Toxicological Profile for

TOTAL XYLENES

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
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Agency for Toxic Substances and Disease Registry

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TOXICOLOGICAL PROFILE FOR TOTAL XYLENES

Prepared by:

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, and on October 17, 1990.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by CERCLA, as amended.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about xylene and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Xylene has been found at 236 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for xylene. As EPA evaluates more sites, the number of sites at which xylene is found may change. The information is important for you because xylene may cause harmful health effects and because these sites are potential or actual sources of human exposure to xylene.

When a chemical is released from a large area such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as xylene, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS XYLENE?

Xylene is primarily a man-made chemical. Chemical industries produce xylene from petroleum and to a smaller extent from coal. Xylene also occurs naturally in petroleum and coal tar, and is formed during forest fires. It is a colorless liquid with a sweet odor. There are three forms of xylene called isomers: meta-xylene, ortho-xylene, and para-xylene (m-, o-, and p-xylene). Mixed xylene is a mixture of the three forms of xylene and smaller amounts of other chemicals, primarily ethylbenzene. Mixed xylene usually contains 6%-15% ethylbenzene, although it may contain higher amounts. The term "total xylenes," as used in the title of this report, refers to the three forms or isomers of xylene (meta-, ortho-, and para-xylene) and also to mixed xylene. In this report, the term "total xylenes" and xylene will be used interchangeably.

1. PUBLIC HEALTH STATEMENT

Solvents (liquids that can dissolve solids) and thinners for paints and varnishes often contain xylene, along with other solvents. Xylene is used as a solvent in the printing, rubber, and leather industries, and as a cleaning agent. It is also found in airplane fuel and gasoline, and is used as a material in the chemical, plastic, and synthetic fiber industries, and as an ingredient in the coating of fabrics and papers. Isomers of xylene are used in the manufacture of certain polymers, such as plastics.

Xylene evaporates and burns easily. Xylene does not mix well with water; however, it does mix with alcohol and with many other chemicals. Xylene is a liquid, and it can leak into soil, surface water (creeks, streams, rivers), or groundwater, where it may remain for 6 months or longer before it is broken down into other chemicals. However, because it evaporates readily, most xylene goes into the air, where it lasts for several days. During these several days in the air, the xylene is broken down by sunlight into other kinds of chemicals. Additional information regarding chemical and physical properties, use, and environmental fate of xylene can be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO XYLENE?

You may become exposed to xylene because of its wide distribution in the environment. Releases of xylene occur primarily from industrial sources, automobile exhaust, and from the use of xylene as a solvent. Hazardous waste disposal sites and spills of xylene into the environment also serve as possible sources of exposure. Levels of xylene measured in industrial areas and cities of the United States and Europe range between 0.0007 and 0.09 parts of xylene per million parts of air (ppm). Xylene is sometimes released into water and soil as a result of the use, storage, and transport of petroleum products. Surface water generally contains less than 1 part of xylene per billion parts of water (ppb), although the level may be higher in industrial areas. Levels of xylene in public drinking water supplies range from 0 to 750 ppb. Because xylene evaporates rapidly, the presence of xylene in upper layers of soil is probably not large. Little information exists about the amount of xylene in food. Levels ranging between 0.05 ppm and 0.12 ppm xylene have been found in fish.

You may also come in contact with xylene from a variety of consumer products, including cigarette smoke, gasoline, paint, varnish, shellac, and rust preventives. Breathing vapors from these types of products can expose you to xylene. Indoor levels of xylene can be higher than outdoor levels, especially in buildings with poor ventilation. Skin contact with products containing xylene, such as solvents, lacquers, paint thinners and removers, and pesticides may also expose you to xylene.

1. PUBLIC HEALTH STATEMENT

In addition to painters (or paint industry workers), biomedical laboratory workers, distillers of xylene, wood processing plant workers, garage workers, metal workers, and furniture refinishers also may be exposed to xylene. Exposure to high levels of xylene is most likely to occur in workers who smoke and routinely come in contact with solvent products. Additional information on the potential for human exposure can be found in Chapter 5.

1.3 HOW CAN XYLENE ENTER AND LEAVE MY BODY?

Xylene is most likely to enter your body through breathing xylene vapors. Less often, xylene enters the body through the skin following direct contact. Exposure to xylene may also take place by eating or drinking xylene-contaminated food or water. Xylene is rapidly absorbed by the lungs following breathing air containing xylene. The amount of xylene retained by the lungs ranges from 50% to 75% of the amount of xylene to which you are exposed. Physical exercise increases the amount of xylene absorbed by the lungs. Absorption of xylene after eating food or drinking water containing it is both rapid and complete. Absorption of xylene through the skin also occurs rapidly following direct contact with xylene or exposure to xylene vapors in the air. At hazardous waste sites, breathing xylene vapors, drinking wellwater contaminated with xylene, and direct contact of the skin with xylene are possible ways you can be exposed. Xylene passes into the blood soon after entering the body.

In humans and laboratory animals, xylene is broken down into other chemicals in the liver and lungs. This process changes most of the xylene that is breathed in or swallowed into a different form. Once xylene has been broken down, the breakdown products rapidly leave the body, mainly in urine but some unchanged xylene also leaves in breath from the lungs. Small amounts of broken down xylene have appeared in urine of humans as soon as 2 hours after breathing air containing xylene. Usually most of the xylene that is taken in leaves the body within 18 hours after exposure ends. Storage of xylene in fat or muscle may prolong the time needed for xylene to leave the body. Additional information on how xylene can enter and leave your body can be found in Chapter 2.

1.4 HOW CAN XYLENE AFFECT MY HEALTH?

Short-term exposure of humans to high levels of xylene or chemical mixtures containing xylene causes irritation of the skin, eyes, nose, and throat; difficulty in breathing; impaired function of the lungs; delayed response to a visual stimulus; impaired memory; stomach discomfort; and possible changes in the liver and kidneys. Death can occur in individuals who are exposed to very high levels of xylene for a short period of time. Both short- and long-term exposure to high concentrations of xylene can also cause

a number of effects on the nervous system, such as headaches, lack of muscle coordination, dizziness, confusion, and changes in one's sense of balance.

Results of studies with animals indicate that large amounts of xylene can cause changes in the liver and adverse effects on the kidney, lung, heart, and nervous system. Short-term exposure to high concentrations of xylene causes death in some animals, as well as muscular spasms, incoordination, hearing loss, changes in behavior, changes in organ weights, and changes in enzyme activity. Long-term exposure to low concentrations of xylene has not been well studied in animals.

Information from animal studies is not adequate to determine whether or not xylene causes cancer in humans. However, exposure of pregnant women to high levels of xylene may cause adverse effects in the fetus. Studies with unborn animals indicate that high levels of xylene may cause increased numbers of deaths, decreased weight, skeletal changes, and delayed skeletal development. In many instances, the levels of xylenes causing these effects also caused the mothers to be ill. The higher the level of exposure and the longer the exposure to xylene, the greater the chance for adverse health effects. Additional information regarding the health effects of xylene can be found in Chapter 2.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Xylene or chemical mixtures containing xylene are deadly to humans if large enough quantities are swallowed or inhaled. However, the levels which cause death in humans are not known. Lower levels (100-299 ppm) of inhaled xylene can cause eye, nose, and throat irritation, delayed response to a visual stimulus, and poor memory. Direct contact of humans with several drops of xylene causes skin irritation. The lowest level at which you can detect the odor (smell) of xylene in air ranges from 0.1 ppm to 2.0 ppm.

In animals, moderate to high levels (1,300-2,000 ppm) of xylene inhaled for short periods of time may cause decreased breathing rate, hearing loss, inactivity, unconsciousness, and biochemical changes in the brain. With longer-term inhalation, adverse health effects in animals generally occur at lower levels (230-800 ppm). In animals breathing high levels of xylene over long-term exposures, possible adverse health effects include changes in heart rate and blood flow, changes in the chemical composition of nerves, and hearing loss. In animals given high levels (5,000 ppm) of xylene orally over short-term exposures, a possible adverse health effect is impaired eye function. In animals exposed by mouth to very high levels (40,000 ppm) of xylene, death can occur.

Tables 1-1 through 1-4 show the relationship between exposure to xylene and known health effects.

TABLE 1-1. Human Health Effects from Breathing Xylene*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects**
100	1 day	Eye, nose, and throat irritation.
299	70 minutes	Delayed response to a visual stimulus and impaired memory during exercise.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects**
		The health effects resulting from long-term exposure of humans to air containing specific levels of xylene are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.
**These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-2. Animal Health Effects from Breathing Xylene

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
1,300	1 minute	Decreased breathing rate in mice.
1,450	8 hours	Hearing loss in rats.
1,940	4.5 hours	Inactivity or unconsciousness in rats.
2,000	3 days	Biochemical changes in brain of rats.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
230	4 weeks	Changes in blood vessels of heart, decreased blood flow in heart, and increased heart rate in rats.
300	18 weeks	Changes in fat and protein composition of nerves in rats.
600	4 weeks	Changes in liver weight in rats.
800	6 weeks	Hearing loss in rats.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-3. Human Health Effects from Eating or Drinking Xylene*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to food containing specific levels of xylene are not known.
Levels in Water		
		The health effects resulting from short-term exposure of humans to water containing specific levels of xylene are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to food containing specific levels of xylene are not known.
Levels in Water		
		The health effects resulting from long-term exposure of humans to water containing specific levels of xylene are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking Xylene

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
5,000	1 day	Impaired eye function in rats.
40,000	14 days	Death in rats.
Levels in Water (ppm)		The health effects resulting from short-term exposure of animals to water containing specific levels of xylene are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of animals to food containing specific levels of xylene are not known.
Levels in Water (ppm)		The health effects resulting from long-term exposure of animals to water containing specific levels of xylene are not known.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

More information about the levels of exposure that have resulted in harmful health effects can be found in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO XYLENE?

Medical tests are available to determine if you have been exposed to xylene at greater than normal background levels. Confirmation of xylene exposure is determined by measuring xylene's breakdown products that are eliminated from the body in the urine. These urinary measurements will specifically determine if you have been exposed to xylene. There is a high degree of agreement between exposure to xylene and the levels of xylene's breakdown products in the urine. A urine sample must be provided soon after exposure ends, because xylene quickly leaves the body. Alcohol and aspirin may affect the test results. Available tests can only indicate exposure to xylene; they cannot be used to predict which health effects, if any, will develop. More information about the detection of xylene can be found in Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The U.S. Environmental Protection Agency (EPA) estimates that for an adult of average weight, exposure to 0.4 milligrams of xylene per liter (mg/L or ppm) of water each day for a lifetime (70 years) is unlikely to result in noncancerous adverse health effects. For a long-term but less than lifetime exposure (about 7 years), 27.3 ppm is estimated to be a level unlikely to result in noncancerous adverse health effects for an adult. Exposure to 12 ppm of xylene in water for 1 day or to 7.8 ppm of xylene in water for 10 days or longer is unlikely to present a noncancerous health risk to a small child. EPA has proposed a recommended maximum level of 0.44 ppm for xylene in drinking water.

To protect individuals from the potential adverse health effects of xylene, the federal government regulates xylene in the environment. The Occupational Safety and Health Administration (OSHA) has set up a legally enforceable occupational exposure limit of 100 ppm of xylene in air averaged over an 8-hour workday, and a 15-minute exposure limit of 150 ppm. The National Institute for Occupational Safety and Health (NIOSH) has recommended an exposure limit of 100 ppm of xylene averaged over a workday up to 10 hours long in a 40-hour work week. NIOSH has also recommended that exposure to xylene not exceed 200 ppm for longer than 15 minutes. NIOSH has classified xylene exposures of 10,000 ppm as immediately dangerous to life or health.

EPA and the Food and Drug Administration (FDA) specify conditions under which xylene may be used as a part of herbicides, pesticides, or articles that are used in contact with food.

EPA reportable quantity regulations require that a spill of 1,000 pounds or more of xylene or used xylene solvents be reported to the Federal Government National Response Center.

More information on government regulations can be found in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to total xylenes. Its purpose is to present levels of significant exposure for total xylenes based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of total xylenes, and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effect. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

2. HEALTH EFFECTS

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1986), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

Tables 2-1 through 2-4 and Figures 2-1 through 2-4 describe the health effects in humans and/or animals associated with inhalation exposure to mixed xylene and xylene isomers.

2.2.1.1 Death

One report was located regarding death in humans following acute inhalation exposure to xylene (Morley et al. 1970). One of three men died after breathing paint fumes for several hours that contained an estimated concentration of 10,000 ppm xylene. Xylene comprised 90% of the solvent in the paint, with solvent comprising 34% of the paint by weight. Clinical signs noted in two exposed men who survived included solvent odor of the breath, cyanosis of the extremities, and neurological impairment (temporary confusion, amnesia). Both of these men recovered completely. The authors hypothesized that anoxia did not contribute to the effects observed because diffusion of oxygen into the area in which the men were working should have been sufficient to maintain the level of oxygen. No studies were located regarding mortality in humans after intermediate or chronic inhalation exposure to mixed xylene or xylene isomers.

Acute inhalation LC_{50} values have been determined in animals for xylene and its isomers (Bonnet et al. 1979; Carpenter et al. 1975; Hine and Zuidema 1970). The 4-hour LC_{50} value for mixed xylene in rats ranged between 6,350 ppm (Hine and Zuidema 1970) and 6,700 ppm (Carpenter et al. 1975). The 4-hour LC_{50} value for p-xylene in rats was reported to be 4,740 ppm (Harper et al. 1975). In mice, the 6-hour LC_{50} values for m-xylene, o-xylene, and p-xylene were determined to be 5,267 ppm, 4,595 ppm, and 3,907 ppm, respectively (Bonnet et al. 1979). According to the toxicity classification system of Hodge and Sterner (1949), these values indicate that mixed xylene and its isomers are slightly toxic by acute inhalation. Death from inhalation of xylene is reportedly caused by respiratory failure and/or sudden ventricular fibrillation (Gosselin et al. 1984).

TABLE 2-1. Levels of Significant Exposure to Mixed Xylene - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4hr/d		580		6700 (LC50)	Carpenter et al. 1975
2	Rat	1 d 4hr/d				6350 (LC50)	Hine and Zuidema 1970
Systemic							
3	Human	1 d 30min/d	Resp Derm/Oc	396 396			Hastings et al. 1986
4	Human	5 d 3d/wk 70min/d	Cardio	299			Gamberale et al. 1978
5	Human	1 d 1x/d	Derm/Oc		460 (eye irritation)		Carpenter et al. 1975
6	Rat	1 d 45min/d	Hemato	15000			Carpenter et al. 1975
7	Mouse	1 d 1min/d	Resp	460	1300[b] (decreased respiratory rate)		Carpenter et al. 1975
Neurological							
8	Human	1 d 30 min/d		396			Hastings et al. 1986
9	Human	5 d 3d/wk 70min/d		299			Gamberale et al. 1978
10	Human	1 d 70min/d			299[a] (impairment in performance tests while exercising)		Gamberale et al. 1978
11	Rat	1 d 4hr/d		1700			Pryor et al. 1987

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
12	Rat	3 d 6hr/d			2000[b] (increased dopamine and catecholamine in brain)		Andersson et al. 1981
13	Rat	1 d 8hr/d			1450[b] (hearing loss)		Pryor et al. 1987
Developmental							
14	Rat	6 d Gd9-14 24hr/d			230 (increased fetal anomalies)		Hudak and Ungvary 1978
15	Rat	9 d 24hr/d Gd7-15			58 (skeletal retardation)	784 (increased fetal death and resorption)	Ungvary and Tatrai 1985
16	Rat	9 d 24hr/d Gd7-15				53 (skeletal retardation, embryolethality)	Balogh et al. 1982
INTERMEDIATE EXPOSURE							
Systemic							
17	Rat	13 wk 5d/wk 6hr/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Other	810 810 810 810 810 810 810 810			Carpenter et al. 1975
18	Rat	4 wk 5d/wk 6hr/d	Cardio		230[b] (coronary changes)		Morvai et al. 1987
19	Rat	90 d 24hr/d	Hepatic	320			Kyrklund et al. 1987

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
20	Rat	18 wk 5d/wk 6hr/d	Hepatic	300			Elovaara et al. 1980
21	Rat	4 wk 5d/wk 6hr/d	Hepatic		600[b] (increased liver weight)		Toftgard et al. 1981
22	Dog	13 wk 5d/wk 6hr/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Other	810 810 810 810 810 810 810 810			Carpenter et al. 1975
Neurological							
23	Rat	6 wk 7d/wk 14hr/d			800[b] (hearing loss)		Pryor et al. 1987
24	Rat	18 wk 5d/wk 6hr/d			300 (CNS effects)		Savolainen et al. 1979a
25	Rat	90 d 24hr/d		320			Kyrklund et al. 1987
26	Rat	18 wk 5d/wk 6hr/d			300[b] (decreased membrane lipids in axon membranes)		Savolainen and Seppalainen 1979
27	Gerbil	3 mo 30d/mo 24hr/d		160	320 (proteins increased in brain)		Rosengren et al. 1986

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Developmental							
28	Rat	166 d 7d/wk 6hr/d			60 (decreased pup weight)		Bio/dynamics 1983
Reproductive							
29	Rat	166 d 7d/wk 6hr/d		500			Bio/dynamics 1983

[a]This concentration is presented in Table 1-1.
[b]This concentration is presented in Table 1-2.

Cardio = cardiovascular; CNS = central nervous system; d = day; Derm/Oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; hr = hour; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; min = minute; mo = month; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; ppm = parts per million; Resp = respiratory; wk = week

TABLE 2-2. Levels of Significant Exposure to m-Xylene - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Mouse	1 d 6hr/d				5267 (LC50)	Bonnet et al. 1979
Neurological							
2	Rat	1 d 4.5hr/d			2100 (narcosis)		Molnar et al. 1986
3	Rat	3 d 6hr/d			2000 (increased brain levels of catecholamine)		Andersson et al. 1981
Developmental							
4	Rat	8 d Gd7-14 24hr/d		345	691 (decreased fetal weight)		Ungvary et al. 1980b
INTERMEDIATE EXPOSURE							
Neurological							
5	Mouse	7 wk 5d/wk 4hr/d			1600 (decreased alpha-adrenergic binding in brain)		Rank 1985

d = day; hr = hour; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ppm = parts per million; wk = week

TABLE 2-3. Levels of Significant Exposure to o-Xylene - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Mouse	1 d 6hr/d				4595 (LC50)	Bonnet et al. 1979
Neurological							
2	Rat	3 d 6hr/d			2000 (increased brain levels of catecholamine)		Andersson et al. 1981
3	Rat	1 d 4.5hr/d			2180 (narcosis)		Molnar et al. 1986
Developmental							
4	Rat	8 d Gd7-14 24hr/d		34.5	345 (decreased fetal weight)		Ungvary et al. 1980b

d = day; Gd = gestation day; hr = hour; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ppm = parts per million; Resp = respiratory

TABLE 2-4. Levels of Significant Exposure to p-Xylene - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 4hr/d				4740 (LC50)	Harper et al. 1975
2	Mouse	1 d 6hr/d				3907 (LC50)	Bonnet et al. 1979
Systemic							
3	Human	5 d 1x/d	Resp Cardio Other	100 100	100[a] (ENT irritation)		Hake et al. 1981
Neurological							
4	Human	5 d 1x/d		100			Hake et al. 1981
5	Rat	1 d 4.5hr/d			1940[b] (narcosis)		Molnar et al. 1986
6	Rat	3 d 6hr/d			2000 (increased brain levels of catecholamine)		Andersson et al. 1981
7	Rat	1.5 wk 5d/wk 6hr/d			800 (decreased axonal transport)		Padilla and Lyerly 1989

TABLE 2-4 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Developmental							
8	Rat	10 d Gd7-16 6hr/d		1612			Rosen et al. 1986
9	Rat	48 hr Gd9-10 24hr/d			691 (decreased fetal weight)		Ungvary et al. 1981

[a]This concentration is presented in Table 1-1.
[b]This concentration is presented in Table 1-2.

1x = one time; Cardio = cardiovascular; d = day; ENT = ear, nose, throat; Gd = gestation day; ppm = parts per million; hr = hour; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week

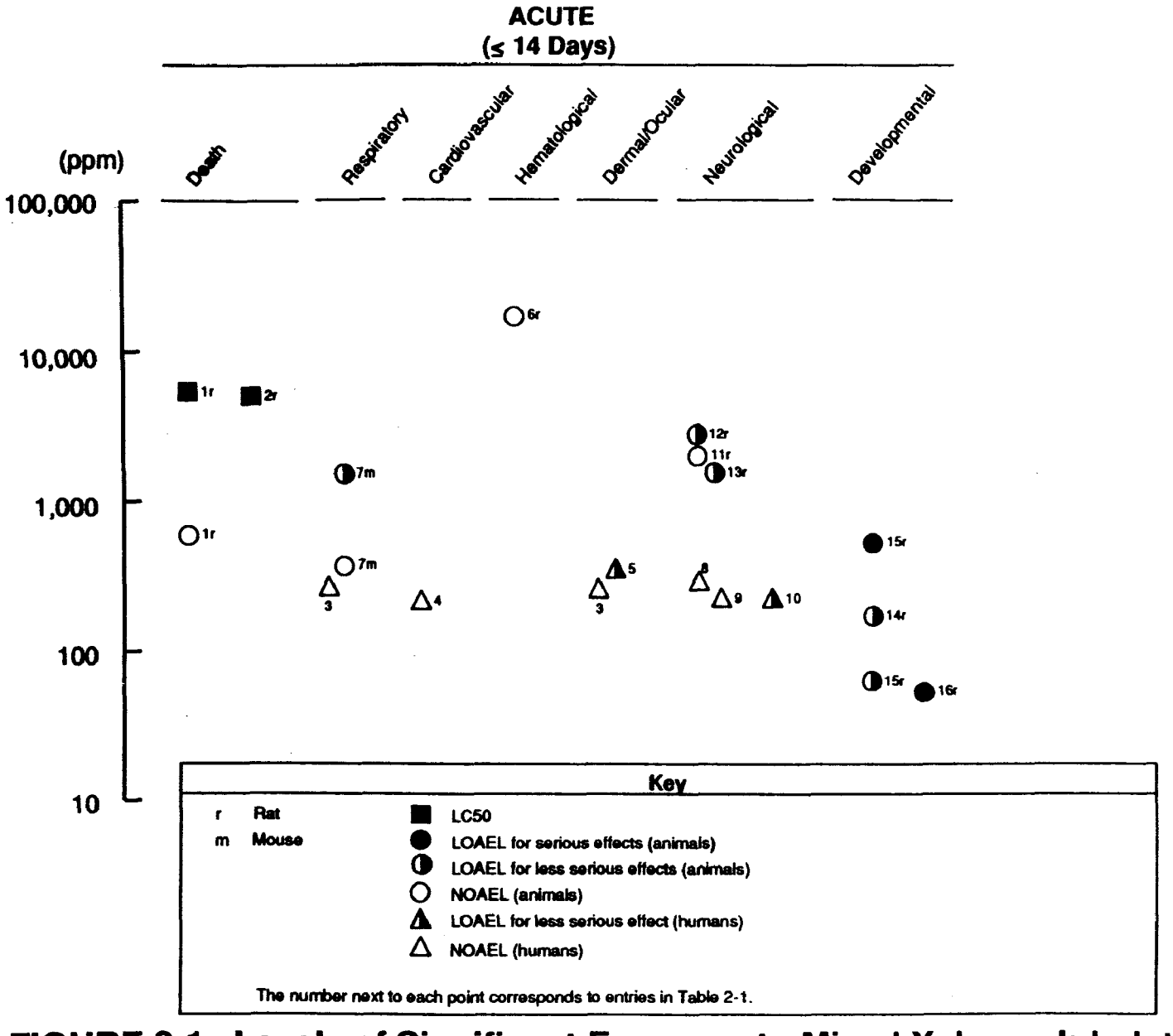

FIGURE 2-1. Levels of Significant Exposure to Mixed Xylene - Inhalation

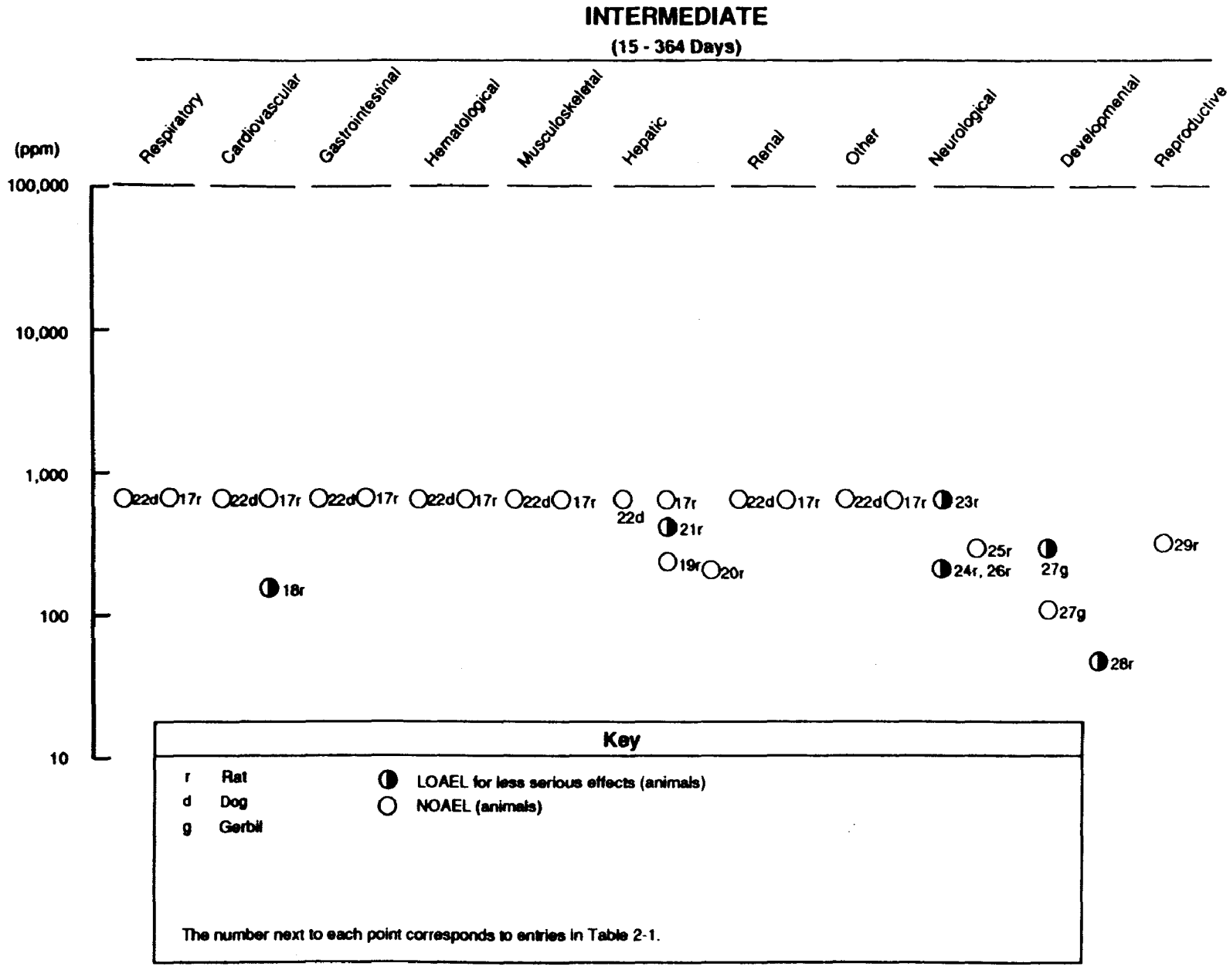

FIGURE 2-1 (Continued)

