IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Sampling and Analysis

Xylene can be directly measured in the field with a calibrated combustible gas indicator, [72,79] but the method is nonspecific, being subject to interference in the presence of other organic compounds. The same disadvantage applies to the interferometer. [1,72] Detector tubes also offer a rapid, simple procedure, but depend upon an estimation of the length of a stain produced in the tube or on the intensity of color produced. Unfortunately, detector tubes are not particularly accurate, and are also nonspecific, other aromatic hydrocarbons also producing colors. [80-82]

Collection in a bubbler containing sulfuric acid and formaldehyde has also been proposed, but this method is little more than semiquantitative. [83,84] Collection in a bubbler containing methanol with subsequent measurement by ultraviolet spectrophotometry has been described, [85] but has the disadvantage of requiring that the sampling unit be placed in dry ice to prevent evaporation. In addition, sampling of breathing zone exposures is more difficult with sampling devices containing liquids.

Silica gel has been used by a number of investigators to collect xylene vapor for laboratory analysis. [86-88] In the presence of water vapor, however, there may be considerable loss. Whitman and Johnston [89] reported that this problem could be overcome by the use of a molecular sieve prefilter.

Plastic bags have also been used to collect xylene and other organic vapors. [90-92] Possible losses with time through reaction of the specific compound with the type of plastic used must be determined in advance.

Adsorption of xylene vapor on activated charcoal has been studied by a number of investigators. [93-95] Activated charcoal is the preferred sampling method since the xylene is not displaced by water vapor, as is the case with silica gel, and because it is a simpler, more convenient procedure than the use of plastic bags or bubblers. White et al [95] have defined the design of activated charcoal tubes suitable for sampling occupational exposures to xylene, and such tubes are commercially available. They reported average desorption efficiencies (percent xylene recovered from the charcoal) of 94% (range 91-96%) for 100 ppm concentrations of xylene sampled alone and 98% (range 97-100%) in the presence of 6 other organic vapors.

Various methods for analyzing the collected samples have been used, including colorimetric, [83,84] infrared analysis, [88] and ultraviolet spectrophotometry. [85,87,96] In recent years, however, gas chromatography has become the method of choice of most investigators for analysis of organic solvents. [86,88,89,93-95,97-99] Gas chromatography also offers suitable specificity and sensitivity. [89,93,95]

Appendices I and II present recommended methods for sampling and analyzing xylene. These include collection of personal samples, using charcoal tubes, desorption with carbon disulfide, and measurement with a gas chromatograph equipped with a flame ionization detector. [94,95,100] The sampling method has the advantages of using a small, portable sampling device and of involving no liquids. Analysis is by means of a quick

instrumental method that can be used for the simultaneous analysis of 2 or more solvents in the same sample. Disadvantages include the fact that the amount of sample that can be collected is limited by the number of milligrams that the tube will hold before overloading, and the fact that volatile compounds can migrate to the backup section during storage before analysis. The precision of the method is limited by the reproducibility of the pressure drop across the charcoal tubes. Nevertheless, the accuracy of the overall sampling and analytical method is 10%. [100,101] Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions.

Control of Exposure

Engineering design and work practices for xylene should have, as their main objectives, controlling vapor concentrations, minimizing skin contact, and preventing fires.

Closed systems, properly operated and maintained, should be used, where practicable, to achieve all 3 of these objectives. Where closed systems are not feasible, well-designed local exhaust ventilation should be provided. [6] Guidance for design can be found in Industrial Ventilation--A Manual of Recommended Practice, [102] or more recent revisions, and in ANSI Z9.2-1971. [103] Exhaust air should not be recirculated, and should be scrubbed to prevent pollution of the outdoor air. Respiratory protective equipment is not an acceptable substitute for proper engineering controls, but should be available for emergency purposes, and for nonroutine maintenance and repair situations.

Sparkproof equipment in exhaust hoods, stands, booths, or similar

arrangements should be employed where xylene-containing paints or lacquers are sprayed. Exposures should be minimized by isolating painting and drying areas.

