

## 2. HEALTH EFFECTS

### 2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of xylene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Commercial xylene is a mixture of three isomers of xylene: *m*-, *o*-, and *p*-xylene. In the following discussion of the health effects of xylene, the effects of both the mixture and the individual isomers are presented. Where possible, the effects of individual isomers will be identified and presented separately.

### 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure - inhalation, oral, and dermal; and then by health effect - death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods - acute (14 days or less, including a single exposure), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration 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” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are reversible, that are not expected

## 2. HEALTH EFFECTS

to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary 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 in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed.

Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike. Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for xylene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in

## 2. HEALTH EFFECTS

development or acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

### 2.2.1 Inhalation Exposure

#### 2.2.1.1 Death

One report was located regarding death in humans following acute inhalation exposure to xylene (composition unspecified) (Morley et al. 1970). One of three men died after breathing paint fumes for several hours that contained an estimated atmospheric concentration of 10,000 ppm xylene. Xylene comprised 90% of the solvent in the paint (small amounts of toluene were also present), with the total solvent comprising 34% of the paint by weight. An autopsy of the man who died showed severe pulmonary congestion, interalveolar hemorrhage, and pulmonary edema; the brain showed hemorrhaging and evidence of anoxic damage. Clinical signs noted in the two exposed men who survived included solvent odor of the breath, cyanosis of the extremities, and neurological impairment (temporary confusion, amnesia). Both men recovered completely. The authors hypothesized that anoxia did not contribute to the effects observed in the survivors because the flow of oxygen into the area in which the men were working should have been adequate. The study was inconclusive for evaluating the toxic effects of xylene because the subjects were concurrently exposed to other chemicals in the paint. No studies were located regarding mortality in humans after intermediate or chronic inhalation exposure to mixed xylene or xylene isomers.

Acute inhalation LC<sub>50</sub> values have been determined in animals for xylene and its isomers (Bonnet et al. 1979; Carpenter et al. 1975a; Harper et al. 1975; Hine and Zuidema 1970; Ungvary et al. 1980b). The 4-hour LC<sub>50</sub> value for mixed xylene in rats ranged from 6,350 ppm (Hine and Zuidema 1970) to 6,700 ppm (Carpenter et al. 1975a). The 4-hour LC<sub>50</sub> value for *p*-xylene in rats was reported to be 4,740 ppm (Harper et al. 1975). In mice, the 6-hour LC<sub>50</sub> 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). These data suggest that *p*-xylene may be slightly more toxic than the other xylene isomers. According

## 2. HEALTH EFFECTS

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.

Mice appear to be more sensitive than rats to the lethal effects of the *m*- and *o*-isomers of xylene (Cameron et al. 1938). While no rats died following a 24-hour exposure to 2,010 ppm *m*-xylene, 6 of 10 mice died as a result of a similar exposure. Similarly, a 24-hour exposure of rats to 3,062 ppm *o*-xylene resulted in a death rate of only 1 in 10, whereas in mice, 4 of 10 died. It is unclear whether differential sensitivities exist for the *p*-isomer of xylene in mice and rats (Cameron et al. 1938).

Information regarding lethality following intermediate-duration exposures is limited to the results of a single study examining mortality in rats, guinea pigs, monkeys, and dogs following intermittent and continuous exposure to *o*-xylene (Jenkins et al. 1970). Continuous exposure to 78 ppm *o*-xylene for 90-127 days resulted in the death of only 1 of 15 rats. Intermittent exposure to 780 ppm *o*-xylene resulted in deaths of 3 of 15 rats; none of the 15 guinea pigs, 3 monkeys, or 2 dogs died. No data were located regarding death following chronic-duration exposure to mixed xylene or its isomers.

All LC<sub>50</sub> values and LOAEL values from each reliable study for death in each species and duration category are recorded in Tables 2-1, 2-2, 2-3, and 2-4 and plotted in Figures 2-1, 2-2, 2-3, and 2-4.

