% xylene and toluene, with xylene predominating. The impurities were several acetates, but these were not identified. The day after ingestion, the urine had a specific gravity of 1.055, was positive to Fehling's test for dextrose in the urine, and contained urobilinogen. There was serological evidence (abnormal sulfobromphthalein retention) of a toxic hepatitis, but total recovery took place within 20 days. In the opinion of these authors, it could not be assumed that similar liver damage would necessarily arise

from the inhalation of xylene vapor, but they emphasized the need for liver function testing in cases of ingestion.

Joyner and Pegues [26] in 1961 described an outbreak of upper respiratory irritation with evidence of "a mild nephrotoxic action" in all of 6 men who became ill (out of a total of 8 exposed) while demolishing some epoxy-resin concrete. Substantial amounts of xylene were detected by infrared and mass spectrometric analyses of decomposition products of the concrete material and the odor of xylene was present during the demolition process. The urinary findings indicative of kidney damage were albuminuria, microhematuria, and pyuria in all 6 cases.

In 1956 Schmid [27] reviewed earlier reports of corneal disease in workers exposed to volatile solvents and discussed his own observations in furniture polishers. He reported that workers suffered eye irritation and photophobia primarily in the morning, but that these symptoms abated after a few hours of work. Slit lamp examination revealed minute vacuoles in the corneal epithelium, but the cornea healed completely in a few days with no scars remaining, even in workers who were frequently affected. Whenever the lesion occurred, workers had been exposed to a number of volatile solvents, including xylene, toluene, butyl acetate, butanol, ethylene alcohol, and ethylene acetate at unknown concentrations.

When Schmid [27] exposed 6 humans to xylene, toluene, methyl acetate, ethylene acetate, and butyl acetate evaporating from saturated filter paper, toluene was the most irritating to the eyes and xylene was the least irritating. Apparently, the exposures were not sufficient to produce corneal vacuolization in any of the humans.

Matthaus [28] described a furniture polisher who complained of burning, sensation of pressure, sensation of a foreign body, and dazzling in both eyes, with slight limitation of vision. On examination both eyes showed marked conjunctival injection, but the corneas were clear and sparkling. However, under high magnification a large number of minute, dewdrop-like vacuoles were seen in the deeper layers of the corneal epithelium opposite the palpebral fissure. The little vesicles were particularly concentrated in the pupillary and subcentral zones. Matthaus was amazed that the patient had only slight visual disturbance. The subjective eye complaints had developed within 2-3 days from the time he started working with a new lacquer solvent. Seven fellow workers were also involved but had only slight subjective eye problems. However, on ophthalmic examination, 4 of these had similar alterations in their corneas and 3 had isolated vacuole formation, despite mild subjective complaints. The cases were followed up and the corneal changes fully recovered leaving no scars after removal from exposure for an average of 8-11 days. Gas chromatographic analysis of the lacquer solvent showed it to be "practically pure" xylene. Contamination by toluene and benzene "was so minor that it could be ignored." Whether this effect is totally reversible on intermittent exposure or whether it may eventually lead to permanent damage is not known. Unfortunately no environmental data were offered as to the concentration of the xylene vapor to which these workers were exposed.

A 1957 Polish paper [29] reported troubles of heart function and electrocardiographic changes indicative of cardiac muscle damage in a 17-year-old worker who was overcome by xylene vapor. He had been exposed for an unspecified time at an unstated concentration and was unconscious for 3

hours. According to the authors, this complication was "characteristic" of the susceptibility of juveniles to the action of aromatic hydrocarbons, but they did not document this characteristic susceptibility.

In 1965 Michon [30] reported a survey of the menstrual history of 500 Polish women, aged 20-40 years, working in a shoe factory in an atmosphere contaminated by benzene, toluene, and xylene at unstated concentrations. The aromatic hydrocarbon concentrations were said to be within the Polish permissible limits (31 ppm for benzene, 67 ppm for toluene, and 58 ppm for xylene). Compared with 100 women not working in shoe production, the subjects exposed to the aromatic hydrocarbons showed some increased intensity and duration of the menstrual flow, but no alteration in menstrual rhythm. It is impossible to say which of the contaminants in the air was responsible for this influence upon menstruation, or to evaluate the significance of such menstrual disturbance.

Kucera [31] investigated the incidence of spinal malformations (sacrococcygeal agenesis, or caudal regression syndrome), in all human malformations recorded in Czechoslovakia from 1959-1966. In over 1,500,000 live and stillborn infants, more than 20,000 were malformed. Skeletal malformations included the caudal regression syndrome in 9 of these infants. Five of the 9 mothers involved had been exposed to fat solvents (xylene in 1 case) during their pregnancy. After observing teratogenic effects among chick embryos exposed to xylene vapors (discussed in Animal Toxicity), Kucera concluded that fat solvents, including xylene, may have a teratogenic effect causing caudal agenesis in man. However, his data are not adequate to support such a contention.

In 1956 Giammarinaro [32] reported a fatal case of what was described as osteosclerotic anemia with aplastic myelosis in a 46-year-old typographer. Giammarinaro gave no details of the patient's exposure except to state that he "worked since youth as a printer and had constant contacts with xylene." Without knowing the purity of the xylene or the concentration to which the man was exposed, the author considered both the bone condition and the aplastic anemia to be independent effects resulting from xylene intoxication. However, as suggested by Browning [2] in her review of this report, an alternate and reasonable explanation of the case is that the anemia was secondary to idiopathic osteosclerosis.