Protective clothing should be worn wherever required to prevent skin contact. Equipment made of natural rubbers should be avoided since it is subject to solvent action by xylene. Neoprene or other materials resistant to xylene should be used for gloves, aprons, or other protective clothing. [8]

Xylene is a flammable liquid that vaporizes at normal temperature. At 25 C, the vapor pressures of the isomers range from 5.2 mm Hg for o-xylene to 8.6 mm Hg for p-xylene, and the lower explosive limit is 1.1% by volume. [1] The vapor can travel a considerable distance to a source of ignition and flash back. Ignition sources include open flames, chemical reactions, lightning, smoking, hot surfaces, radiant heat, and spontaneous combustion. Static electricity can also present a hazard. [8] All metal dispensing containers should be properly grounded when pouring.

Structures and operations should be designed with the objectives of reducing the possibilities of fires, and of limiting the size or spread of any which might occur. Storage of materials is also an important factor. Firefighting procedures should be developed in advance, and local fire departments, as well as plant employees, should be informed of the hazards involved. [8]

Biologic Evaluation

The first report on xylene metabolism apparently was that of Schultzen and Naunyn [104] in 1867. They demonstrated toluric acid (the

glycine conjugate of toluic acid) in the urine of dogs and men after ingestion of xylene. In 1892, Curci [105] reported that xylenols were also formed as metabolites of xylenes. This was confirmed in 1914 by Filippi, [106] who also showed that the ortho isomer had greatest chronic toxicity in the dog.

Bray et al [107] investigated the metabolism in rabbits of the xylene isomers, administered by stomach tube. They reported that all 3 isomers were primarily oxidized to the corresponding toluic acid (60%, 81%, and 88% of the administered dose, respectively, for o-, m-, and p-xylene). The o-toluic acid was excreted mainly unconjugated and as an ester glucuronide, with a small amount excreted as a glycine conjugate. The m- and p-toluic acids were excreted chiefly as glycine conjugates with only small amounts excreted free or conjugated with glucuronic acid. There was some evidence of hydroxylation: 6% of o- and 4% of m-xylene doses were excreted as ethereal sulfate and 10-15% of the p-xylene dose was probably excreted as an ether glucuronide. Additionally, there was some evidence that p-xylene may have given rise to a xylenol.

In a later paper, Bray et al [108] presented additional data on the fate of xylenes and xylenols in the rabbit. They concluded that it seemed most likely that the phenolic material excreted after the administration of xylenes consisted mainly of xylenols, both free and conjugated. When the xylenols were administered directly to rabbits only small amounts of further oxidation or hydroxylation products were detected. The authors considered this evidence that the amount of the xylenols formed from the metabolism of xylene was probably very small.

Fabre et al [109] administered pure xylene isomers to rabbits, rats, and guinea pigs by stomach tube. Their results confirmed the oxidation of each isomer to the corresponding toluic acid and indicated that the second methyl group resisted oxydation, since no phthalic acids were isolated. In the case of o- and p-xylene, the phenolic metabolites were identified as 3,4-dimethylphenol (asymmetrical o-xylenol) and 2,5-dimethylphenol (p-xylenol), respectively. A xylenol metabolite of m-xylene was isolated but not identified.

Bakke and Scheline [110] administered each of the 3 xylene isomers to rats in an oral dose of 100 mg/kg body weight, and phenolic metabolites were quantitatively estimated in hydrolyzed urine samples by gas chromatography. o-Xylene was metabolized to 3,4-dimethylphenol (0.1% of the dose) and to very small amounts of 2,3-dimethylphenol (approximately 0.03% of the dose). m-Xylene was metabolized to 2,4-methylphenol (0.9% of the dose), and p-xylene to 2,5-dimethylphenol (1.0% of the dose). In addition, 2-methyl benzyl alcohol was a metabolite of o-xylene. This had not been previously reported. This work confirmed the earlier work of Bray et al [107] suggesting oxidation of a methyl group to give toluic acids as a major pathway for xylene. Bakke and Scheline [110] noted that the conversion of aromatic hydrocarbons to phenols by hydroxylation "is accompanied by an appreciable increase in acute toxicity," but they considered this of little importance because the metabolites occurred in small quantities which were partly eliminated as glucuronides and ethereal sulfates.