### 2.2.1.2 Systemic Effects

No human or animal data were available regarding dermal effects following inhalation exposure to mixed xylene or xylene isomers. The systemic effects observed after inhalation exposure to xylene are discussed below. The highest NOAEL value and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 2-1, 2-2, 2-3, and 2-4 and are plotted in Figures 2-1, 2-2, 2-3, and 2-4.

**Respiratory Effects.** In humans, acute-duration inhalation exposure to mixed xylene and *p*-xylene has been associated with irritation of the nose and throat (Carpenter et al. 1975a; Hake et al. 1981; Klaucke et al. 1982; Nelson et al. 1943; Nersesian et al. 1985). Nose and throat irritation has been reported following exposure to mixed xylene at 200 ppm for 3-5 minutes (Nelson et al. 1943) and to *p*-xylene at 100 ppm for 1-7.5 hours/day for 5 days (Hake et al. 1981). However, no increase in reports of nose and throat irritation and no change in respiratory rate were seen in a study of subjects

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat Harlan- Wistar	4 hr				6700 M (LC50)	Carpenter et al. 1975a
2	Rat Long-Evans	4 hr				6350 M (LC50)	Hine and Zuidema 1970
<b>Systemic</b>							
3	Human	0.25 hr	Resp	460	690 (throat irritation)		Carpenter et al. 1975a
			Ocular	230	460 (eye irritation)		
4	Human	2 or 3 d 70min/d	Cardio	299 M			Gamberale et al. 1978
5	Human	30 min	Resp	396 M			Hastings et al. 1986
			Ocular	396 M			
6	Human	3-5 min	Resp		200 (nose and throat irritation)		Nelson et al. 1943
			Ocular		200 (eye irritation)		
7	Rat Harlan- Wistar	0.75 hr	Hemato	15000 M			Carpenter et al. 1975a
8	Rat Sprague- Dawley	3 d 6hr/d	Resp		2000 M (decreased cytochrome P-450)		Toftgard and Nielsen 1982
9	Rat Wistar	9 d 5hr/d	Hemato	2764			Wronska-Nofer et al. 1991

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
10	Mouse Swiss- Webster	1 min	Resp	460 M		1300 M (50% decrease in respiratory rate)	Carpenter et al. 1975a
11	Mouse	6 min	Resp			2440 M (50% decrease in respiratory rate)	Korsak et al. 1988
<b>Neurological</b>							
12	Human	0.25 hr		460	690 (dizziness)		Carpenter et al. 1975a
13	Human	4 hr			100 <sup>b</sup> M (increased reaction time)		Dudek et al. 1990
14	Human	2 d 70min/d		299 M			Gamberale et al. 1978
15	Human	1 d 70min/d			299 M (impairment in reaction time and short-term memory after exercising; not without exercising)		Gamberale et al. 1978
16	Human	30 min		396 M			Hastings et al. 1986
17	Rat Sprague- Dawley	3 d 6hr/d			2000 M (increased dopamine and catecholamine in brain)		Andersson et al. 1981
18	Rat NS	4 hr		580 M		1300 M (incoordination)	Carpenter et al. 1975a
19	Rat F344	5 hr		99 M			Ghosh et al. 1987
20	Rat F344	3 d 6hr/d			114 M (transiently decreased operant responding)		Ghosh et al. 1987

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

Key to <sup>a</sup> figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
21	Rat F344	1 d 3x/d 2hr/x			113 M (transiently decreased operant responding)		Ghosh et al. 1987
22	Rat NS	4 hr		2010 M		2870 M (impairment of rotarod performance)	Korsak et al. 1988
23	Rat NS	1.5 wk 5d/wk 6hr/d			800 M (decreased axonal transport)		Padilla and Lyerly 1989
24	Rat NS	4 hr		1700 M			Pryor et al. 1987
25	Rat NS	8 hr				1450 M (hearing loss)	Pryor et al. 1987
26	Rat F344	2 hr		102 M	192 M (decreased self-stimulation behavior)		Wimolwattanapun et al. 1987
27	Cat NS	2 hr				9500 M (salivation, ataxia, seizures, anesthesia)	Carpenter et al. 1975a
<b>Reproductive</b>							
28	Rat (CFY)	8 d 24h/d Gd 7-15				775 (8% decrease in fertility; increase in resorptions)	Balogh et al. 1982
<b>Developmental</b>							
29	Rat (CFY)	8 d 24hr/d Gd 7-14			53 (reduced ossification)	775 (postimplantation loss)	Balogh et al. 1982