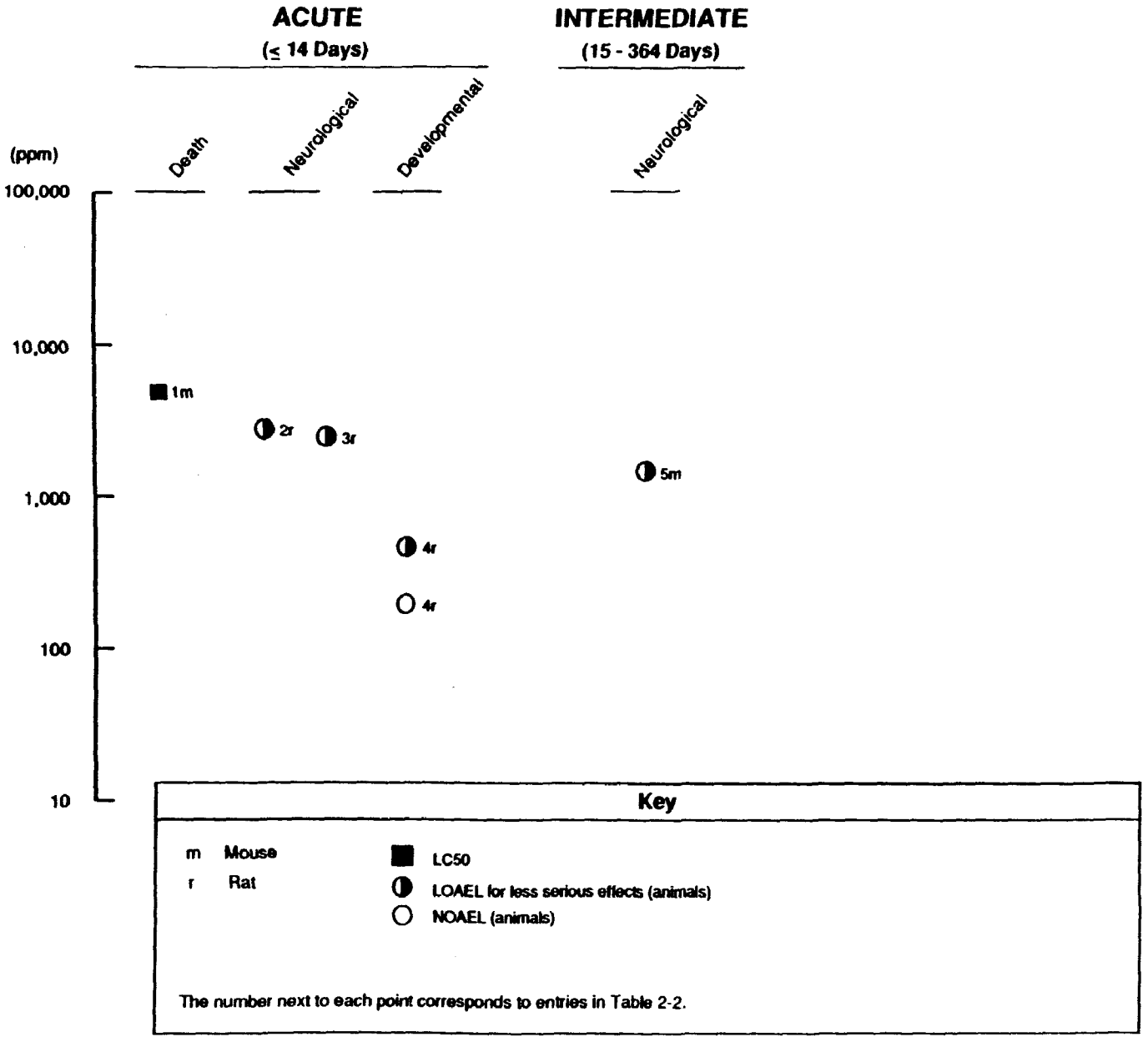

FIGURE 2-2. Levels of Significant Exposure to m - Xylene - Inhalation

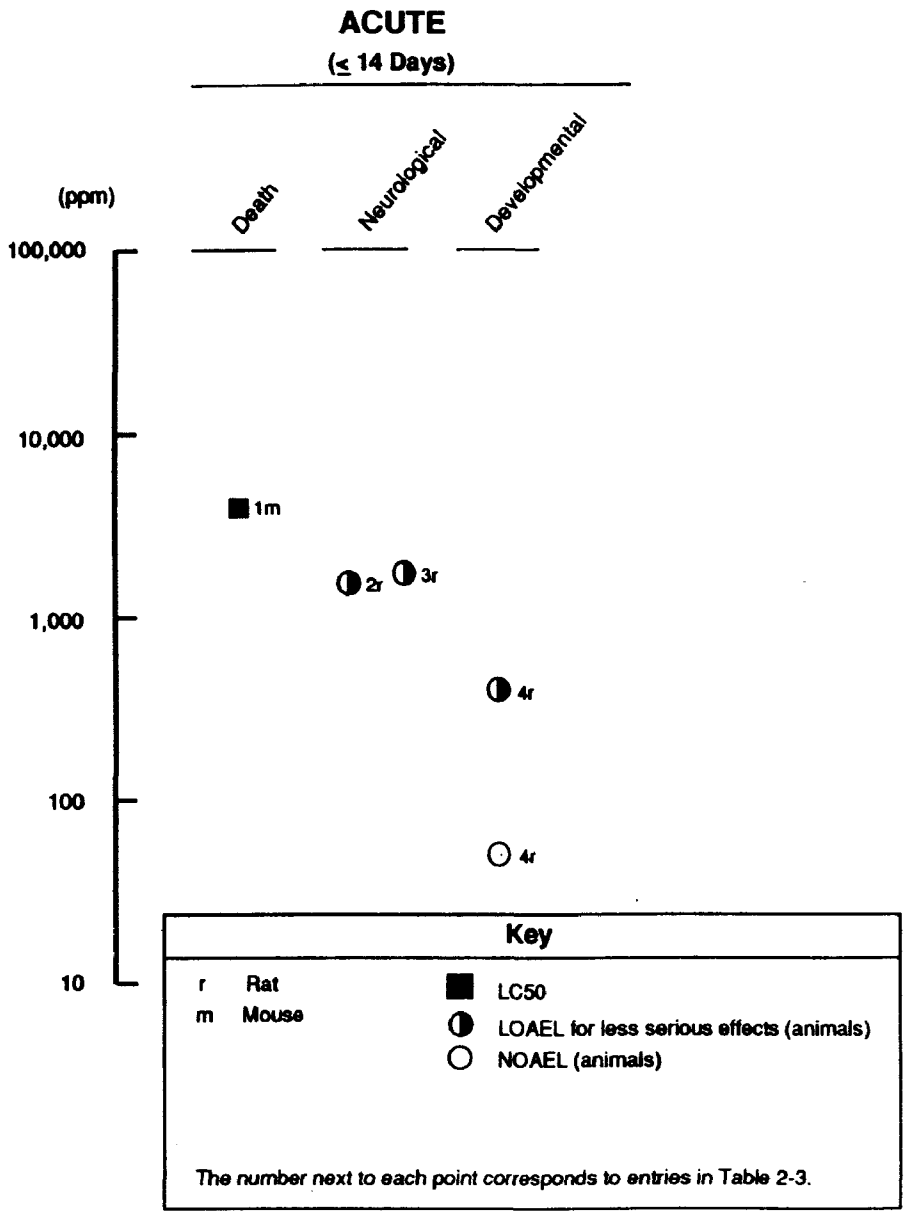

FIGURE 2-3. Levels of Significant Exposure to o - Xylene - Inhalation

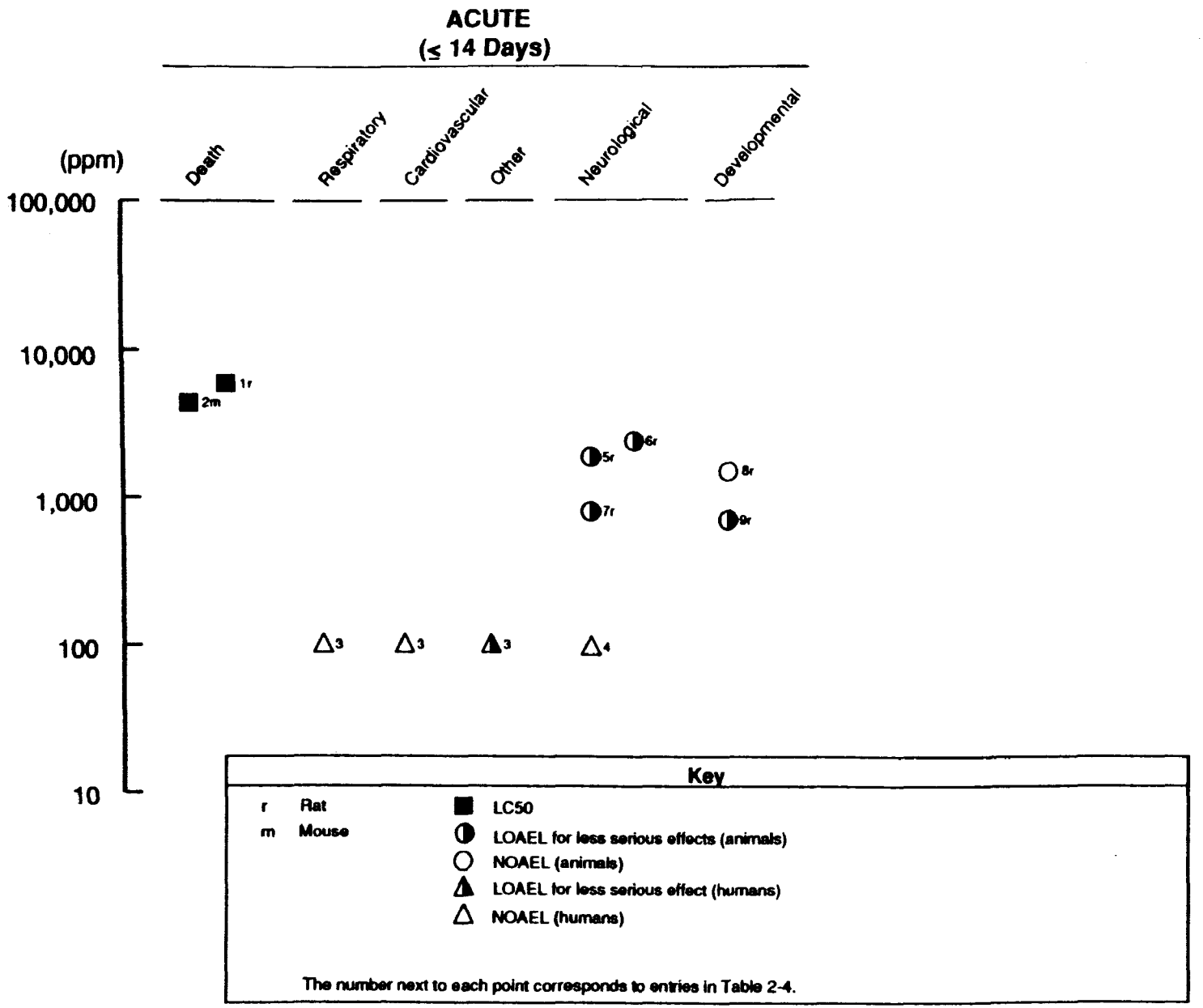

FIGURE 2-4. Levels of Significant Exposure to p - Xylene - Inhalation

Other acute studies with rats and mice have shown that animal lethality is determined by length of exposure and concentration. No deaths occurred after exposure to concentrations ranging from 1,005 ppm m-xylene over a period of 14 days to 8,982 ppm p-xylene for only 1 hour (Cameron et al. 1938; Klimisch et al. 1988). No studies were located regarding death in animals after intermediate or chronic inhalation exposure to mixed xylene or xylene isomers.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Tables 2-1 through 2-4 and plotted in Figures 2-1 through 2-4.

2.2.1.2 Systemic Effects

Respiratory Effects. Respiratory effects following inhalation exposure to xylene have been observed in humans and animals. In humans, inhalation exposure to mixed xylene and p-xylene has been associated with dyspnea and irritation of the nose and throat at a concentration as low as 100 ppm p-xylene for an acute exposure period (Goldie 1960; Hake et al. 1981; Klaucke et al. 1982; Nersesian et al. 1985). However, no increase in reports of nose and throat irritation and no change in respiratory rate were obtained in a study of subjects exposed to mixed xylenes at concentrations as high as 398 ppm (Hastings et al. 1986). An autopsy revealed that exposure to 10,000 ppm of xylene produced severe lung congestion with focal intra-alveolar hemorrhage and pulmonary edema in one worker who died following exposure to xylene fumes for several hours while painting (Morley et al. 1970). Human subjects exposed to concentrations ranging from 20 ppm to 150 ppm p-xylene for 6 weeks had nose and throat irritation, but no pulmonary ventilation effects (Hake et al. 1981). Chronic occupational exposure of workers to vapors of mixed xylene has also been associated with labored breathing and impaired pulmonary function (Hipolito 1980; Roberts et al. 1988).

Adverse respiratory effects noted in rats, mice, and guinea pigs following acute and intermediate inhalation exposure to xylene are similar to those observed in humans. They include decreased respiration, labored breathing, irritation of the respiratory tract, pulmonary edema, pulmonary hemorrhage, and pulmonary inflammation (Carpenter et al. 1975; De Ceaurriz et al. 1981; Furnas and Hine 1958). Concentrations of 1,300 ppm mixed xylene (Carpenter et al. 1975) or 1,467 ppm o-xylene (De Ceaurriz et al. 1981) produced a 50% decrease in respiratory rate in mice. No histopathological changes in the lungs were evident in rats, guinea pigs, or monkeys following intermediate exposure to concentrations ranging between 78 ppm and 810 ppm mixed xylene or o-xylene (Carpenter et al. 1975; Jenkins et al. 1970). No

animal studies were located that evaluated the respiratory effects of mixed xylene or single isomers following chronic inhalation exposure.

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Tables 2-1 and 2-4 and plotted in Figures 2-1 and 2-4.

Cardiovascular Effects. Limited human and animal data are available regarding the cardiovascular effects of xylene following inhalation exposure. Chronic occupational exposure to xylene along with other chemical agents resulted in complaints of increased heart palpitation, severe chest pain, and an abnormal ECG (Hipolito 1980; Sukhanova et al. 1969). No cardiovascular effects were noted in humans exposed for an acute or intermediate period to either 100 or 150 ppm p-xylene (Hake et al. 1981) or exposed acutely to 299 ppm mixed xylene (Gamberale et al. 1978).

Data regarding cardiovascular effects in animals are limited. Morphological changes in coronary microvessels (increased vascular tone), decreased myocardial blood flow, and increased heart weight were noted in rats exposed to 230 ppm xylene (unspecified composition) for 4 weeks (Morvai et al. 1987). Other effects seen in rats inhaling unspecified high (lethal) concentrations of xylene of unknown composition included ventricular repolarization disturbances, atrial fibrillation, arrhythmias, cardiac arrest, and ECG changes (Morvai et al. 1976). However, histopathological examination of rats, guinea pigs, or monkeys exposed for an intermediate period (13-18 weeks) to concentrations of mixed xylene or o-xylene ranging between 78 ppm and 810 ppm revealed no adverse effects upon the heart (Carpenter et al. 1975; Jenkins et al. 1970). No information was located regarding cardiovascular effects in animals after chronic exposure to mixed xylene or its isomers.

The highest NOAEL values and all reliable LOAEL values for cardiovascular effects in each species and duration category are recorded in Tables 2-1 and 2-4 and plotted in Figures 2-1 and 2-4.

Gastrointestinal Effects. Symptoms of nausea, vomiting, and gastric discomfort have been noted in case reports of workers exposed by inhalation to xylene (Goldie 1960; Klaucke et al. 1982; Nersesian et al. 1985). These symptoms subsided after cessation of the xylene exposure. Samples of air taken from the sites at which persons experienced these symptoms revealed that air concentrations of xylene ranged from 1.8 to 18.7 ppb in one case of gastric disturbance (Nersesian et al. 1985). Other quantitative estimates of xylene concentrations were not provided. The isomeric composition of xylene in these case studies also was not reported.

Limited data were located regarding gastrointestinal effects in animals. No lesions were observed in the gastrointestinal tract of rats and dogs exposed to concentrations as high as 810 ppm mixed xylene for an intermediate period of time (Carpenter et al. 1975). These NOAEL values are recorded in Table 2-1 and plotted in Figure 2-1. No studies were located regarding gastrointestinal effects in animals after acute or chronic inhalation exposure to mixed xylene or the isomers of xylene.

Hematological Effects. Human and animal data provide no indication of adverse hematological effects following inhalation of xylene.

Previously, chronic occupational exposure to xylene by inhalation was thought to be associated with a variety of hematological effects. However, exposure in all cases was to solvent mixtures known or suspected to contain benzene. Because benzene is an agent strongly suspected of causing leukemia and other blood dyscrasias in humans, these effects cannot be solely attributed to xylene (ECETOC 1986). More recent epidemiological studies suggest a possible relationship between coal-based xylene exposure and hematological effects (leukemia) (Arp et al. 1983; Wilcosky et al. 1984). Both of these studies examined workers in the rubber and tire manufacturing industry and were limited by the small number of subjects, unknown composition of xylene, exposure to other chemicals, and imprecise historical exposure estimates.

No adverse hematological effects have been observed in rats or dogs following acute or intermediate inhalation exposure to concentrations of mixed xylene as high as 810 ppm for blood chemistry parameters (intermediate exposure) or 15,000 ppm for erythrocyte fragility (acute exposure) (Carpenter et al. 1975). The highest NOAEL values for hematological effects are recorded in Table 2-1 and plotted in Figure 2-1.

Musculoskeletal Effects. No data were available regarding musculoskeletal effects in humans following inhalation exposure to mixed xylene or individual isomers. Animal data regarding musculoskeletal effects following inhalation of xylene provide no indication that xylene produces musculoskeletal effects. No lesions were observed in the skeletal muscle of rats and dogs exposed for an intermediate period of time to concentrations as high as 810 ppm mixed xylene (Carpenter et al. 1975). These NOAEL values are recorded in Table 2-1 and plotted in Figure 2-1.

Hepatic Effects. Human data regarding hepatic effects following inhalation of xylene are limited to several case and occupational studies (Dolara et al. 1982; Kurppa and Husman 1982; Morley et al. 1970). These studies are inadequate for evaluating the hepatic effects of xylene, because

their subjects were concurrently exposed to other chemical agents in addition to xylene.

Animal studies using rats indicate that mixed xylene, m-xylene, o-xylene, or p-xylene generally induce a wide variety of hepatic enzymes, as well as increase hepatic cytochrome P-450 content in rats (Elovaara 1982; Elovaara et al. 1980; Patel et al. 1979; Savolainen et al. 1978; Toftgard and Nilsen 1981, 1982; Toftgard et al. 1981; Ungvary et al. 1980a). Many hepatic effects appear after intermediate exposure. They include increased hepatic weight in rats (Tatrai and Ungvary 1980; Toftgard et al. 1981), increased transient liver-to-body weight ratios in rats (Kyrklund et al. 1987; Toftgard et al. 1981); decreased hepatic glycogen in rats (Tatrai and Ungvary 1980; Ungvary et al. 1980b), ultrastructural changes in size hepatic endoplasmic reticulum in rats (Tatrai and Ungvary 1980); and changes in the distribution of hepatocellular nuclei in rats (Tatrai and Ungvary 1980). Conversely, upon histopathologic examination, no treatment-related effects were noted in rats, guinea pigs, or monkeys following intermediate exposure to concentrations as high as 810 ppm mixed xylene or o-xylene (Carpenter et al. 1975; Jenkins et al. 1970). Increased liver weight and microsomal enzyme activity were reported in a study in which rats were exposed to o-xylene for one year (Tatrai et al. 1981). Electron microscopic examination of liver tissue revealed a proliferation of the endoplasmic reticulum and only very minor toxic effects on mitochondria as exemplified by increased numbers of perixosomes. These authors concluded that the increase in liver weight produced by chronic exposure to o-xylene is an adaptive rather than a toxic effect.

The highest NOAEL values and a reliable LOAEL value for hepatic effects in rats exposed for an intermediate period to mixed xylene are recorded in Table 2-1 and plotted in Figure 2-1.

Renal Effects. Limited data from case reports and occupational studies suggest that inhalation exposure to solvent mixtures containing xylene may be associated with renal effects in humans (Askergren 1981, 1982; Askergren et al. 1981b, 1981c; Franchini et al. 1983; Martinez et al. 1989; Morley et al. 1970). These effects included increased blood urea concentrations, decreased urinary clearance of endogenous creatinine, increased lysozymuria, increased urinary levels of β-glucuronidase, and increased urinary excretion of albumin, erythrocytes, and leukocytes. However, no definitive conclusions can be made from these renal effects from xylene inhalation exposure because of confounding exposures to other solvents.

The renal effects of mixed xylene and xylene isomers following inhalation exposure have been evaluated in acute and intermediate studies with rats, guinea pigs, dogs, and monkeys (Carpenter et al. 1975; Elovaara 1982; Jenkins et al. 1970; Toftgard and Nilsen 1982). Effects noted in these

studies at xylene concentrations of 50-2,000 ppm have included increased renal enzyme activity, increased renal cytochrome P-450 content, and increased kidney-to-body weight ratios (o-xylene exposed rats) (Elovaara 1982; Toftgard and Nilsen 1982). However, histopathologic examination of rats, guinea pigs, dogs, and monkeys did not reveal any renal lesions after inhalation of 810 ppm mixed xylene or 78 ppm o-xylene for an intermediate period of time (Carpenter et al. 1975; Jenkins et al. 1970).

No chronic animal studies were located regarding renal effects following inhalation exposure to mixed xylene, m-, o-, or p-xylene.

The highest NOAEL values for renal effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Dermal/Ocular Effects. No human or animal data were available regarding dermal effects following inhalation exposure to mixed xylene or xylene isomers. However, limited human data indicate that acute inhalation exposure to mixed xylene and p-xylene vapors produces mild transient eye irritation following inhalation at concentrations ranging from 100 ppm p-xylene to 460 ppm mixed xylene (Carpenter et al. 1975; Hake et al. 1981; Nelson et al. 1943). However, exposure to concentrations of mixed xylene as high as 396 ppm produced no increase in subjective reports of eye irritation or in the number of eyeblinks in human subjects (Hastings et al. 1986). The highest NOAEL value and all reliable LOAEL values for dermal/ocular effects are recorded in Tables 2-1 and 2-4 and plotted in Figures 2-1 and 2-4.

No studies were located regarding dermal/ocular effects in animals following inhalation exposure to mixed xylene or individual isomers.

2.2.1.3 Immunological Effects

No determination can be made regarding the association between inhalation of xylene and immunological effects from available human studies, because workers were concurrently exposed to other chemical agents (Moszczynski and Lisiewicz 1983; Smolik et al. 1973; Sukhanova et al. 1969). No studies were located regarding immunological effects in animals following inhalation exposure to mixed xylene or xylene isomers.

2.2.1.4 Neurological Effects

The neurological effects of xylene in humans following inhalation exposure have been evaluated in a number of experimental studies, case reports, and occupational studies. Results of experimental studies with humans indicate that acute inhalation exposure to mixed xylene or m-xylene causes impaired short-term memory, impaired reaction time, performance decrements in

numerical ability, and alterations in equilibrium and body balance (Gamberale et al. 1978; Riihimaki and Savolainen 1980; Savolainen and Riihimaki 1981b; Savolainen and Linnavuo 1979; Savolainen et al. 1979b, 1984, 1985).

Acute exposure to 299 ppm mixed xylene while performing physical exercise produced impairment in a variety of tests of central nervous system performance. However, exposure to 299 ppm (Gamberale et al. 1978) or 398 ppm (Hastings et al. 1986) mixed xylene at rest had no effect on performance tests. Exercise appears to increase the uptake of xylene. Concentrations of m-xylene fluctuating between 64 and 400 ppm produced impairment in human body balance (Savolainen and Riihimaki 1981b; Savolainen et al. 1979b) and concentrations fluctuating between 135 and 400 ppm produced slight decrease in the latency of visual evoked potentials (Seppalainen et al. 1989). Other studies also reported impaired body balance following acute exposure to m-xylene (Riihimaki and Savolainen 1980; Savolainen et al. 1984, 1985).

Neurological effects following acute or intermediate inhalation exposure to p-xylene have not been observed in experimental studies with humans at concentrations ranging from 64-150 ppm (Hake et al. 1981; Olson et al. 1985). Differences in such factors as the xylene isomer, the neurological parameter, exposure conditions and concentrations, rapid development of tolerance, and total xylene uptake may account for the disagreements in results.

Available case reports and occupational studies are difficult to evaluate because exposure conditions in the studies generally are not well characterized and/or subjects may have been exposed to other chemical agents in addition to xylene (Arthur and Curnock 1982; Goldie 1960; Hipolito 1980; Klaucke et al. 1982; Morley et al. 1970; Nersesian et al. 1985; Roberts et al. 1988). Available case reports and occupational studies together provide suggestive evidence that acute and chronic inhalation exposure to xylene or solvent mixtures containing xylene may be associated with neurological effects and symptoms. They include headache, nausea, dizziness, fatigue, agitation, confusion, tremors, labored breathing, incoordination, and sensitivity to noise. In several case reports, isolated instances of unconsciousness, amnesia, brain hemorrhage, and epileptic seizure have been associated with acute inhalation exposure to solvent mixtures containing xylene (Arthur and Curnock 1982; Goldie 1960; Morley et al. 1970). Because other chemicals were present with xylenes in many of these studies, the effects observed cannot be conclusively attributed to xylene exposure.

Results of experimental studies with animals also provide evidence that mixed xylene and its isomers are neurotoxic following inhalation exposure. Signs of neurotoxicity observed in rats, mice, and gerbils following acute and intermediate inhalation exposure to the various xylene isomers include narcosis, prostration, incoordination, tremors, muscular spasms, labored breathing, behavioral changes, hyperreactivity to stimuli, elevated auditory

thresholds, hearing loss, changes in brain enzyme activity, and biochemical changes in the brain (Andersson et al. 1981; Bushnell 1989; Carpenter et al. 1975; De Ceaurriz et al. 1983; Furnas and Hine 1958; Ghosh et al. 1987; Kyrklund et al. 1987; Molnar et al. 1986; Pryor et al. 1987; Rank 1985; Rosengren et al. 1986; Savolainen and Seppalainen 1979; Savolainen et al. 1978, 1979b; Wimolwattanapun et al. 1987).

Exposure levels associated with neurological effects in animals are well defined. Acute concentrations inducing behavioral changes in rats and mice ranged from 113 ppm for effects of mixed xylene on operant conditioning or self-stimulation behavior (Ghosh et al. 1987; Wimolwattanapun et al. 1987) to 1,010 ppm for o-xylene-induced immobility in a "behavioral despair swimming test" (De Ceaurriz et al. 1983). Acute exposure to 1,600 ppm p-xylene produced hyperactivity (Bushnell 1989) and 1,300 ppm mixed xylene produced incoordination in rats which did not persist after exposure ended; no overt signs of toxicity were noted at 580 ppm (Carpenter et al. 1975). Acute exposure to p-xylene caused decreased axonal transport at concentrations as low as 800 ppm (Padilla and Lyerly 1989), however no such decrease was apparent three days after exposure had ceased. At concentrations of 1,600 ppm, however, the decrease in axonal transport persisted for 13 days after exposure. All three isomers produced narcosis in rats after 1-4 hours' exposure to concentrations of approximately 2,000 ppm (Molnar et al. 1986). Hearing loss occurred in rats exposed to 1,450 ppm mixed xylene for 8 hours, whereas exposure to 1,700 ppm for 4 hours produced no effects on hearing (Pryor et al. 1987) indicating that the duration of exposure is important for the observation of ototoxic effects. Acute inhalation of 2,000 ppm mixed xylene produced increased dopamine and/or noradrenaline levels in the hypothalamus of rats; no behavioral changes were assessed (Andersson et al. 1981). Levels of catecholamine in the hypothalamus of rats were increased following inhalation of 2,000 ppm mixed xylene, m-, o-, or p xylene (Andersson et al. 1981).

In intermediate inhalation studies with animals, neurological effects have been observed following exposure to approximately 300 ppm of xylene. Brain concentrations of DNA and/or astroglial proteins increased in rats and gerbils after intermediate exposure to 300-320 ppm xylene (Rosengren et al. 1986; Savolainen and Seppalainen 1979). In addition, increased levels of brain enzymes, changes in nerve axon membranes, and behavioral changes occurred in rats after exposure to 300 ppm of mixed xylene for 18 weeks (Savolainen and Seppalainen 1979; Savolainen et al. 1979a). Hearing loss was also evident after exposure for 6 weeks to 800 ppm (Pryor et al. 1987). However, no significant long-term alterations in fatty acid levels were noted in the brains of rats after intermediate exposure to 320 ppm mixed xylene (Kyrklund et al. 1987).

No animal studies were located regarding neurological effects following chronic inhalation exposure to mixed xylene or its isomers.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Tables 2-1 through 2-4 and plotted in Figures 2-1 through 2-4.

2.2.1.5 Developmental Effects

Human data are limited for assessing the relationship between inhalation of xylene and developmental effects, because the available studies involved concurrent exposure to other chemical agents in addition to xylene in the workplace (Holmberg and Nurminen 1980; Kucera 1968; Taskinen et al. 1989) and because of the small number of subjects (Taskinen et al. 1989).

Both mixed xylene and the individual isomers produce fetotoxic effects in laboratory animals. Effects of mixed xylene observed in rats and mice included increased incidences of skeletal variations in fetuses, delayed ossification, fetal resorptions, hemorrhages in fetal organs, and decreased fetal body weight (Balogh et al. 1982; Bio/dynamics 1983; Hudak and Ungvary 1978; Litton Bionetics 1978a; Mirkova et al. 1983; Ungvary and Tatrai 1985). The levels at which these effects were observed depended upon the composition and concentration of mixed xylene, and the choice of strain and test species used. In addition, animals in a number of studies were exposed 24 hr/day (Balogh et al. 1982; Hudak and Ungvary 1979; Ungvary and Tatrai 1985), whereas animals in other studies (Bio/dynamics 1983; Litton Bionetics 1978a; Mirkova et al. 1983) were exposed 6 hr/day. The study conducted by Litton Bionetics (Litton Bionetics 1978a) used a formulation of mixed xylene with a comparatively high percentage (36%) of ethylbenzene. Developmental effects occurred following maternal exposure to concentrations as low as 12 ppm mixed xylene in rats (Mirkova et al. 1983), but the health of the test animals may have been compromised. This is suggested by the relatively low conception rates and the high incidence of fetal hemorrhages seen in the controls. Maternal toxicity was observed at 775 ppm in the study by Balogh et al. (1982) whereas no maternal toxicity occurred in the studies by Bio/dynamics (1983), Hudak and Ungvary (1978) and Litton Bionetics (1978a). Insufficient evidence was presented to determine whether maternal toxicity occurred in the studies by Mirkova et al. (1983) and Ungvary and Tatrai (1985). Many of the studies (Bio/dynamics 1983; Hudak and Ungvary 1978; Mirkova et al. 1983; Ungvary and Tatrai 1985) had limitations that made them difficult to assess (e.g., unknown composition of xylene and insufficient number of doses to form a dose-response relationship; lack of detail with regard to both methods and data obtained). An increase in placental weight was seen at 438 and 775 ppm in the study by Balogh et al. (1982). The biological significance of this effect is unknown.

Inhalation of m-, o-, or p-xylene at concentrations similar to those at which mixed xylenes caused fetal toxicity, produced decreased fetal weight, skeletal retardation and post-implantation loss in rats following maternal exposure (Ungvary and Tatrai 1985; Ungvary et al. 1980b, 1981). Both increases and decreases in placental weight were evident in rats following inhalation of 345 ppm o-xylene and p-xylene (Ungvary et al. 1980b). As noted above, the biological significance of changes in placental weight is unknown. A NOAEL value of 1,612 ppm p-xylene for developmental effects was determined from one study with rats (Rosen et al. 1986). The large variation in concentrations of xylene producing developmental effects and those producing no developmental effects may be influenced by a number of factors (e.g., strain and species of animal, purity of xylene, method of exposure, exposure duration, etc.). For example, Rosen et al. (1986) exposed animals for 6 hr/day whereas animals were exposed 24 hr/day in studies by Ungvary and Tatrai (1985) and Ungvary et al. (1980b, 1981). No information on maternal toxicity was available for the studies by Ungvary and Tatrai (1985) or Ungvary (1981); however, in the studies by Rosen et al. (1986) and Ungvary et al. (1980b) signs of maternal toxicity in rats following inhalation of the isomers included decreased weight gain, decreased food consumption, and increased liver-to-body weight ratios. m-Xylene was the only isomer that resulted in lasting maternal growth inhibition or maternal mortality (Ungvary et al. 1980b).

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Tables 2-1 through 2-4 and plotted in Figures 2-1 through 2-4.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to mixed xylene or to xylene isomers.

In male and female rats, no adverse reproductive effects were noted following inhalation exposure of mixed xylene at concentrations as high as 500 ppm during premating, mating, pregnancy, and lactation (Bio/dynamics 1983). This NOAEL value is recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

Limited human and animal data are available regarding the genotoxic effects of mixed xylene following inhalation exposure. No inhalation studies were available on the genotoxicity of m-xylene, o-xylene, or p-xylene. Results of a study by Pap and Varga (1987) suggests that inhalation exposure of humans to mixed xylene is not associated with the induction of sister-chromatid exchanges or chromosomal aberrations. Results of other investigations were also negative for chromosomal aberrations in humans or

rats exposed by inhalation to xylene; however, the isomeric composition of the xylene in these studies was not reported (Haglund et al. 1980; Zhong et al. 1980). The negative findings of these inhalation studies are supported by the consistently negative results found in other genotoxicity assays in which bacteria, yeast, insects, mammals, and mammalian cells have been exposed *in vitro* or *in vivo* to mixed xylene or to individual isomers (See Section 2.4).

2.2.1.8 Cancer

Human data regarding cancer are limited to occupational studies. These studies examined the cancer and leukemia risks among solvent-exposed workers (Arp et al. 1983, Wilcosky et al. 1984). Both contain limitations (e.g., small number of subjects, no exposure concentrations, unknown composition of xylene) that preclude a definitive conclusion regarding inhalation of xylene and cancer. No studies were located regarding cancer in animals exposed via inhalation to mixed xylene or xylene isomers.

2.2.2 Oral Exposure

Tables 2-5 through 2-8 and Figures 2-5 through 2-8 describe the health effects in humans and/or animals associated with oral exposure to mixed xylene and xylene isomers. The exposure level and exposure duration associated with these health effects are also presented.

2.2.2.1 Death

Death in humans following accidental or intentional ingestion of xylene or mixtures containing xylene was reported (Abu al Ragheb et al. 1986; Bernardelli and Gennari 1987). In one case, levels of xylene found in blood and gastric and duodenal contents were 110 mg/L, 8,800 mg/L, and 33,000 mg/L, respectively, indicating ingestion of a large, but undetermined, quantity of xylene (Abu Al Ragheb et al. 1986).

Mortality was observed in laboratory animals following the ingestion of mixed xylene and isomers of xylene. Two females from a group of ten that were given *p*-xylene (2,000 gm/kg) orally for ten days died (Condie et al. 1988). Acute LD50s have been determined for mixed xylene and *m*-xylene in rats and mice (Table 2-9). Reported acute oral LD50s in rats for mixed xylene range from 3,523 mg/kg when administered in corn oil (NTP 1986) to 8,600 mg/kg when administered as an undiluted sample (Hine and Zuidema 1970). The acute oral LD50 for mixed xylene in male and female mice was determined to be 5,627 mg/kg and 5,251 mg/kg, respectively (NTP 1986). An LD50 for *m*-xylene in rats was reported as 6,631 mg/kg (Smyth et al. 1962). The wide range of LD50 values in rats may be due to differences in xylene composition, strain, sex, nutritional status (fasted or nonfasted), and/or vehicle. According to the toxicity

TABLE 2-5. Levels of Significant Exposure to Mixed Xylene - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	14 d 1x/d		1000		2000[a] (8/10 died)	NTP 1986
2	Rat	(G)	1 d 1x/d		2000M 4000F		3523 (LD50 in males)	NTP 1986
3	Rat	(G)	1 d 1x/d				8600 (LD50)	Hine and Zuidema 1970
4	Rat	(G)	1 d 1x/d		5100		5950 (4/6 died)	Muralidhara and Krishnakumari 1980
5	Mouse	(G)	1 d 1x/d		4000		5627M (LD50) 5251F (LD50)	NTP 1986
6	Mouse	(G)	14 d 1x/d		2000		4000 (10/10 died)	NTP 1986
Systemic								
7	Mouse	(GO)	1 d	Other	1000			Feldt 1986
Developmental								
8	Mouse	(G)	10 d Gd6-15 3x/d		1030		2060 (cleft palate)	Marks et al. 1982
INTERMEDIATE EXPOSURE								
Death								
9	Rat	(G)	13 wk 5d/wk 1x/d		1000			NTP 1986
10	Mouse	(G)	13 wk 5d/wk 1x/d		2000M			NTP 1986

TABLE 2-5 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
Systemic								
11	Rat	(GO)	90 d 1x/d	Hemato	750	1500 (polycythemia and leukocytosis)		Condie et al. 1988
				Hepatic		150 (increased liver weight in males)		
				Renal	150	750 (increased kidney weight)		
				Other	750	1500 (increased spleen weight)		
12	Rat	(G)	13 wk 5d/wk 1x/d	Resp	1000			NTP 1986
				Cardio	1000			
				Gastro	1000			
				Hemato	1000			
				Musc/skel	1000			
				Hepatic	1000			
				Renal	1000			
				Derm/Oc	1000			
				Other	1000			
13	Mouse	(G)	13 wk 5d/wk 1x/d	Resp	2000			NTP 1986
				Cardio	2000			
				Gastro	2000			
				Hemato	2000			
				Musc/skel	2000			
				Hepatic	2000			
				Renal	2000			
				Derm/Oc	2000			
				Other	2000			
Neurological								
14	Rat	(G)	13 wk 5d/wk 1x/d		1000			NTP 1986
15	Mouse	(G)	13 wk 5d/wk 1x/d		2000			NTP 1986

TABLE 2-5 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
Reproductive								
16	Rat	(G)	13 wk 5d/wk 1x/d		1000			NTP 1986
17	Mouse	(G)	13 wk 5d/wk 1x/d		2000			NTP 1986
CHRONIC EXPOSURE								
Death								
18	Rat	(G)	103 wk 5d/wk 1x/d				500 (decreased survival, males)	NTP 1986
19	Mouse	(G)	103 wk 5d/wk 1x/d		1000			NTP 1986
Systemic								
20	Rat	(G)	103 wk 5d/wk 1x/d	Resp	500			NTP 1986
				Cardio	500			
				Gastro	500			
				Musc/skel	500			
				Hepatic	500			
				Renal	500			
				Derm/Oc	500			
21	Mouse	(G)	103 wk 5 d/wk 1x/d	Resp	1000			NTP 1986
				Cardio	1000			
				Gastro	1000			
				Musc/skel	1000			
				Hepatic	1000			
				Renal	1000			
				Derm/Oc	1000			
				Other	1000			

TABLE 2-5 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
Neurological								
22	Rat	(G)	103 wk 5d/wk 1x/d		500			NTP 1986
23	Mouse	(G)	103 wk 5d/wk 1x/d		500	1000 (hyperactivity)		NTP 1986
Reproductive								
24	Rat	(G)	103 wk 5d/wk 1x/d		500			NTP 1986
25	Mouse	(G)	103 wk 5 d/wk 1x/d		1000			NTP 1986

[a]Converted to an equivalent concentration of 40,000 ppm in food for presentation in Table 1-4.

Cardio = cardiovascular; d = day; Derm/Oc = dermal ocular; F = female; Gastro = gastrointestinal; (G) = gavage; (GO) = gavage-oil; Gd = gestation day; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mg/kg/day = milligrams per kilogram per day; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week.