Lachnit and Reimer [33] described 2 fatal cases of panmyelopathy. One was in a 20-year-old girl who had been employed 1 year in a textile factory where she used an adhesive containing 27% toluene and xylene with some esters and benzene. During pregnancy she developed severe anemia, leukopenia, and thrombocytopenia. The bone marrow was generally aplastic. She died 6 weeks after the birth of a healthy child. After her death, air samples collected in the workplace revealed 8 ppm benzene and 11.1 ppm toluene, but these apparently represented an improvement over conditions prevailing during the woman's employment. No xylene concentrations were reported. In a second case, a man who had worked as a printer for 30 years was possibly acutely overexposed when a fire burned 40 liters of xylene. His health deteriorated thereafter and he died from aplastic anemia 1 year later. In an examination approximately 8 years before his death, the blood picture was essentially normal, but because his printing career had begun in 1922 there no doubt was a history of benzene exposure.

Epidemiologic Studies

Lob [34] in 1952 published a study of 19 photogravure workers, including 2 women, who had been exposed to ink-diluent vapors for periods ranging from several months to 21 years. In the 4 cases selected as being clearly pathological, the workers had been exposed for 7, 9 (a woman with intermittent exposure), 18, and 20 years. No further correlation was made between the observed abnormalities and either the degree or length of exposure. Overall results included hemoglobin levels of 70-85% in 11 subjects, including 1 of the women. The total white cell count was reported to be below 5,000/cu mm in 11 cases, below 4,000 in 1 case, and below 3,000 in 2 cases; whether this refers to a total of 11 or 14 cases is not clear. Granulocytes were below 3,000/cu mm in 9 cases, below 2,000 in 4 cases, and below 1,500 in 2 cases; whether this refers to 9 or 15 cases is unclear. Bone marrow examinations were also performed and mild general hypoplasia was found in 2 cases, severe general hypoplasia in 2 cases, and aplasia in 2 cases. In the erythropoietic series there was evidence of some hyperplasia in 7 cases and of hypoplasia in 1 case, with inhibition of maturation in 14 cases. In 15 cases the myeloid series showed inhibition of maturation. These results are suggestive of mild myelotoxicity, but once more the nature of the exposure is suspect. The ink solvent in use was described as a mixture of toluene and xylene with "no more than a minimal trace of benzene." The author stated that benzene was not used in that print shop in "appreciable quantity" except for 1 month, 5 years before this paper was published. Because of the nature of photogravure work and the previous experience in printing normally required, prior exposure to solvents had undoubtedly occurred and it seems reasonable to

suggest that there had been benzene exposure.

Sukhanova et al [35] studied 45 young to middle-aged men who manufactured xylene from gasoline. Employment ranged from 6 months to 5 years. Xylene vapor in the work atmosphere was considered to present the chief hazard, although other hydrocarbons such as gasoline were also present. The xylene concentrations ranged from 1.5-4 times the MAC in 35-40% of the samples taken, and the remainder of the air samples were below the MAC. The MAC for xylene in the USSR at that time was 50 mg/cu m (about 10 ppm). [36] Therefore, the air levels were below 50 mg/cu m in 60-65% of the samples but ranged as high as 200 mg/cu m (approximately 45 ppm). On being questioned, "approximately one-third" of the workers complained of headaches, irritability, insomnia, tachycardia, and dyspepsia. In 9 workers (20%) nervous system alterations of the type of "neurasthenic or asthenoautonomic syndromes" were established, and "autonomic-vascular dysfunction" was observed in 6 (13%). There were no other significant symptoms, and these potentially psychosomatic clinical findings were not compared with the incidence in a control population. The amount of phenols excreted in the urine was higher than normal in all cases. There were no changes in the erythrocyte, reticulocyte, or thrombocyte counts or in hemoglobin. Both the glycogen and peroxidase contents of neutrophils were found to be decreased in comparison with controls, and the decrease became more pronounced with increased duration of exposure. The authors inferred from these cytochemical changes a disturbance of the functional capacity of the leukocytes and predicted an eventual disturbance of immunologic processes.

Animal Toxicity

Chassevant and Garnier [37] observed in 1903 that toluene, ethylbenzene, and benzene, in the order of decreasing toxicity, were more toxic than xylene when administered in one intraperitoneal dose to guinea pigs. The toxic (probably meaning lethal) doses of the xylene isomers were 1.20 g/kg for p-xylene, 1.43 g/kg for m-xylene, and 1.98 g/kg for o-xylene. The toxic doses for toluene, ethylbenzene, and benzene were 0.44, 0.57, and 0.66 g/kg, respectively.

Batchelor [38] injected rats intraperitoneally and reported lethal doses of 2.0-2.5 cc/kg for xylene, 1.75-2.0 cc/kg for toluene, and 1.5-1.75 cc/kg for benzene. Xylene and toluene at doses up to 0.75 cc/kg produced no signs except apathy, but benzene at doses as low as 0.25 cc/kg produced tremor and muscular twitchings. None of these solvents had an appreciable effect on the blood counts in animals that survived the acute toxic effects.