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
30	Rat CFY	6 d Gd 9-14 24hr/d				230 F (increased fused sternbrae and extra ribs)	Hudak and Ungvary 1978
31	Rat CFY	9 d 24hr/d Gd 7-15			58 (reduced ossification)	784 (increased fetal death and resorption)	Ungvary and Tatrai 1985
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
32	Rat NS	10 wk 5d/wk 6hr/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Endocr Bd Wt	810 M 810 M 810 M 810 M 810 M 810 M 810 M 810 M			Carpenter et al. 1975a
33	Rat NS	5, 9, 14, or 18 wk 5d/wk 6hr/d	Hepatic	300 M			Elovaara et al. 1980
34	Rat CFY	4 wk 5d/wk 6hr/d	Cardio			230 M (increased wall thickness in coronary micro-vessels)	Morvai et al. 1987
35	Rat Sprague-Dawley	4 wk 5d/wk 6hr/d	Hepatic		600 M (11% increase in relative liver weight)		Toftgard et al. 1981

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
36	Dog	13 wk 5d/wk 6hr/d	Resp	810 M			Carpenter et al. 1975a
			Cardio	810 M			
			Gastro	810 M			
			Hemato	810 M			
			Musc/skel	810 M			
			Hepatic	810 M			
			Renal	810 M			
			Endocr	810 M	(adrenal, thyroid, parathyroid)		
<b>Neurological</b>							
37	Rat Albino	30 d 24hr/d			800 M (decreased acetylcholine in striatum, increased glutamine in midbrain, and norepinephrine in hypothalamus)		Honma et al. 1983
38	Rat Sprague-Dawley	61 d 7d/wk 8hr/d			1009 M (reversible decrease in auditory brainstem response)		Nylen and Hagman, 1994
39	Rat Fischer-344	6 wk 7d/wk 14hr/d				800 M (hearing loss)	Pryor et al. 1987
40	Rat Wistar	18 wk 5d/wk 6hr/d			300 M (decreased membrane lipids in axon membranes)		Savolainen and Seppalainen 1979
41	Rat Wistar	18 wk 5d/wk 6hr/d			300 M (transient decreases in preening behavior)		Savolainen et al. 1979a

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
42	Gerbil Mongolian	3 mo 30d/mo 24hr/d			160	(regional increases in DNA and astro-glial proteins)	Rosengren et al. 1986
<b>Reproductive</b>							
43	Rat Sprague- Dawley	61 d 7d/wk 18h/d		1000			Nylen et al. 1989
<b>Developmental</b>							
44	Rat CD	166 d 7d/wk 6hr/d		250	500 F	(7% decrease in fetal weight)	Bio/dynamics 1983
45	Rat Wistar	Gd 4-20 6hr/d			200 <sup>c</sup>	(decreased rotarod performance of pups)	Hass and Jakobsen 1993
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
46	Human	Average 7 yr 8 hr/d	Resp Gastro			14 M (nose and throat irritation) 14 M (increased prevalence of nausea and poor appetite)	Uchida et al. 1993
			Hemato	14 M			
			Hepatic	14 M			
			Renal	14 M			
			Ocular		14 M	(eye irritation)	

**TABLE 2-1. Levels of Significant Exposure to Mixed Xylene - Inhalation (continued)**

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
<b>Neurological</b>							
47	Human	Average 7 yr 8 hr/d			14 <sup>d</sup>	(increased prevalence of anxiety, forgetfulness, inability to concentrate and other subjective symptoms)	Uchida et al. 1993

<sup>a</sup>The number corresponds to entries in Figure 2-1.

<sup>b</sup>Used to derive an acute duration inhalation Minimal Risk Level (MRL) of 1 ppm; concentration divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

<sup>c</sup>Used to derive an intermediate duration inhalation Minimal Risk Level (MRL) of 0.7 ppm; concentration divided by an uncertainty factor of 300 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, 3 for human variability).