TABLE 2-6. Levels of Significant Exposure to m-Xylene - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	1 d 1x/d				6631 (LD50)	Smyth et al. 1962
Systemic								
2	Rat	(GO)	10 d 1x/d	Hepatic	250	1000 (increased liver weight)		Condie et al. 1988
				Other	1000	2000 (decreased spleen weight)		
INTERMEDIATE EXPOSURE								
Systemic								
3	Rat	(G)	13 wk 7d/wk 1x/d	Resp	800			Hazleton Labs 1988a
				Cardio	200	800 (decreased absolute heart weight in males)		
				Gastro	800			
				Hemato	800			
				Musc/skel	800			
				Hepatic	800			
				Renal	200	800 (increased relative kidney weight in males)		
				Derm/oc	800			
				Other		200 (decreased weight gain and food consumption in males)		

TABLE 2-6 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
Neurological								
4	Rat	(G)	13 wk 7d/wk 1x/d		200	800 (increased brain-to-body weight ratio in males)		Hazleton Labs 1988a
Reproductive								
5	Rat	(G)	13 wk 7d/wk 1x/d		800			Hazleton Labs 1988a

Cardio = cardiological; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; (G) = gavage; (GO) = gavage-oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; mg/kg/day = milligrams per kilogram per day; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week

TABLE 2-7. Levels of Significant Exposure to o-Xylene - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect, Less Serious (mg/kg/day))	LOAEL (Effect, Serious (mg/kg/day))	Reference
ACUTE EXPOSURE								
Systemic								
1	Rat	(GO)	10 d 1x/d	Hepatic	250	1000 (increased liver weight)		Condie et al. 1988
				Other	1000	2000 (decreased spleen weight)		

d = day; (GO) = gavage-oil; LOAEL = lowest-observed-adverse-effect level; mg/kg/day = milligrams per kilogram per day; NOAEL = no-observed-adverse-effect level

TABLE 2-8. Levels of Significant Exposure to p-Xylene - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(GO)	10 d 1x/d		1000		2000 (death)	Condie et al. 1988
Systemic								
2	Rat	(GO)	10 d 1x/d	Hepatic		250 (increased liver weight)		Condie et al. 1988
				Other	1000	2000 (decreased thymus weight)		
Neurological								
3	Rat	(G)	1 d 1x/d		125	250[a] (impaired visual function)		Dyer et al. 1988
INTERMEDIATE EXPOSURE								
Systemic								
4	Rat	(G)	13 wk 7d/wk 1x/d	Resp	800			Hazleton Labs 1988b
				Cardio	800			
				Gastro	800			
				Hemato	800			
				Musc/skel	800			
				Hepatic	800			
				Renal	800			
				Derm/oc	800			
				Other	200	800 (salivation)		

TABLE 2-8 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
Neurological								
5	Rat	(G)	13 wk 7d/wk 1x/d		800			Hazleton Labs 1988b
Reproductive								
6	Rat	(G)	13 wk 7d/wk 1x/d		800			Hazleton Labs 1988b

[a]Converted to an equivalent concentration of 5,000 ppm in food for presentation in Table 1-4.

Cardio = cardiological; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; (G) = gavage; (GO) = gavage-oil; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; mg/kg/day = milligrams per kilogram per day; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week

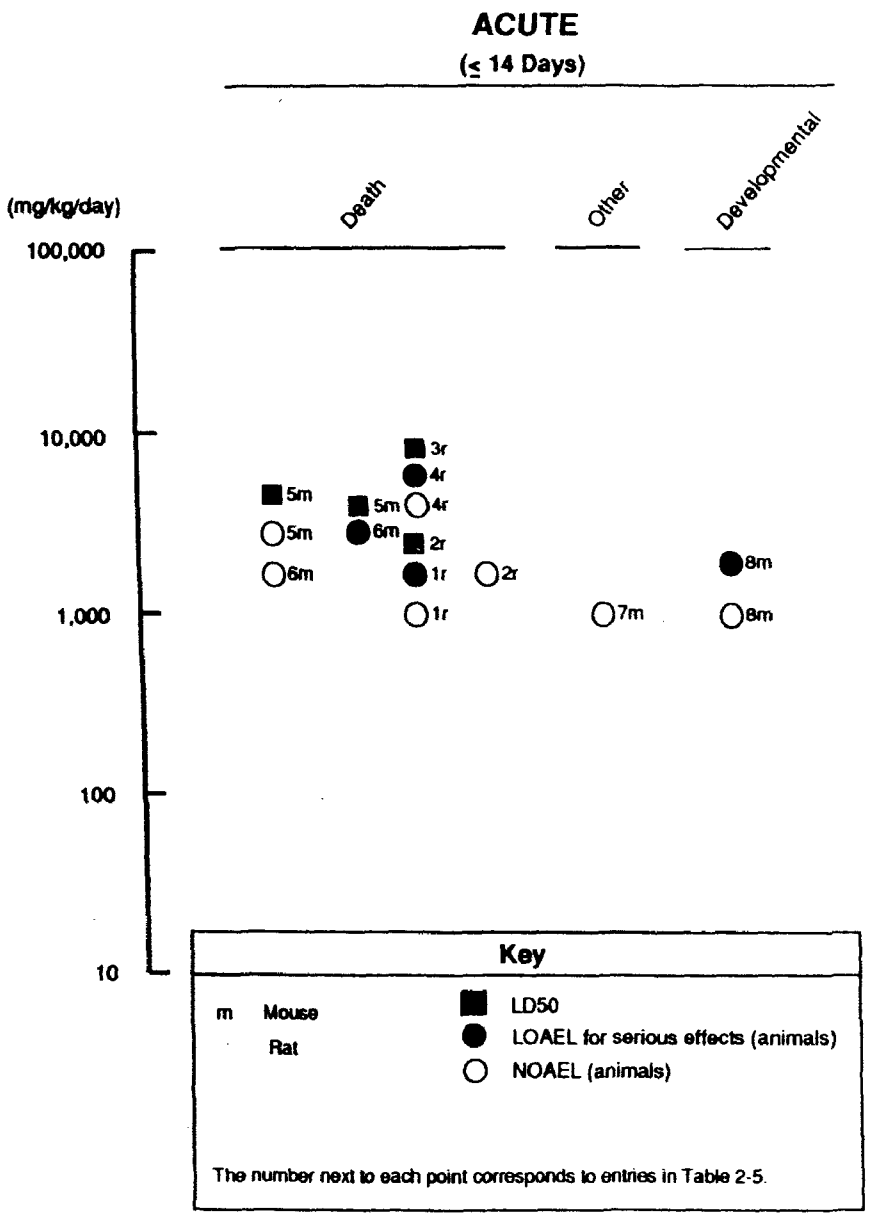

FIGURE 2-5. Levels of Significant Exposure to Mixed Xylene - Oral

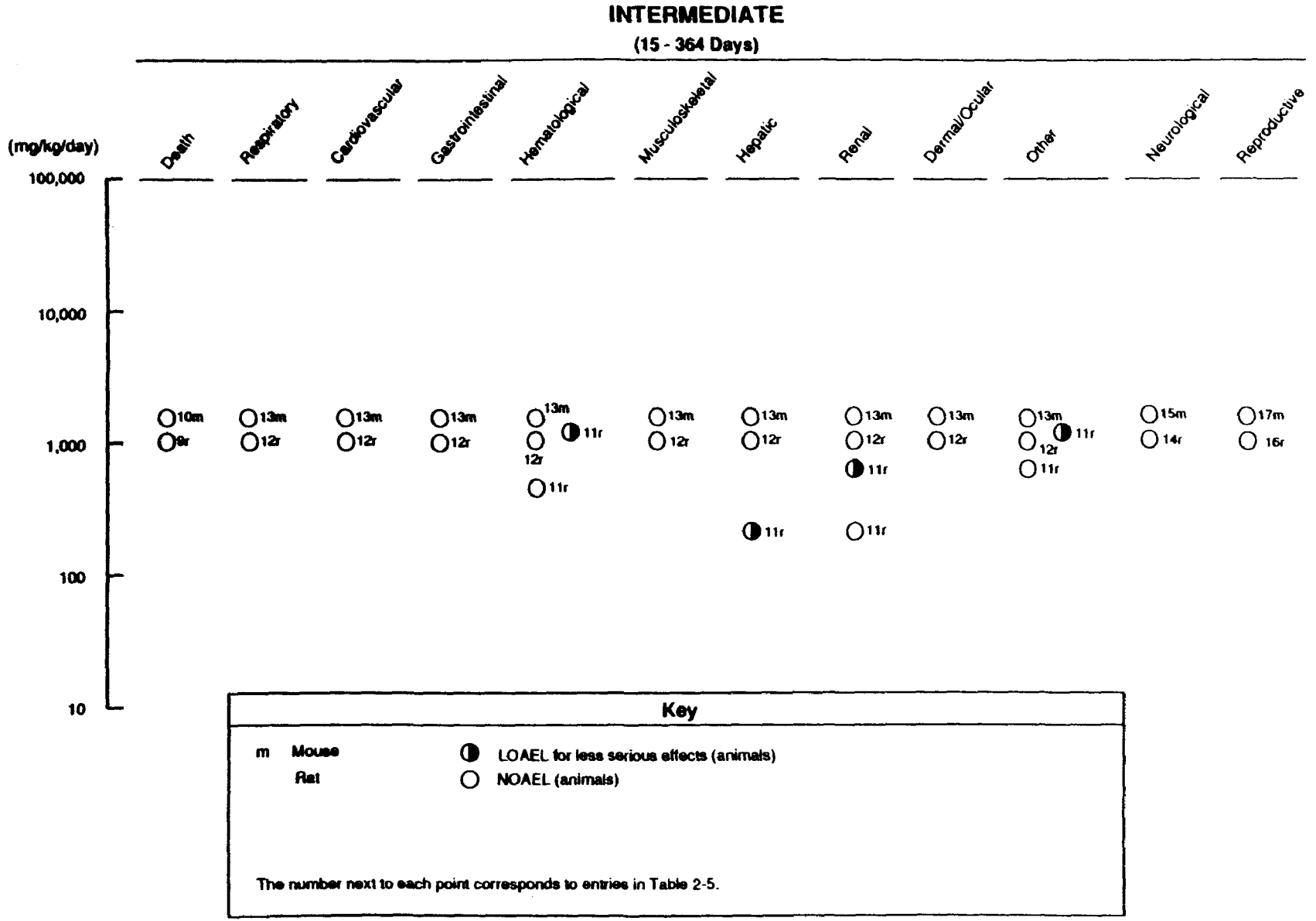

FIGURE 2-5 (Continued)

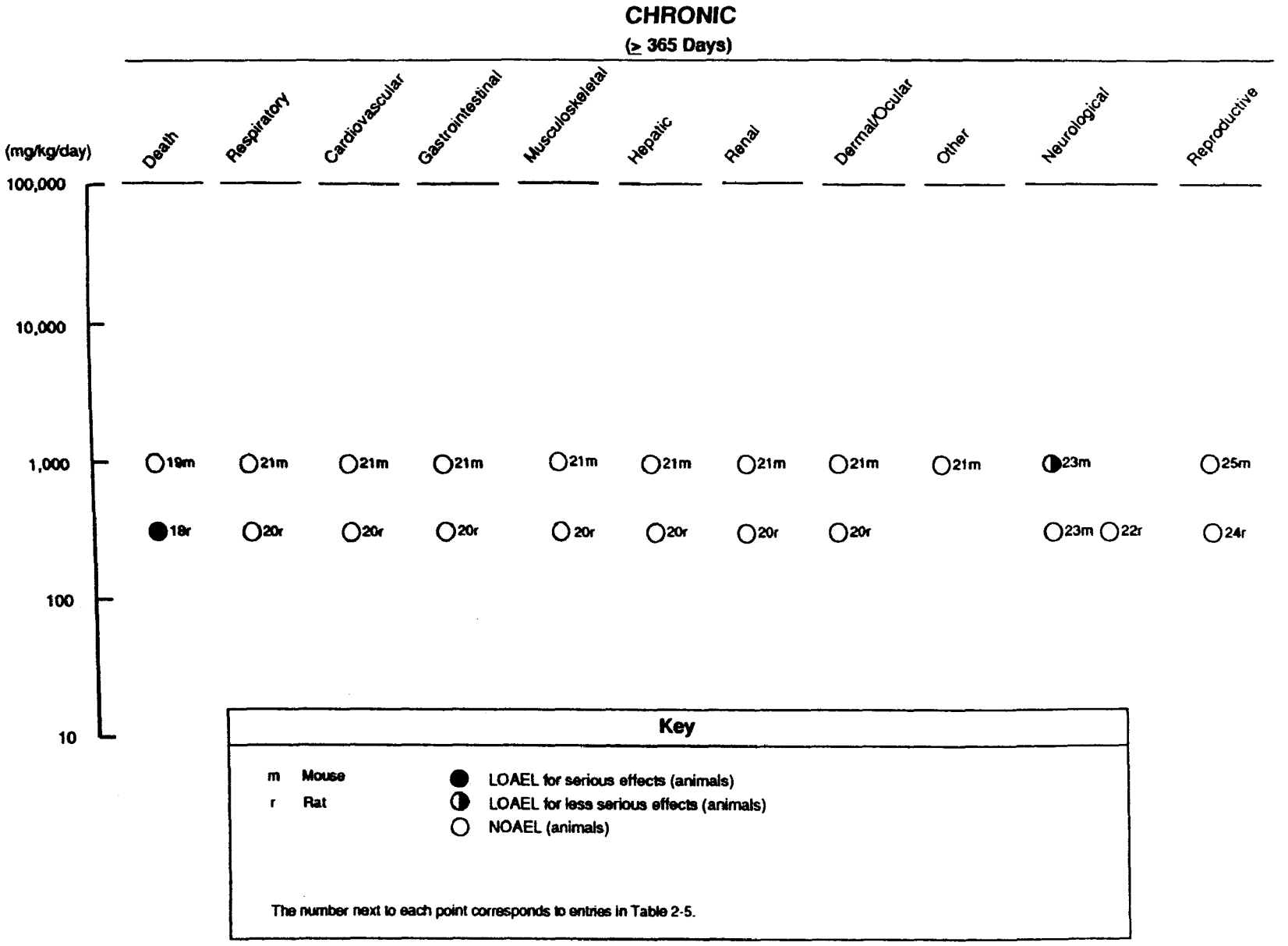

FIGURE 2-5 (Continued)

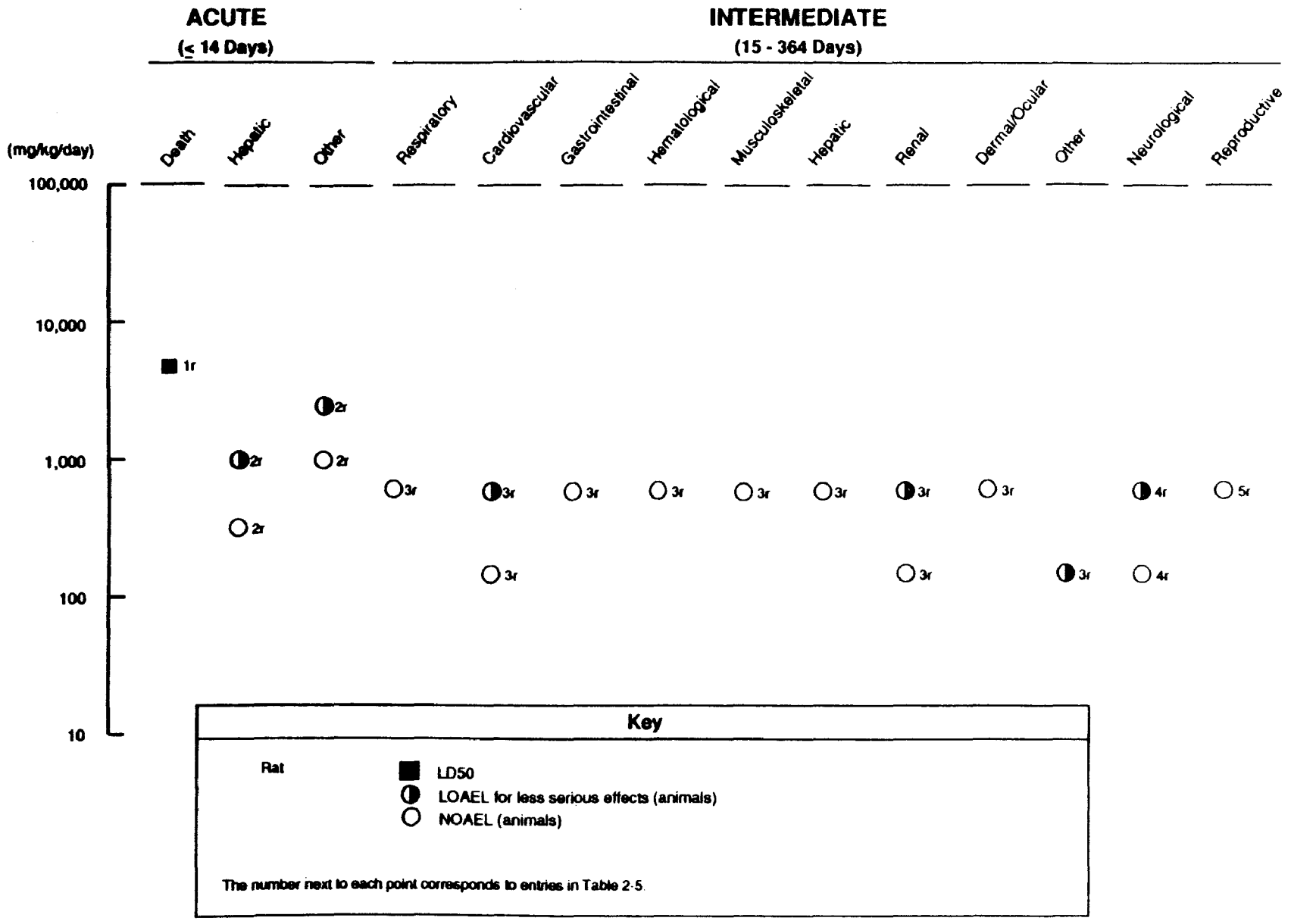

FIGURE 2-6. Levels of Significant Exposure to m - Xylene - Oral

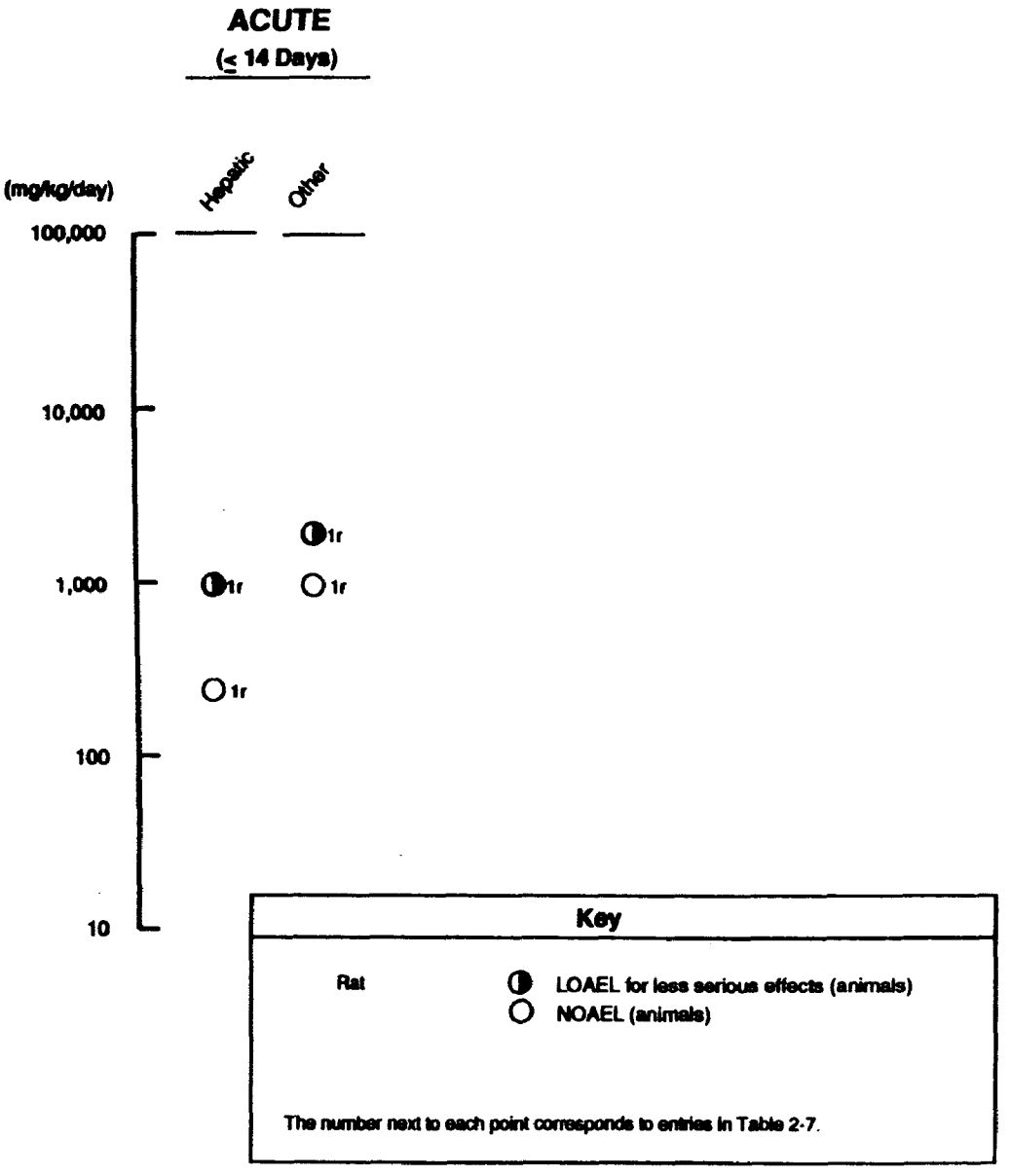

FIGURE 2-7. Levels of Significant Exposure to o - Xylene - Oral

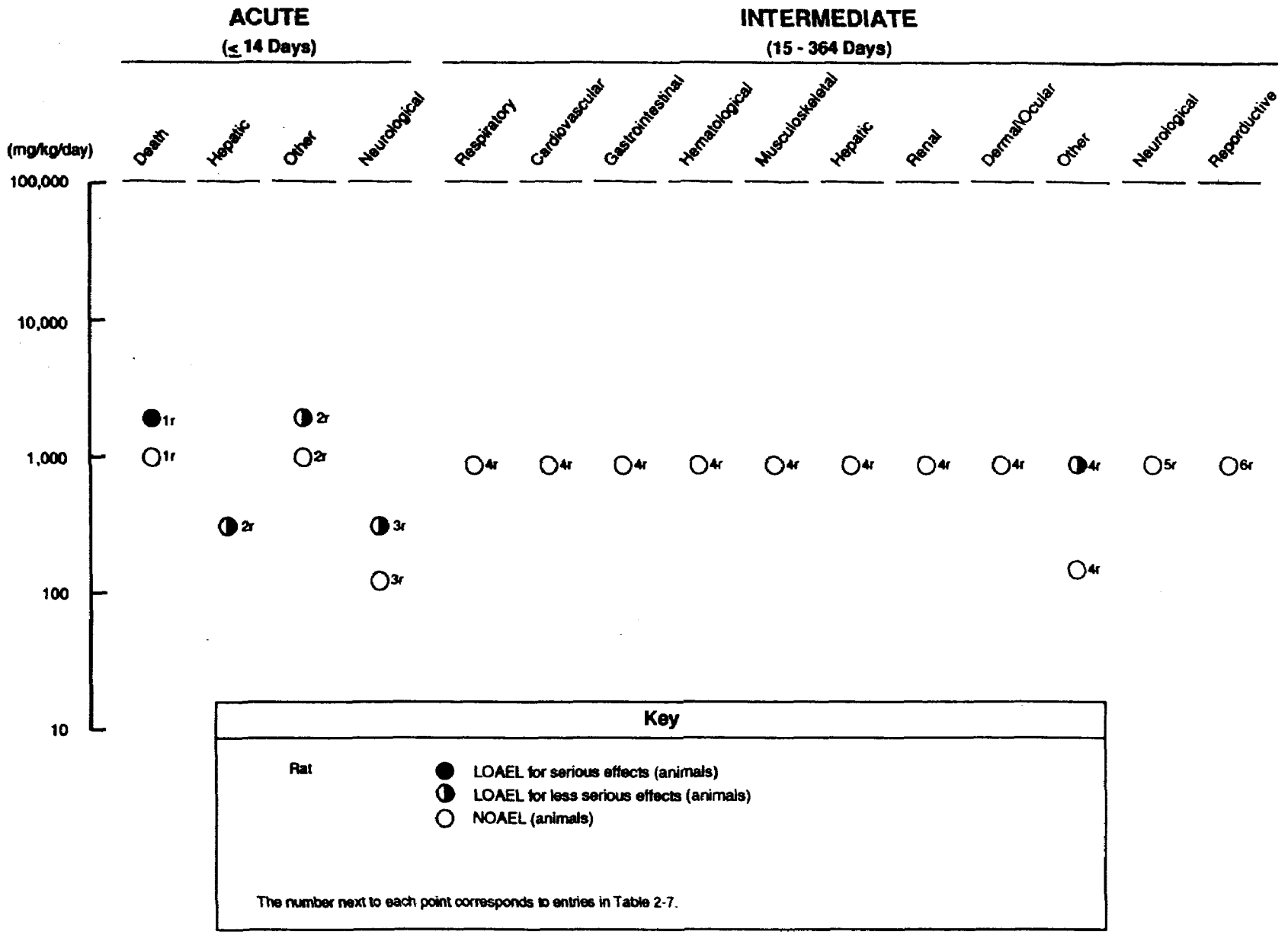

FIGURE 2-8. Levels of Significant Exposure to p - Xylene - Oral

TABLE 2-9. Reported Acute Oral LD_{50} Values for Xylene

Xylene Isomer	Species/Strain	Sex	Acute Oral LD_{50} Value	Reference
Mixed xylene	Rat/Long-Evans	Male	8,600 mg/kg	Hine and Zuidema 1970
Mixed xylene	Rat/F344/N	Male	3,523 mg/kg	NTP 1986
m-Xylene	Rat/Carworth-Wistar	Male	6,631 mg/kg	Smyth et al. 1962
Mixed xylene	Mice/$B6C3F_1$	Male Female	5,627 mg/kg 5,251 mg/kg	NTP 1986

classification system of Hodge and Sterner (1949), these LD50 values indicate that mixed xylene and m-xylene are slightly toxic by acute oral exposure.

No deaths were observed in rats following intermediate oral administration of mixed xylene doses as high as 1,000 mg/kg/day (NTP 1986). Survival was significantly lowered in male rats exposed to mixed xylene at chronic oral doses of 500 mg/kg/day but not at 250 mg/kg/day (NTP 1986). Although mortality was dose related in the treated rats, many of the early deaths were gavage related. No significant increase in mortality was observed in mice treated chronically with mixed xylene at oral doses up to 1,000 mg/kg/day (NTP 1986).

According to a study by Gerarde (1959), m-xylene may be slightly less toxic than the other two isomers. A single oral dose of 8,650 mg/kg m-xylene, o-xylene, or p-xylene produced death in 3/10, 7/10, and 6/10 rats, respectively.

All reliable NOAEL and LOAEL values for death in each species and duration category are recorded in Tables 2-5, 2-6, and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

2.2.2.2 Systemic Effects

Respiratory Effects. No human studies were located regarding respiratory effects following oral exposure to mixed xylene or xylene isomers. Histopathological examination of the lungs and mainstem bronchi of rats and mice administered mixed xylene at doses as high as 500 mg/kg/day in rats and 1,000 mg/kg/day in mice for up to 2 years revealed no adverse effects (NTP 1986). Gross and histopathological examination of rats administered m-xylene or p-xylene for 13 weeks at doses as high as 800 mg/kg/day revealed no treatment-related effects (Hazleton Labs 1988a, 1988b). The highest NOAEL values for respiratory effects are recorded in Tables 2-5, 2-6 and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to mixed xylene or its isomers. No adverse cardiovascular effects were noted following histopathological examination of the heart in rats and mice exposed to mixed xylene for 13 or 103 weeks (NTP 1986). No treatment-related effects were noted upon gross or histopathological examination of the heart in rats administered m-xylene or p-xylene at doses as high as 200 mg/kg/day for 13 weeks (Hazleton Labs 1988a, 1988b). However, absolute heart weight was decreased in male rats administered 800 mg/kg/day m-xylene for 13 weeks. The highest NOAEL values and all reliable LOAEL values for cardiovascular effects

are recorded in Tables 2-5, 2-6, and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

Gastrointestinal Effects. No superficial erosions, deep ulcerations, or other lesions were observed after histopathological examination of the gastric mucosa of a person following ingestion of a "large quantity" of xylene (Abu Al Ragheb et al. 1986). Histopathological examination of rats administered doses as high as 1,000 mg/kg/day of mixed xylene and mice administered doses as high as 2,000 mg/kg/day of mixed xylene for an intermediate or chronic exposure period revealed no adverse effects on the stomach, small intestine, or colon (NTP 1986). Administration of doses of m- or p-xylene as high as 800 mg/kg/day for an intermediate period had no significant effect on the organs of the gastrointestinal system (Hazleton Labs 1988a, 1988b). The highest NOAEL values for gastrointestinal effects are recorded in Tables 2-5, 2-6, and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

Hematological Effects. No human studies were located regarding hematological effects following oral exposure to mixed xylene or xylene isomers. Acute exposure to o- and m-xylene at 2000 mg/kg/day for ten days produced a decrease in the spleen weight of male rats (Condie et al. 1988), however, no hematological effects were observed in rats and mice upon histopathological examination of the bone marrow of the femur following intermediate or chronic exposure to doses of mixed xylene as high as 2,000 mg/kg/day (for 13 weeks in mice) and 1,000 mg/kg/day (for 103 weeks in mice) (NTP 1986). At termination of an intermediate study (13 weeks), no adverse hematological effects were noted in rats administered m- or p-xylene (Hazleton Labs 1988a, 1988b). Mild polycythemia and leukocytosis in both male and female rats and an increase in spleen weight in females were observed in rats exposed to 1,500 mg/kg mixed xylene for 90 days (Condie et al. 1988). The NOAEL and LOAEL values for hematological effects are recorded in Tables 2-5, 2-6 and 2-8 and plotted in Figures 2-5, 2-6 and 2-8.

Musculoskeletal Effects. No human studies were located regarding musculoskeletal effects following oral exposure to mixed xylene or xylene isomers. In two animal bioassays, no musculoskeletal effects were observed in rats and mice upon histopathological examination of the femur, sternebrae, or vertebrae following intermediate or chronic exposure to doses of mixed xylene as high as 2,000 mg/kg/day (for 13 weeks in mice) and 1,000 mg/kg/day (for 103 weeks in mice) (NTP 1986). No adverse effects were observed in the sternum (with marrow), thigh musculature, or femur upon histopathological examination of rats administered m- or p-xylene at doses as high as 800 mg/kg/day for 13 weeks (Hazleton Labs 1988a, 1988b). The highest NOAEL values for musculoskeletal effects are recorded in Tables 2-5, 2-6, and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to mixed xylene or xylene isomers. However, in acute and intermediate studies with rats, oral exposure to xylene has been associated with hepatic enzyme induction and increased hepatic weight (Condie et al. 1988; Pyykko 1980). In the study by Condie et al. 1988, acute exposure to p-xylene at 250 mg/kg/day and m- and o-xylene at 1000 mg/kg/day caused increases in liver weight. Administration of doses as low as 1,060 mg/kg/day of all three xylene isomers for an acute exposure period also produced increased liver weight, increased cytochrome P-450 and b_5 content and increased activities of liver enzymes in rats (Pyykko 1980). The different isomers generally showed different potencies of enzyme induction. Administration of mixed xylenes to rats for 90 days caused increased liver weight ratios in males at doses as low as 150 mg/kg/day and in females at doses as low as 750 mg/kg/day (Condie et al. 1988). No treatment related histopathological changes were observed in liver tissue samples. Also, no effects were noted upon histopathological examination of the liver of rats and mice orally administered mixed xylene for a chronic or intermediate period of time to doses as high as 2,000 mg/kg/day (for 13 weeks in mice) and 1,000 mg/kg/day (for 103 weeks in mice) (NTP 1986). Administration of doses as high as 800 mg/kg/day of m- or p-xylene in rats for 13 weeks produced no adverse hepatic effects (Hazleton Labs 1988a, 1988b).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in rats and mice for each duration category are recorded in Tables 2-5, 2-6, 2-7, and 2-8 and plotted in Figures 2-5, 2-6, 2-7, and 2-8.

Renal Effects. No human studies were located regarding renal effects following oral exposure to mixed xylene or xylene isomers. No adverse effects were noted upon histopathological examination of the kidney of rats and mice following intermediate or chronic exposure to doses of mixed xylene as high as 2,000 mg/kg/day (for 13 weeks in mice) and 1,000 mg/kg/day (for 103 weeks in mice) (NTP 1986). Increased relative kidney weight in male rats administered 800 mg m-xylene/kg/day for an intermediate period was the only treatment-related effect noted in rats of both sexes exposed to m- and p-xylene (Hazleton Labs 1988a, 1988b). Increased relative kidney weight also was increased in male rats given mixed xylenes at 750 mg/kg/day and in female rats at 1500 mg/kg/day (Condie et al. 1988). Gross and histopathology revealed symptoms consistent with early chronic nephropathy. The NOAEL and LOAEL values for these studies are recorded in Tables 2-5, 2-6, and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

Dermal/Ocular Effects. No human studies were located regarding dermal/ocular effects following oral exposure to mixed xylene or xylene isomers. No adverse effects were noted during microscopic examination of the eyes of rats and mice administered doses as high as 2,000 mg/kg/day in mice

and as high as 1,000 mg/kg/day in rats of mixed xylene for an intermediate (13 weeks) or chronic (103 weeks) period of time (NTP 1986). Upon histopathologic examination, the skin of rats and mice exposed to mixed xylene for up to 2 years appeared comparable to that of controls. The eyes and skin of rats administered doses as high as 800 mg/kg/day of m- or p-xylene for 13 weeks appeared without effect upon histopathological examination (Hazleton Labs 1988a,b). These NOAEL values are recorded in Tables 2-5, 2-6, and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

Other Systemic Effects. Salivation was frequently observed in rats exposed orally to 800 mg m- or p-xylene/kg/day for 13 weeks (Hazleton Labs 1988a, 1988b). Average body weights were slightly decreased in male and female rats at 800 mg p-xylene/kg/day, but this decrease was not significant. Food consumption and body weight gain were significantly decreased during intermediate exposure at a dose as low as 200 mg m-xylene/kg/day in males (Hazleton Labs 1988a). Decreased relative thymus weights were observed in rats exposed for 10 days to 2,000 mg/kg p-xylene (Condie et al. 1988).