Fridlyand [111] injected guinea pigs and rats subcutaneously with 90 mg doses of benzene, toluene, o-, m-, or p-xylene, then collected urine for

analysis. According to Fridlyand, toluene and xylene were demethylated and phenol was formed. In rats, the quantity of phenol excreted was greatest after injection of benzene and decreased in the order p-xylene, toluene, m-xylene, and o-xylene. The relationship was the same for guinea pigs except that o- and m-xylene, in that order, resulted in the least phenol.

Recent quantitative inhalation experiments by Ogata et al [112] showed that 72% of absorbed m-xylene was excreted in the urine of male volunteers as m-methylhippuric acid during and within 18 hours after the end of exposure. Attempting to relate excretion data to exposure levels, the authors found that total excretion during and for 18 hours after exposure was most accurate, followed by excretion rates (in mg methylhippuric acid/minute) during exposure. Least accurate but still useful were urine concentrations of methylhippuric acid, corrected to a specific gravity of 1.024, during the afternoon and morning exposure periods. Concentrations uncorrected for specific gravity were too variable to be of use.

Subjects were exposed in groups of 4 or 5 for 7 hours, with a 1-hour break after the 3rd hour, to m- or p-xylene at 100 ppm, or to m-xylene at 200 ppm. [112] Urinary excretion of methylhippuric acid rose during exposure, peaking 6-7 hours after exposure began. The results are summarized in Table X-3. Based on these results, the authors proposed "screening levels" 2 standard deviations below the average excretion after exposure at 100 ppm. They suggested that if methylhippuric acid excretion by an exposed worker was above the screening level, it should be taken as evidence that the person might have been exposed above 100 ppm (according to their statistical interpretation, this would be true in 5% of the cases). Separate screening levels were given for samples taken in the

morning and afternoon, as well as a screening level for the rate of excretion over a 7-hour exposure period. These proposed screening levels are given in Table X-4.

This report by Ogata et al [112] contains the only published data found by NIOSH that quantitatively correlate the urinary excretion of xylene metabolites with exposure levels. Unfortunately, this work was done using pure m- or p-xylene. Thus, there are no data correlating urinary excretion with o-xylene exposure, and the excretion resulting from exposure to mixed xylene isomers is unknown. If mixtures do not alter the relative metabolism and excretion of the isomers, it is possible that the excretion of, for example, m-methylhippuric acid could be used to compute total xylene exposure based on the percentage composition of the mixture in use. The suitability of this procedure has not been verified experimentally.

Ogata et al [113] also developed 2 analytical procedures for the determination of m- and p-methylhippuric acid in urine, based on colored azlactone formation. A silica gel method involved extraction of the methylhippuric acids with an ethyl ether/ethyl alcohol solution, drying with silica gel, and azlactone formation using p-dimethylaminobenzaldehyde in acetic anhydride. The azlactones were extracted with ethyl ether and the absorbance read at 460 nm. Standard solutions prepared by the same extraction procedure were applied to aqueous solutions of m- or p-dimethyl-aminobenzaldehyde reagent and gave a positive reaction with urea. However, the extraction procedure using ethyl ether/ethyl alcohol did not extract urea from urine. The sensitivity of this method was 4 μg/ml urine. The other method, using benzenesulfonyl chloride, was less sensitive (20 μg/ml urine), but was much simpler to use. The methylhippuric acids were

extracted with ethyl acetate or ethyl ether/ethyl alcohol solution and the azlactones formed by reaction with benzenesulfonyl chloride in pyridine solution. The absorbance was then read at 380 nm against a pyridine-benzenesulfonyl chloride blank. Recoveries by both methods were 94-100%. Hippuric acid, a urinary metabolite of toluene, is also determined by both methods, but hippuric acid, m-, and p-methylhippuric acid can be separated by paper or thin-layer chromatography and then determined spectrophotometrically.