<sup>d</sup>Used to derive a chronic duration inhalation Minimal Risk Level (MRL) of 0.1 ppm; concentration divided by an uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability)

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); DNA = deoxyribonucleic acid; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x=time(s)

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat CFY	7 d 24hr/d				700 F (4/30 died)	Ungvary et al. 1980b
2	Mouse SPF-Of1	6 hr				5267 F (LC50)	Bonnet et al. 1979
3	Mouse NS	24 hr				2010 (6/10 died)	Cameron et al. 1938
<b>Systemic</b>							
4	Human	2-6 d 5-5.5hr/d	Resp Cardio Hemato	200 M 200 M 200 M			Laine et al. 1993
5	Human	7 hr	Cardio	200 M			Ogata et al. 1970
6	Human	4 d 3.67hr/d	Resp Cardio	200 M 200 M			Seppalainen et al. 1989
7	Rat Wistar	1 or 2 wk 5d/wk 6hr/d	Hepatic	750 M			Elovaara 1982
8	Rat NS	24 hr	Resp		75 M (decrease in P-450 and 7-ethoxycoumarin O-deethylase activity)		Elovaara et al. 1987
9	Rat Sprague- Dawley	3 d 6hr/d	Resp		2000 M (decreased cytochrome P-450)		Toftgard and Nielsen 1982

TABLE 2-2. Levels of Significant Exposure to *m*-Xylene - Inhalation (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
10	Rat CFY	7 d 24hr/d Gd 7-14	Hepatic  Bd Wt	700 F  350 F			Ungvary et al. 1980b
					700 F (16% decrease in body weight gain)		
11	Mouse Balb/C	6 min	Resp		2700 M (transient decrease in respiratory rate)		Korsak et al. 1990
12	Mouse Balb/c	Once 6 min	Resp			1361 M (respiratory rate decreased 50%)	Korsak et al. 1993
<b>Neurological</b>							
13	Human	2-6 d 5-5.5hr/d		200 M			Laine et al. 1993
14	Human	7 hr		200 M			Ogata et al. 1970
15	Human	2x/dose 1x/wk 4hr/x		281 M			Savolainen 1980
16	Human	4 hr				400 M (impaired body balance and impaired reaction times)	Savolainen et al. 1984
17	Human	4 d 3.67hr/d			200 M (altered visual evoked potentials)		Seppalainen et al. 1989
18	Rat Sprague- Dawley	3 d 6hr/d			2000 M (increased brain levels of catecholamine)		Andersson et al. 1981
19	Rat	6 hr				3000 M (impaired rotorod performance)	Korsak et al. 1990
20	Rat Wistar Imp:DAK	Once 4hr				1982 M (LC50 for decreased rotarod performance)	Korsak et al. 1993

TABLE 2-2. Levels of Significant Exposure to *m*-Xylene - Inhalation (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
21	Rat	4 hr				2100 M (narcosis)	Molnar et al. 1986
<b>Developmental</b>							
22	Rat	8 d 24hr/d Gd 7-14		350 F	700 F (fetal and maternal weight decreased, decreased implantation)		Ungvary et al. 1980b
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
23	Rat Wistar	3 mo 5 d/wk 6hr/d	Hemato Bd Wt	1000 M 1000 M			Korsak et al. 1992
24	Rat Wistar	6 mo 5d/wk 6h/d	Hepatic	100 M			Rydzynski et al. 1992
25	Rat Wistar	3 mo 5d/wk 6h/d	Hepatic	1000 M			Rydzynski et al. 1992
<b>Neurological</b>							
26	Rat Wistar	3 mo 5 d/wk 6hr/d			1000 M (decreased rotarod performance and spontaneous motor activity)		Korsak et al. 1992
27	Rat Wistar	6 mo 5 d/wk 6 hr/d			100 M (decreased rotarod performance and spontaneous motor activity)		Korsak et al. 1992

TABLE 2-2. Levels of Significant Exposure to *m*-Xylene - Inhalation (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
28	Mouse NMRI- BOM	7 wk 5d/wk 4hr/d			1600 F (decreased alpha-adrenergic binding in brain)		Rank 1985