In 1928 Smyth and Smyth [39] exposed "at least 3" guinea pigs to m-xylene vapor, initially at 450 ppm. One animal died the first day and the others were prostrate, so the exposure concentration was reduced to 300 ppm for the remainder of a total of 64 exposures. The first 2 weeks, exposures were made daily. Thereafter, animals were exposed for 4 hours a day, 6 days a week. There was "not much evidence of definite harm," although at necropsy slight degeneration of the liver and inflammation of the lungs were noted. The experiment was repeated later at 300 ppm for 58 exposures, again with few effects. Guinea pigs also were exposed to toluene and suffered no serious effects after 35 exposures at 1,000 ppm, suggesting that for this species xylene was the more toxic solvent.

Lazarew [40] reported lethal concentrations for white mice of 30 mg/liter (6,900 ppm) for o-xylene, 50 mg/liter (11,500 ppm) for m-xylene, and 15-35 mg/liter (3,450-8,050 ppm) for p-xylene. The lethal concentration of toluene was 30-35 mg/liter (8,010-9,345 ppm). These data were incorrectly cited by Browning [2] and in a Report of the International Labour Office, [41] probably because of transposition of figures from Lazarew's table. Narcotic effects were noted [40] at concentrations of 15-20 mg/liter (3,450-4,600 ppm) for o-, 10-15 mg/liter (2,300-3,450 ppm) for m-, and 10 mg/liter (2,300 ppm) for p-xylene. Exposure to m-xylene at a concentration of 15 mg/liter (3,450 ppm) resulted in the abolition of (undescribed) reflexes in the mice.

Inhalation experiments with rats and mice were described by Cameron et al. [42] Rats and mice in groups of 10 were exposed at various concentrations of toluene and to each xylene isomer. Mice appeared to be more sensitive than rats, with some mice dying after 24-hour exposures at concentrations of 2,010 ppm of m-xylene or 3,062 ppm of o-xylene. Mice survived 24-hour exposures at 4,912 ppm of p-xylene and at 6,100 ppm of toluene.

By subcutaneous injection, [42] the lethal dose in rats and mice was 5-10 cc/kg of toluene, p- or m-xylene, while the lethal dose of o-xylene was about half as large. The lethal dose for each was about half as much when injected intraperitoneally, but the relative toxicities remained the same. Although the number of animals used was not given, the authors concluded that "no definite effect" was produced when rabbits received 1-ml subcutaneous injections of o-, m-, or p-xylene on 3 consecutive days. All variations observed were considered well within the limits of normality.

Wolf et al [43] found that xylene had greater acute oral toxicity to rats than either toluene or benzene. The LD50 for xylene was 4.3 g/kg while the LD50s for toluene and benzene were 7.0 and 5.6 g/kg, respectively. Xylene and benzene caused more necrosis and were more irritating to the skin of rabbits than toluene. As indicated by the appearance, body weight, and behavior of the rabbits, these solvents apparently were not absorbed through the skin in acutely toxic amounts. Two drops of xylene instilled into rabbits' eyes produced slight conjunctival irritation with very slight and transient corneal injury, but Wolf et al [43] gave few details of the changes observed in the eyes of the rabbits.

Temporary corneal effects were also noted by Schmid, [27] who described the formation of vacuoles in the corneas of cats exposed to xylene vapor. The vacuoles reportedly disappeared within a day when exposure to xylene was stopped. The vacuoles were similar to those reported by Schmid [27] and Matthaus [28] in the eyes of furniture polishers exposed to xylene.

In a more recent study [CP Carpenter, DL Geary, written communication, April 1974] corneal vacuolization was not observed in the eyes of adult male New Zealand rabbits exposed to a mixture of xylene isomers. Xylene was instilled in the right eye of a rabbit once daily for 2 days and then 3 times daily on 3 days. Although the lids were swollen and partially denuded, the cornea appeared normal at all times on fluorescein staining and on examination by hand slit lamp and ophthalmoscope. To examine the possibility that a metabolic product might cause vacuolization, 2 rabbits were given 8 ml/kg per os and both died within 3 days. When eyes were examined with the hand slit lamp and ophthalmoscope, there was no evidence

of vacuolization prior to or following death. One rabbit was exposed at a metered concentration of 60 mg/liter (13,800 ppm) for 3 hours (the actual concentration probably was 7,000-8,000 ppm). The rabbit was prostrate after 30 minutes and the left eyelid apparently was held open against the side of the exposure chamber. Consequently, the right eye was normal but the left eye appeared rough and dry. The entire left cornea stained with fluorescein and on the following day appeared dull to the unaided eye. However, both corneas were normal within 1 week and no corneal vacuolization was seen in either eye at any time.

According to Schumacher and Grandjean, [44] the LD50s by intraperitoneal injection in mice were 1.15 ml/kg for benzene, 1.3 ml/kg for toluene, 1.4 ml/kg for a 2:1 mixture of toluene and xylene, and 1.8 ml/kg for xylene. In inhalation experiments with rats, the time in seconds of exposure to produce narcotic effects was uniformly greater for xylene than for toluene and benzene. The starting concentration in each case was 15,000 ppm. Benzene was rated in a group of substances with strong affinity for the nervous system, while toluene was in an intermediate group, and xylene was in the group with the least affinity for the central nervous system.