A more recent paper by Buchet and Lauwerys [114] described a gas chromatographic technique for the determination of both hippuric acid and m-methylhippuric acid in urine. Comparison indicated that this technique was as specific and as sensitive as that reported by Ogata et al, [113] but it was much more rapid. A known amount of heptadecanoic acid, as the internal standard, was added to urine before its extraction with ethyl acetate. After evaporation of the solvent, the acids were methylated with diazomethane and the residue was taken up in methanol and injected into the gas chromatograph. The ratio of the height of the m-methylhippuric acid peak to the height of the heptadecanoic acid peak was calculated and by reference to a calibration curve prepared in the same conditions the urine concentration of the acid was determined. This technique could simultaneously determine both hippuric and m-methylhippuric acid, but was not described in connection with the metabolites of o- and p-xylene. Therefore, while this method seems promising, its applicability to mixtures of o-, m-, and p-methylhippuric acid is unknown.

These reports indicate that the major metabolic pathway for xylene involves oxidation of a single methyl group followed by conjugation with

glycine or glucuronic acid. [104,105,107,109,112] The relatively low toxicity of these major metabolites was cited in reviews by Laham [115] and Gerarde [75] as an explanation for the apparent lack of myelotoxicity on the part of xylene and other alkylbenzenes. In review articles, Browning, [2] Laham, [115] and Gerarde [75] have attributed the myelotoxicity of benzene to its phenolic metabolites. However, as pointed out in the recent NIOSH benzene criteria document, [116] the phenolic metabolites do not produce hematopoietic toxicity when administered directly. In any event, while some hydroxylation of xylene apparently occurs, [107-110] the amount of phenolic metabolites produced is small. [109,110]

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The earliest US standard for xylene appeared in a list of toxic limits published in 1943, [117] in which the value of 200 ppm was recommended as a Maximum Allowable Concentration (MAC). In 1945 Cook, [118] in his then comprehensive list of recommended MACs, cited 200 ppm for xylene in all the states mentioned (California, Connecticut, Massachusetts, New York, Oregon, Utah) as well as for the USPHS and the "American War Standard." This MAC was established by analogy with toluene, but Cook commented that "xylene vapor is somewhat more irritating to the eyes than that of toluene and it is probable that a somewhat lower limit of exposures may be required to permit comfort of the worker." [118]

In 1946, the American Conference of Governmental Industrial Hygienists (ACGIH) recommended a MAC of 200 ppm for xylene. [119] In 1948 the terminology was changed to Threshold Limit Value (TLV), but the level remained at 200 ppm. According to the 1962 documentation, [120] the effects of xylene were considered to be similar to those of toluene. The 200 ppm TLV was based on the report by Nelson et al [17] of irritation at 200 ppm and on the suggestion of Greenburg and Moskowitz. [121] In 1963, the ACGIH for the first time added a "C" (ceiling) notation to a number of TLVs, including that for xylene. [122] This 200 ppm ceiling remained in effect until the TLV was changed to a time-weighted average (TWA) of 100 ppm, proposed in 1965 [123] and adopted in 1967. [124] The basis given in the 1966 [125] and 1971 [126] documentation was Gerarde's opinion [3] that 100 ppm would be more acceptable from the standpoint of comfort and worker

performance, as well as the report by Nelson et al [17] of irritation at 200 ppm. The current TLV remains a TWA of 100 ppm, except that in 1974 the "Skin" notation was added, [127] which was intended to suggest the need to prevent skin absorption.

In 1951 Elkins [128] listed the maximum allowable concentration (presumably for Massachusetts) as 150 ppm, based in part on the concentration found to be irritating.

The American National Standards Institute (ANSI) [1] acceptable concentrations of xylene in 1971 were 100 ppm as an 8-hour TWA, 200 ppm as a ceiling, and 300 ppm as an acceptable maximum for a peak above the ceiling (not more than 30 minutes' duration and encountered not more than once a day). The TWA level was intended to prevent irritation, based on human experience as reported by Nelson et al. [17] The basis for the ceiling level was also human experience [17] and a review by Gerarde. [3] No basis was given for the 300 ppm peak, but it was said that there would be no health damage, provided that such an exposure would not be encountered more than once a day, although irritation of the eyes, nose, and throat was expected.