The highest NOAEL values and all reliable LOAEL values for other systemic effects are recorded in Tables 2-5, 2-6 and 2-8 and plotted in Figures 2-5, 2-6 and 2-8.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans and animals after oral exposure to mixed xylene or xylene isomers.

2.2.2.4 Neurological Effects

Information concerning possible neurological effects associated with the ingestion of xylene is limited. Xylene produced a coma that persisted for more than 26 hours in a person who accidentally ingested xylene (Recchia et al. 1985). The composition of the xylene was unknown.

Impairment of visual function, as evidenced by significant decreases in flash-evoked potentials, was noted in rats treated one time at doses of 250 mg p-xylene/kg/day and higher (Dyer et al. 1988). Histopathological examination of the brain and spinal cord of rats and mice administered doses as high as 1,000 mg/kg/day (rats) or 2,000 mg/kg/day (mice) of mixed xylene for up to 2 years revealed no adverse effects (NTP 1986). However, following gavage of 1,000 mg/kg/day in the chronic bioassay, hyperactivity was noted for 5-30 minutes in weeks 4-103 of study in both male and female mice (NTP 1986). No adverse effects were noted in the spinal cord of rats administered doses of m- or p-xylene as high as 800 mg/kg/day for 13 weeks (Hazleton Labs 1988a,b), however, the brain-to-body weight ratio was increased in males dosed with

800 mg/kg/day of m-xylene. Clinical signs included hyperactivity, convulsions, salivation, and epistaxis.

The highest NOAEL values and all reliable LOAEL values for neurological effects in rats and mice and for each exposure duration are recorded in Tables 2-5, 2-6, and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

2.2.2.5 Developmental Effects

No studies were located regarding developmental or teratogenic effect in humans following oral exposure to mixed xylene or xylene isomers.

Significantly increased incidences of cleft palate and decreased body weight were reported following maternal exposure during gestation to doses of 2,060 mg/kg/day mixed xylene in rats (Marks et al. 1982). Mixed xylene was also toxic to the dams, producing 31.5% mortality at 3,100 mg/kg/day. It is unclear whether the observation of cleft palate in this study is associated with a predisposition of mice under stress to give birth to offspring with this birth defect. In a teratology screening study, 2000 mg/kg/day of m-xylene produced no evidence of fetal toxicity (Seidenberg 1986). Given the limited amount of animal data, no conclusion can be made regarding the relationship between oral exposure of xylene and adverse developmental effects. The highest NOAEL value and a reliable LOAEL value for developmental effects are recorded in Table 2-5 and plotted in Figure 2-5.

2.2.2.6 Reproductive Effects

No human studies were located regarding reproductive effects following oral exposure to mixed xylene or individual isomers. No studies directly examining reproductive effects of xylene after oral exposure exist, however, histological examination of rats and mice administered mixed xylene at doses as high as 500 mg/kg/day in rats and 1,000 mg/kg/day in mice for up to 2 years revealed no adverse effects in the prostate/testes (male), ovaries/uterus, or mammary glands (female) (NTP 1986). The reproductive system organs of rats administered doses of m- or p-xylene as high as 800 mg/kg/day appeared comparable to controls after 13 weeks of treatment (Hazleton Labs 1988a, 1988b). The NOAEL values for reproductive effects are recorded in Tables 2-5, 2-6, and 2-8 and plotted in Figures 2-5, 2-6, and 2-8.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to mixed xylene or xylene isomers. No chromosomal aberrations or change in the incidence of micronuclei were observed in reticulocytes isolated from mice receiving doses of xylenes as high as 1000 mg/kg in a 24 hour period (Feldt 1986). Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No data were located regarding the development of cancer in humans following oral exposure to mixed xylene or xylene isomers.

The carcinogenicity of mixed xylene following oral exposure has been evaluated in chronic studies with rats and mice; however, no animal studies were available on the carcinogenic effects of m-xylene, o-xylene, or p-xylene following oral exposure. Results of the chronic oral studies with mixed xylene have been negative (NTP 1986) or equivocal (Maltoni et al. 1983, 1985). The interpretation of the results of the NTP bioassay was compromised by the large number of gavage-related deaths early in the study in the high dose male rats. The Maltoni studies were weakened because of methodological flaws such as failure to report site-specific neoplasia, insufficient toxicity data, and absence of statistical analyses. Therefore, given the limited data, no definitive conclusion can be made regarding the carcinogenicity of mixed xylene following oral exposure.

EPA has classified mixed xylene as a Group D agent (not classifiable as to human carcinogenicity) (IRIS 1989). This classification applies to those chemical agents for which there is inadequate evidence of carcinogenicity in animals. No cancer potency factor (q1*) or other quantitative estimate of carcinogenicity has been developed by EPA for mixed xylene, m-xylene, o-xylene, or p-xylene.

2.2.3 Dermal Exposure

2.2.3.1 Death

No reports of death in humans following dermal exposure to xylene were located. Limited animal data suggest that mixed xylene and m-xylene can cause death when applied dermally (Hine and Zuidema 1970; Pound and Withers 1963; Smyth et al. 1962). The acute dermal LD_{50} in rabbits has been determined to be 14.1 mL/kg for m-xylene and greater than 5.0 mL/kg for mixed xylene (Hine and Zuidema 1970; Smyth et al. 1962). The studies contain limitations which compromise their reliability for assessing a dose-response relationship between dermal exposure to xylene and death.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic or renal effects in humans and animals after dermal exposure to mixed xylene or xylene isomers.

Dermal/Ocular Effects. Acute dermal exposure of human subjects to m-xylene in hand immersion studies has been associated with transient skin erythema (irritation), vasodilation of the skin, and dryness and scaling of the skin (Engstrom et al. 1977; Riihimaki 1979). The concentrations at which these dermal effects occurred were not well characterized. No human data were available regarding ocular effects following dermal exposure to mixed xylene or xylene isomers.

Mild to moderate skin irritation was noted in rabbits and guinea pigs treated topically with mixed xylene in acute studies (Anderson et al. 1986; Hine and Zuidema 1970). Localized edema, dryness, and scaling, along with cellular proliferation of the skin was observed in mice following intermediate dermal exposure to undiluted xylene (Pound and Withers 1963). No chronic animal studies evaluating the dermal effects of xylene were located.

No studies were located regarding the ocular effects in humans and animals after dermal exposure to mixed xylene or xylene isomers.

2.2.3.3 Immunologic Effects

No studies were located regarding immunologic effects in humans and animals after dermal exposure to mixed xylene or xylene isomers.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans and animals after dermal exposure to mixed xylene or xylene isomers.

2.2.3.5 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to mixed xylene or its isomers.

Dermal exposure of rats to a 1% solution of xylene (isomeric components not specified) caused no evidence of fetal toxicity (Rumsey et al. 1969). This study was limited by the coapplication of the surfactant alkylphenoxy polyethoxyethanol with xylene. Another study indicated that dermal exposure of pregnant rats to doses as low as 200 mg xylene/kg/day produced decreases in enzyme activity (cholinesterase, cytochrome) in fetal and maternal brain tissue (Mirkova et al. 1979). Pregnant dams exposed to xylene also showed impaired motor activity in behavioral tests suggesting a neurotoxic effect of xylene. The doses in this study appear to be unusually high. Other limitations of this study are the absence of information on the composition of xylene used and the frequency of application.

2.2.3.6 Reproductive Effects

No studies were located regarding reproductive effects in humans and animals after dermal exposure to mixed xylene or xylene isomers.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans and animals after dermal exposure to mixed xylene or xylene isomers.

2.2.3.8 Cancer

No human and no adequate animal data were available for evaluating the carcinogenicity of mixed xylene or xylene isomers.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Evidence for absorption of xylene by humans following inhalation exposure is provided by the observation that metabolite levels in the urine increase in proportion to exposure (Ogata et al. 1970; Riihimaki and Pfaffli 1978; Riihimaki et al. 1979b; Sedivec and Flek 1976b; Senczuk and Orlowski 1978; Wallen et al. 1985) and in proportion to increased ventilatory rates during exercise (Astrand 1982; Astrand et al. 1978; Engstrom and Bjurstrom 1978; Riihimaki et al. 1979b; Riihimaki and Savolainen 1980). Absorption of the retained isomers appears to be similar, regardless of exposure duration or dose. There appear to be two phases of absorption; the first is apparently short, occurring within 15 minutes of initiation of exposure. The second phase is longer and represents the establishment of an equilibrium between the inhaled xylene and blood.

Many authors have measured the retention of xylene following inhalation exposure. It is this retained xylene that is available for absorption into the systemic circulation. In experimental studies with human subjects, retention of the various isomers was similar following inhalation of either m-, o-, or p-xylene, and averaged 63.6% (Sedivec and Flek 1979b). Other authors have estimated that between 49.8% and 72.8% of inhaled xylene is retained (David et al. 1979; Ogata et al. 1970; Riihimaki and Pfaffli 1978; Riihimaki and Savolainen 1980; Riihimaki et al. 1979b; Wallen et al. 1985). Pulmonary retention does not appear to differ on the basis of sex (Senczuk and Orlowski 1978). Physical exertion, as the result of exercising or working, and increased dose can increase the amount of xylene retained and subsequently absorbed into the body due to enhanced pulmonary ventilation and cardiac

output (Astrand et al. 1978, Riihimaki et al. 1979b). The study by Astrand et al. (1978) suggests that retention efficiency decreases as exposure duration increases.

In pregnant mice, approximately 30% of an administered inhalation dose of 600 ppm p-xylene was absorbed following a 10-minute exposure period (Ghantous and Danielsson 1986). Absorption was not quantified in the other animal studies, but effects on microsomal enzyme systems suggested that absorption occurred following inhalation of xylene (Carlsson 1981; David et al. 1979; Elovaara 1982; Elovaara et al. 1987; Patel et al. 1978).

2.3.1.2 Oral Exposure

Limited information is available on the absorption of xylene in humans and animals following ingestion. Excretion of urinary metabolites indicated that absorption had occurred following oral doses of either 40 or 80 mg/kg/day of o-xylene or m-xylene in humans (Ogata et al. 1980). However, absorption was not quantified.

Animal data indicate that xylene is absorbed following oral exposure. Almost complete absorption (87%-92%) occurred following ingestion of a dose of 1.8 grams m-xylene, or of 1.74 grams o- or p-xylene (Bray et al. 1949). Evidence of absorption was indirect and minimally estimated from the amount of metabolites excreted in different fractions of the urine; no estimate of the amount of metabolites exhaled was available. The various fractions included the ether-soluble acid, the ester glucuronide, and the ethereal sulphate. The results of other studies qualitatively indicate absorption following ingestion by animals because metabolites were detected and identified in urine (Bakke and Scheline 1970; Patel et al. 1978; Pyykko 1980).

2.3.1.3 Dermal Exposure

Results of experimental studies with humans indicate that m-xylene is absorbed following dermal exposure; however, the extent of penetration and absorption of m-xylene through skin is not nearly as great as that resulting from inhalation (Engstrom et al. 1977; Riihimaki 1979; Riihimaki and Pfaffli 1978). Absorption of m-xylene vapor through the skin was approximately 0.1%-2% that of inhalation exposure (Riihimaki and Pfaffli 1978). In addition to dermal absorption following exposure to m-xylene vapors, m-xylene can be absorbed through the skin following direct dermal contact with the solvent (Engstrom et al. 1977; Riihimaki 1979; Riihimaki and Pfaffli 1978). In humans, the estimated absorption rate following immersion of both hands in m-xylene for 15 minutes was approximately 2 $\mu g/cm^2/min$ (Engstrom et al. 1977). It is generally accepted that absorption of xenobiotics is greater in persons with diseased or damaged skin than in persons with normal skin (Riihimaki and Pfaffli 1978).

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Limited information is available regarding the absorption of xylene following dermal exposure in animals. Permeability of m-xylene across rat skin was estimated from blood levels obtained during exposure to m-xylene vapors by McDougal et al. (1990) and permeability constants were calculated. The permeability constant for rats was approximately twice that calculated for humans using data from Riihimaki and Pfaffli (1978). Also, the absorption of o-xylene was examined in the excised abdominal skin of rats (Tsuruta 1982). As the time of contact with o-xylene increased, the amount of o-xylene that penetrated the excised skin also increased. The penetration rate was estimated to be 0.967 nmol/cm^2/min (Tsuruta 1982). However, dermal absorption studies using excised skin are limited by the lack of an intact blood supply, cell death and the resultant alterations in membrane permeability, as well as the lack of nervous system control over blood flow.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Xylenes are very soluble in blood and therefore are absorbed easily into the systemic circulation during exposure (Astrand 1982). The majority (90%) of an absorbed dose of xylene is predominantly associated with serum proteins and the remainder is associated with the serum (Riihimaki et al. 1979b). Following systemic circulation, xylene is distributed primarily to adipose tissue.

The distribution of xylene in fat following inhalation exposure has been studied in humans (Astrand 1982; Engstrom and Bjurstrom 1978; Riihimaki et al. 1979a, 1979b). Estimates of the amount of xylene accumulated in human adipose tissue range from 5% to 10% of the absorbed dose (Astrand 1982, Engstrom and Bjurstrom 1978). Exercise may increase the amount of m-xylene distributed to body fat (Riihimaki et al. 1979a, 1979b). It has been suggested that following prolonged occupational exposure to xylene, significant amounts of the solvent could accumulate in adipose tissue (Astrand 1982; Engstrom and Bjurstrom 1978).

Studies in mice (Ghantous and Danielsson 1986) and in rats (Carlsson 1981) indicate that the distribution of p-xylene and m-xylene is characterized by high uptake in lipid-rich tissues, such as brain, blood, and fat. High uptake also occurs in well-perfused organs, such as the liver and kidney.

According to a chronic animal study, the level of xylene stored in body fat may decrease as exposure continues due to an increase in metabolic rate (Savolainen et al. 1979a). Levels of m-xylene in perirenal fat of rats exposed to 300 ppm technical xylene decreased from 67.6 to 36.6 μg/g tissue as exposure duration increased from 5 to 18 weeks (Savolainen et al. 1979a). p-Xylene readily crossed the mouse placenta and was distributed in embryonic

and fetal tissues (Ghantous and Danielsson 1986). The level detected in fetal tissues, which are low in lipids, was only 2% of that detected in the maternal brain tissue, which contains large amounts of lipids (Ghantous and Danielsson 1986).

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans or animals following oral exposure to mixed xylene, or xylene isomers.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals following dermal exposure to mixed xylene or individual isomers.

2.3.3 Metabolism

The biotransformation of xylene in humans proceeds primarily by the oxidation of a side-chain methyl group by microsomal enzymes (mixed function oxidases) in the liver to yield toluic acids (methylbenzoic acids). These toluic acids conjugate with glycine to form toluric acids (methylhippuric acids) that are excreted into the urine (Astrand et al. 1978; Norstrom et al. 1989; Ogata et al. 1970; Riihimaki et al. 1979a, 1979b; Sedivec and Flek 1976b; Senczuk and Orlowski 1978). This metabolic pathway accounts for almost all of the absorbed dose of xylene, regardless of the isomer, the route of administration, the administered dose, or the duration of exposure. Results of both human and animal studies indicate that xylene is a phenobarbital-like inducer of liver microsomal cytochrome P-450 (David et al. 1979; Toftgard et al. 1981). Minor metabolic pathways that account for less than 10% of the absorbed dose include the elimination of unchanged compound in the exhaled breath and in the urine, and the urinary elimination of methylbenzyl alcohols, o-toluylglucuronides (o-toluic acid glucuronide), and of xylenols (dimethylphenols). The metabolism of the various xylene isomers in humans is presented in Figure 2-9.

The metabolism of xylene in animals is qualitatively similar to that of humans, though quantitative differences do exist (Bakke and Scheline 1970; Bray et al. 1949; Ogata et al. 1980; Sugihara and Ogata 1978; van Doorn et al. 1980). The metabolism of the various isomers in animals is presented in Figure 2-10. The major quantitative difference occurs in the metabolism of the metabolic intermediate methylbenzoic acid (toluic acid). In rats given m-, o-, or p-xylene by i.p. injection, 10% to 56.6% of the administered dose of o-xylene was excreted in the urine as o-toluylglucuronide; whereas approximately 1% of the administered doses of m-xylene and p-xylene were metabolized to the appropriate toluylglucuronide (Ogata et al. 1980; van Doorn et al. 1980). The amounts of m-methylhippuric acid and p-methylhippuric acid

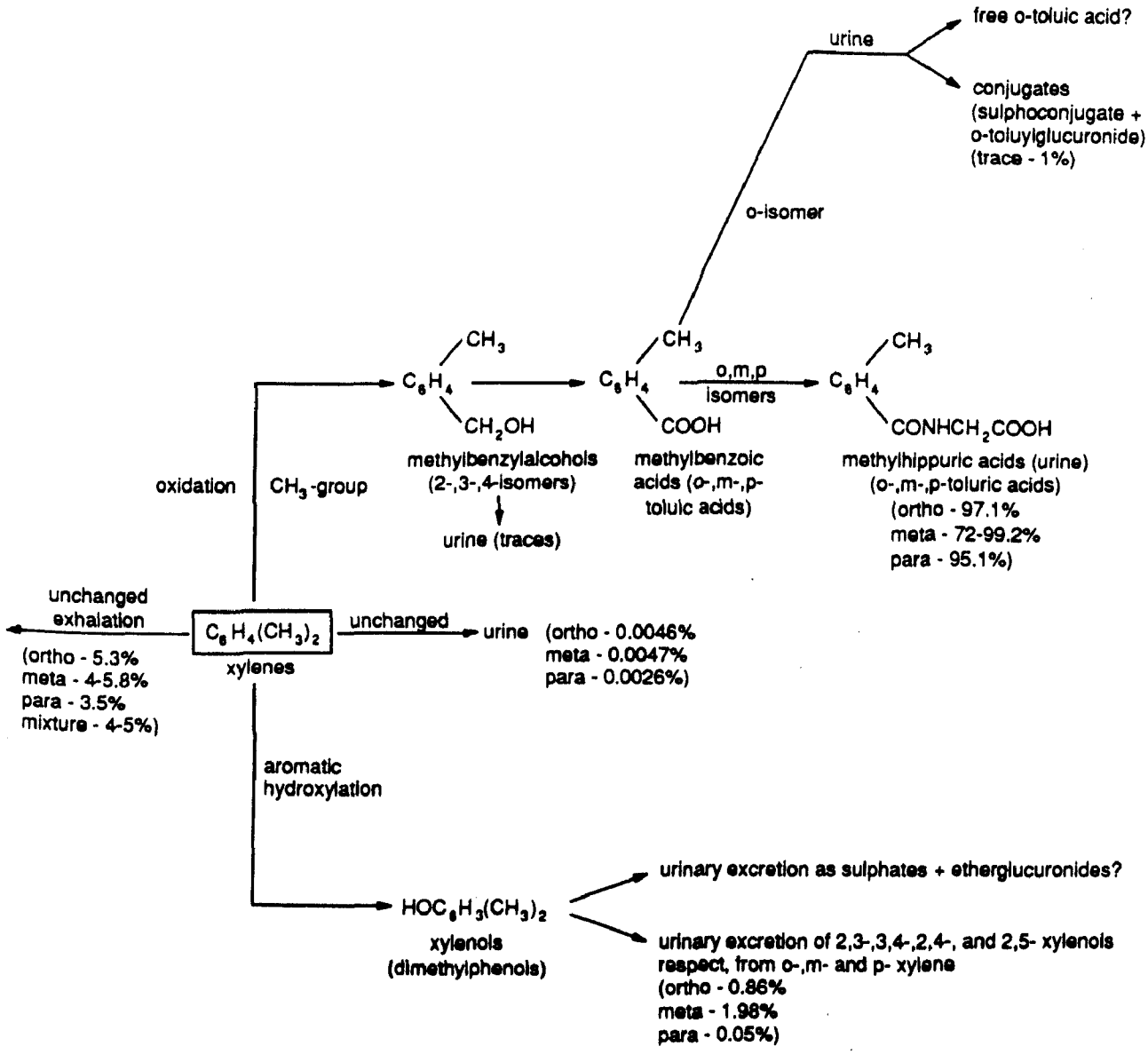

FIGURE 2-9. Metabolic Scheme For Xylenes - Humans

Source: Astrand et al. 1978, Ogata et al. 1980, Riihimaki et al. 1979a, b, Sedivec and Flek 1976b, Senczuk and Orlowski 1978, Toftgard and Gustafsson 1980.

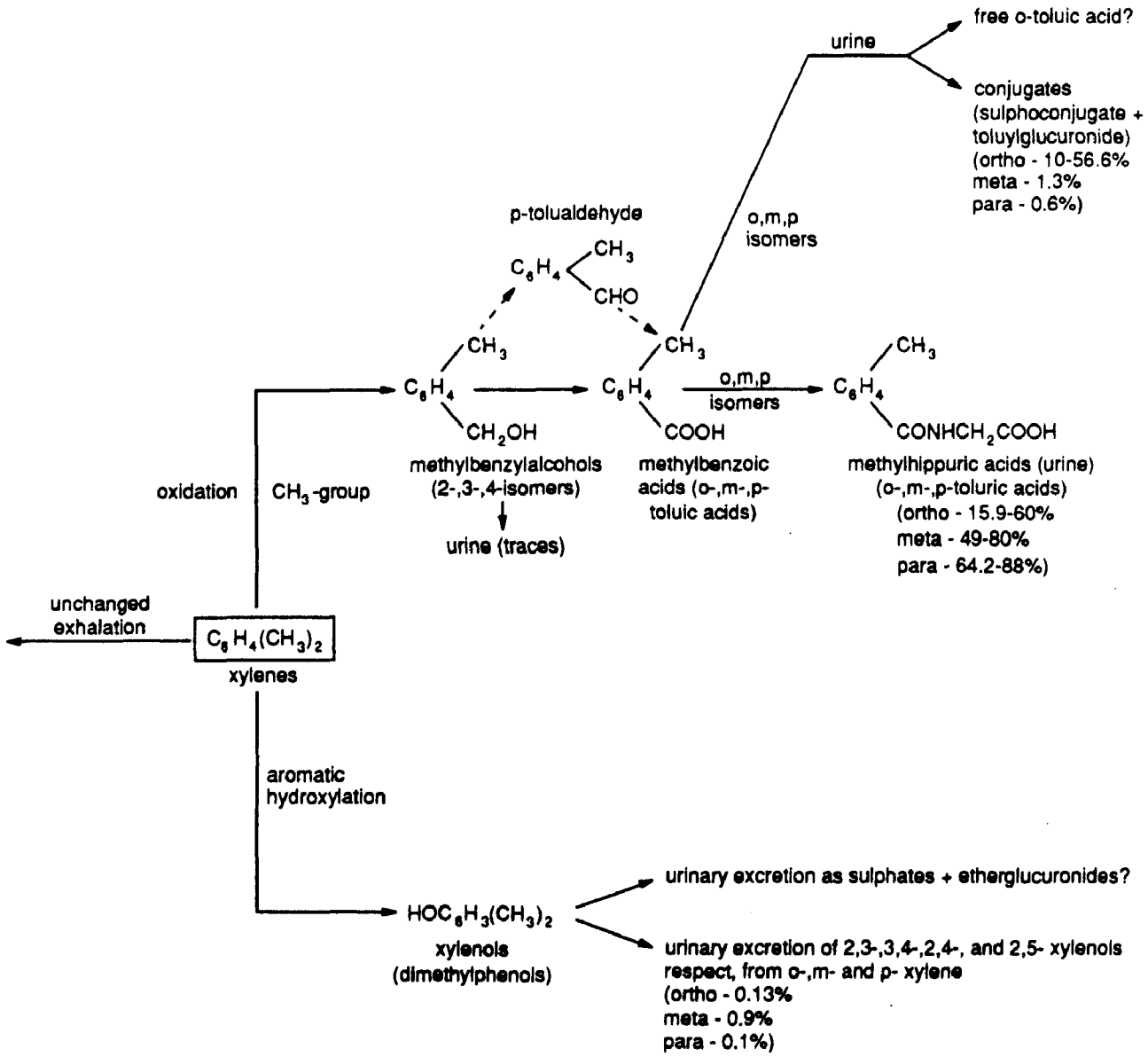

FIGURE 2-10. Metabolic Scheme For Xylenes - Animals

Source: Bakke and Scheline 1970, Bray et al. 1949, Ogata et al. 1980, Sugihara and Ogata 1978, Toftgard and Gustafsson 1980, van Doorn et al. 1980.

excreted in the urine accounted for 49% to 62.6% and 64% to 75% of the administered dose, respectively (Ogata et al. 1980; Sugihara and Ogata 1978). In studies with rabbits, 60% of an administered o-xylene dose, 81% of a m-xylene dose, and 88% of a p-xylene dose were excreted in the urine as methylhippuric acids (Bray et al. 1949). Minor quantities of methylbenzyl alcohols and xylenols have also been detected in the urine of experimental animals administered xylene isomers (Bakke and Scheline 1979; Ogata et al. 1980; van Doorn et al. 1980).

A toxic metabolite of p-xylene in animals appears to be p-methylbenzaldehyde (p-tolualdehyde) (Carlone and Fouts 1974; Patel et al. 1978; Smith et al. 1982). It is formed by the action of alcohol dehydrogenase on p-methylbenzyl alcohol in lung and liver tissues. The presence of p-methylbenzaldehyde has not been confirmed in humans. Lung tissue can be damaged by this intermediate because of its selective inactivation of enzymes involved in microsomal electron transport (mixed function oxidases, cytochrome P-450). A reactive intermediate of p-xylene (probably p-methylbenzaldehyde) is capable of binding to lung proteins in rabbits (Smith et al. 1982). This binding may be associated with the reported destruction of pulmonary cytochrome P-450. This selective inactivation does not occur in the liver where p-methylbenzaldehyde is metabolized to p-methylbenzoic acid and subsequently excreted as p-methylhippuric acid (Patel et al. 1978; Smith et al. 1982).

The route of exposure (i.e., inhalation, oral, or dermal) does not influence the metabolism of xylene once it is absorbed. The differences in xylene metabolism observed between humans and animals may, in part, be explained by differences in the size of the doses given to humans and animals in experimental studies (David et al. 1979; Ogata et al. 1980; van Doorn et al. 1980). The formation of glucuronic acid derivatives may be an emergency mechanism that is activated when the organism can no longer conjugate all acids with glycine (Ogata et al. 1980; Sedivec and Flek 1976b; van Doorn et al. 1980). Humans dosed with 19 mg/kg xylene excreted only methylhippuric acids in the urine, whereas rabbits exposed to 600 mg/kg excreted both methylhippuric acids and derivatives of glucuronic acid (Sedivec and Flek 1976b). The second-phase conjugation of the main oxidized intermediate (methylbenzoic acid with glycine to form methylhippuric acid) may be the rate-limiting step in humans. It is limited by the amount of available glycine in normal physiology, 200 μmol/minute (Riihimaki et al. 1979b). If this limit is approached, other elimination pathways may be activated, such as conjugation with glucuronic acid or aromatic hydroxylation to form xylenols. The capacity of the first-phase oxidation reaction, encompassing both side-chain and aromatic oxidation, is not known. Aromatic oxidation of xylene could possibly produce toxic intermediates and phenolic end-metabolites (Riihimaki et al. 1979b); however, this is a minor metabolic pathway.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

In humans, about 95% of absorbed xylene is biotransformed and excreted as urinary metabolites, almost exclusively as methylhippuric acids; the remaining 5% is eliminated unchanged in the exhaled breath (Astrand et al. 1978; Ogata et al. 1980; Riihimaki et al. 1979a, 1979b; Sedivec and Flek 1976b; Senczuk and Orlowski 1978). Less than 0.005% of the absorbed dose of xylene isomers is eliminated unchanged in the urine, and less than 2% is eliminated as xylenols (Sedivec and Flek 1976b). The excretion of methylhippuric acids is rapid and a significant amount is detected in the urine within 2 hours of exposure. The amount of methylhippuric acid increases with time and reaches a maximum at the termination of exposure. Differences in the amount of the metabolites excreted depend on the interpersonal differences in lung ventilation and retention, not on the isomer of xylene (Sedivec and Flek 1976b).

There appear to be at least two distinct phases of elimination, a relatively rapid one and a slower one. These phases of elimination are consistent with the distribution of xylene into three main tissue compartments; the rapid and slower elimination phases correspond to elimination from the muscles and the adipose tissue, respectively, whereas the elimination of xylene from the parenchymal organs is so rapid that the available studies could not monitor it (Ogata et al. 1970; Riihimaki et al. 1979a, 1979b). It is also possible that the renal excretion of the most common xylene metabolite, methylhippuric acid, takes place via the tubular active secretion mechanism of organic acids. Renal excretion is not a rate-limiting step in the elimination of absorbed xylene under normal physiological conditions (Riihimaki et al. 1979b).

Human volunteers acutely exposed by inhalation to 100 or 200 ppm m-xylene for 7 hours had excreted 54% and 61%, respectively, of the administered dose by 18 hours after exposure ended (Ogata et al. 1970). Following intermittent acute exposure of men and women to 23, 69, or 138 ppm m-xylene, excretion of m-methylhippuric acid peaked 6-8 hours after exposure began. It decreased rapidly, regardless of exposure level or sex, after exposure had ended. Almost no xylene or m-methylhippuric was detected 24 hours later (Senczuk and Orlowski 1978).

Exercise increased the amount of xylene absorbed and thus increased the amount of m-methylhippuric acid and 2,4-xylenol eliminated in the urine of men exposed to m-xylene (Riihimaki et al. 1979b). The excretion of m-methylhippuric acid appeared to correspond very closely to the estimated xylene uptake and expired xylene represented about 4%-5% of the absorbed xylene in all exposure groups (Riihimaki et al. 1979b).

Limited information was available on the elimination of the metabolites of xylene following inhalation exposure of experimental animals. m-Methylhippuric acid was detected in the urine of rats exposed for 6 hours to various doses of m-xylene (David et al. 1979). The authors did not analyze for other urinary metabolites.

2.3.4.2 Oral Exposure

Limited information is available on the elimination of the metabolites of xylene following ingestion in humans. In male volunteers given oral doses of 40 mg/kg/day of o-xylene or m-xylene, the molar excretion ratios (total excretion [mol] in urine during appropriate interval/dose administered [mol] x 100[%]) for o-methylhippuric acid and m-methylhippuric acid were 33.1 and 53.1, respectively (Ogata et al. 1980). More of the m-xylene is eliminated as m-methylhippuric acid than is o-xylene. The molar excretion ratio for o-toluic acid glucuronide (o-toluylglucuronide) was 1.0 in men given o-xylene as an oral dose of 40 mg/kg/day. The amount of o-methylhippuric acid (o-toluric acid) and of o-toluic acid glucuronide excreted in the urine attained a maximum level in 3-6 hours of exposure, while that of m-methylhippuric acid attained a maximum in 1-3 hours (Ogata et al. 1980). These results indicate that the major elimination pathway of o-xylene is the formation of o-methylhippuric acid in humans. The formation of o-toluic acid glucuronide is a minor pathway for the elimination of o-toluic acid. It is expected that at much higher doses, this minor pathway would be used to a greater degree as the major pathway becomes saturated.

Limited information was available on the elimination of the metabolites of xylene following ingestion in animals. Rats administered 100 mg/kg doses of m-, o-, or p-xylene eliminated in the urine 0.1% of a dose of o-xylene as 3,4-xylenol and 0.03% as 2,3-xylenol, 0.9% of a dose of m-xylene as 2,4-xylenol, and 1% of a dose of p-xylene as 2,5-xylenol. A trace of methylbenzyl alcohol was also detected in the urine of rats given o-xylene and m-xylene (Bakke and Scheline 1970).

2.3.4.3 Dermal Exposure

The elimination of liquid m-xylene absorbed dermally in humans following a 15 minute exposure was through the exhaled breath and urine (Engstrom et al. 1977; Riihimaki and Pfaffli 1978). Elimination in the exhaled breath followed a 2-phase elimination curve with a rapid half-life of 1 hour and a longer half-life of 10 hours. Excretion of m-methylhippuric acid in the urine following a dermal exposure to m-xylene was delayed and prolonged by 2-4 hours, though elimination of the dermally absorbed m-xylene was similar to that following inhalation absorption (Riihimaki and Pfaffli 1978). In humans, the rate of excretion of m-methylhippuric acid was approximately 50 μmol/hour at 2 hours following immersion of both hands in m-xylene for 15 minutes

(Riihimaki 1979). It decreased to approximately 1 nmol/L at the 6th post-exposure hour. These results indicate that although absorption was delayed, it was gradual and protracted.

2.3.4.4 Other Routes of Exposure

Limited information was available on the elimination of xylene metabolites in rats following intraperitoneal injection (Ogata et al. 1980; Sugihara and Ogata 1978; van Doorn et al. 1980). The urinary metabolites of xylene are similar regardless of route of exposure; however, the amounts of various metabolites differ. Elimination of xylene isomers is related more to absorption than it is with dose or duration of exposure. In rats, 49% to 62.6% of various doses of m-xylene or 64.2% to 75% of various doses of p-xylene were excreted in the urine as m-methylhippuric acid or p-methylhippuric acid, respectively (Sugihara and Ogata 1978). Rats that were administered an intraperitoneal dose of 1,240 mg o-xylene/kg/day excreted o-toluic acid glucuronide and o-methylhippuric acid in the urine in molar excretion ratios of 56.6 and 15.9, respectively (Ogata et al. 1980). The amount of o-toluic acid glucuronide and o-methylhippuric acid excreted reached a maximum 8-24 hours after dosing. Mercapturic acid derivatives (sulphoconjugates) were present in the urine of rats following an intraperitoneal dose of m-, o-, or p-xylene (van Doorn et al. 1980). The percentages ranged from 0.6% (p-xylene) to 10% (o-xylene).