Hine and Zuidema [45] tested the toxicity of 10 hydrocarbon solvents representative of those used in industry. One of these was a mixture of 8-carbon aromatic solvents (the 3 xylene isomers and ethylbenzene). This sample contained at least 98% aromatics and had a boiling range of 138-141 C. The LD50 for rats when injected intragastrically was 10.0 ml/kg. By inhalation the 4-hour LC50 was 6,350 ppm, with all deaths occurring during exposure. Survivors were comatose but recovered shortly after removal from

the chamber. Rabbits were used to test for primary skin irritation, eye irritation, percutaneous toxicity, and for irritation after repeated skin applications. The xylene mixture was rated as moderately irritating and practically nontoxic by percutaneous absorption. Overall, the xylene mixture was considered by these authors to be relatively harmless under these experimental conditions.

In 1940 Rigdon [46] postulated an increase in the permeability of capillaries in rabbit skin, based on the localization of dyes, antitoxins, and carbon particles following cutaneous application of xylene. In a second paper, [47] he showed that intravenously injected staphylococci localized and concentrated in areas of skin treated with xylene. Subsequently Rigdon [48] demonstrated the localization of antibodies in areas pretreated with xylene. Finally, in 1949 Rigdon [49] reported that antihistamines did not modify the xylene localization effects, which therefore might be due to a "variation in the absorptive ability of the tissue cells" in addition to increased capillary permeability.

Falck and Moller [50] applied solvents and ultraviolet light to the shaved skin of rabbits. There was a highly significant increase in the water content of skin treated with xylene. A decrease in the catecholamines was also noted in the skin.

In 1960 Mikiska [51] and Mikiskova [52] described a technique for evaluating narcotic effects by measuring the threshold of excitability of the cerebral motor cortex. Stimulation electrodes were attached to guinea pigs, and threshold determinations were made before and after intraperitoneal injection of benzene, toluene, or xylene. Each hydrocarbon increased the excitation threshold, with the most significant elevation

caused by xylene. No change followed injection of physiological saline. Clonic muscle contractions and tremors were observed in some cases after the injection of xylene and in all cases after benzene, but not after toluene was injected. This apparently represented a second phase of action, which was accompanied by increased cortical excitability. Often the tremors and muscle contractions were observed during the narcotic state, suggesting to Mikiskova [52] that parts of the central nervous system were not subject to the same inhibition.

Battig and Grandjean [53] tested the effects of xylene exposure on avoidance conditioning in 6 experimental and 6 control rats. The conditioning stimulus was a phone buzzer, followed by an electrical shock which the rats could avoid by moving into a safe part of the cage. Experimental animals were exposed to xylene at initial concentrations of 800 ppm. Concentrations fell to 550-750 ppm in the first 2.5 hours, after which no further decrease was observed. Avoidance response tests began 2 hours after xylene exposure began. The authors observed no clear effect by xylene on any phase of the avoidance testing. There appeared to be no difference between test and control groups in acquiring the conditioned response, and in the consolidation phase the xylene-exposed animals were reported to have an insignificantly higher avoidance response rate. In the extinction phase, the exposed rats had a slightly slower extinction of the avoidance response when the buzzer was not followed by the electric shock.

Desi et al [54] investigated central nervous system dysfunction as evidenced by maze learning ability in rats given xylene. Untrained rats were injected subcutaneously either with xylene or with physiologic saline at a dose of 0.05 ml/100 g body weight. From the beginning, the xylene-

injected rats ran the maze much more slowly than the controls, and their running times declined at a slower rate. Although test scores fluctuated, the differences between test and control groups were highly significantly different in every instance. Pretrained rats were subcutaneously injected with physiologic saline (0.05 ml/100 g) or with xylene at doses of 0.02, 0.05, or 0.10 ml/100 g. Ataxia and death in experimental animals given xylene at 0.10 ml/100 g led to discontinuation of experiments at that level. The rate of weight gain was reduced compared to controls and the running times for the xylene groups were longer, but the differences were not statistically significant. Thus, the ability to learn a maze seemed to suffer more than the ability to perform trained behavior.

Investigating the role of irritation in carcinogenesis, Berenblum [55] exposed white mice to 3,4-benzpyrene with xylene, and to xylene alone as a control. Berenblum concluded that the addition of xylene did not produce a significant difference in the yield of tumors. He also concluded that xylene was probably not carcinogenic, although one minute tumor (which regressed) was observed in a control animal treated with xylene. Xylene applied at a concentration which produced irritation similar to that produced by croton oil showed no evidence of being co-carcinogenic.

In experiments by Pound and Withers, [56] mice received daily right-side subcutaneous injections of 0.25 ml of xylene from 1-6 days prior to injection of 25 mg urethane. Seven days following urethane injection, and once a week thereafter, the entire back of each mouse was painted with 0.25 ml of croton oil in acetone (0.5% solution). The numbers of survivors and the number and location of papillomata were counted each week for 20 weeks. Xylene showed some toxicity, as 8 mice died within 2 weeks. Groups of mice

treated with xylene gave significantly ($p = 0.005$) higher yields of left-sided tumors than mice treated with acetic acid, trichloroacetic acid, turpentine, or scarification. The relative severity of changes in the skin produced by the various irritant substances correlated with the increases in tumor yield observed in animals treated with these substances. The authors concluded that, in addition to a local influence, xylene and some other substances "appeared to have a general effect that influenced the tumor yields." Pound [57] reviewed this work and commented that the augmenting effect was not related to carcinogenic or promoting properties but to the inflammation and hyperplasia produced in the skin. This seems to be a more reasonable explanation.