A number of limits have been set by foreign countries. In 1968 the Joint ILO/WHO Committee on Occupational Health [36] compiled the recommendations (listed in Table X-5) from 11 countries and 6 states in the United States, with values ranging from 10-200 ppm (50-870 mg/cu m). No basis was given for any of these limits. According to Bardodej, [129] the Czechoslovakian MAC was established on the basis of experience showing that the mean MAC of 200 mg/cu m (45 ppm) posed no hazard of damage after long-term exposure, and that the peak MAC of 1,000 mg/cu m (230 ppm) presented

no risk of acute poisoning. Bardodej cited his own unpublished work showing no health damage after exposure at 200 mg/cu m, although there were "single complaints by employees about headache and loss of appetit (sic), in exceptional cases drowsiness...." He also reported that unacclimatized persons complained of slight irritation of the eyes and "airways."

The present federal standard for occupational exposure to xylene is 100 ppm as a TWA. [29 CFR 1910.93, published in the Federal Register, vol 39, June 27, 1974] This was based on the ACGIH TLV in 1968.

Basis for Recommended Environmental Standard

Xylene can have a narcotic effect, apparently at relatively high levels, but actual air concentrations have not been reported. Johnstone and Miller [77] speculated that workers would not voluntarily remain in such an atmosphere long enough for the symptoms to develop because of the irritating nature of xylene. While this may make narcosis less probable, Morley et al [24] reported 3 cases (1 of which was fatal) and Sikora and Gala [29] reported 1 case in which workers, who were not trapped and could have escaped, were overcome by xylene vapor. No atmospheric concentrations were reported, but Morley et al [24] estimated the air level had reached 10,000 ppm. Glass [23] reported that a worker intermittently exposed for 2 weeks at concentrations of 270-350 ppm, and probably at higher concentrations on occasion, developed giddiness and vomiting, followed by anorexia for 1 week.

Liver damage [24] and kidney damage [24,26] have been reported after inhalation of xylene and liver damage [25] after the accidental ingestion of a small amount of a xylene-toluene thinner. In all these cases,

exposure was sufficient to cause unconsciousness [24] or illness, [25,26] but all those involved recovered fully. No published evidence was found of irreversible liver or kidney damage. Liver necrosis and diffuse nephritis have been reported after xylene was injected intraperitoneally in rats, and moderate cloudy swelling of the kidneys followed exposure by inhalation. [38] DiVincenzo and Krasavage [71] recently reported lipid deposition in the liver and increased serum OCT activity after xylene was injected intraperitoneally in guinea pigs.

There have been reports of reversible corneal vacuolization resulting from exposure to xylene [28] or xylene plus other volatile solvents [27] in the furniture polishing industry. Two investigators reported similar transient vacuolization when cats were exposed to xylene vapor [27] and when xylene was instilled in the eyes of rabbits. [43] More recently, efforts to produce this effect failed [CP Carpenter, DL Geary, written communication, April 1974] when rabbits were exposed to xylene vapor, had xylene instilled in an eye, or were given xylene by intratracheal tube.

In the past, xylene was thought to be myelotoxic based on reports that occupational exposures had led to leukopenia, [10] relative lymphocytosis, [10,12] and aplastic anemia. [12-15] In animal studies, changes that have been reported include transitory leukopenia, [38] leukocytosis, [65] and hyperplasia of the bone marrow. [38,64,66] Aplasia of the bone marrow has not been reported after administration of xylene, but has followed benzene exposure. [38,68,69]