2.4 RELEVANCE TO PUBLIC HEALTH

The concentrations of mixed xylene and xylene isomers used in animal studies are much higher than the ambient levels encountered in urban and industrial areas. However, information about the effects observed at high concentrations of xylenes is important because potentially high levels may be present at hazardous waste sites. In addition, subgroups of the population may be extremely sensitive and effects seen at high levels in animals may be a predictor of effects seen in these subgroups when they are exposed at much lower levels.

Both human and animal data suggest that mixed xylene, m-xylene, o-xylene, and p-xylene all produce similar effects, although the individual isomers are not necessarily equal in potency with regard to a given effect. Human data indicate that both short and long-term xylene exposure result in a variety of nervous system effects that include headache, mental confusion, narcosis, alterations in body balance, impaired short-term memory, dizziness, and tremors. In animals, xylene also produces nervous system effects. The respiratory system may also be affected. Higher doses of xylene have produced unconsciousness and death in humans and animals. The liver and kidney may also be targets of xylene toxicity in humans, although more thorough data are needed to better assess the relationship.

Death. Xylene can be fatal to both humans and animals following inhalation and oral exposure. Death has been observed in animals following dermal exposure to xylene, but no cases have been reported in humans. Death in humans and animals appears to be caused by either respiratory failure or ventricular fibrillation. The amount of xylene necessary to cause death is relatively large in both animals and humans, and reports of death in humans following inhalation of xylene occurred in areas of poor ventilation. Therefore, it is highly unlikely that inhalation or ingestion of the small amounts of xylene likely to be present in contaminated water or air would pose a risk of death.

Systemic Effects. In humans, acute inhalation of xylene produced nose and throat irritation (Goldie 1960; Hake et al. 1981; Klaucke et al. 1982; Nersesian et al. 1985). Severe lung congestion with pulmonary hemorrhages and edema were noted in a worker who died following acute inhalation of paint fumes containing xylene (Morley et al. 1970). In addition, chronic occupational exposure to xylene vapors has been associated with labored breathing and impaired pulmonary function (Hipolito 1980; Roberts et al. 1988).

Animal data provide supporting evidence for the respiratory effects observed in humans following exposure to xylene. Adverse respiratory effects noted in rats, mice, and guinea pigs following acute and intermediate inhalation exposure to xylene included decreased respiratory rate, labored breathing, irritation of the respiratory tract, pulmonary edema, and pulmonary inflammation (Carpenter et al. 1975; De Ceaurriz et al. 1981; Furnas and Hine 1958; Smyth and Smyth 1928).

Chronic occupational exposure of workers to xylene by inhalation has been associated with increased heart palpitation and abnormal ECGs (Hipolito 1980; Sukhanova et al. 1969). However, these particular reports provide no conclusive evidence that xylene causes cardiovascular effects in humans because exposure conditions were not well characterized and workers may have been exposed to other chemical agents in addition to xylene.

Data from animal studies provide limited evidence that humans could be at increased risk of developing cardiovascular effects following exposure to xylene. Cardiovascular effects observed in rats following acute and intermediate inhalation exposure to xylene have included ventricular repolarization disturbances, atrial fibrillation, arrhythmias, occasional cardiac arrest, changes in ECG, morphological changes in coronary microvessels, decreased myocardial blood flow, and increased heart weight (Morvai et al. 1976, 1987). However, histopathologic lesions of the heart have not been observed in other studies (Carpenter et al. 1975; Hazleton Labs 1988a, 1988b; Jenkins et al. 1970; NTP 1986).

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Symptoms of nausea, vomiting, and gastric discomfort have been noted in workers following inhalation of xylene. Gastrointestinal effects have not been reported in animals. However, there are sufficient human data to conclude that exposure to xylene could produce such effects (e.g., nausea and vomiting).

Human and animal data provide no indications of adverse hematological effects following inhalation of xylene. In the past, chronic occupational exposure to xylene by inhalation was thought to be associated with a variety of hematological effects. However, exposure in all cases was to solvent mixtures known or suspected to contain benzene. Because benzene is an agent strongly suspected of causing leukemia and other blood dyscrasias in humans, these effects cannot be attributed solely to xylene.

Hematological effects have not been observed in rats, dogs, or guinea pigs exposed by inhalation to mixed xylene or o-xylene for an intermediate period (Carpenter et al. 1975; Jenkins et al. 1970). These negative results from animal studies suggest that humans might not develop hematological effects from intermediate inhalation of xylene; however, the hematological effects from chronic inhalation, oral, and dermal exposure are not known.

No data were available regarding the musculoskeletal effects of xylene in humans following inhalation exposure to mixed xylene, m-, o-, or p-xylene. Animal da· regarding musculoskeletal effects following xylene exposure are limited. ..icroscopic examination of skeletal muscle of rats exposed for an intermediate period of time to mixed xylenes, m-xylene, or p-xylene revealed no treatment-related lesions (Carpenter et al. 1975; Hazleton Labs 1988a, 1988b; NTP 1986). Skeletal anomalies, delayed ossification, and extra ribs have been observed in the fetuses and offspring of pregnant mice and rats exposed by inhalation to mixed xylene and o-xylene (Mirkova et al. 1983; Ungvary et al. 1980b). These latter results suggest that the human fetus might be at increased risk of such skeletal effects following maternal exposure to high levels of xylene. The above studies are not definitive, however, in terms of possible skeletal effects.

Human data regarding the hepatic effects following inhalation of xylene are limited to several case and occupational studies (Dolara et al. 1982; Kurppa and Husman 1982; Morley et al. 1970). However, these studies provide limited evidence for evaluating the hepatic effects of xylene in humans because these subjects were concurrently exposed to other chemical agents in addition to xylene.

Available animal studies indicate that mixed xylene and individual isomers produce a variety of mild hepatic effects, and they provide evidence that humans might be at increased risk of developing such effects following xylene exposure. Effects seen in animals have included increased hepatic

cytochrome P-450 and b5 content, increased hepatic weight, increased liver to body weight ratios, decreased hepatic glycogen, ultrastructural changes in hepatic endoplasmic reticulum, changes in the distribution of hepatocellular nuclei, congestion of liver cells, and/or degeneration of the liver (Bowers et al. 1982; Condie et al. 1988; Elovaara 1982; Elovaara et al. 1980; Muralidhara and Krishnakumari 1980; Patel 1979; Pyykko 1980; Smyth and Smyth 1928; Tatrai and Ungvary 1980; Tatrai et al. 1981; Toftgard and Nilsen 1981, 1982; Toftgard et al. 1981; Ungvary et al. 1980a). Many of the observed hepatic effects in animals following inhalation and oral exposure to xylene are likely due to increased metabolism of the solvent and are not necessarily adverse effects (EPA 1985a; Tatrai et al. 1981).

The available human studies that investigate the renal effects following inhalation of xylene are of limited value because exposure conditions were not well characterized and subjects were exposed to other solvents in addition to xylene. However, they provide suggestive evidence that subjects exposed by inhalation to solvent mixtures containing xylene may be at an increased risk of developing renal dysfunction and/or renal damage (Askergren 1982; Franchini et al. 1983; Morley et al. 1970). Indications of renal effects in humans exposed to solvent mixtures containing xylene have included increased blood urea concentrations, decreased urinary clearance of endogenous creatinine, increased lysozymuria, increased urinary levels of β-glucuronidase, and increased urinary excretion of albumin, erythrocytes, and leukocytes (Askergren 1982; Franchini et al. 1983; Morley et al. 1970). No human data were available regarding the renal toxicity of xylene following oral or dermal exposure.

Data from animal studies provide additional evidence that humans could be at risk of developing renal effects following inhalation exposure to xylene. Effects noted in studies with rats, guinea pigs, dogs, and monkeys have included increased renal enzyme activity, increased renal cytochrome P-450 content, increased renal microsomal protein, and increased kidney-to-body weight ratios (Condie et al. 1988; Elovaara 1982; Toftgard and Nilsen 1982). In the study by Condie et al. (1988), tubular dilation and atrophy consistent with early chronic nephropathy were observed, however in studies by Carpenter et al. (1975) and Jenkins et al. (1970), the biochemical changes were not associated with any histopathologic lesions of the kidney.

It has been suggested that xylene induces renal effects by causing increased capillary (at the glomerulus) and/or tubular permeability (EPA 1985a). Increased renal permeability caused by irritant or fluidization effects could result in physiological and possibly histological effects (EPA 1985a). In humans exposed to solvent mixtures containing xylene, the increased urinary levels of β-glucuronidase may be due to a faster cellular turnover in the renal tubular epithelium because of a mild toxic effect (Franchini et al. 1983). The lysozymuria and increase in urinary excretion of

albumin may be indicative of potential damage to the renal tubules and renal glomeruli, respectively (Askergren 1982; Franchini et al. 1983). Increased urinary excretion of erythrocytes and leukocytes are also indicators of potential toxic injury to the kidney (Askergren 1982).

Dermal exposure of humans to xylene causes skin irritation, dryness and scaling of the skin, and vasodilation of the skin (Engstrom et al. 1977; Riihimaki 1979). Exposure of humans to xylene vapors causes ocular irritation (Carpenter et al. 1975; Hake et al. 1981; Klaucke et al. 1982; Nelson et al. 1943).

Animal data provide additional evidence that dermal exposure to xylene produces dermal and ocular effects. These included skin erythema and edema, eschar formation in some animals, and epidermal thickening (Hine and Zuidema 1970). No studies were available regarding potential dermal/ocular effects in animals following exposure to xylene vapor.

Immunological Effects. Very limited human and no animal data are available to evaluate the immunological effects of xylene. Therefore, the relevance to public health is not known.

Neurological Effects. Neurological effects in humans following oral or dermal exposure to xylene have not been studied, although one case was reported of a man who developed a coma following ingestion of xylene (Recchia et al. 1985). Results of experimental studies with humans indicate that acute inhalation exposure to mixed xylene or m-xylene causes impaired short-term memory, impaired reaction time, performance decrements in numerical ability, and alterations in equilibrium and body balance (Gamberale et al. 1978; Riihimaki and Savolainen 1980; Savolainen et al. 1985; Savolainen et al. 1979b; Savolainen and Riihimaki 1981b; Savolainen and Linnavuo 1979; Savolainen et al. 1984). Available case and occupational studies together provide suggestive evidence that acute and chronic inhalation exposure to xylene or solvent mixtures containing xylene may be associated with many neurological effects and symptoms (Arthur and Curnock 1982; Goldie 1960; Hipolito 1980; Klaucke et al. 1982; Morley et al. 1970; Nersesian et al. 1985; Roberts et al. 1988). In several case reports, isolated instances of unconsciousness, amnesia, brain hemorrhage, and epileptic seizure have been associated in a limited number of individuals with acute inhalation exposure to solvent mixtures containing xylene (Arthur and Curnock 1982; Goldie 1960; Morley et al. 1970).

Results of experimental studies with animals provide further evidence that mixed xylene and individual isomers are neurotoxicants following inhalation exposure. Signs of neurotoxicity observed in rats, mice, and gerbils following acute and intermediate inhalation exposure to the various

xylene isomers have included narcosis, prostration, incoordination, tremors, muscular spasms, labored breathing, behavioral changes, hyperactivity, elevated auditory thresholds, hearing loss, changes in brain enzyme activity and changes in levels of brain proteins (Andersson et al. 1981; Carpenter et al. 1975; De Ceaurriz et al. 1983; Furnas and Hine 1958; Ghosh et al. 1987; Kyrklund et al. 1987; Molnar et al. 1986; NTP 1986; Pryor et al. 1987; Rank 1985; Rosengren et al. 1986; Savolainen and Seppalainen 1979; Savolainen et al. 1978; Savolainen et al. 1979a; Wimolwattanapun et al. 1987). No animal studies evaluating the neurological effects of xylene following chronic inhalation exposure were available.

Although a number of mechanisms of action have been proposed, the toxic mechanism of xylene on the nervous system is not fully understood. Because xylene is lipid soluble, it can distribute to the central nervous system. A number of investigators have noted the affinity of xylene for nervous system tissue, such as myelin and axonal membrane, in humans and animals (Desi et al. 1967; EPA 1985a; Gerarde 1959; Savolainen and Pfaffli 1980).

Neurological effects, including narcosis and anesthesia, are noted after acute exposure to high concentration of xylene when high blood and brain levels of the solvent occur (EPA 1985a). It has been suggested that xylene and other alkylbenzenes act simply by being in the nervous system at sufficiently high concentrations to inhibit normal function (Desi et al. 1967; EPA 1985a; Gerarde 1959). A number of experimental studies with humans on CNS function indicate that the first observable effects of m-xylene are on the central vestibular system, which controls equilibrium and body balance (Riihimaki and Savolainen 1980; Savolainen and Linnavuo 1979; Savolainen et al. 1979b; Savolainen and Riihimaki 1981b; Savolainen et al. 1984; Savolainen et al. 1985).

Also, xylene may directly affect nerve conductivity by altering the lipid components of the axonal membrane (EPA 1985a; Savolainen and Seppalainen 1979). Altered lipid components in turn could alter sodium permeability and decrease action potentials, resulting in signs of intoxication (EPA 1985a).

Results of experimental studies with rats suggest that mixed xylene and m-, o-, or p-xylene can cause alterations in dopamine and/or noradrenaline levels in the brain (Andersson et al. 1981). These changes can produce disturbances in catecholamine neurotransmission, which in turn can potentially alter brain function, particularly mental, motor, and neuroendocrine control (Andersson et al. 1981). Two possible modes of action have been suggested. Xylene or a metabolite of xylene could act directly on adrenergic receptors in the brain, causing increased catecholamines and postsynaptic stimulation. The second possibility involves alteration of axonal membrane fluidity, which causes permeability changes and alters neurotransmitter release (Andersson et al. 1981; EPA 1985a).

Some authors have also suggested that metabolic intermediates, such as arene oxides or methylbenzaldehyde, may be responsible for the toxic effects of xylene (Savolainen and Pfaffli 1980). Oxidation of xylene to these intermediates by microsomal enzyme systems may occur within brain cells (Savolainen and Pfaffli 1980).

Developmental Toxicity. Limited human studies were available regarding the developmental or teratogenic effects of xylene. However, because of concurrent exposure with chemical agents in addition to xylene, they cannot be used to assess the relationship between xylene exposure and developmental effects in humans. Findings in animal studies suggest that adverse effects might occur in the unborn and offspring of women exposed to xylene or its isomers. Results of studies with rats and mice indicate that inhalation exposure to mixed xylene or xylene isomers may induce increased fetal death, decreased fetal weight, delayed skeletal development, skeletal anomalies, enzymatic changes in fetal organs, and maternal toxicity (Hudak and Ungvary 1978; Marks et al. 1982; Mirkova et al. 1983; Ungvary et al. 1980b, 1981). Oral exposure to mixed xylene has been associated with cleft plate and decreased fetal weight (Marks et al. 1982). Dermal exposure of rats to xylene has been associated with biochemical changes in fetal and maternal brain tissue (Mirkova et al. 1979). However, p-xylene produced no developmental effects, with maternal toxicity, in rats (Rosen et al. 1986). These studies were generally limited but, taken together, suggest fetotoxic effects, although most of these may have been secondary to maternal toxicity.

The exact mechanism by which mixed xylene or its individual isomers produce toxic effects in fetuses has not been fully investigated. Based on results of studies with rats, p-xylene-induced delayed fetal development may have been caused by decreased levels of progesterone and estradiol (Ungvary et al. 1981). The titers of these hormones were apparently lowered due to xylene's inductive effect on metabolism, which caused increased hormone catabolism.

Reproductive Toxicity. The relevance to public health regarding xylene exposure and adverse reproductive effects is not known because of the limitations of the human and animal data. Occupational exposure of men to xylenes, in addition to other solvents, was found to increase the potential for their wives to experience spontaneous abortions, however, this study was limited by exposure of the men to other solvents and the limited size of the population studied (Taskinen et al. 1989). No reproductive effects were found in rats following inhalation of xylene before mating and during gestation and lactation (Bio/dynamics 1983). Histopathological examination following intermediate and chronic oral bioassays revealed no adverse effects on the reproductive organs of rats and mice (Hazleton Labs 1988a, 1988b; NTP 1986).

No other studies were located regarding reproductive effects in animals following inhalation or dermal exposure to xylene or its isomers.

Genotoxicity. Mixed xylene, as well as each of the individual xylene isomers, has been tested for genotoxicity in a variety of *in vitro* and *in vivo* assays. Results of the various assays indicate that mixed xylene and xylene isomers are nongenotoxic (Tables 2-10 and 2-11). As summarized in Table 2-10, the results of the various assays indicate that mixed xylene and xylene isomers are nongenotoxic following *in vitro* exposure (Bos et al. 1981; Connor et al. 1985; Florin et al. 1980; Haworth et al. 1983; Litton Bionetics 1978b; McCarroll et al. 1981a, 1981b; NTP 1986; Shimizu et al. 1985).

The induction of genotoxic effects following *in vivo* exposure to xylene has been evaluated in the bone marrow chromosomal aberration test with rats (Litton Bionetics 1978b), the bone marrow micronucleus test with mice (Mohtashamipur et al. 1985), and the sperm morphology test with rats (Washington et al. 1983). The incidence of sister-chromatid exchanges and chromosomal aberrations in the peripheral lymphocytes of workers exposed occupationally to xylene also has been evaluated (Haglund et al. 1980; Pap and Varga 1987). Both human studies involved occupational exposure to other chemicals in addition to xylene. As summarized in Table 2-11, the results of these studies indicate that mixed xylene, *m*-, *o*-, and *p*-xylene are nongenotoxic following *in vivo* exposure.

No mutagenic activity was demonstrated for any of the various metabolites of xylene in bacterial test systems. *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without S9 metabolic activation, have been used to test the mutagenic activity of *p*-xylenol (Epler et al. 1979; Florin et al. 1980; Hejtmankova et al. 1979; Pool and Lin 1982), *m*-xylenol (Epler et al. 1979; Florin et al. 1980), and *o*-methylbenzyl alcohol (Bos et al. 1981). 2,4-Dimethylphenol has been evaluated in a gene reversion assay with *E. coli* strain Sd-4-73 (Szybalski 1958).

Ethylbenzene, a common component of many technical grades of mixed xylene, also demonstrated no mutagenic effects in the gene reversion assay with *S. cerevisiae* (Nestmann and Lee 1983), the *Salmonella*/microsome assay with strains TA98, TA100, TA1535, TA1537, and TA1538 (Florin et al. 1980; Nestmann et al. 1980), or in cytogenic assays with cultured Chinese hamster ovary cells (NTP 1986). However, in studies with cultured human lymphocytes, ethylbenzene induced a slight but statistically significant ($p<0.01$) increase in the number of the sister-chromatid exchanges (Norppa and Vainio 1983). The authors of this latter study suggested that ethylbenzene may be a "weak, ineffective mutagen." Ethylbenzene is the subject of a separate toxicological profile, and the reader should refer to that document for a more detailed review of its genotoxicity potential.

TABLE 2-10. Genotoxicity of Xylene In Vitro

Endpoint	Species/Test System	Isomer	Purity/Composition	Result: With Activation	Result: Without Activation	Reference
Prokaryotic Systems						
Mutation	*Salmonella typhimurium* TA97, TA98, TA100, TA1535/plate incorporation assay	Mixed Xylene	60% m-xylene, 9% o-xylene, 14% p-xylene, 17% ethylbenzene	Negative	Negative	NTP 1986
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537/plate incorporation assay	m-Xylene o-Xylene p-Xylene	Not Reported Purity = 97% Purity = 99%	Negative Negative Negative	Negative Negative Negative	Haworth et al. 1983
Mutation	*S. typhimurium* TA98, TA100, UTH8414, UTH8413/plate incorporation assay	m-Xylene o-Xylene p-Xylene	Not Reported Purity = 97% Purity = 99.7%	Negative Negative Negative	Negative Negative Negative	Connor et al. 1985
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538/plate incorporation assay	m-Xylene o-Xylene p-Xylene	Not Reported Not Reported Not Reported	Negative Negative Negative	Negative Negative Negative	Bos et al. 1981
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537/spot and plate incorporation assays	m-Xylene p-Xylene	Purity ≥ 97% Purity ≥ 97%	Negative Negative	Negative Negative	Florin et al. 1980
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538/suspension and plate incorporation assays	Mixed Xylene	52.1% m-xylene, 11.4% o-xylene, 0.3% p-xylene, 36.1% ethylbenzene	Negative	Negative	Litton Bionetics 1978b
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538/plate incorporation assay	p-Xylene	Purity = 98%	Negative	Negative	Shimizu et al. 1985
Mutation	*Escherichia coli* WP2uvrA/plate incorporation assay	p-Xylene	Purity = 98%	Negative	Negative	Shimizu et al. 1985
DNA Damage	*E. coli* WP2, WP2uvrA, WP67, CM611, WP100, W3110polA$^+$, p3478pola$^-$/DNA repair microsuspension assay	Not Reported (technical grade)	Not Reported	Negative	Negative	McCarroll et al. 1981b
DNA Damage	*Bacillus subtilis* H17, M45/modified rec assay	Not Reported (technical grade)	Not Reported	Negative	Negative	McCarroll et al. 1981a

TABLE 2-10 (Continued)

Endpoint	Species/Test System	Isomer	Purity/Composition	Result		Reference
				With Activation	Without Activation	
Eukaryotic Systems						
Mitotic Gene Conversion	Saccharomyces cerevisiae D4/suspension and plate incorporation assays	Mixed Xylene	52.1% m-xylene, 11.4% o-xylene, 0.3% p-xylene 36.1% ethylbenzene	Negative	Negative	Litton Bionetics 1978b
Mammalian Systems						
Mutation	Cultured mouse lymphoma cells (L5178Y, TK+/-)/forward mutation assay	Mixed Xylene	52.1% m-xylene, 11.4% o-xylene, 0.3% p-xylene, 36.1% ethylbenzene	Negative	Negative	Litton Bionetics 1978b
Sister chromatid exchange and chromosomal aberrations	Cultured human lymphocytes	Not Reported	Not Reported	Not tested	Negative	Gerner-Smidt and Friedrich 1978

TABLE 2-11. Genotoxicity of Xylene In Vivo

Endpoint	Species/Test System	Exposure Route	Isomer	Purity/composition	Result	Reference
Mammalian Systems						
Sister Chromatid Exchange and Chromosomal Abberations	Human Peripheral Lymphocytes	Inhalation (Occupational exposure)	Not Reported	Not Reported	Negative	Haglund et al. 1980
Sister Chromatid Exchange	Human Peripheral Lymphocytes	Inhalation (Occupational exposure)	Mixed Xylene	6-15% ethylbenzene	Negative	Pap and Varga 1987
Chromosomal Aberrations	Rat Bone Marrow	Intraperitoneal (single exposure)	Mixed Xylene 11.4% o-xylene, 0.3% p-xylene, 36.1% ethylbenzene	52.1% m-xylene,	Negative	Litton Bionetics 1978b
Chromosomal Aberrations	Rat Bone Marrow	Intraperitoneal (5 exposures)	Mixed Xylene 0.3% p-xylene, 36.1% ethylbenzene	52.1% m-xylene, 11.4% o-xylene,	Negative	Litton Bionetics 1978b
Micronuclei Formation	Mouse Bone Marrow Polychromatic-Erythrocyte Assay (Micronucleus Test)	Intraperitoneal (two exposures)	m-Xylene o-Xylene p-Xylene	purity = 98% purity = 98% purity = 98%	Negative Negative Negative	Mohtashamipur et al. 1985
Sperm-Head Abnormalities	Rat Sperm-Head Morphology Assay	Intraperitoneal	o-Xylene	Not Reported	Negative	Washington et al. 1983

In summary, genotoxicity studies on mixed xylene and the individual isomers of xylene have provided consistently negative results in a variety of in vitro and in vivo assays and test systems (bacteria, yeast, insects, cultured mammalian cells, mice, rats, and humans). Based on the genotoxicity studies conducted to date, there is sufficient evidence to conclude that mixed xylene, m-xylene, o-xylene, and p-xylene are nonmutagenic. There is also limited evidence from bacterial test systems that suggest that xylene metabolites, specifically m-xylenol, p-xylenol, 2,4-dimethylphenol, and o-methylbenzyl alcohol, are nonmutagenic as well.

Cancer. No data were available regarding the development of cancer in humans following inhalation, oral, or dermal exposure to mixed xylene or individual isomers. Animal carcinogenicity data for the xylenes are limited to oral studies with mixed xylene (Maltoni et al. 1983, 1985; NTP 1986) and dermal studies in which the isomeric composition of the xylene was not specified, exposures were less than lifetime, and involved multiple chemicals (Berenblum 1941; Pound 1970; Pound and Withers 1963). No animal carcinogenicity data for the xylenes were available for inhalation exposure. Because of the limited data, no conclusions can be drawn regarding the relationship between xylene exposure and cancer in humans.

EPA has classified mixed xylene as a Group D agent (not classifiable as to human carcinogenicity) (IRIS 1989). This classification applies to those chemical agents for which there is inadequate evidence of carcinogenicity in animals. No cancer potency factor (q1*) or other quantitative estimate of carcinogenicity has been developed by EPA for mixed xylene, m-xylene, o-xylene, or p-xylene.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the results of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on

the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It maybe difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to xylene are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g. increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by xylene are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Xylenes

Xylene levels in the blood and levels of its metabolite, methylhippuric acid, in the urine are the primary markers used to detect exposure to xylenes. Xylene is very soluble in the blood and is readily absorbed into the circulation during exposure (Astrand 1982). Measurement of blood levels of xylene is limited by the rapid metabolism of xylene. Xylene is metabolized almost exclusively to methylhippuric acid in humans. Detection of methylhippuric acid in the urine is the most widely used indicator of xylene exposure (ACGIH 1986). Within 2 hours of an inhalation exposure, methylhippuric acid may be detected in the urine (Sedivec and Flek 1976b). The excretion of methylhippuric acid is complete within a day or two of exposure to xylenes, limiting the utility of this biomarker to the detection of only very recent exposures. With chronic exposure to xylene, the metabolism is enhanced, further limiting the time following exposure that xylene levels may be measured in the blood (Savolainen et al. 1979a). For additional information on the kinetics of xylene absorption, distribution, metabolism, or excretion, see Section 2.3.

Xylenes cause a number of physiological effects such as hepatic enzyme induction and a wide spectrum of nervous system effects ranging from cognitive dysfunction and anesthetic-like symptoms to hyperactivity and convulsions. However, none of these effects is specific for xylene exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by Xylenes

The following changes are potential biomarkers of effect for xylenes; however, none of the changes are unique to xylene exposure. Xylenes have been observed to enhance the activity of a variety of microsomal enzymes and increase hepatic cytochrome P-450 content (Elovaara 1982; Elovaara et al. 1980; Patel et al. 1979; Savolainen et al. 1978; Tatrai et al. 1981; Toftgard and Nilsen 1981, 1982; Toftgard et al. 1981). Increases in liver-to-body weight ratios and proliferation of endoplasmic reticulum are also characteristic responses to xylene exposure (Condie et al. 1988; Kyrklund et al. 1987; Tatrai et al. 1981; Toftgard et al. 1981). Scores consistent with memory impairment and decreased reaction time have been observed using standard intelligence tests and measures of reaction time (Gamberale et al. 1978; Riihimaki and Savolainen 1980; Savolainen and Riihimaki 1981b; Savolainen et al. 1979b; 1984, 1985). Decreases in flash-evoked potentials have been observed as a result of xylene exposure (Dyer et al. 1988). Also, decreased axonal transport has been observed following xylene exposure (Padilla and Lyerly 1989). Increased hypothalamic catecholamine levels have been observed following xylene exposure (Andersson et al. 1981). Further study may indicate that one or a combination of the above effects may be a more specific biomarker of the effects of xylenes.

2.6 INTERACTIONS WITH OTHER CHEMICALS

The interaction of xylene with alcohol, drugs (aspirin, phenobarbital), and various solvents (1,1,1-trichloroethane, benzene, ethylbenzene) has been evaluated in experimental studies with humans and animals.

The effects from combined exposure to xylene and ethanol have been studied most extensively because of the high potential for workers to consume alcoholic beverages and to be exposed to xylene occupationally by inhalation. Results of studies with humans and animals indicate that metabolic interaction between xylene and ethanol occurs. Ethanol appears to inhibit the metabolism of xylene and delay microsomal oxidation (Elovaara et al. 1980; Riihimaki et al. 1982a, 1982b; Romer et al. 1986; Savolainen 1980; Savolainen et al. 1978, 1979b, 1980).

Possibly because of competition for the enzymes involved in conjugation with glycine during the concurrent metabolism of m-xylene and aspirin by human volunteers, saturation of the conjugation pathway occurred that led to decreases in the metabolism of both aspirin and m-xylene (Campbell et al.

1988). Administration of aspirin to pregnant rats which were being exposed to xylene caused a potentiation of maternal and fetal toxic effects above that observed in the presence of either xylene or aspirin alone (Ungvary 1985). This was postulated to be due to the delayed metabolism of aspirin by xylene.

Exposure to xylene combined with benzene or ethylbenzene may produce mutual inhibition of the metabolism of both solvents (Engstrom et al. 1984; Gut 1981; Nakajima and Sato 1979). Ethylbenzene is found in mixed xylene. Co-exposure to m-xylene and methyl ethyl ketone also produced inhibition of the metabolism of m-xylene (Liira et al. 1988). In contrast, ethyl acetate exposure in combination with exposure to m-xylene caused a reduction in the blood of xylene levels (Freundt et al. 1989).

Inhalation of m-xylene following pretreatment with phenobarbital was associated with both increased pulmonary retention of m-xylene and increased urinary excretion of m-methylbenzoic acid (David et al. 1979). Surprisingly, inhalation of m-xylene and 1,1,1-trichloroethane has been associated with slight improvements in certain psychophysiological parameters, including reaction time and equilibrium in humans as compared with pre-exposure measurements (Savolainen et al. 1982a, 1982b) and impairment in others such as visual evoked potentials and equilibrium (Savolainen et al. 1982a; Seppalainen et al. 1983). Also, a protective effect of xylene on n-hexane-induced testicular atrophy was observed when rats were exposed to n-hexane and xylene simultaneously (Nylen et al. 1989).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Available data indicate that subsets of the human population may be unusually susceptible to the toxic effects of xylene. Pregnant women, fetuses, and very young children may be at greater risk of adverse health effects from xylene exposure than the population in general (Barlow and Sullivan 1982; Holmberg and Nurminen 1980; Hudak and Ungvary 1978; Kucera 1968; Marks et al. 1982; Mirkova et al. 1982; Mirkova et al. 1983; Ungvary et al. 1980b, 1981). Although no human studies were located indicating maternal or fetal toxicity following total xylenes exposure, animal studies suggest there may be a relationship between exposure to the agents and developmental effects (Hudak and Ungvary 1978; Marks et al. 1982; Ungvary et al. 1980b, 1981). The ability of fetuses and very young children to metabolize certain xenobiotics, including possibly xylene, is reduced because of their immature enzyme detoxification systems (Calabrese 1978). This reduced ability to biotransform and excrete these compounds efficiently may increase or decrease their toxic effect, depending on whether the parent compound or one or more metabolites is the actual toxic form. The biotransformation of xylene varies with the exposure concentration.

People with subclinical and clinical epilepsy are at increased risk of seizures if exposed to xylene due to its excitatory CNS effects (Arthur and Curnock 1982; Goldie 1960; Riihimaki and Hanninen 1987). It has also been demonstrated in human studies (Goldie 1960; Riihimaki et al. 1982a; Savolainen 1980; Savolainen et al. 1978; Savolainen et al. 1980) and animal studies (Elovaara et al. 1980; Savolainen et al. 1979b) that alcohol consumption potentiates xylene toxicity. Some people appear particularly susceptible to the interaction and may develop dizziness, nausea, and dermal flush (Riihimaki et al. 1982b; Savolainen et al. 1980).

People with clinical or subclinical renal, hepatic, and cardiac disease may be more susceptible to the effects of xylene. Evidence from occupational and case studies indicate that exposure to xylene might cause renal impairment and some hepatic effects, as well as cardiac manifestations, including tachycardia and ECG abnormalities (Goldie 1960; Hipolito 1980; Morley et al. 1970; NIOSH 1975; Sikora and Gala 1957; Sukhanova et al. 1969; von Burg 1982). However, exposure to xylene in these studies was confounded with exposure to other chemical agents.

Limited human data suggest that people with respiratory diseases, such as asthma, could potentially be at risk to the adverse effects of xylene following inhalation exposure (Hipolito 1980; Morley et al. 1970; Muller and Greff 1980).