In 1970, Pound [58] described further experiments using ultraviolet light to attempt to initiate tumor formation in mice. Single short exposures did not produce tumors, but tumors developed when the exposure was followed by application of croton oil. Ultraviolet light apparently was acting as an initiator. If the skin of experimental mice was pretreated with xylene, acetic acid, or croton oil before irradiation, then the number of tumors increased. Pound concluded [58] that cells which had been induced to proliferate were more susceptible to induction of tumors by ultraviolet light than normal cells.

Experiments by Jellinek were reported by Kucera in 1968. [31] The possible implication of fat solvents as etiological agents in human sacral agenesis led to experiments in which chick embryos were exposed at an unstated concentration of xylene vapor for 60-240 minutes. A significant increase in malformations and mortalities was observed, and this correlated positively with the length of exposure to xylene. Younger chick embryos

were more susceptible. The author concluded that xylene had a teratogenic effect. [31] In view of the results of Kucera's survey of human sacrococcygeal agenesis, this seems to be an effect, if real, of fat solvents in general, rather than of xylene in particular.

To investigate possible embryotoxic or teratogenic effects, Krotov and Chebotar' [59] exposed pregnant white rats to dimethylterephthalate, "paratoluic methylate (PT-ether)" (apparently this was methyl (p-toluic acid) ether), or p-xylene vapor during gestation. Twenty-nine rats were exposed to p-xylene at 500 mg/cu m (115 ppm) for 20 days, 24 hours a day. On the 20th day of pregnancy, the experimental and 17 control rats were killed. A count was made of corpora lutea in the ovaries, the number of implantation points, and the number of living and dead fetuses. Fetuses were examined grossly and microscopically for abnormalities. Experimental rats experienced significantly greater preimplantation mortality (32.1%) than controls (11.3%). Postimplantation mortality was also higher (38.9% vs 4.8%). No teratogenic effects were observed, the only malformed fetus (shortened tail and adactylia of the 5th toe of a rear foot) being 1 of 110 living fetuses in the "PT-ether" group.

Kashin et al [60] in 1968 exposed 9 chinchilla rabbits at 200 mg/cu m (46 ppm) for 2 hours daily, and a second group of 9 was exposed at 50 mg/cu m (12 ppm) for 4 hours daily, both groups for 10-12 months. They suggested 3 periods of change due to long-term action by small concentrations of xylene. The first, or compensation period of 1-3 months, was characterized by increases in hemoglobin content, erythrocytes and leukocytes, increases in common proteins and especially in gamma globulins, increased activity of blood acetylcholinesterase, and increased excretion of 17-ketosteroids in

urine. At the same time, inhibitory effects were exhibited by weight loss and by decreased immunological response. A second or normalization phase then occurred during the 4th-8th months of exposure. The authors interpreted the changes to indicate weakening of adrenal cortex functions, disturbance of intermediary metabolism, and decreased immunobiological activity, and they concluded that these reflected overstraining of defense mechanisms and adaptation systems. The final or physiological decompensation phase occurred with decreases in the activity of several systems. The authors concluded [60] that more pronounced changes were caused by a long exposure to a low concentration of xylene than by shorter exposure to a higher concentration. They considered a concentration of 50 mg/cu m (12 ppm) with 4 hours daily exposure to be an unacceptable exposure limit. It is difficult to evaluate the significance of these findings in light of an inadequate description of the experiment, including results in control animals.

Batchelor [38] exposed rats to benzene, toluene, xylene, or high-flash naphtha by inhalation, subcutaneous injection, or intraperitoneal injection. This work was supported by the National Safety Council, who also published the results, [61] and it was reviewed and discussed by Winslow. [62] In the inhalation experiments, rats were exposed for 18-20 hours a day at various concentrations of solvent vapor. Batchelor did not report analyzing the xylene for benzene contamination, but the boiling point of the xylene used was 139 C, suggesting that there probably was little benzene present. Of 4 rats exposed to xylene at 1,600 ppm, 1 died after 2 days and 1 after 4 days. The remaining 2 were removed after 2 days of exposure and recovered. [61] Initial signs of exposure were instability

and incoordination with evidence of mucous membrane irritation. Narcosis prevented ingestion of food and water, leading to weight loss, anhydremia, and death. The white blood count was reduced by 27% in the rat that died after 4 days of exposure. There was no effect on the white count of rats exposed only 2 days. An increased red blood cell count was attributed to the anhydremia. Four rats exposed at 980 ppm for 7 days exhibited similar signs but narcosis did not result. The bone marrow and spleen were hyperplastic and kidneys showed acute congestion with moderate cloudy swelling but no signs of an acute nephritis. One rat had a 32% reduction in the white count. No signs of toxicity were observed in 8 rats exposed at 620 ppm for 7 days, with the exception of a 30% reduction in the white count of 1 rat. In contrast, benzene at high concentrations (1,000-2,440 ppm) did not produce narcosis and death, but after 6-7 days of exposure the rats' skeletal muscles became hypertonic and rats suffered clonic spasms and a spastic gait. This condition persisted for 3-4 days after exposure ended. Leukopenia and destruction of the bone marrow bordering on aplasia were observed after exposure at all benzene concentrations used (2,440, 1,035, 815, and 460 ppm). [38,61,62]