In all of the occupational exposures to xylene, concomitant benzene exposure was either known or suspected at some time in the individual's career. Since benzene is known to cause the kinds of blood dyscrasias

reported, [116] the myelotoxicity can be attributed to benzene rather than xylene exposure. This conclusion is supported by 2 recent animal studies [19,70] in which exposure to pure xylene did not produce significant hematologic changes in rats, dogs, guinea pigs, or monkeys, although benzene has induced aplasia in other animal studies. [38,68,69] On this basis, it is concluded that xylene is not myelotoxic when uncontaminated with substances such as benzene. This conclusion that xylene is not myelotoxic was also expressed in review articles by Browning, [2,73] Gerarde, [3,72,74,75] Johnstone and Miller, [77] Lederer, [78] and by Lehmann and Flury. [76]

Thus, the only well-documented effects which a xylene standard should protect against are the irritating and narcotizing properties of xylene. There are no data available from actual occupational exposures, but these effects have been investigated experimentally. One study [40] indicated that narcotic effects were observed in mice at concentrations over 2,000 ppm, while another [42] reported that some mice died after a 24-hour exposure to m-xylene at a concentration of 2,010 ppm. For humans, only one report was found which associated possible narcotic effects with a known xylene concentration. One of 7 volunteers exposed at 1.0 mg/liter (230 ppm) and 1 of 6 exposed at 2.0 mg/liter (460 ppm) [19] experienced slight lightheadness without loss of equilibrium or coordination at the end of the 15-minute exposure period.

Estimates of the odor threshold for xylene range from 0.6 mg/cu m (0.14 ppm) [21] to 20 ppm. [18] Although there was a wide difference in the odor thresholds, these authors [18,21] both reported a lower threshold for xylene than for toluene. Similarly, Nelson et al [17] found that

xylene was more irritating than toluene to the eyes and mucous membranes during a 3- to 5-minute exposure. Based on this brief exposure, these subjects estimated that 100 ppm would be satisfactory for an 8-hour exposure. Based on 15-minute exposures, Carpenter et al [19] concluded that 1.0 mg/liter (230 ppm) should not be objectionable to most people.

While there are no adequate data available with which to establish a xylene limit, neither are there data which indicate any need to alter the existing federal limit of 100 ppm. However, this TWA limit does not restrict excursions so long as the 8-hour TWA limit is not exceeded. Such a restriction is needed for xylene not only because of its irritant properties, but also because as a central nervous system depressant, xylene might at briefly high concentrations affect attention, judgment, or perception sufficiently that if an emergency were to occur the worker might not respond appropriately. The study by Carpenter et al [19] suggests the possibility of minimal narcotic effects at a xylene concentration of 230 ppm. Therefore, in addition to the 100 ppm TWA, NIOSH recommends a 10-minute ceiling of 200 ppm for xylene.

It is recognized that many workers handle small amounts of xylene or work in situations where, regardless of the amount used, there is only negligible contact with the substance. Under these conditions, it should not be necessary to comply with many of the provisions of this recommended standard, which has been prepared primarily to protect worker health under more hazardous circumstances. Concern for worker health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. For these reasons, "exposure to xylene" has been defined as exposure above half the environmental limit, thereby

delineating those work situations which do not require the expenditure of health resources, of environmental and medical monitoring, and associated recordkeeping. Half the environmental limit has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard may exist. However, because of nonrespiratory hazards such as those resulting from skin irritation or eye contact, it is recommended that appropriate work practices and protective measures be required regardless of the air concentration.

The absence of data either in support of or in opposition to the existing limit of 100 ppm (or the prior ACGIH TLV of 200 ppm) apparently is due to the fact that no epidemiological studies have been attempted. While exposures to a pure solvent are rare, some effort is needed to describe what effects, if any, result from occupational exposures under current conditions. Some investigators have suggested effects on the liver, [12,24,25] the kidney, [24,26] the cardiovascular system, [12,29] and the gastrointestinal tract [23] after inhalation of xylene vapor. Effects on these organs and systems should be investigated to confirm or deny any involvement of xylene. Additionally, studies should be conducted to investigate the possibility of interaction between xylene and alcohol. Earlier reports [27,28] of corneal vacuolization were not confirmed by a recent animal study [19] but workers exposed to xylene should be examined to verify that no hazard exists for them. Although the recommended standard should prevent any narcotizing effects, including impaired judgment or reaction time, studies are needed for confirmation.

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