2.8 ADEQUACY OF THE DATABASE

Section 104(i)5 of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of xylene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of xylene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 Existing Information on Health Effects of Xylene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to xylene are summarized in Figure 2-11. The

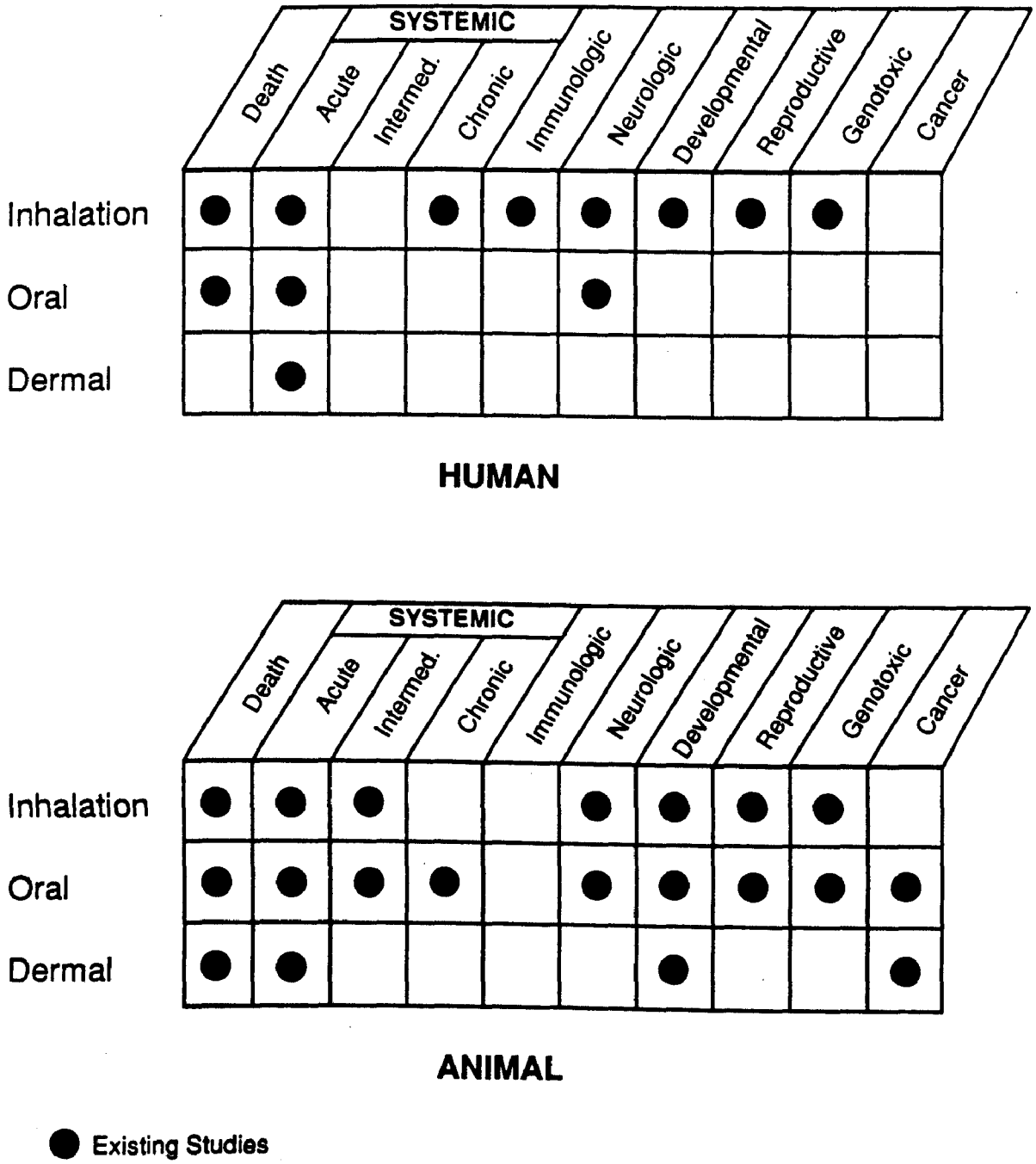


Figure 2-11. Existing Information on Health Effects of Total Xylenes

purpose of this figure is to illustrate the existing information concerning the health effects of xylene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

Figure 2-11 graphically depicts the existing health effects information for total xylenes for a specific route and duration of exposure.

Persons may be exposed to xylene at hazardous waste sites by inhalation of contaminated air, drinking contaminated water, or dermal contact with contaminated water or subsurface soils and sediments. Volatilization of xylenes from surface water and soil occurs rapidly; therefore, inhalation is the most likely source of exposure to xylenes at these sites. The health effects of xylenes by inhalation exposure have been studied to the greatest extent. There is little information available regarding health effects in humans following oral or dermal exposure to xylene. As noted above, ingestion of xylene may be of concern because of the potential for xylene to contaminate sources of drinking water (groundwater). Dermal exposure to xylene is of concern not only because of potential workplace exposures, but also because members of the general public are potentially exposed to xylene contained in paints, glues, and other household products. As noted above, dermal exposure to soils and water contaminated with xylene at waste sites could also occur.

Human fatalities following both inhalation and ingestion of xylene have been reported in the literature. Acute exposure to xylene has resulted in the development of both systemic effects, such as hepatic and cardiovascular effects, and neurologic effects following inhalation or oral exposure. Data regarding the systemic health effects of intermediate human exposure to xylene were not reported in the literature. Also, no human carcinogenicity data were reported in the literature. Very little information is available on the chronic systemic, immunologic, developmental, reproductive, and genotoxic health effects of xylene exposure in humans. Interpretation of the large number of human studies examining the health effects of inhaled xylene vapor is difficult due to study design limitations, e.g., inadequate characterization of exposure, and concurrent exposure to other solvents, such as toluene and benzene.

Studies conducted on experimental animals have been fairly extensive (Figure 2-11), and have focused on the adverse health effects following inhalation and oral exposure to xylene. Data are comprehensive on neurological and systemic effects. There are several developmental studies in animals, although most have limitations. Limited information exists on the carcinogenicity of xylene. A large number of studies on the genotoxicity of xylene are available, with the majority reporting negative results.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. There are acute exposure data in humans and/or animals that indicate that the central nervous system and possibly the developing fetus are the major targets of acute xylene toxicity by the inhalation and oral routes. No information is available on the nervous system effects of dermal exposure to xylenes. Death has been observed to occur as a result of exposure by inhalation, oral, and dermal exposure, and lethal and nonlethal levels of total xylenes have been determined. Acute studies have demonstrated that xylene is irritating to the skin and eyes. Inhalation of xylenes has also been shown to cause irritation of the respiratory tract and dyspnea. Data on NOAELs and LOAELs from acute studies were not sufficient for deriving either inhalation or oral MRLs for xylene. Additional information on the effects observed after acute dermal exposure would be helpful due to the likelihood that acute duration skin contact with xylenes could occur in the home, workplace, and possibly at hazardous waste sites. Pharmacokinetic data and toxicity data indicate that xylenes are absorbed through the skin, although the relative absorption by this route is difficult to ascertain due to the rapid evaporation of xylenes from the skin. Because short-term inhalation or oral exposure is likely in the home, workplace, and at hazardous waste sites, additional acute-duration inhalation and oral studies also would be helpful in determining the threshold levels at which toxicity occurs.

Intermediate-Duration Exposure. Intermediate-duration inhalation and oral studies have identified the central nervous system, liver, kidneys, and possibly the developing fetus as the primary targets of intermediate- duration xylene exposure. No studies were available that examined the effects associated with intermediate-duration dermal exposure to xylenes. Pharmacokinetic data indicate that absorption of xylenes occurs through the skin; however, it is difficult to determine whether similar end points would be expected after repeated dermal exposure to xylenes. Human skin may be repeatedly exposed to xylenes as a result of occupational and home use. Repeated exposure of the skin to contaminated media at hazardous waste sites may also occur. Therefore, a well-designed and well-conducted intermediate-duration dermal study would be helpful in estimating the human health hazard associated with this type of exposure. No inhalation or oral studies were sufficient to determine intermediate-duration MRLs. Additional inhalation and oral studies examining the threshold levels associated with adverse health effects would be helpful since there are populations surrounding hazardous waste sites that might be repeatedly exposed to xylene.

Chronic-Duration Exposure and Cancer. Few epidemiological or animal studies were available regarding the health effects associated with chronic exposure to xylenes. The central nervous system and the liver appear to be the primary targets of chronic xylene exposure; however, no study had

sufficient information on threshold levels associated with these health effects to allow calculation of a chronic MRL. No information is available on the health effects of chronic dermal exposure to xylenes. Since the inhalation and oral routes are potential means of exposure for individuals living near hazardous waste sites, more information on the health effects associated with chronic low-level exposure by these routes would be helpful.

No epidemiological studies were available regarding the development of cancer in humans following inhalation, oral, or dermal exposure to mixed xylene or xylene isomers. Several oral carcinogenicity bioassays involving lifetime exposure have been conducted with mixed xylene in rats and mice; however, all of these bioassays contained limitations that preclude a definitive conclusion regarding the carcinogenicity of xylene. Several dermal studies are available in which xylene (unspecified isomeric content) was evaluated for its ability to enhance tumor induction by tumor-initiating and tumor-promoting agents; however, these studies are less than lifetime and have often involved exposures to more than one chemical agent. No animal cancer bioassays involving inhalation exposure to mixed xylene or isomers of xylene have been conducted. Because the issue of the potential carcinogenicity of xylenes has not been resolved, additional bioassays are desirable. Chronic inhalation and oral bioassays to low levels would be helpful because chronic exposure by these routes may be encountered in the workplace, home, or in the vicinity of hazardous waste sites.

Genotoxicity. Limited data is available regarding the genotoxicity of inhalation of xylenes in humans. No data is available regarding the potential genotoxicity of xylenes in humans following oral or dermal exposure. Animal studies examining the genotoxicity of inhalation or oral exposure to xylenes have been uniformly negative. Also, a variety of *in vitro* assays have negative results. Because of the large number of negative studies that exist, additional *in vivo* or *in vitro* assays of the genotoxicity potential of xylenes are not required at this time.

Reproductive Toxicity. One epidemiological study suggested that paternal exposure to xylenes in the workplace may increase the likelihood of abortions; however this study was limited by the size of the sample population (Taskinen et al. 1989). Only one animal inhalation study has been conducted to test the potential reproductive toxicity of mixed xylene (Bio/dynamics 1983). No reproduction studies have been conducted on either mixed xylene or the individual xylene isomers in animals following exposure via oral or dermal routes. Histopathological examination of reproductive organs of rats and mice following intermediate and chronic oral bioassays revealed no adverse effects; however, given the high potential for human exposure to xylene and its isomers and their ability to cross the placenta, additional studies in animals and

epidemiological studies in humans would be useful to assess more fully the reproductive toxicity of xylene and its isomers.

Developmental Toxicity. Congenital defects of the central nervous system in children whose mothers were exposed occupationally to mixed xylene vapors were reported in two case studies (Holmberg and Nurminen 1980; Kucera 1968). However, the studies have many limitations, and no conclusion can be made. Animal inhalation, oral, and dermal studies have provided some information on the developmental effects of xylene and its isomers; however the quality of many of these studies precludes drawing definitive conclusions. Additional animal studies examining the relationship between developmental effects and xylene exposure would provide useful information because of the developmental effects evident in inhalation and oral studies and the ability of xylene to cross the placenta. More information is needed on the mechanism of xylene-induced developmental toxicity.

Immunotoxicity. Several occupational studies have been conducted to evaluate the immunological effects of xylene; however, workers in these studies were exposed to other chemical agents in addition to xylene. No animal studies involving exposure by any route have been conducted examining the immunotoxicity of mixed xylene or the xylene isomers. Inhalation exposure studies in animals employing only xylene or its isomers may remove uncertainties about the immunotoxicity potential of xylene. Dermal sensitization tests may also provide useful information on whether an allergic response to xylene is likely, since the potential for skin contact by humans occurs in occupational settings and in soil and water at hazardous waste sites.

Neurotoxicity. Human and animal studies regarding neurologic effects have been conducted following oral and inhalation exposures to xylene. Data from such studies indicate that xylene adversely affects the nervous system. The majority of studies in humans and animals concentrated on the neurobehavioral effects of xylene. Further studies attempting to elucidate the mechanism of action of xylenes on the nervous system would be helpful in understanding the neurotoxic effects produced by xylenes. Additional well-conducted studies in animals on the histopathologic changes of the central nervous system following intermediate or chronic exposure also may provide useful information on permanent structural alterations induced by xylene.

Epidemiological and Human Dosimetry Studies. Limited epidemiological studies and no human dosimetry studies on any of the xylenes have been conducted. Much of the available information on the effects of xylene in humans comes from case reports and occupational studies in which subjects were exposed to other chemical agents in addition to xylene. Many of the case reports and occupational studies were also limited in that exposure conditions

(concentration, duration) were not reported and/or well characterized. Well-designed and well-controlled epidemiological studies of people living near waste sites or industries using xylene, or occupational studies in which xylene exposure conditions are better characterized, would be useful. Epidemiological studies examining the nervous system, developmental, and renal effects associated with xylene exposure would be particularly useful since reports of human exposure and animal studies have suggested that persons living in the vicinity of hazardous waste sites may be at risk for developing these types of effects.

Biomarkers of Exposure and Effect. Methods are available for determining xylene and its metabolite, methylhippuric acid, in biological tissues and fluids. These biomarkers of exposure are specific for xylene exposure and are sufficient for determining recent exposure to xylenes but are incapable of distinguishing short-term from chronic exposures. A number of physiological effects occur as a result of xylene exposure, but none of these effects is specific for xylenes, and, therefore, their occurrence would have very little usefulness in determining exposure to xylenes. Further study of the effects associated with xylene exposure may reveal additional biomarkers that are specific to xylene exposure.

No specific biomarkers of effects have been identified for xylenes. Xylenes have been demonstrated to cause a number of adverse health effects including central nervous system disturbances. A number of neurological and cognitive function tests exist and have been used to identify central nervous system changes produced by xylenes. However, until the mechanism for nervous system disruption is identified, it is unlikely that a specific test could predict xylene-specific intoxication. Assessment of hepatic enzyme induction is difficult without obtaining liver tissue. Demonstration of enhanced metabolism of substances by the microsomal enzyme system could be interpreted as microsomal induction; however, a large number of substances other than xylenes also induce enhanced enzyme activity. Renal impairment also has been associated with xylene exposure. Increased excretion of albumin, leukocytes, and erythrocytes demonstrates kidney damage of the type ascribed to xylene exposure, but these effects are not specific for xylenes. However, limited data are available associating levels of xylene in human tissues and fluids with adverse health effects. Available human studies have focused on the blood concentrations of m-xylene associated with central nervous system effects. Additional animal studies evaluating the association between xylene (or xylene metabolite) levels in other human tissues or fluids and adverse health effects would be useful.

Absorption, Distribution, Metabolism, and Excretion. The absorption, metabolism, and excretion of xylenes following inhalation exposure in humans and animals have been well characterized. The distribution of xylenes has

been well characterized in animals and identified to a small extent in humans. The database for oral and dermal absorption, distribution, and excretion of xylene isomers in humans and/or animals consists primarily of qualitative information from experimental and occupational studies. A few quantitative studies exist that examined the toxicokinetics following oral or dermal exposure. Differences in the rate of metabolism of xylenes after short-term or chronic exposure have been identified. Additional information on the dermal absorption, distribution, metabolism, and excretion would be helpful for predicting the fate of xylene in persons exposed by this route.

Comparative Toxicokinetics. The target organs and adverse health effects of xylenes are similar across species. Toxicokinetic studies have been performed in humans, rats, mice, rabbits, and monkeys. There is reasonable correlation between the end points examined in these studies. The metabolism of m- and p-xylenes is similar in rats and humans. However, a difference between the metabolism of o-xylene in rats and in humans exists. Whereas o-xylene is almost exclusively metabolized to o-methylhippuric acid in humans, 10%-56% of o-xylene is also conjugated by glucuronide and glutathione in rats. Additional studies would be helpful for determining whether other differences exist in the metabolism of xylenes among species. Study of the health effects of the glucuronide and glutathione metabolites of o-xylene may answer this question.

2.8.3 On-going Studies

On-going studies regarding the health effects of xylene were reported in the Federal Research in Progress File (FEDRIP) database and in the Directory of On-Going Research in Cancer Epidemiology (Parkin and Wahrendorf 1987). P. Moszczynski (Provincial Immunology Lab, Poland) is continuing to examine the hematological and immunological functions of workers occupationally exposed to benzene, toluene, and xylene. To date, no effects have been recorded. J.M. Russo of NIOSH is conducting neurobehavioral tests on several chemicals including xylene. The results will be used to assess neurological effects from acute and chronic exposures in high-risk occupations.

On-going studies on mixed xylene and individual xylene isomers are also being conducted by the Health Effects Research Laboratory in Cincinnati for EPA's Office of Research and Development (NTP 1988). Testing was to be started in 1988 on the subchronic, systemic/organ, neurologic/behavioral, and pulmonary toxicity of mixed xylene. Testing was in progress in 1988 on the neurologic/behavioral toxicity and systemic/organ toxicity of m-xylene, the systemic/organ toxicity of o-xylene, and the biochemical/cellular/tissue effects, neurologic/behavioral toxicity, and pulmonary toxicity of p-xylene (NTP 1988).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The synonyms and identification numbers for mixed, m-, o-, and p-xylene are listed in Tables 3-1 through 3-4.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of mixed, m-, o-, and p-xylene are presented in Tables 3-5 through 3-8.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Mixed Xylene

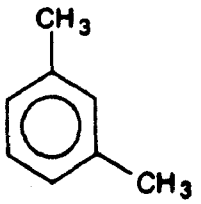
	Value	Reference
Chemical name	Xylene	Windholz 1983
Synonyms	Dimethylbenzene; xylol; benzene, dimethyl-; Ksylen (Polish); Xiloli (Italian); Xylenen (Dutch); Xylole (German); methyl toluene	Windholz 1983; HSDB 1988 Sax and Lewis 1989
Trade names	Violet 3	Sax and Lewis 1989
Chemical formula	C_8H_{10}	HSDB 1988
Chemical structure[a]		
Identification numbers:		
CAS Registry	1330-20-7	HSDB 1988
NIOSH RTECS	ZE 2100000	HSDB 1988
EPA Hazardous waste	U239	HSDB 1988
OHM/TADS	No data	
DOT/UN/NA/IMCO Shipping	UN 1307; Xylene (xylol) IMCO 3.2 IMCO 3.3	HSDB 1988
HSDB	4500	HSDB 1988
NCI	C55232	HSDB 1988
STCC	49 093 50; Xylene	HSDB 1988

[a]Mixture of m-xylene, o-xylene, p-xylene, and ethylbenzene. See Tables 3-2, 3-3, and 3-4 for chemical structures of m-, o-, and p-xylene.

HSDB = Hazardous Substances Data Bank; CAS = Chemical Abstracts Service; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; NCI = National Cancer Institute; STCC = Standard Transport Commodity Code.

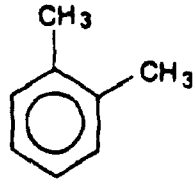
3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Chemical Identity of m-Xylene

	Value	Reference
Chemical name	m-Xylene	Windholz 1983
Synonyms	1,3-Dimethylbenzene; 1,3-xylene; benzene, 1,3-dimethyl; m-dimethylbenzene, m-xylol; m-methyltoluene; meta-xylene	HSDB 1988 ECETOC 1986
Trade names	No data	
Chemical formula	C_8H_{10}	HSDB 1988
Chemical structure		ECETOC 1986
Identification numbers:		
CAS Registry	108-38-3	HSDB 1988
NIOSH RTECS	ZE 2275000	HSDB 1988
EPA Hazardous Waste	U239; Xylene F003; Xylene	HSDB 1988
OHM/TADS	7216953	HSDB 1988
DOT/UN/NA/IMCO Shipping	UN 1307; m-Xylene; m-Xylol IMCO 3.2 Xylenes IMCO 3.3 Xylenes	HSDB 1988
HSDB	135	HSDB 1988
NCI	No data	
STCC	49 093 50; Xylenes	HSDB 1988

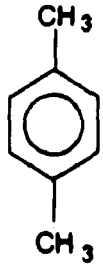
HSDB = Hazardous Substances Data Bank; CAS = Chemical Abstracts Service; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances;. EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; NCI = National Cancer Institute; STCC = Standard Transport Commodity Code.

TABLE 3-3. Chemical Identity of o-Xylene

	Value	Reference
Chemical name	o-Xylene	Windholz 1983
Synonyms	1,2-Dimethylbenzene; 1,2-xylene; benzene, 1,2-dimethyl-; o-dimethylbenzene; o-methyltoluene; o-xylol; ortho-xylene	HSDB 1988 ECETOC 1986
Trade names	No data	
Chemical formula	C_8H_{10}	HSDB 1988
Chemical structure		ECETOC 1986
Identification numbers:		
CAS Registry	95-47-6	HSDB 1988
NIOSH RTECS	ZE 2450000	HSDB 1988
EPA Hazardous Waste	U239; Xylene F003; Xylene	HSDB 1988
OHM/TADS	7216952	HSDB 1988
DOT/UN/NA/IMCO Shipping	UN 1307; Xylene; Xylol IMCO 3.2 Xylenes IMCO 3.3 Xylenes	HSDB 1988
HSDB	134	HSDB 1988
NCI	No data	HSDB 1988
STCC	49 093 50; Xylene	HSDB 1988

HSDB = Hazardous Substances Data Bank; CAS = Chemical Abstracts Service; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; NCI = National Cancer Institute; STCC = Standard Transport Commodity Code.

TABLE 3-4. Chemical Identity of p-Xylene

	Value	Reference
Chemical name	p-Xylene	Windholz 1983
Synonyms	1,4-Dimethylbenzene; 1,4-xylene; p-dimethylbenzene; p-methyltoluene; p-xylol; para-xylene	HSDB 1988; ECETOC 1986
Trade names	Scintillar	HSDB 1988
Chemical formula	C_8H_{10}	HSDB 1988
Chemical structure		ECETOC 1986
Identification numbers:		
CAS Registry	106-42-3	HSDB 1988
NIOSH RTECS	ZE 2625000	HSDB 1988
EPA Hazardous Waste	U239; Xylene F003; Xylene	HSDB 1988
OHM/TADS	7216951	HSDB 1988
DOT/UN/NA/IMCO Shipping	UN 1307; p-Xylene; p-Xylol IMCO 3.2 Xylenes IMCO 3.3 Xylenes	HSDB 1988
HSDB	136	HSDB 1988
NCI	No data	
STCC	49 093 51; Xylene (para-xylene)	HSDB 1988

HSDB = Hazardous Substances Data Bank; CAS = Chemical Abstracts Service; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; NCI = National Cancer Institute; STCC = Standard Transport Commodity Code.

TABLE 3-5. Physical and Chemical Properties of Mixed Xylene

Property	Value	Reference
Molecular weight	106.16	Windholz 1983
Melting point	No data	
Boiling point	137°-140°C	Windholz 1983
	138.5°C	Sax and Lewis 1989
Density	About 0.86	Windholz 1983
at 20°C/4°C	0.864	Sax and Lewis 1989
	0.8685	Dawson et al. 1974
Physical state	Liquid	Windholz 1983
Color	Clear	Sax and Lewis 1989
Odor	Sweet	Environment Canada 1981
Odor threshold:		
Air	0.0045 mg/L (1.0 ppm)	Carpenter et al. 1975
	0.6 mg/m^3 (0.1 ppm)	Gusev 1967
	0.73 mg/m^3 (0.17 ppm)	Gusev 1965
Water	No data	
Solubility:		
Water	Practically insoluble	Windholz 1983
at 25°C	0.013 g/100 g (130 ppm)	Stephan and Stephen 1963
Organic solvents	Miscible with absolute alcohol, ether, and other organic liquids	Windholz 1983
	Very soluble in alcohol, very soluble in ether	Sandmeyer 1981
Partition coefficients:		
Log octanol/water	3.12-3.20	Hansch and Leo 1979
	3.33	Leo 1982
Log K_{oc}	No data	
Vapor pressure at 7.5°C	2.5 mmHg	Dawson et al. 1974
at 20°C	6-16 mmHg	Sandmeyer 1981
at 21°C	6.72 mmHg	Sax and Lewis 1989
Henry's law constant	No data	
Autoignition temperature	464°C (867°F)	General Electric 1980
Flashpoint	17°-25°C (C.C.)	Maxwell 1978
	27°-46°C (O.C.)	Hawley 1977
	29°C	Windholz 1983
	37.6°C (100°F) (T.O.C)	Sax and Lewis 1989, Sandmeyer 1981

TABLE 3-5 (Continued)

Property	Value	Reference
Flammability limits	1%-7%	General Electric 1980
Conversion factors	1 mg/m^3 = 0.23 ppm 1 ppm = 4.41 mg/m^3	Verschueren 1977

T.O.C = tag open cup; C.C. = closed cup; and O.C. = open cup.

TABLE 3-6. Physical and Chemical Properties of m-Xylene

Property	Value	Reference
Molecular weight	106.16	Windholz 1983
Melting point	-47.4°C	Windholz 1983
	-47.9°C	Sax and Lewis 1989; Weast 1988
	-48°/53°C	Verschueren 1983
Boiling point	139.3°C	Windholz 1983
	139.1°C	Weast 1988
Density at 15°C	0.8684	Windholz 1983
at 20°C	0.8642	Weast 1988
Physical state	Liquid	Windholz 1983
Color	Colorless	Windholz 1983
Odor	Sweet	Environment Canada 1981
Odor threshold:		
Air	16 mg/m^3 (3.7 ppm)	Verschueren 1977
Water	1.1 mg/L (1.1 ppm)	Rosen et al. 1962
Solubility:		
Water	Insoluble	Windholz 1983
at 25°C	146 mg/L (146 ppm)	NAS 1980
at 20°C	160 mg/L (160 ppm)	Chernoglazova and Simulin 1976
at 25°C	161 ppm	Sanemasa et al. 1982
at 25°C	173 ppm	Andrews and Keefer 1949
at 20°C	0.00003 g/100g (0.3 ppm)	Mackison et al. 1981
at 25°C	134.0 ppm	Price 1976
Organic solvents	Miscible with alcohol, ether, and many other organic solvents	Windholz 1983
Partition coefficients:		
Log octanol/water (Log K_{ow})	3.09 (estimated)	Konemann 1981
	3.20	Hansch and Leo 1979; Verschueren 1983
	3.28 (estimated)	Yalkowsky and Valvani 1976
K_{oc}	166	Abdul et al. 1987

TABLE 3-6 (Continued)

Property	Value	Reference
Vapor pressure at 20°C	6 mmHg	Verschueren 1983
at 28.3°C	10 mmHg	Sax and Lewis 1989
at 30°C	11 mmHg	Verschueren 1983
Henry's law constant at 25°C	7.19×10^{-3} atm-m^3/mol	SRC 1988
Autoignition temperature	527°C	NFPA 1978
Flashpoint	25°C (C.C.)	Windholz 1983
	27°C (C.C.)	NFPA 1978
Flammability limits	1.1%-7.0%	NFPA 1978
Conversion factors	1 mg/m^3 = 0.23 ppm	Verschueren 1983
	1 ppm = 4.41 mg/m^3	Verschueren 1983

C.C. = closed cup.

TABLE 3-7. Physical and Chemical Properties of o-Xylene

Property	Value	Reference
Molecular weight	106.16	Windholz 1983
Melting point	-25°C	Windholz 1983
Boiling point	144°C	Windholz 1983
Density at 20°C	0.8801	Windholz 1983
Physical state	Liquid	Windholz 1983
Color	Colorless	Windholz 1983
Odor	Sweet	Verschueren 1983
Odor threshold:		
Air	0.08 ppm	Verschueren 1977
	0.17 ppm	Gerarde 1959
Water	1.8 ppm	Verschueren 1983
Solubility:		
Water	Insoluble	Windholz 1983
at 0°C	142 mg/L (142 ppm)	Polak and Lu 1973
at 20°C	175 mg/L (175 ppm)	Verschueren 1983
at 25°C	175 ppm	OHM/TADS 1988
at 25°C	178 ppm	Sanemasa et al. 1982
at 25°C	213 mg/L (213 ppm)	Polak and Lu 1973
Organic solvents	Miscible with alcohol, ether	Windholz 1983
Partition coefficients:		
Log octanol/water	2.77	Verschueren 1983
	3.09 (estimated)	Konemann 1981
	3.12	Hansch and Leo 1979
	3.18 (estimated)	Yalkowsky and Valvani 1976
Koc		
at 25°C	47.7-68.1	Nathwani and Phillips 1977
at 110°C	82.2-117	Nathwani and Phillips 1977
	129	Abdul et al. 1987
Vapor pressure at 20°C	5 mmHg	Verschueren 1983
at 25°C	6.8 mmHg	Sandmeyer 1981
at 30°C	9 mmHg	Verschueren 1983
Henry's law constant at 25°C	5.19×10^{-3} atm-m^3/mol	Sanemasa et al. 1982
Autoignition temperature	463°C	NFPA 1978
	463.89°C	OHM/TADS 1988
	464°C	Hawley 1977
	465°C	Sax 1979

TABLE 3-7 (Continued)

Property	Value	Reference
Flashpoint	17°C (C.C.)	Windholz 1983
	17.2°C (C.C.)	US DOT 1978
	23.9°C (O.C.)	US DOT 1978
	32°C (C.C.)	NFPA 1978
	32.2°C (C.C.)	Mackison et al. 1981; Sax 1979
	46.1°C (O.C.)	Hawley 1977
Flammability limits	1.0%-6.0%	NFPA 1978
Conversion factors	1 mg/cm^3 = 0.23 ppm	Verschueren 1983
	1 ppm = 4.41 mg/m^3	

C.C. = closed cup; and O.C. = open cup.

TABLE 3-8. Physical and Chemical Properties of p-Xylene

Property	Value	Reference
Molecular weight	106.16	Windholz 1983
Melting point	13°-14°C	Windholz 1983
Boiling point	137°-138°C	Windholz 1983
Density at 20·C	0.86104	Windholz 1983
	0.8611	Weast 1988
Physical state	Liquid	Hawley 1981
at low temperatures	Solid (plates or prisms)	Windholz 1983
	Monoclinic prisms	Weast 1988
Color	Colorless	Windholz 1983
Odor	Sweet	US DOT 1978
Odor threshold:		
Air	0.47 ppm	Verschueren 1977
Water	0.53 ppm	Rosen et al. 1962
Solubility:		
Water at	Insoluble	Windholz 1983
25°C	198 mg/L (198 ppm)	Verschueren 1983
25°C	162.4 ppm	Sanemasa et al. 1982
25°C	185 mg/L (185 ppm)	Polak and Lu 1973
Organic solvents	Soluble in alcohol, ether, and other organic solvents	Windholz 1983
Partition coefficients:		
Log octanol/water	3.08 (measured)	Hutchinson et al. 1978
	3.09 (estimated)	Konemann 1981
	3.15 (estimated)	Hansch and Leo 1979
	3.28 (estimated)	Yalkowsky and Valvani 1976
Koc	260	Vowles and Mantoura 1987
Vapor pressure at 20°C	6.5 mmHg	Verschueren 1983
at 20°C	9 mmHg	Mackison et al. 1981
at 25°C	8.82 mmHg	Hine and Mookerjee 1975
at 25°C	8.84 mmHg	Chao et al. 1983
at 30°C	12 mmHg	Verschueren 1983
at 27.3°C	10 mmHg	OHM/TADS 1988

TABLE 3-8 (Continued)

Property	Value	Reference
Henry's law constant at 25°C	7.60×10^{-3} atm-m^3/mol	SRC 1988
Autoignition temperature	528°C	NFPA 1978
Flashpoint	25°C (C.C.)	Windholz 1983
	27°C (C.C.)	NFPA 1978
	27.2°C (T.O.C.)	Hawley 1981; Mackison et al. 1981
Flammability limits	1.1%-7.0%	NFPA 1978
Conversion factors	1 mg/m^3 = 0.23 ppm	Verschueren 1983
	1 ppm = 4.41 mg/m^3	

T.O.C = tag open cup; and C.C. = closed cup.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Mixed xylene consists of a mixture of ethylbenzene and the m-, o-, and p-isomers of xylene; m-xylene predominates. Mixed xylene may contain non-xylene hydrocarbons in addition to ethylbenzene, such as benzene, toluene, trimethylbenzene, phenol, thiophene, and pyridine (Gerarde 1960; Riihimaki and Hanninen 1987; Sandmeyer 1981). However, the product has been relatively free of benzene (less than 0.001%) since the late 1950s (Gosselin et al. 1984; Riihimaki and Hanninen 1987). The exact composition of mixed xylene depends on the manufacturing method used. Currently, nearly all mixed xylene is produced as a catalytic reformate of petroleum and consists of approximately 20% o-xylene, 44% m-xylene, 20% p-xylene, and 15% ethylbenzene (HSDB 1988; NIOSH 1975). Mixed xylene may also be manufactured from coal tar, yielding a mixture of approximately 10%-15% o-xylene, 45%-70% m-xylene, 23% p-xylene, and 6%-10% ethylbenzene; by gasoline pyrolysis, or by disproportionation of toluene, producing a mixture free of ethylbenzene (HSDB 1988; NIOSH 1975; Ransley 1984). U.S. manufacturers have an estimated annual capacity to produce over one billion gallons of mixed xylene (SRI 1988). In 1987, U.S. petroleum refiners produced 649,428,000 gallons of high-purity (98%-100%) mixed xylene (USITC 1988).

The isomers of xylene are produced from mixed xylene. m-Xylene is obtained from mixed xylene via crystallization and fractionation or via complexing with hydrofluoric acid and boron trifluoride (HSDB 1988). o-Xylene is isolated from mixed xylene via distillation, but can also be produced by the isomerization of the meta isomer (HSDB 1988). p-Xylene is derived from mixed xylene by crystallization, solvent extraction, or adsorption (HSDB 1988; Hawley 1981). U.S. production capacity is estimated at 920 million and 5,525 million pounds annually for o-xylene and p-xylene, respectively (SRI 1988). In 1987, over 939 million pounds of o-xylene and greater than 5,155 million pounds of p-xylene were produced in the United States (USITC 1988). Current values are not reported for m-xylene; U.S. production of m-xylene was estimated as 5.59×10^{10} gallons for 1980 (HSDB 1988).

4.2 IMPORT

In 1982, 1.31×10^{11} gallons of mixed xylene and 1.02×10^{9} gallons of m-xylene were imported to the United States (HSDB 1988). In 1985, 1.48×10^{7} gallons of o-xylene and 6.53×10^{10} gallons of p-xylene were imported (HSDB 1988).

4.3 USE

Approximately 70% of mixed xylene is used in the production of ethylbenzene and the meta, ortho, and para isomers of xylene. The remaining mixed xylene is used in solvents, such as for paints and coatings, or is blended into gasoline (HSDB 1988; Riihimaki and Hanninen 1987; Santodonato et al. 1985).