Mixed in equal volumes of olive oil, the solvents were also injected subcutaneously. [38] Xylene was injected for 10 consecutive days at doses of 1 and 2 cc/kg. This resulted in slightly reduced activity and a transient reduction in the red blood cell count, but had no effect on the white blood cell count. At autopsy, the bone marrow was found to be hyperplastic, and mild necrosis of the liver and diffuse nephritis were seen. Benzene at a dose of 1 cc/kg caused a reduction in the white count to below 2,000/cu mm after 4-21 daily injections. A reduction in the red blood cell

count appeared later, accompanied by bone marrow aplasia. General signs, which appeared early and became progressively more severe as benzene injections continued, included apathy, extreme weight loss, great weakness, and tonic and clonic muscle contractions of the body and extremities.

In 1924 Woronow [63] reported experiments in which he injected rabbits subcutaneously twice daily with benzene in olive oil at a dose of 1.5 ml (units are assumed since none were given in the article). Leukopenia developed rapidly, and a leukocyte count of zero reportedly was observed after 9-11 days. When xylene in olive oil was injected subcutaneously in the same dosage, the leukocyte count dropped in the first 4-5 days then rose markedly to 20,000-30,000 by the 9th or 10th day. The elevation was due primarily to increased numbers of monocytes and neutrophils. Myelocytes and juvenile forms were not observed. By the 5th day, the granules of neutrophils were reported to be exclusively basophilic, and monocytes reportedly began to show basophilic granulation. Bone marrow was hyperplastic. Similar results were observed after rabbits were injected with toluene. Cumene produced a less pronounced leukocytosis with a shift to the left. Woronow [63] concluded that the methyl groups acted on leukocytes and on the hematopoietic organs, and suggested that increasing the number of methyl groups on the benzene ring produced changes increasingly similar to myeloid leukemia, but it seems more likely that these changes in xylene-treated animals were a normal response to toxic insult.

Farber [64] in 1933 reported similar experiments that had been conducted to verify Woronow's [63] findings. After rabbits were subcutaneously injected twice daily with 1.5 ml xylene in olive oil, there

was an immediate reduction in the white count, followed by an increase to about 60% above the initial values. No increases as high as those reported by Woronow were observed. Farber noted that the same initial drop in leukocytes occurred when a rabbit was injected with olive oil alone. The responses after xylene injections were summarized as a definite leukocytosis, a shift to the left, monocytosis, atypical cells in the granulocyte series (similar to a degeneration), disturbed red cell analysis (polychromasia and increased numbers of normoblasts), and hyperplasia of the bone marrow.

Because injection of xylene caused necrosis which led to the skin sloughing off in patches, Farber [64] exposed rabbits to xylene by inhalation to rule out effects due to irritation, infection, and necrosis. Rabbits were placed in a bell jar, with xylene evaporating from a filter paper, until they were unconscious. In this case there was no leukocytosis, shift to the left, or monocytosis. Changes in the red blood series were similar to those observed after injections, but were much less severe. The bone marrow was not hyperplastic. Farber therefore concluded that the skin irritation and severe inflammatory processes were responsible for the blood changes observed in the injection experiments. The possibility of benzene contamination is an additional factor that complicates the interpretation of these studies reported in 1929 by Woronow, [63] and in 1933 by Farber. [64]

Engelhardt [65] exposed cats and rabbits at xylene concentrations of 10 mg/liter (2,300 ppm) and 25 mg/liter (5,750 ppm), and observed a reduction in the number of red blood cells and a pronounced leukocytosis. After cats and rabbits were injected with xylene, Engelhardt saw a distinct

shift to the left and leukocytosis, but like Farber [64] he attributed these changes to local effects such as inflammation and necrosis at the injection site. Engelhardt concluded that toluene and xylene were less toxic than benzene.

Fabre et al [66] exposed rats and rabbits for 8 hours a day, 6 days a week to a benzene-free mixture of the xylene isomers. Six rabbits were exposed at 5 mg/liter (1,150 ppm) for 40-55 days, and 12 rabbits and 9 rats were exposed at 3 mg/liter (690 ppm) for 110-130 days. At 3 mg/liter there were no significant changes in the blood. At 5 mg/liter there were decreases in both red and white cells. At both concentrations of xylene the bone marrow was hyperplastic, but there was no tendency to aplasia. Microscopic examination revealed vascular congestion in the liver, kidney, heart, adrenals, lungs, and spleen of animals exposed at each concentration. The renal lesions (chronic subacute glomerulonephritis) were observed after exposure at both concentrations and were considered the most important observations. Based on this observation, the authors recommended caution in the use of xylenes, and suggested that such effects in man would be indicated by an increase in blood urea and the appearance of albumin and blood in the urine.