The isomers of xylene are used as industrial solvents and serve as intermediates in synthetic reactions. m-Xylene is a chemical intermediate in the production of isophthalic acid, m-toluic acid, and isophthalonitrile; isophthalic acid, in turn, is used in polyesters. o-Xylene is a chemical intermediate in the synthesis of phthalic anhydride (for plasticizers), phthalonitrile, 4,4-(trifluoro-1-(trifluoromethyl)ethylidene) diphthalic anhydride (for polyimide polymers), terephthalic acid (for polyesters), isophthalic acid, vitamins, and pharmaceuticals. p-Xylene is a chemical intermediate for the synthesis of dimethyl terephthalate, terephthalic acid (for polyesters), dimethyl tetrachloroterephthalate, vitamins, and pharmaceuticals. Both o- and p-xylene are used as components of insecticides (HSDB 1988; Hawley 1981).

4.4 DISPOSAL

Various methods of incineration are used in the disposal of xylene isomers (EPA 1981b; HSDB 1988); the addition of a more flammable solvent has been suggested to make the process easier (HSDB 1988).

Criteria for the disposal of xylenes are currently subject to significant revision. Under the Resource Conservation and Recovery Act, the waste product, off-specification batches, and spill residues of xylene greater than 1,000 pounds are subject to handling, reporting, and recordkeeping requirements; this applies also to spent xylene solvents and still bottoms from the refining of these solvents (EPA 1980b, 1981c).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Xylenes are released to the atmosphere primarily as fugitive emissions from industrial sources (e.g., petroleum refineries, chemical plants), in automobile exhaust, and through volatilization from their use as solvents. Discharges into waterways and spills on land result primarily from use, storage, and transport of petroleum products and waste disposal. Most of the xylenes released to the environment partition to the atmosphere. Xylenes are moderately mobile in soil and can leach into the groundwater, where they may persist for several years. Xylenes are rapidly transformed in the troposphere where photooxidation by hydroxyl radicals is the dominant process. Xylenes are stable to hydrolysis and oxidation in the aquatic environment, but some evidence indicates that they may be biotransformed by microorganisms in groundwater. Biotransformation of xylene in surface waters is probably not significant due to the volatility of the compound. Biotransformation will be an important process mainly in subsurface soils, since xylenes in surface soils will undergo photooxidation or will volatilize to the atmosphere. Sorption of xylene to soils is more important in dry soils and will increase in soils and sediments as organic matter content increases. Xylenes have been found to bioaccumulate to very modest levels (e.g., bioconcentration factors of less than 100), but food-chain biomagnification has not been observed. Xylene or its metabolites have been detected in human urine, blood, and expired air samples among members of the general population. Human exposure to xylenes is believed to occur via inhalation of indoor and workplace air, inhalation of automobile exhausts, ingestion of contaminated drinking water, smoking, and inhalation and dermal absorption of solvents containing xylenes.

5.2 RELEASES TO THE ENVIRONMENT

Xylenes are ubiquitously distributed in the environment. They have been detected in the atmosphere, rainwater, soils, surface waters and sediments, drinking water, aquatic organisms, and human blood, urine, and expired breath. Xylenes do not occur in the environment naturally except in smoke from forest fires or as constituents of petroleum which may seep into the oceans from underground deposits (Merian and Zander 1982). To date total xylenes have been identified at 236 of the total 1,177 NPL sites (VIEW 1989). The frequency of these sites within the United States can be seen in Figure 5-1. Xylene has been detected at 38% of the 2,738 hazardous waste sites that have had samples of all media analyzed by EPA's Contract Laboratory Program (CLP) at a positive geometric mean concentration of 25 ppb (CLP 1988).

Releases of xylenes into the environment each year are estimated to total nearly 3 million tons (2.7 million metric tons) (Merian 1982). In 1978,

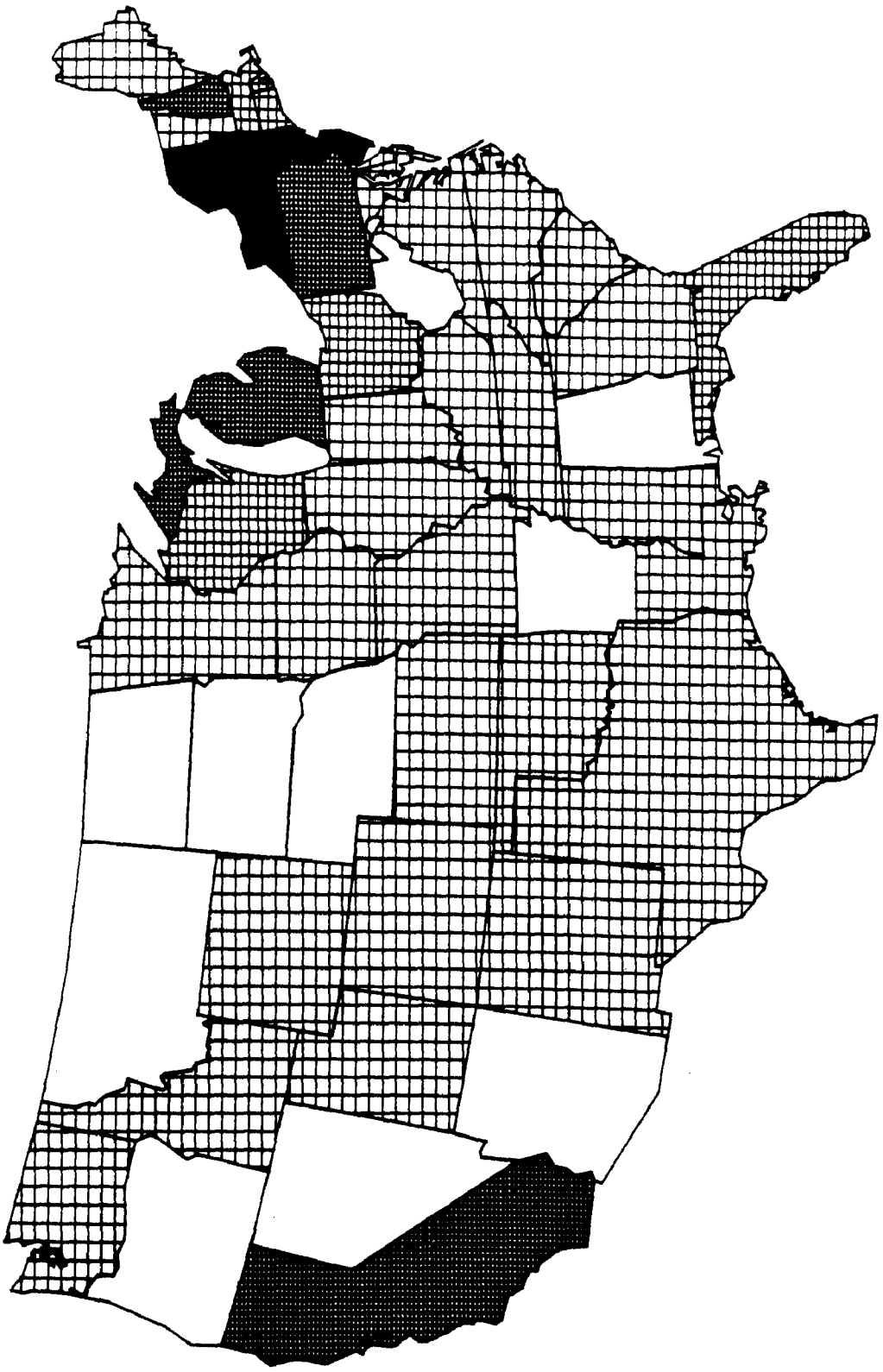


FIGURE 5-1. FREQUENCY OF SITES WITH TOTAL XYLENES CONTAMINATION

total U.S. emissions of mixed xylenes were estimated to be 480,000 tons (435,000 metric tons) (SAI 1981). Major emissions of mixed xylenes occur during production (principally from catalytic reforming of petroleum stock) and end-use as a solvent in a variety of industrial applications. Total emission of mixed xylenes from catalytic reformate production in the United States in 1978 was estimated to have been approximately 9 million pounds (4,500 tons) (Anderson et al. 1980). The breakdown of individual isomers in these emissions was 16.7% p-xylene, 20.5% o-xylene, and 35.7% m-xylene. In 1978, the estimated U.S. mixed xylene emissions were 330,400 pounds from pyrolysis gasoline production, 39,600 pounds from toluene disproportionation, and 41,250 pounds from coal-derived production (Anderson et al. 1980). Individual xylene isomers are produced by extraction of mixed xylenes (Anderson et al. 1980). In 1978, U.S. emissions of xylene isomers from extraction production processes were estimated to have been approximately 2.7 million pounds, 6.4 million pounds, and 176,000 pounds for o-, p-, and m-xylene, respectively (Anderson et al. 1980).

5.2.1 Air

About 3 million tons of total xylenes are lost annually into the global environment (Merian 1982). Volatilization is the dominant process which governs the environmental behavior of xylenes, so most of the xylene released will ultimately partition into the atmosphere. The total annual xylene loss consists of 0.5 million tons from solvent losses, 2 million tons from refinery losses into the atmosphere during the production, transportation, and processing of petroleum, and 0.5-1 million tons as a component of automobile exhaust gases (Merian and Zander 1982). Evaporation of gasoline into the air during its transportation and distribution accounts for 10,000 tons of the total annual xylene releases. Another 50,000 tons are released from the chemical industry (Merian and Zander 1982).

5.2.2 Water

Xylenes may be introduced into groundwater by fuel oil, gasoline, or solvent spills, by infiltration of polluted surface waters, by leaking underground storage tanks, or by leaching from disposed wastes (Giger and Schaffner 1981). It is estimated that over 10,000 water-polluting spills of oil and hazardous substances occur annually in the United States (Faust 1977). EPA ranked xylene as 16th out of the 20 most hazardous soluble substances based on the lowest concentration range at which a material impairs any of the beneficial uses of water, the quantity shipped annually by each mode of transport, and the probability of an accidental spill to surface waters (Faust 1977). Annual losses into the sea have been estimated to account for approximately 0.6 million tons of the total global losses into the environment (Merian and Zander 1982).

Total xylene and the individual o-, m-, and p-xylene isomers have been detected primarily in finished drinking water (at both the source and the tap), effluent from chemical plants and oil refineries, well water (not specified), river water, and landfill leachate effluent (Shackelford and Keith 1976). Xylenes have been detected in petroleum refinery effluents in the United States at concentrations of 6 μg/L (ppb) (CEC 1976). A total xylene concentration (concentration includes ethylbenzene) of 1.2 ppb was detected in effluent from containment ponds in the containment area of an oil spill that accumulated along the banks of the Atigun River, Alaska (Lysyj et al. 1980). Treated effluents from offshore oil drilling platforms in the Gulf of Mexico contained an average concentration of 0.3 mg/L (ppm) (concentration includes ethylbenzene) (Lysyj et al. 1980). Final effluent from the Los Angeles County wastewater treatment plant sampled from November 1980 to August 1981 contained o- and p-xylene at concentrations of 40 and 30 μg/L, respectively (Gosset et al. 1983).

According to EPA's Contract Laboratory Program (CLP) statistical database (CLP 1988), total xylenes have been detected in surface water and groundwater samples of approximately 3.9% and 11.6%, respectively, of the 2,783 hazardous waste sites that have had samples analyzed through the CLP. The geometric mean concentrations of the positive surface water and groundwater samples were 11.4 and 216.6 μg/L, respectively.

5.2.3 Soil

No quantitative information was available in the literature regarding total releases of xylenes to soil. Atmospheric xylenes may reach soils either by wet deposition in precipitation or dry deposition of material adsorbed to particulate matter in air. Xylenes may also reach soils from the introduction of man-made wastes (e.g. landfills) or as a result of accidental releases (e.g., spills).

According to EPA's CLP database (CLP 1988), total xylenes have been detected in the soil of approximately 22.5% of the 2,783 hazardous waste sites that have had samples analyzed through the CLP. The geometric mean concentration of xylene in the positive soil samples was 19 μg/kg (ppb).

5.3 ENVIRONMENTAL FATE

Volatilization is the dominant transport mechanism for xylene. Therefore, most xylene releases will ultimately partition into the atmosphere. The major transformation process in the atmosphere is photooxidation by hydroxyl radicals. Hydrolysis and oxidation of xylenes in the aquatic environment are not expected to be significant. Xylenes are relatively mobile in soil and may leach into groundwater depending upon soil conditions (e.g., degree of saturation, percent of organic matter). Sorption is more important

in soils or sediments with high organic matter contents. Once in groundwater, xylenes are known to persist for several years despite evidence that they biodegrade in both soil and groundwater. Bioconcentration of xylenes has been reported but is not expected to be significant.

5.3.1 Transport and Partitioning

In a global sense, most (99.68%) of the xylenes released into the environment will ultimately partition into the atmosphere as shown by the applied calculations of fugacity (Jori et al. 1986). Table 5-1 shows the calculated equilibrium distribution for releases of xylenes to the environment. As the magnitude of the Henry's Law Constant for xylenes presented in Chapter 3 indicates, xylenes are highly volatile and are likely to partition readily into the atmosphere from water. Because of their volatility, xylenes are generally not persistent in surface water in high concentrations. The half-life associated with volatilization from surface waters for o-xylene at a depth of one meter is reported to be 5.6 hours but will vary in accordance with turbulence and water depth (Mackay and Leinonen 1975).

When spilled on land, xylenes will volatilize or leach into the ground. Volatilization half-lives for the three xylene isomers in soil are not available in the literature. Using an estimated soil organic carbon partition coefficient (Koc) of 2.40×10^2 and a dimensionless Henry's law constant (H) of 2.12×10^{-1}, the calculated air-soil partition coefficient (Kas) for total xylene is 1,100, where Kas = Koc/H. In general, calculated Kas values of 10,000 or less correlate well with chemicals which volatilize completely from soil in one year or less as determined by iterative modeling using a time dependent soil volatilization model with reservoir depletion (Hwang et al. 1986). However, calculated air-soil partition coefficients for individual soils suggest that as soil organic content increases beyond 1%, xylene residence time in soil increases correspondingly. In soils and sediments, xylene tends to be adsorbed to organic matter since the octanol:water partition coefficient is about 1,100:1 (Chiou et al. 1982). A general increasing trend for the relative retention of xylene in soil with increasing soil organic matter has been observed by a number of investigators (Green et al. 1981; Nathwani and Phillips 1977; Seip et al. 1986). In subsurface soils with low organic carbon content, xylenes are more likely to infiltrate into groundwater from soil (EPA 1985a). According to the Exposure Analysis Modeling System (EXAMS) model of Burns et al. (1981), total steady state xylene accumulation in bottom sediments from surface waters ranged from 4.5% to 70% of the total xylene load from the model, depending upon the percent organic matter present.

When xylene was spilled at an application depth of 7.2×10^{-2} m or less on loam-textured soil at moisture contents ranging from 0.15 to 0.26 kg/kg, 1%-4%

TABLE 5-1. Characteristics of Different Environmental Compartments and Xylene Concentrations on Emission of 100 mol

Compartment	Volume (m^3)	Amount (%)	Concentration (mol/m^3)	Concentration (ppm)
Air	10^{10}	99.6837	0.99×10^{-8}	880×10^{-6}
Soil	9×10^{3}	0.0089	98.88×10^{-8}	70×10^{-6}
Water	7×10^{6}	0.2656	3.79×10^{-8}	4×10^{-6}
Biomass	3.5	0.1261×10^{-4}	360.28×10^{-8}	382×10^{-6}
Suspended solids	35	0.6942×10^{-4}	198.34×10^{-8}	140×10^{-6}
Sediments	2.1×10^{4}	0.0416	198.09×10^{-8}	140×10^{-6}
Total amount	--	99.9999	--	--

Source: Jori et al. 1986.

volatilized, 0.5%-35% leached, 50%-85% degraded, and 6%-12% remained after about 80 days in the soil (Aurelius and Brown 1987). Most of the observed volatilization occurred immediately after application. The fractions of applied xylene that were retained, volatilized, or degraded were greatest in the driest soil. Increased sorption of xylene in dry soils results in greater retention and allows for subsequent loss by volatilization or degradation. Estimated degradation rates ranged from 45.7 to 137.8 g/day, with the greatest degradation in the soil with the highest application rate and the least degradation in the wettest soil with the lowest application rate.

Xylene moves through unsaturated soil faster than water and other polar solvents (Amoozegar et al. 1986; Barbee and Brown 1986). Additional field data suggesting that concentrated organics may leach 10 to 1,000 times faster than water in unsaturated soil were provided by Griffin et al. (1984). This increased conductivity is probably due to the formation of cracks in the soil through which the organics move rapidly (Aurelius and Brown 1987). At high water contents, water displaces a number of organics from mineral surfaces (Rhue et al. 1988). Because xylene is hydrophobic, it does not easily diffuse through water films into the soil matrix (Barbee and Brown 1986). Thus, in the presence of a hydraulic gradient, xylene likely moves as a separate immiscible organic phase floating on the water films in the soil pores (Aurelius and Brown 1987). Xylene moved as a relatively uniform front through loamy sand; however, in silt loam and clay, xylene moved preferentially through large pores in the soil structure (Barbee and Brown 1986). Because of its ability to desiccate clays, xylene may have further opened these natural macropores, thereby facilitating rapid movement. Even though xylene may move slowly through a wet clay by diffusion and convection, there is, in principle, a danger that it will eventually cause shrinking and cracking and thereby allow fluid transmission in bulk (Green et al 1981).

The measured log octanol-water partition coefficients (as log K_{ow}) are reported by Chiou et al. (1982) as 2.77, 3.15, and 3.20 for o-, m-, and p-xylene, respectively. Although bioaccumulation has been predicted for all isomers of xylene because of their tendency to partition into the octanol phase of the octanol-water system (EPA 1978b), the rapid oxidation of xylenes to their corresponding polar metabolites seems to preclude bioaccumulation in higher animal systems (NRC 1980). Bioconcentration factors (BCFs) for o-, m-, or p-xylene have been estimated to be 45, 105, and 95, respectively (EPA 1985a). The calculated log BCF range for fish is reported to be 2.14-2.20 (HSDB 1988). Bioconcentration of xylenes has been observed in shrimp (Pandalus platyceros) (Sanborn and Malins 1980), manila clams (Tapes semidecussata) (Nunes and Benville 1979), and eels (Anguilla japonica) (Ogata and Miyake 1978). A bioaccumulation factor of 6 has been reported for tissue accumulation in clams throughout an 8-day exposure to o-, m-, and p-xylene (Nunes and Benville 1979), and bioaccumulation factors of 21.4, 23.6, and 23.6 have been reported for eels exposed to 50 ppm of o-, m-, or p-xylene,

respectively (Ogata and Miyake 1978). Tissue accumulation reached a steady state after 10 days.

5.3.2 Transformation and Degradation

Xylenes undergo photooxidation and biodegradation as their main environmental transformation reactions. Phototransformation in the atmosphere is believed to be the most quantitatively important transformation process for xylene in terms of the percentage of substance transformed (an estimated 99.96%) (Jori et al. 1986). The remainder of the total xylene transformed is primarily photooxidized in soils or biodegraded in groundwater and sediments (Jori et al. 1986). Hydrolysis and oxidation are not significant transformation processes for xylene in the aquatic environment.

5.3.2.1 Air

Xylenes are transformed in the atmosphere by photooxidation. Direct photolysis is not expected because these compounds do not significantly absorb light at wavelengths greater than 290 nm (Jori et al. 1986). Based on an estimated rate constant of 0.0287 hr^{-1} (Jori et al. 1986), the half-life for the photooxidation of xylene in the atmosphere is estimated to be 24.1 hour. The transformation of xylene by reaction with hydroxyl radicals prevails over that of reaction with ozone or peroxy radical and is likely to be the only significant atmospheric removal process for xylene (Atkinson et al. 1982; Fox et al. 1984; Mill 1980; Roberts et al. 1984). Reported half-lives for the oxidation of o-, m-, and p-xylene by hydroxyl radicals range from 0.4 to 1.0 day (ECETOC 1986; Mill 1980). The reported half lives for the reaction with ozone are much greater, ranging from 5,000 to 6,200 days (ECETOC 1986). The products of photoreaction with hydroxyl radicals are ultimately degraded to carbon dioxide and water after absorption in the hydrosphere (Guisti et al. 1974).

5.3.2.2 Water

Oxidation reactions are not expected to be significant transformation processes for xylene in aquatic systems (Mill 1980). In addition, xylenes are reported to be resistant to hydrolysis (HSDB 1988). Biodegradation may be the only significant transformation process for xylene in water, but it appears to vary according to the source of the microbial population and whether or not the microbial population was conditioned to utlize xylene by pre-exposure to the chemical (acclimation) (Bridie et al. 1979). Acclimation increased degradation in a filtered sewage seed to 57% and 74% from 52% and 44% of the theoretical 5-day BOD value for o- and p-xylene, respectively (Bridie et al. 1979). A concentration of 500 mg/L of o-, m-, or p-xylene was toxic to unacclimatized activated sludge microorganisms during the first 24 hours of aeration (Marion and Malaney 1964). In other studies, m-xylene was found to

be toxic to microorganisms, yielding only about 10% of the theoretical Biological Oxygen Demand (BOD) after 8 days, while o-Xylene and p-xylene were more degradable, varying between 63% and 26% of the theoretical BOD (Malaney 1960; Malaney and McKinney 1966; Marion and Malaney 1964). The relatively high concentrations of xylene used in some of these studies may account for the low degradation rates as a result of toxicity to test microorganisms (EPA 1985a).

Although xylenes have been observed to completely degrade in groundwater in one study (Kappeler and Wuhrmann 1978a), forming methylbenzyl alcohol intermediates, xylenes appear to be only poorly to moderately biodegraded in most aquatic systems. The estimated half-life for biodegradation of xylenes in water (247.5 hr) (Jori et al. 1986) is considerably greater than most of the half-lives predicted for volatilization of xylene from water (5.6 hr-264 hr). Xylene concentrations detected in tap water during several monitoring studies were not significantly different than those at the source (Keith et al. 1976; Otson et al. 1982a; Saunders et al. 1975; Williams et al. 1982), which supports the conclusion that biodegradation of xylenes in water is limited and that little or no oxidation or hydrolysis occurs. In addition, xylenes are known to persist for many years in groundwater at least at sites where the initial xylene concentration is quite high (HSDB 1988). In a field study following an oil spill from the Trans-Alaskan Pipeline in the Atigun Pass, Alaska on June 10, 1979, xylenes were not detected in the 40 km long watershed of the containment area 18 days after the spill. This suggested xylene persistence in the groundwater of the containment area as opposed to movement in the groundwater to the watershed area (Lysyj 1980).

5.3.2.3 Soil

In surface soils, photo-induced oxidation is likely to be a significant transformation process for xylenes. Based on an estimated rate constant of 0.0287 hr^{-1} (Jori et al. 1986), the half-life for the photooxidation of xylene in soils is estimated to be 24.1 hr. No other quantitative information was found in the available literature regarding photooxidation of xylenes in surface soils.

Biodegradation is considered to be the only significant transformation mechanism for xylene in sub-surface soil but is likely to be a slow process based on its rate of degradation in other media (EPA 1984, 1985a). Biodegradation half-lives for xylene in soil were not found in the available literature; however, numerous bacteria (including several strains of Pseudomonas, Flavobacterium, and Norcardia) capable of utilizing p- and m-xylene as a carbon source in the growth medium have been isolated from soils (Davis et al. 1968; Gibson et al. 1974). According to several degradative pathways that have been proposed, both m- and p- isomers are oxidized to their respective intermediate products, which in turn undergo aromatic ring cleavage

(Davis et al. 1968; Davey and Gibson 1974; Gibson et al. 1974; Omori and Yamada 1970). Since many of the decomposition products of microbial degradation of xylene are hydrophilic (e.g., xylenols, benzoic acids, etc.), they are easily subject to further microbial biodegradation (Merian and Zander 1982). The importance of the methyl group position to breakdown of xylene isomers is indicated by the fact that p-xylene grown cultures of Pseudomonas were capable of oxidizing both m-xylene and toluene, but neither p- nor m-xylene grown cultures were capable of oxidizing o-xylene (Davis et al. 1968).

Based on an estimated rate constant of 0.0028 hr^{-1} (Jori et al. 1986), the half-life for the biodegradation of xylene in sediments is estimated to be 247.5 hr. Quantitative measurements of anaerobic breakdown of xylene in sediments were not found in the available literature. However, field evidence of xylene transformation during transport in anoxic groundwater at a landfill in North Bay, Ontario, suggests that anaerobic transformation of xylene likely occurs in landfills and their leachate plumes (Barker 1987).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

As a result of its large production and widespread use as a solvent, xylene is ubiquitously distributed in the environment. The compound has been detected in indoor and outdoor air, surface water, groundwater, drinking water, soils, and rainwater.

5.4.1 Air

Ambient air concentrations of xylenes in industrial and urban areas of the United States range from 0.003 to 0.38 mg/m^3 (Merian and Zander 1982). Since one of the largest sources of xylene release into the atmosphere comes from auto emissions, atmospheric concentrations are related to urbanization. Median o-xylene concentrations calculated from a compilation of the available published and unpublished atmospheric data on organic chemicals were 0.41 $\mu g/m^3$ in rural/remote areas (114 observations), 5.2 $\mu g/m^3$ in urban/suburban areas (1,885 observations), and 3.5 $\mu g/m^3$ in source dominated areas (183 observations) (Brodzinsky and Singh 1983). The median concentrations for the combined isomers m- and p-xylene were 0.38 $\mu g/m^3$ in rural/remote areas (115 observations), 12 $\mu g/m^3$ in urban/suburban areas (1,911 observations), and 7.4 $\mu g/m^3$ in source dominated areas (186 observations) (Brodzinsky and Singh 1983). The maximum concentrations reported for o-xylene and combined m- and p-xylene were 38,000 and 43,000 $\mu g/m^3$, respectively (Oldham et al. 1979). Both values were measured at a source dominated location.

Recent studies have revealed that xylene is also a common contaminant of indoor air. Concentrations of m- and p-xylene measured in homes at 15 locations in the United States ranged from 10 to 47 $\mu g/m^3$ (Seifert and Abraham

1982). Similar results were reported during a 1981 study of the correlation between breath concentration and personal and outdoor air concentrations of 350 New Jersey residents (Wallace et al. 1986). The weighted median indoor air concentrations of o-xylene and the combined m- and p-xylene isomers were 4.9 and 14 $\mu g/m^3$, respectively. Breath concentrations showed significant correlation with personal air concentrations but only weak correlation with outdoor air concentrations. Concentrations in indoor air were usually higher than in outdoor air, indicating that the source of the xylenes was building materials or household products (e.g., cleaning agents) (Wallace et al. 1986, 1987a).

5.4.2 Water

Limited monitoring data are available on ambient concentration of xylenes in surface waters. In view of the rapid volatilization of xylenes, their presence in surface waters is unlikely to be significant. Surface waters generally contain average xylene concentrations of <1 ppb total xylenes except in areas where there are fuel processing activities, such as petroleum refining (ECETOC 1986; Otson et al. 1982b; Sauer et al. 1978). Typical surface water concentrations range from not detected to 2 $\mu g/L$ (ppb) (Otson et al. 1982b; Sauer et al. 1978).

Data on the occurrence of xylene in public drinking water supplies are available from several federal, regional, and state surveys (EPA 1985a). In most cases, less than 6% of the groundwater and surface water systems sampled contained detectable levels of xylenes (EPA 1983b, 1985a; NJDEP 1984, 1985). Typical xylene concentrations detected (all isomers) ranged from 0.2 to 9.9 $\mu g/L$ (ppb) with mean concentrations of less than 2 $\mu g/L$ (ppb) (EPA 1978a, 1985a; Keith et al. 1976; NJDEP 1984, 1985; Williams et al. 1982). However, m-xylene was detected in public drinking water in Rhode Island with concentrations ranging from 1 ppb to 30 ppb (RIDH 1989). Xylene was detected in private well water in Rhode Island with concentrations ranging from 1 ppb to 6,000 ppb (RIDH 1989).

5.4.3 Soil

Although several investigators (Aurelius and Brown 1987; Barbee and Brown 1986; Griffin et al. 1984) refer to leaching of xylene from waste disposal sites as a source of xylene levels in groundwater samples, very little data are available on actual measurements of xylene in soil. Diluted aliquots were made from samples (e.g., used oil, spent solvents, paint wastes, and polymer formulations) collected under contract to the EPA Contract Laboratory Program (CLP). These came from a variety of waste materials including contaminated soils at 221 hazardous waste disposal sites. In these samples, o-xylene was detected 223 times out of 600 analyses (37.2% frequency of detection) at a mean concentration of 8,388 ppm (mg/L) (Blackman et al.

1984). o-Xylene was second among the most prevalent organic chemicals and had the third highest reported maximum concentration (790,000 mg/L) (Blackman et al. 1984).

No other quantitative data on the presence of xylenes in soil were found in the available literature. However, in view of the rapid volatilization of xylenes, their presence in surface soils is unlikely to be significant. In addition, much of the xylene that is present in sub-surface soils probably becomes degraded by microorganisms or leached in groundwater.

5.4.4 Other Media

Xylene has been detected in both cigarette smoke and consumer products. The gas phase delivery of p-xylene in ultra-low tar delivery cigarette smoke ranges from <0.01 to 8 μg/cigarette, while the ranges for m- and o-xylene, respectively, are from <0.01 to 20 μg/cigarette and from <0.005 to 10 μg/cigarette (Higgins et al. 1983). The 1,095 household products surveyed by the Consumer Product Safety Commission (Fishbein 1985) contained an average of 9.5% mixed xylenes. The largest number of mixed xylene-containing products were found in household aerosols and paints, varnishes, shellac, and rust preventatives.

Xylene has also been detected in distillates of rainbow trout, and carp tissue samples from three rivers not known to be contaminated (Hiatt 1983). The estimated tissue concentrations of m- and p-xylene in rainbow trout and carp were 0.05 and 0.12 mg/kg, respectively (Hiatt 1983).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The principal population at risk of significant xylene exposure is the occupational work force. This group can be exposed to mixed xylenes during their production as well as their end use as an industrial solvent. Occupational exposures result from inhalation or dermal exposure and are usually associated with process, storage, or fugitive emissions at chemical, paint, and plastics plants (Fishbein 1985). Average daily intake from individual occupational exposure sources has not been estimated.

The National Occupational Hazard Survey (NOHS) conducted by the National Institute for Occupational Safety and Health (NIOSH), ranked xylenes 13th in concentration in workplace air out of approximately 7,000 chemicals (NIOSH 1976). The NOHS estimated that 1,016,020 workers in 99,920 U.S. plant sites were potentially exposed to total xylenes in the workplace in 1970 (NIOSH 1976). An estimated 5,778 workers in 179 plants, 4,621 workers in 96 plants, and 1,912 workers in 62 plants were potentially exposed to o-, m-, and p-xylene, respectively. These estimates were derived from observations of the actual use of total xylenes and the individual isomers and the use of trade

name products known to contain xylenes (see Table 5-2 for composition breakdown of the estimates). The largest numbers of workers exposed to total xylenes were employed by automotive dealers, service stations, or special trade contractors and in the chemical and allied products, transportation equipment, machinery (except electrical), fabricated metal products, and electrical equipment and supplies industries. In addition, the largest numbers of workers exposed to single xylene isomers were employed in the rubber and plastics products, printing and publishing, petroleum and coal products, chemicals and allied products, and fabricated metal products industries.

Preliminary data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 1,106,789 workers, including 211,806 women, in 74,063 plants were potentially exposed to total xylenes in the workplace in 1980 (NIOSH 1984). An estimated 5,596 workers (including 1,314 women) in 331 plants, 16,863 workers (including 1,194 women) in 1,610 plants, and 1,160 workers (including 545 women) in 178 plants were potentially exposed to o-, m-, and p-xylene, respectively. The largest numbers of workers exposed to total xylenes were employed in the machinery (except electrical), special trade contractors, fabricated metal products, and health services industries and as assemblers, janitors, and cleaners, painting and paint-spraying machine operators, and automobile mechanics. The largest numbers of workers exposed to o-xylene were employed in the chemical and allied products industry and as machine operators (not specified), chemical technicians, production inspectors, checkers, and examiners. The largest numbers of workers exposed to m-xylene were employed in the electric, gas, and sanitary services and business services industries and as electrical power installers and repairers, supervisors, plumbers, pipe fitters, and steam fitters, order clerks, and chemists (except biochemists). The largest numbers of exposed workers exposed to p-xylene were employed in the health services industries and as clinical laboratory technologists and technicians. These estimates were derived from observations of the actual use of xylenes and the individual isomers and the use of trade name products known to contain xylenes (see Table 5-2 for percentage breakdown).

Neither the NOHS nor the NOES databases contain information on the frequency, level, or duration of exposure of workers to any of the chemicals listed therein. The surveys only provide estimates of workers potentially exposed to the chemicals.

Members of the general population are exposed to low levels of xylenes primarily by breathing ambient air, particularly in areas with heavy traffic, near filling stations, near industrial sources such as refineries, or where xylenes are used as solvents. Exposure may also arise from ingestion of contaminated drinking water. Common activities identified with increased

TABLE 5-2. Percentage Breakdown of NIOSH Occupational Exposure Estimates from the NOHS and NOES Databases[a]

Chemical	NOHS		NOES	
	Actual[b] (%)	Trade Name[c] (%)	Actual (%)	Trade Name (%)
o-Xylene	14	86	96	4
m-Xylene	--	100	23	77
p-Xylene	41	59	75	25
Total Xylene	9[d]	35[d]	19	81

[a]Source: NIOSH 1976, 1984.
[b]Actual observations are surveyor observations in which the surveyor observed the use of the specific agent.
[c]Trade name observations are surveyor observations in which the surveyor observed the use of a trade name product known to contain the specific agent.
[d]Remainder is composed of generic observations (i.e., observations of the use of generic products suspected of containing xylene), which are not included in the total exposure estimates provided.