In 1968, Speck and Moeschlin [67] were unable to demonstrate any myelotoxic effects in rabbits from toluene or xylene. Rabbits received toluene or xylene subcutaneously in doses of 300 mg/kg/day for 6 weeks or 700 mg/kg/day for 9 weeks. Erythrocyte, reticulocyte, leukocyte, and thrombocyte counts were made twice weekly, and all values fluctuated within normal limits. Cytopenia was not induced in any cell type. Using tritiated methyl thymidine and autoradiographic techniques, the authors

determined that neither toluene nor xylene affected DNA synthesis in the bone marrow. Earlier, similar experiments with benzene had resulted in aplastic anemia, and autoradiographic analysis had demonstrated arrested DNA synthesis in the bone marrow. [68,69] The authors suggested [67] that earlier reports of aplastic anemia caused by toluene or xylene could be attributed to benzene contamination, and stated that their results presented "a substantial argument for the lack of myelotoxicity of toluene and xylene."

In 1970, Jenkins et al [70] reported the results of long-term inhalation studies of benzene, toluene, and o-xylene using rats, guinea pigs, monkeys, and dogs. Pre- and postexposure body weight, hematologic data, and mortalities were reported. Experiments with o-xylene were conducted at 3,358 mg/cu m (770 ppm) and 337 mg/cu m (78 ppm), while studies with toluene were conducted at 4,095 mg/cu m (1,085 ppm) and 389 mg/cu m (105 ppm). With benzene, exposure levels were 817 mg/cu m (255 ppm) and 98 mg/cu m (30 ppm). At the higher concentration in each case, there were 30 repeated exposures for 8 hours a day, 5 days a week, while at the lower concentration there was continuous exposure for 90 days. Animals were also continuously exposed to benzene at a concentration of 56 mg/cu m (17 ppm) for 127 days. At the end of the exposures, animals were killed and necropsied. Sections of heart, lung, liver, spleen, and kidney were taken from all species; sections of brain and spinal cord were obtained from dogs and monkeys for microscopic examination. Results of microscopic examinations were negative and no significant changes were noted in body weight or hematologic data. However, the authors reported only leukocyte counts rather than complete differential white blood counts and they did

not examine the bone marrow, so these results are not negative evidence of benzene effects.

In 1974 Carpenter et al, [19] using a solvent sample containing 80.5% mixed xylenes (65.0% m-xylene) and 19.3% ethylbenzene, exposed male rats and dogs at measured concentrations of 3.5, 2.0, and 0.77 mg/liter (805, 460, and 175 ppm) for 6 hours a day, 5 days a week for 13 weeks. Blood analyses (including hematocrit, total erythrocyte count, reticulocyte count, total and differential leukocyte counts, serum alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxalacetic transaminase, and blood urea nitrogen) were determined initially, at intervals during exposure, and at the end of the exposure period. Rats were killed at intervals and all surviving rats and dogs were killed at the end of 65-66 exposure days. No gross or microscopic lesions were ascribed to inhalation of the mixed xylenes. Blood counts and blood analyses likewise did not differ significantly from baseline levels or from levels in unexposed controls.

Using serum ornithine carbamyl transferase (OCT) activity to screen for liver damage, DiVincenzo and Krasavage [71] injected guinea pigs intraperitoneally with organic solvents and collected blood samples 24 hours later. In 117 control animals, serum OCT activity averaged 2.0 ± 1.6 international units (IU), but after injection with 1,000 mg/kg of xylene, the OCT activity of 4 guinea pigs averaged 18.4 IU. At a dose of 2,000 mg/kg, 3 of 4 animals died, and mean OCT activity was reported as 25.2 IU. As a positive control, carbon tetrachloride was administered in doses of 5-150 mg/kg. The OCT activity in the 5 mg/kg group was 3.8 IU, and in the other groups (25-150 mg/kg) ranged from 37.1-64.4 IU. Liver sections from

each test animal were examined microscopically, and showed signs of lipid deposition in the hepatocytes at both xylene dosages, but no evidence with hematoxylin-eosin stain of hepatocellular damage.

Many of these studies of xylene have examined its toxicological properties in comparison with those of benzene or toluene. Reports regarding the relative toxicity of the isomers of xylene and toluene and benzene are conflicting. Smyth and Smyth [39] and Wolf et al [43] published results suggesting that xylene was more toxic than toluene. The data of Chassevant and Garnier, [37] Batchelor, [38] and Schumacher and Grandjean [44] showed the opposite. The work of Lazarew [40] and of Cameron et al [42] indicated that toluene was less toxic than some but more toxic than other xylene isomers, but these papers did not agree in detail. No clear pattern emerges from these studies, and it is only possible to conclude that the acute toxicity of xylene is of the same order of magnitude as that of toluene. This does not necessarily reflect the relative chronic toxicities.

Changes in the blood [38,64] and hyperplasia of the bone marrow [38,64,66] have been reported in animals injected subcutaneously with xylene. Leukocytosis and a reduced red count were reported in a 1935 inhalation study. [65] However, blood changes were not seen in 1 of these older studies when the animals were exposed to xylene by inhalation, [64] and the author attributed, probably correctly, the blood changes seen after injection to the expected response to inflammatory processes. More recent studies have shown no blood changes after exposure by inhalation [19,66,70] or by injections. [67] In contrast, benzene has produced aplasia after subcutaneous injection [68,69] and after inhalation. [38]

Correlation of Exposure and Effect

Like most organic solvents xylene has irritant effects on the skin, [2,3,72] and on the mucous membranes, [24] including the conjunctiva [28] and respiratory tract. [24] Xylene also has narcotic effects on the central nervous system, [21,24] variable effects on the liver [12,24,25] and kidneys, [24,26] and rather nonspecific, probably irritant, effects on the gastrointestinal tract. [22,23] Questionable effects on the cardiovascular system [12,29] and female reproductive endocrine system [30] have been reported. In the past, xylene was thought to have significant deleterious effects on the bone marrow and hemopoietic system in general, [10,12-15] but in the light of more recent research, this appears doubtful. [19,66,67,70] The better controlled studies of Speck and Moeschlin [67-69] give strong support to the conclusion that xylene uncontaminated by benzene does not have such effects.

The narcotic and other effects of xylene at high concentrations were well established by the incident described by Morley et al. [24] Three painters working in the confined space of a ship's fuel tank were overcome by xylene vapor from the paint they were using, in which the solvent was 90% xylene. The authors estimated that the xylene concentration had reached 10,000 ppm. It was not known how long it took the men to lose consciousness, because they were not found until 18.5 hours after they entered the tank. One died shortly after discovery and at autopsy showed pulmonary edema and intra-alveolar hemorrhages. The other 2 men survived and recovered completely in about 2 days. They both had temporary hepatic impairment (inferred from elevated serum transaminase levels) and 1 had evidence of temporary renal impairment (increased blood urea and reduced

endogenous creatinine clearance).

Giddiness, anorexia, and an episode of vomiting were observed in a paint-pot cleaner who used a solvent containing 75% xylene (the remaining 25% consisting of ethylbenzene, methylethylbenzenes, and trimethylbenzenes). [23] At head height above the paint-pots, the xylene concentration ranged from 60-100 ppm when the pots were cold but from 270-350 ppm when the pots were warm. It was believed that the worker was exposed frequently to an even higher level when he placed his head inside the warm pots during cleaning.

Nelson et al [17] exposed a group of volunteers, usually 10, of both sexes to various solvent vapors, including xylene, in an exposure chamber for 3-5 minutes. The subjects were questioned about the subjective effects of eye, nose, and throat irritation. They were also asked the highest concentration which they considered satisfactory for an 8-hour exposure. The majority of subjects found a xylene concentration of 200 ppm irritating to eyes, nose, and throat and judged 100 ppm to be the highest concentration subjectively satisfactory for an 8-hour exposure.

In a Soviet xylene extraction plant, xylene concentrations were below 50 mg/cu m (about 10 ppm) in 60-65% of the air samples taken, and ranged from 75-200 mg/cu m (about 15-45 ppm) in the remaining samples. [35] Forty-five workers had been exposed for periods ranging from 5 months to 6 years. [35] One-third of these workers complained of occasional headaches, insomnia, irritability, tachycardia, and dyspepsia. If any were made, similar observations were not reported for unexposed workers. What were called neurasthenic or asthenoautonomic syndromes were observed in 9 workers (20%) and autonomic-vascular dysfunction (not further defined) was

observed in 6 workers. Again there were no similar observations in a control group. The amount of phenols excreted in the urine was higher than normal in all cases (the actual amount and the "normal" were not given). Peripheral blood polymorphonuclear leukocytes had a decreased glycogen and peroxidase content, compared with unidentified controls. These decreases were more marked in those employed 3-5 years than in those employed 1-3 years. The authors projected that such cytochemical changes might eventually lead to disturbance of the immunological processes.

In the first 30-40 years of this century a variety of blood changes, including aplastic and pseudopernicious anemia, were attributed to xylene exposure. [10,12-15] However, because the xylene of that era was contaminated with benzene and other hydrocarbons, [9,15,16] these reports can be regarded only as evidence that a health problem existed at that time. More recent studies that have reported blood changes in exposed workers have involved known exposure to benzene as well as xylene [33,34] or employment in a print shop during the time when benzene contamination of xylene was probable. [32-34] In animal experimentation, changes in the blood and bone marrow have been reported after injections of xylene [38,64] and in a 1935 study [65] after inhalation. More recent studies do not report blood changes after injections [67] or after exposure by inhalation, [19,66,70] and studies [67-69] with good controls strongly support the conclusion that uncontaminated xylene does not have myelotoxic effects.

In 1950 Browning [73] called xylene "innocuous to the haematopoetic system." In a 1965 review, [2] she pointed out what she considered to be the dubious nature of practically all the reports of bone marrow effects since the exposures described were either admitted to involve concomitant

exposure to benzene, or were suspected of involving significant amounts of benzene as a contaminant. In a series of papers reviewing available data and presenting his own results, Gerarde [3,72,74,75] reviewed the evidence and concluded that the myelotoxic properties of benzene were destroyed by alkylation of the benzene ring. Lehmann and Flury in 1943, [76] Johnstone and Miller in 1960, [77] and Lederer in 1972 [78] all expressed the view that there was little or no evidence that xylene was a myelotoxicant.