NIOSH = National Institute for Occupational Safety and Health; NOES = National Occupational Hazard Survery; NOHS = National Occupational Exposure Survey

potential exposure include pumping gasoline, visiting service stations, traveling in a car, painting, scale model building, pesticide use, and smoking (Wallace et al. 1986; 1987a). The level of exposure associated with living near hazardous waste sites has not been assessed, but it is expected to be elevated above ambient background levels determined in areas not near hazardous waste sites.

General population exposure to xylene can also occur through dermal contact with the many consumer products containing xylene, including cleaning solvents, insecticides, lacquers, paint thinners and removers, and pesticides (Gleason et al. 1969; Fishbein 1985; EPA 1985a). Dermal absorption is reported to be minor following exposure to xylene vapor but may be significant following contact with the liquid (EPA 1985a). The percutaneous absorption rate of m-xylene in humans was approximately 2 $\mu g/cm^2/min$ through the skin of the hands (Engstrom et al. 1977).

Assuming a daily intake of 2 liters drinking water and that total xylene (sum of m-, o-, and p-xylene isomer concentrations) is present at the highest concentration reported, the adult maximum daily intake for total xylene through consumption of drinking water is estimated to be 2,760 μg/day or 39.4 μg/kg/day (EPA 1985a). Assuming a typical xylene concentration in drinking water of 0-1 ppb, the average daily intake of xylenes from drinking water is estimated to be 2 μg or less than 0.03 μg/kg/day (HSDB 1988).

Based on the estimates of Brodzinsky and Singh (1983) of median atmospheric concentrations of xylene in rural, urban, and source dominated areas (see Section 5.4.1) and assuming inhalation of 23 m^3/d by a 70-kg adult, the daily o-xylene intake from air for adults exposed to the median levels in rural, urban, and source dominated areas would be 0.1, 1.7, and 1.2 μg/kg/day, respectively. The median m- and p-xylene intake would be 0.1, 3.9, and 2.4 μg/kg/day, respectively (EPA 1985a). Assuming a typical ambient air xylene concentration of 4.0 ppb, the average daily intake of xylenes from air is estimated to be 353 μg (HSDB 1988).

Exposure to xylenes in indoor environments can constitute a significant source of human exposure (Krotoszynski et al. 1979; Seifert and Abraham 1983; Wallace et al. 1986, 1987b). Xylene isomers were consistently present in personal air (indoor air) and breath samples at higher concentrations than in outdoor samples in recent surveys of approximately 400 residents of New Jersey, North Carolina, and North Dakota. They appeared in exhaled breath at approximately 50% of their average concentration in the air inhaled during the previous 12 hours (Wallace et al. 1986, 1987a). The major reason for the high levels of personal exposures seen in these studies appears to be elevated indoor air levels at work and at home caused by a variety of sources, including consumer products, building materials, and personal activities such as smoking (Wallace et al. 1986, 1987a). In most cases, exposures to indoor

air levels at work and at home were greater than exposures to outdoor air levels found near traditional "major" point sources (e.g., chemical plants, petroleum refineries, petrochemical plants) and area sources (e.g., dry cleaners and service stations) (Wallace et al. 1987a).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in certain occupational groups appear to have the greatest potential for exposure to high concentrations of xylenes. Based on the available case reports of xylene toxicity in humans, painters (or paint industry workers) and laboratory workers appear to be most frequently affected (EPA 1985a). In general, workers involved in the distillation and purification of xylene or employed in industries using xylene as a raw material (e.g., gasoline blending) may be at higher risk of exposure (EPA 1985a). The use of xylene in improperly ventilated areas is often the cause for toxic levels of exposure. Significant relationships with increased exposures or breath concentrations have been observed for wood processing plant workers, gas station employees, metal workers, and furniture refinishers. Among the general population, individuals who smoke or routinely come into contact with solvent products appear to be potentially exposed to the highest concentrations of xylenes. Populations living near chemical waste sites where xylene is improperly stored are also likely to be at risk of increased exposure.

5.7 ADEQUACY OF THE DATABASE

Section 104(i) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of xylene is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of xylene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of xylene have been well studied, and reliable values for key parameters are

available for use in environmental fate and transport models. On this basis, further studies of the physical-chemical properties of xylene are not essential at the present time.

Production, Use, Release, and Disposal. Potential for human exposure to xylenes is expected to be quite high based on the high volume of production and the widespread use of xylenes in the home and industry.

Recent estimates of production capacity of xylenes indicate that over 1 billion gallons of mixed xylenes and over 50 billion gallons of xylene isomers may be produced in the United States each year. Information on the actual production levels, however, is limited. More information on current production levels as well as past and projected production volumes would be helpful in estimating potential human exposure.

Xylenes are widely used in industry as solvents and as precursors of other products (i.e., polyester). Exposure of individuals may occur as a result of releases to the environment (approximately 3 million tons per year) and as a result of the presence of xylenes in gasoline, paint products, insecticides and cigarette smoke. No information was obtained on the occurrence of xylenes in food. Consequently, dietary intake and its contribution to total exposure could not be evaluated. This information would be helpful in estimating potential human exposure.

Because of their widespread use and release into the environment, xylenes have been distributed to most environmental media. They have been detected in air, rainwater, soil, surface water and sediments, drinking water, and aquatic organisms. Reports of levels in the various environmental media are dated within the last 10 years, with some as current as 1989. Information on the most recent distribution of xylenes would be helpful in estimating exposure.

According to the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRTKA), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxics Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

Incineration is the primary method for disposal of xylenes, although information on the disposal methods is not detailed. Information on the amount of xylenes disposed of by incineration as well as the amount of xylene disposed of or abandoned at hazardous waste sites is important for estimating the potential human exposure. Criteria for the disposal of xylenes are currently subject to frequent revision.

5. POTENTIAL FOR HUMAN EXPOSURE

Environmental Fate. The information available regarding transport and partitioning of xylene among environmental compartments indicates that volatilization is the most important fate process. Xylene released to surface water will primarily volatilize. Xylene will also sorb to soils and sediments and leach into groundwater; however, there is considerable variation and uncertainty in estimates of persistence in these media. Photooxidation appears to be the most important transformation process in the atmosphere and in surface soils. Biodegradation is likely to be the only significant degradation process for xylene in subsurface soils and aquatic systems. Additional data on the partitioning of xylene released to soil and groundwater and on the rates of biotransformation in soils, sediments, and groundwater would be useful to further define potential pathways of human exposure and to estimate ambient concentrations in environmental media.

Bioavailability from Environmental Media. Xylenes are absorbed during inhalation, oral, and dermal contact. Approximately 50% of the xylene that is inhaled is absorbed into the body. However, limited information was found in the available literature regarding the uptake of xylene components by living organisms from contaminated media such as soil and sediments to which the xylenes are sorbed or from contaminated surface waters. Information on uptake would be helpful in estimating human exposure from contaminated environmental media.

Food Chain Bioaccumulation. Xylenes are bioconcentrated in aquatic organisms to variable extents. The degree of concentration is believed to be limited by the rapid metabolism and excretion of xylenes from some aquatic species. However, additional data on the bioconcentration of xylene by aquatic organisms from contaminated surface waters and sediments would be useful. No information was found in the available literature regarding the bioconcentration of xylenes in plants or biomagnification of xylene among food chain trophic levels. Although bioaccumulation has been predicted for all isomers of xylene because of their tendency to partition into the octanol phase of the octanol-water system, the rapid oxidation of xylenes during metabolism seems to preclude bioaccumulation in higher animal systems. Thus, biomagnification is not expected to be important for xylenes. However, data on the bioaccumulation of xylene in commercially important fish and shellfish would be useful, since consumption of contaminated fish and shellfish may be a potential source of human exposure.

Exposure Levels in Environmental Media. The presence of xylenes in the environment has been assessed mainly together with other volatile organic compounds and characteristic components of oil. There is thus little data available on environmental levels of total xylenes, and data on the individual isomers are even scarcer. In particular, very few estimates of the levels of xylenes in soils and surface waters in the vicinity of industrial sites (such

as fuel processing plants) were found in the available literature. More monitoring data are needed to better characterize ambient concentrations of xylene in soils, surface water, and groundwater, particularly in the vicinity of hazardous waste sites and petroleum refineries. These data would be useful to estimate the exposure of populations coming into contact with xylene through inhalation of contaminated air or consumption of contaminated surface water or groundwater.

The available data allow characterization of human exposure to xyle s from most exposure pathways. Estimates of human intake of xylenes from contaminated air and drinking water have been made based on background levels that have been recorded in the environment. In addition, estimates exist for the absorption from dermal contact that results from immersion in xylenes. More information of the levels of xylenes in contaminated media in the vicinity of hazardous waste sites is necessary before estimates of human intake from these sites may be calculated.

Exposure Levels in Humans. Xylenes have been detected in human blood, urine, and exhaled breath. However, exposure associated with living or working near hazardous waste sites and refineries has not been assessed. The most important human exposure sources, inhalation of workplace and ambient air, are reasonably well understood. Additional monitoring programs involving analysis of human breath or urine would be useful in assessing the magnitude of environmental exposures and in estimating the average daily dose associated with various sources, particularly for populations exposed in the vicinity of hazardous waste sites.

Exposure Registries. Several sectors of the occupational work force have the greatest levels of exposure to xylenes. Total xylene exposure has been found to be greatest among those employed in the machinery (except electrical), special trade contracting, fabricated metal products, and health services industries and as assemblers, janitors and cleaners, painting and paint-spraying machine operators, and automobile mechanics. Exposure to o-xylene is greatest among those employed in the chemical and allied products industry and as machine operators; chemical technicians; and production inspectors, checkers, and examiners. Exposure to m-xylene is greatest among those employed in the electrical, gas, and sanitary services and as electrical power installers, repairers, and supervisors; plumbers; pipe fitters; steam fitters; order clerks; and chemists. Exposure to p-xylene is greatest among those employed in the health services industries and as clinical laboratory technologists and technicians.

No exposure registries for xylene were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future

when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No on-going studies on the environmental fate of xylene or of occupational or general population exposures to xylene were located in the available literature. However, remedial investigations and feasibility studies on the 236 NPL sites which are known to be contaminated with total xylene should add to the current knowledge regarding the transport and transformation of the compound in the environment. In addition, environmental monitoring and human exposure assessments conducted in conjunction with these should add to the current database on environmental levels of xylene in media and humans.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for total xylenes and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe briefly the analytical methods that are available for detecting and/or measuring and monitoring xylene in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify xylene concentrations. Rather, the intention is to identify well established or common analytic techniques that are used as the standard methods of analysis. Some of the reported methods in this section are currently used by EPA or by State environmental agencies to detect xylene in environmental samples. On-going research efforts to develop new or improved analytical methods have also been identified.

The analytical methods used to quantify xylene in biological and environmental samples are summarized below. Table 6-1 lists the applicable analytical methods used for determining xylene in biological fluids and tissues, and Table 6-2 lists the methods used for determining xylene in environmental samples.

6.1 BIOLOGICAL MATERIALS

Extensive commercial, industrial, and domestic use of volatile organic chemicals such as xylene virtually assures that the general population will be exposed to some extent to this class of chemicals. The determination of trace amounts of xylene in biological tissues and fluids has been restricted to only a limited number of analytical methods. These include gas chromatography coupled with mass spectrometry (GC/MS), gas chromatography coupled with hydrogen flame ionization detection (GC/FID), and high-performance liquid chromatography (HPLC).

Recent work conducted by Cramer et al. (1988) indicates that m-xylene can be detected at parts-per-trillion (ppt) levels in whole human blood using a GC/MS technique. Antifoam agents do not have to be used in this technique; however, the use in this method of a dynamic headspace purge at room temperature reduces the absolute recoveries of the late eluting compounds. An advantage of this GC/MS technique is that it can be used in conjunction with limited mass scanning (LMS) to obtain better sensitivity of target compounds (such as National Priority List Pollutants) at ppt levels. LMS is a technique which involves scanning for a smaller number of ions than in the full-scan GC/MS method. Some analytes (including m-xylene) can be detected by LMS but not by full-scan GC/MS because of the inherent differences in sensitivity between the two methods (Cramer et al. 1988).

The use of GC/FID followed by a combination of packed and open tubular capillary GC and GC/MS to detect and quantify the isomers of xylene in human

TABLE 6-1. Analytical Methods for Determining Xylene in Biological Materials

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Human blood	Purge-and-trap sample on Tenax TA trap	GC/MS	m-xylene 1 ng/ml	No data	Cramer et al. 1988
	Purge-and-trap sample on sorbent	GC/MS	5.2 ng/ml	No data	Antoine et al. 1986
Tissues and body fluids	Saturate sample with sodium chloride and seal in a vial; inject into GC	GC/FID and GC/MS	m,p-xylene 0.05 mg/100 g o-xylene 0.01 mg/100 g	No data	Bellanca et al. 1982
Urine	Acidify sample and extract with ethyl acetate and methylating solution	GC/FID	5 mg/L	o-MHA 81.5% recovery m-MHA 82.2% recovery p-MHA 84.8% recovery	Caperos and Fernandez 1977
	Adjust pH of sample to 2.0; extract with ethylacetate	GC/FID	No data	m-MHA 98% recovery	Engstrom et al. 1976
	Acidify sample with HCL and extract with ethylacetate; add MeOH to ethylacetate extract; methylate extract with diazomethane in diethyl ether solution	GC/FID	No data	m-MHA 88.7%-95% recovery p-MHA 79.3-82% recovery	Morin et al. 1981
	Acidify sample with HCL; extract with n-butyl chloride: isopropanol (9:1)	HPLC	m-MHA 0.1 mg/ml	No data	Poggi et al. 1982
	Adjust pH of sample to 2.0; extract with methyl ethyl ketone; add phenacyl bromide solution to extract and heat	HPLC	m-MHA 0.02 µg/sample p-MHA 0.02 µg/sample	No data No data	Sugihara and Ogata 1978

TABLE 6-1 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
	Add sample specimen to MeOH; centrifuge	HPLC	o-MHA 6 mg/L	o-MHA 102% recovery	Ogata and Taguchi 1987
			m-MHA 8 mg/L	m-MHA 102.4% recovery	
			p-MHA 8 mg/L	p-MHA 99.5% recovery	
	Acidify sample; extract with chloroform and concentrate	TLC	m-MHA 6 µg/ml	m-MHA 100% recovery	Bieniek and Wilczok 1981
Whole body (mice)	Kill mice and inject with solvent sample; homogenize sample in liquid nitrogen; evaporate liquid nitrogen and extract with carbon disulfide	GC/FID	No data	m-xylene 86% recovery	Tsurata and Iwasaki 1984

GC/MS = gas chromatography/mass spectrometry; GC/FID = gas chromatography/flame ionization detector; HPLC = high performance liquid chromatography; TLC = thin layer chromatography; MHA = methylhippuric acid.

TABLE 6-2. Analytical Methods for Determining Xylene in Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Air	Draw sample through copper tubing with a diaphragm pump	GC/PID	0.3 ppb	No data	Hester and Meyer 1979
	Absorption on Tenax GC air sampler	GC/MS	No data	No data	Hampton et al. 1982
	Collect vulcanized air on activated charcoal; desorb with carbon disulfide	GC/FID	0.1-1.5 ppm	No data	Rappaport and Fraser 1977
	Pump air sample through charcoal tubes; extract charcoal with carbon disulfide	GC/FID	o-xylene <0.05 ppm	o-xylene 51%-86% recovery	Otson et al. 1983
			p-xylene <0.05 ppm	p-xylene 51%-86% recovery	
	Collect sample in tedlar bags by means of an automated sequential large air sampler	GC/FID	No data	No data	Lonneman et al. 1974
	Collect air on activated charcoal; desorb with carbon disulfide; shake with 75% H_2SO_4	GC/FID	1 μg/μL	92%-100% recovery	Esposito and Jacobs 1977
		LC/UV	No data	92%-104% recovery	
	Collect sample in pressurized stainless steel cannister	GC-FID/PID	o-xylene 1.3 pg/sample	No data	Nutmagul et al. 1983
	Collect sample in a pressurized cannister	GC-FID/ECD and GC/MS	<1 ppm	No data	Pleil et al. 1988
Fish	Freeze sample; homogenize in liquid nitrogen; vacuum distillation	GC/MS equipped with fused-silica capillary column	No data	No data	Hiatt 1983
Sediment (clay)	Shake sample with water; purge-and-trap on porapak N cartridges; elute with MeOH	GC-ECD/PID	7 ng/g	p-xylene 70%-77% recovery	Amin and Narang 1985
				o-xylene 68%-79% recovery	
		GC/ECD	1 ng/g	No data	

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Drinking water	Purge-and-trap on sorbent	GC/FID	o-xylene <1 µg/L	o-xylene 75% recovery	Otson and Williams 1982
			m-xylene <1 µg/L	m-xylene 87% recovery	
	Extract sample in hexane	GC/FID	o-xylene 2 µg/L	o-xylene 80%-96% recovery	Otson and Williams 1981
			m-xylene 2 µg/L	m-xylene 80%-83% recovery	
			p-xylene 2 µg/L	p-xylene 78%-85% recovery	
	Purge sample with a counter-current flow of helium gas	GC/MS	<5 ppb	No data	Saunders et al. 1975
	Purge-and-trap on sorbent	GC/PID	0.05 µg/L	No data	EPA 1981a
	No data	GC/PID and GC/MS	m-xylene 0.2-2.0 ppb o-xylene 0.2-2.0 ppb p-0.2-3.0 ppb	No data	NJDEP 1985 (EPA method 602/503.1 and 625)
Waste	Extract waste with hexane	GC/MS	No data	No data	Austern et al. 1975
	Add sample to a small volume of ethanol and dilute with water or raw wastewater; adjust the pH; extract with Freon-TF	GC/FID	No data	No data	Austern et al. 1975

GC/MS = gas chromatography/mass spectrometry; GC/FID = gas chromatography/flame ionization detector; GC/PID = gas chromatography/photoionization detector; LC/UV = liquid chromatography/ultraviolet spectrometry; and GC/ECD = gas chromatography/electron capture detector.

tissues and fluids has been reported in the literature. Brain, liver, lung, kidney, and blood samples of individuals who died following occupational exposure to several organic solvents were analyzed using a combination of capillary columns (Bellanca et al. 1982). The sensitivity and resolution of the isomers of xylene were increased and detection limits of 0.05 mg, 0.05 mg, and 0.01 mg per 100 gram of sample were obtained for m-, o-, or p-xylene, respectively (Bellanca et al. 1982). Despite this increased resolving power, adequate separation of m-xylene and p-xylene was unattainable.

In addition to direct measurement of xylene in biological tissues and fluids, it is also possible to determine the concentration of metabolites in biological fluids. A simple, sensitive and specific automated HPLC technique was developed for direct and simultaneous quantification of o-, m-, and p-methylhippuric acids, the metabolites of o-, m-, and p-xylene, respectively (Ogata and Taguchi 1987, Sugihara and Ogata 1978). The authors noted that a possible disadvantage of the HPLC technique is that at low concentrations (less than 0.6 mg/liter) in urine, these methylhippuric acids may not be distinguishable from other compounds closely resembling these acids.

Other techniques that have been successful in quantitatively determining urinary concentrations of metabolites of xylene include GC/FID, GC/MS, and thin layer chromatography (TLC).

GC/FID and GC/MS offer the possibility of excellent analytical sensitivity and specificity for urinary metabolites of xylene. However, all GC analytical methods require the urinary metabolites to be chemically transformed into methyl esters or trimethyl silyl derivatives. This transformation is a very critical reaction and may subsequently cause low reproducibility (Caperos and Fernandez 1977; Engstrom et al. 1976; Morin et al. 1981; Poggi et al. 1982).

A simple and highly reproducible TLC method has been developed for the detection and separation of m- or p-methylhippuric acid in the urine of individuals exposed to a mixture of volatile organic solvents (Bieniek and Wilczok 1981). However, the authors noted that this analytical technique is time-consuming. Furthermore, the developing agent used in this technique (p-dimethylamine benzaldehyde in acetic acid) has a disadvantage in that it is irritating to the eyes and mucous membranes.

6.2 ENVIRONMENTAL SAMPLES

A gas chromatograph equipped with an appropriate detector is the basic analytical method used for determining the levels of xylene in soil, water, air, and fish. Precautions in the isolation, collection, and storage of xylene in environmental media are necessary to prevent loss of the volatile xylene compounds to the air.

6. ANALYTICAL METHODS

An automated gas chromatograph with photoionization detector (GC/PID) has been developed by Hester and Meyer (1979) to identify gas-phase hydrocarbons (including xylene) for complex systems such as vehicle exhaust gas. The GC/PID method allows for measurement of sub-part-per billion level concentrations of air contaminants and does not require trapping or freeze-concentration of samples before analysis. These latter preconcentration steps are usually necessary because of the limited sensitivity of flame ionization detection (FID) techniques commonly used in the analysis of environmental samples. A limitation of the GC/PID technique is that m- and p-xylene isomers are detected but not well separated. A GC/PID in tandem with a flame ionization detector was constructed to obtain a more sensitive method to determine xylene levels in the air (Nutmagul et al. 1983). A detection limit of 1.3×10^{-12} g of o-xylene per sample was achieved.

A purge-and-trap gas chromatographic method involving photoionization detection has been developed by EPA to analyze volatiles in drinking water (EPA 1981a). A confirmatory analysis by a second analytical column or by GC/MS is advised by EPA. The purge-and-trap gas chromatographic method (EPA method 602/503.1 and 625) can detect the isomers of xylene and has a detection limit for o-, m-, and p-xylene of 0.2 ppb (NJDEP 1985; Otson and Williams 1981, 1982; Saunders et al. 1975).

A gas chromatograph equipped with both electron capture and photoionization detectors (GC-ECD/PID) has been employed to determine xylene levels in sediment samples (Amin and Narang 1985). The authors indicated that their method involved transfer of samples between containers and a considerable loss of volatile compounds was obtained.

A procedure has been developed to characterize volatile xylene compounds from fish samples by GC/MS using a fused-silica capillary column (FSCC) and vacuum distillation (Hiatt 1983). FSCC provides a more attractive approach than packed columns for chromatographic analysis of volatile aromatic organic compounds. A FSCC can be heated to a higher temperature (350°C) than that recommended for packed column, thereby improving the resolution (in ppb levels) of compounds and reducing column retention times. A physical limitation for compounds that can be detected, however, is that the vapor pressure of the compound must be greater than 0.78 torr (~50°C) in the sample chamber (Hiatt 1983).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)5 of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of xylene is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a

program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of xylene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The methods for determining xylene levels in blood and tissue samples, GC/MS or GC/FID, have sufficient sensitivity to measure xylene levels associated with background levels of exposure as well as exposure levels at which biological effects occur. GC/MS has been employed to detect o-xylene at ppm levels in the blood. However, development of a GC/MS method that incorporates a less rigorously heated purge would be useful. Heated purges currently used in GC/MS have the disadvantage of reducing the absolute recoveries of volatile organic solvents. Better resolution and sensitivity are achievable with the application of a capillary GC/MS column and selection of an appropriate detector or detector combination as an alternative to the packed column approach currently in use. Also, there is a growing need for analytical methods to efficiently separate and quantify trace levels of the isomers of xylene in biological media.

Analytical methods are also available to detect and quantify the xylene metabolites present in the urine. These methods, GC/MS, GC/FID, and HPLC, have been well characterized with respect to their precision, accuracy, reliability, and specificity and have sufficient sensitivity to measure xylene metabolite levels associated with biological effects. However, these methods may not be sensitive enough to measure metabolite levels associated with background exposure levels.

Currently, no methods are available to quantitatively correlate monitored levels of xylene in tissues or fluids with exposure levels or toxic effects in humans. These methods would provide the ability to evaluate possible health effects in humans resulting from exposure to xylene.

No specific biomarkers of effect have been clearly associated with xylene exposure. Some biological parameters such as hepatic microsomal enzyme activities and central nervous system activity (measured by evoked potentials or tests of memory and reaction time) have been tentatively linked with xylene

exposure, but insufficient data exist to adequately assess the analytical methods associated with measurement of these potential biomarkers.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining xylene and its degradation products in environmental media are necessary to identify contaminated areas and to determine whether the levels at contaminated sites constitute a concern for human health. Standardized methods are available to detect xylene in air, waste water, drinking water, fish, and clay sediments. There is growing need for simultaneously achieving lower (< ppb) detection limits, separating meta and para isomers of xylene, and obtaining an adequate sample recovery. Such methods would provide useful information for assessing the biological effects of exposure to xylene and to delineate dose-response relationships. A combination of capillary gas chromatography coupled to a multi-detector system, nuclear magnetic resonance (NMR) spectroscopy, and infra-red (IR) spectroscopy, would be useful for the accurate identification and measurement of the isomers of xylene in complex environmental systems.

6.3.2 On-going Studies

Two on-going studies concerning the identification of xylene in biological samples were reported in the Federal Research in Progress File (FEDRIP) database. R.A. Glaser of NIOSH is developing analytical techniques to establish the identities and concentrations of contaminants within the workplace. A prototype solid sorbent device for the direct collection of exhaled breath samples will be evaluated; this prototype will permit further refinement of its design and use. A complete analytical method for identification of m-xylene in breath will be developed. R.E. Letz of the Mount Sinai School of Medicine in New York is estimating the central nervous system concentrations of various solvents (including xylene) in industrial spray painters. This investigator proposes using industrial hygiene sampling and exhaled breath and urine analyses coupled with biomathematical dose models to estimate these concentrations.

No on-going studies concerning the identification of xylene in environmental samples were identified.

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of total xylenes and other volatile organic compounds in blood. These methods use purge-and-trap methodology and magnetic sector mass spectrometry which gives detection limits in the low-parts per trillion range.

7. REGULATIONS AND ADVISORIES

Xylenes are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987a).

The national and state regulations and guidelines pertaining to xylenes in air, water, and other media are summarized in Table 7-1. No international regulations or guidelines applicable to xylenes were found.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Xylenes

Agency	Description	Value	References
IARC	Carcinogen classification	Group 3[a]	IARC 1989
	National		
Regulations:			
a. Air:			
OSHA	PEL TWA (8-hr)	100 ppm	OSHA 1989 (29 CFR 1910)
	STEL (15 min)	150 ppm	
	m-xylene		
	o-xylene		
	p-xylene		
b. Water:			
EPA	Xylene is exempted from the requirement of a tolerance when used as an aquatic herbicide applied to irrigation conveyance systems in accordance with specified conditions	NA	EPA 1985b (40 CFR 180.1025)
EPA OSW	Ground water monitoring list (Appendix IX) (xylenes)	NA	EPA 1987c
EPA OWRS	General permits under NPDES	NA	EPA 1983a (40 CFR 122) Appendix D
c. Other:			
EPA	Residues of xylene are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as an ingredient in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest	NA	EPA 1971 (40 CFR 180.1001)
	Chemical information rules require manufacturers to report production, use, and exposure-related information on mixed xylene, m-xylene, o-xylene, and p-xylene	NA	EPA 1982b (40 CFR 712.30)
	Health and safety data reporting rules require manufacturers, processors, etc. to submit lists and copies of unpulished health and safety studies for m-, o-, and p-xylene	NA	EPA 1982a (40 CFR 716)
EPA OERR	Reportable Quantity		EPA 1985d (CFR 302.4)
	xylenes	1000 lb	
	spent xylene solvents and still bottoms from the recovery of these solvents	1000 lb	
	distillation bottoms from production of phthalic anhydride from o-xylene	5000 lb	
EPA OSW	Hazardous waste:		
	xylene the commercial chemical products, manufacturing chemical intermediates, or off-specification commercial chemical products		EPA 1981c (40 CFR 261.31)
	spent xylene solvents and still bottoms from the recovery of these solvents		
	distillation light ends and bottoms from production of pthalic anhydride from o-xylene		EPA 1981d (40 CFR 261.32)

TABLE 7-1 (Continued)

Agency	Description	Value	References
FDA	Substance for use only as component of adhesives intended for use in packaging, transporting, or holding food in accordance with specified conditions xylene xylene alkylated with dicyclopentadiene	NA	FDA 1977b (21 CFR 175.105)
	Resin safe for use as a coating for articles intended for use in contact with food xylene-formaldehyde resins condensed with 4,4'-isopropylidene- diphenol-epichlorohydrin epoxy resins	NA	FDA 1977a (21 CFR 175.380)
Advisories:			
a. Air:			
ACGIH	TLV TWA	100 ppm (≈435 mg/m^3)	ACGIH 1986
	STEL	150 ppm (≈655 mg/m^3)	ACGIH 1986
NIOSH	REL TWA (10 hr)	100 ppm	NIOSH 1985
	ceiling (10 min.)	200 ppm	
	IDLH	10,000 ppm	NIOSH 1985
b. Water:			
EPA ODW	Health advisory		EPA 1987b
	1-day (10 kg child)	12 mg/L	
	10-day (10 kg child)	7.8 mg/L	
	Longer-term (70 kg adult)	27.3 mg/L	
	(10 kg child)	7.8 mg/L	
	Lifetime	0.4 mg/L	
	MCLG (proposed)	0.44 mg/L	EPA 1985c
NAS	SNARL		NRC 1980
	1-day (70 kg adult)	21 mg/L	
	7-day (70 kg adult)	11.2 mg/L	
c. Other:			
ACGIH	BEI		ACGIH 1986
	End of shift	1.5 g/g creatinine	
	Over last four hours of shift	2 mg/min	
EPA	Carcinogenic classification	Group D[b]	IRIS 1989
	RfD (oral)	2 mg/kg/day	IRIS 1989

TABLE 7-1 (Continued)

Agency	Description	Value	References
	State		
Regulations and Advisories:			
a. Air:	Acceptable ambient air concentration (mixed xylene)		NATICH 1988
Connecticut		8680 $\mu g/m^3$ (8 hr)	
Indiana		2175 $\mu g/m^3$ (8 hr)	
North Carolina		65.5 mg/m^3 (15 min) 2.6 mg/m^3 (24 hr)	
North Dakota		4.35 mg/m^3 (8 hr) 6.55 mg/m^3 (1 hr)	
Nevada		10.357 mg/m^3 (8 hr)	
New York		1450 $\mu g/m^3$ (1 yr)	
Rhode Island		700 $\mu g/m^3$ (24 hr)	
South Dakota		8700 $\mu g/m^3$ (8 hr)	
Massachusetts		11.8 $\mu g/m^3$ (24 hr) 11.8 $\mu g/m^3$ (annual average)	MDEQE 1989
	Acceptable ambient air concentration (m-xylene)		NATICH 1988
New York		1450 $\mu g/m^3$ (1 yr)	
South Carolina		4350 $\mu g/m^3$ (24 hr)	
Virginia		73 $\mu g/m^3$ (24 hr)	
	Acceptable ambient air concentration (o-xylene)		NATICH 1988
New York		1450 $\mu g/m^3$ (1 yr)	
South Carolina		4350 $\mu g/m^3$ (24 hr)	
Virginia		73 $\mu g/m^3$ (24 hr)	

TABLE 7-1 (Continued)

Agency	Description	Value	References
	Acceptable ambient air concentration (p-xylene)		NATICH 1988
New York		1450 $\mu g/m^3$ (1 yr)	
South Carolina		4350 $\mu g/m^3$ (24 hr)	
Virginia		73 $\mu g/m^3$ (24 hr)	
b. Water:	Drinking water (mixed xylene)		FSTRAC 1988
Arizona		440 $\mu g/L$	
Kansas		440 $\mu g/L$	
Maine		620 $\mu g/L$	
Minnesota		440 $\mu g/L$	
New Mexico		620 $\mu g/L$	
New York		50 $\mu g/L$	
Vermont		620 $\mu g/L$	
Wisconsin		620 $\mu g/L$	
Massachusetts		1,000 $\mu g/L$	MDEQE 1989
New Jersey	Drinking water (STAL) (1 yr)	44 $\mu g/L$	NJDEP 1989
Rhode Island	Drinking water	400 $\mu g/L$	RIDH 1989
Massachusetts	Groundwater standard	620 $\mu g/L$	MDEQE 1989 (310 CMR 6.00)
California	Drinking water (m-xylene)	620 $\mu g/L$	FSTRAC 1988
	Drinking water (o-xylene)	620 $\mu g/L$	FSTRAC 1988
	Drinking water (p-xylene)	620 $\mu g/L$	FSTRAC 1988

[a]Group 3: This chemical cannot be classified as to its carcinogenicity for humans.
[b]Group D: Not classifiable as to human carcinogenicity.

IARC = International Agency for Research on Cancer; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; TWA = Time Weighted Average; STEL = Short Term Exposure Limit; EPA = Environmental Protection Agency; NA = not applicable; OSW = Office of Solid Waste; FDA = Food and Drug Administration; OSW = Office of Solid Waste; OWRS = Office of Water Regulations and Standards; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; ACGIH = American Conference of Governmental Industrial Hygienists; TLV = Threshold Limit Value; NIOSH = National Institute for Occupational Safety and Health; REL = Recommended Exposure Limit; IDLH = Immediately Dangerous to Life or Health; ODW = Office of Drinking Water; MCLG = Maximum Contaminant Level Goal; NAS = National Academy of Sciences; SNARL = Suggested-No-Adverse-Response Level; NRC = National Research Council; BEI = Biological Exposure Index; IRIS = Integrated Risk Information System; RfD = Reference Dose; NATICH = National Air Toxics Information Clearinghouse; MDEQE = Massachusetts Department of Environmental Quality Engineering; STAL = short-term action level; NJDEP = New Jersey Department of Environmental Protection; RIDH = Rhode Island Department of Health; FSTRAC = Federal-State Toxicology and Regulatory Alliance Committee.

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the toxicological profiles.

Adsorption Coefficient (Koc) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

9. GLOSSARY

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

9. GLOSSARY

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (Kow) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

9. GLOSSARY

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX

PEER REVIEW

A peer review panel was assembled for xylene. The panel consisted of the following members: Dr. Sanford W. Bigelow, President, MultiSciences, Inc.; Dr. Harvey Checkoway, Department of Environmental Health, School of Public Health, University of Washington; Dr. Lloyd Hastings, Department of Environmental Health, College of Medicine, University of Cincinnati; Dr. Ronald Hood, Biology Department, The University of Alabama; and Dr. Charles O. Ward, private consultant. These experts collectively have knowledge of xylene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientist from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.