<sup>a</sup>The number corresponds to entries in Figure 2-2.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); EC50 = effective concentration, 50% kill; F = female; Gd = gestation day; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = males; *m*-xylene = *meta*-xylene; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x=time(s)

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat Wistar	24 hr				3062 (1/10 died)	Cameron et al. 1938
2	Mouse SPF-Of1	6 hr				4595 F (LC50)	Bonnet et al. 1979
3	Mouse NS	24 hr				3062 (4/10 died)	Cameron et al. 1938
<b>Systemic</b>							
4	Rat Sprague- Dawley	3 d 6hr/d	Resp			2000 M (decreased cytochrome P-450)	Toftgard and Nilsen 1982
			Renal			2000 M (decreased relative kidney weight)	
5	Rat CFY	7 d 24hr/d Gd 7-14	Hepatic	700 F			Ungvary et al. 1980b
			Bd Wt	700 F			
6	Mouse Swiss Of1	5 min	Resp			1467 M (50% decrease in respiratory rate)	De Ceaurriz et al. 1981
7	Mouse Balb/C	6 min	Resp			2513 M (32% decrease in respiratory rate)	Korsak et al. 1990
<b>Neurological</b>							
8	Rat Sprague- Dawley	3 d 6hr/d				2000 M (increased brain levels of catecholamine)	Andersson et al. 1981

TABLE 2-3. Levels of Significant Exposure to *o*-Xylene - Inhalation (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
9	Rat	6 hr				3000 M (impaired rotarod performance)	Korsak et al. 1990
10	Rat	4 hr				2180 M (narcosis)	Molnar et al. 1986
11	Mouse Swiss Of1	4 hr			1010 M (altered behavior in swimming test)		De Ceaurriz et al. 1983
<b>Developmental</b>							
12	Rat CFY	8 d Gd7-14 24hr/d		35	350 (9% decrease in fetal weight)		Ungvary et al. 1980b
<b>INTERMEDIATE EXPOSURE</b>							
<b>Death</b>							
13	Monkey Squirrel	6 wk 5d/wk 8hr/d				780 M (1/3 died)	Jenkins et al. 1970
14	Rat Sprague- Dawley Long- Evans	6 wk 5d/wk 8hr/d				780 (3/15 died)	Jenkins et al. 1970

TABLE 2-3. Levels of Significant Exposure to *o*-Xylene - Inhalation (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
<b>Systemic</b>							
15	Rat Sprague- Dawley Long- Evans	90-127 d 24hr/d	Resp	78			Jenkins et al. 1970
			Cardio	78			
			Hemato	78			
			Hepatic	78			
			Renal	78			
16	Rat Sprague- Dawley Long- Evans	6 wk 5d/wk 8hr/d	Resp	780			Jenkins et al. 1970
			Cardio	780			
			Hemato	780			
			Hepatic	780			
			Renal	780			
17	Rat CFY	6 mo 7d/wk 8hr/d	Hepatic	1096 M			Tatrai et al. 1981
			Bd Wt		1096 M (12% decrease in body weight)		
<b>Neurological</b>							
18	Monkey Squirrel	6 wk 5d/wk 8hr/d		780 M			Jenkins et al. 1970

TABLE 2-3. Levels of Significant Exposure to *o*-Xylene - Inhalation (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
19	Monkey Squirrel	90-127 d 24hr/d		78 M			Jenkins et al. 1970
20	Dog Beagle	6 wk 5d/wk 8hr/d				780 M (tremor)	Jenkins et al. 1970
21	Dog Beagle	90-127 d 24hr/d		78 M			Jenkins et al. 1970
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
22	Rat CFY	1 yr 7d/wk 8hr/d	Hepatic  Bd Wt	1096 M		1096 M (12% decrease in body weight)	Tatrai et al. 1981

<sup>a</sup>The number corresponds to entries in Figure 2-3.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = female; Gd = gestation day; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; *o*-xylene = *ortho*-xylene; Resp = respiratory; wk = week(s); y = year(s)

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat Wistar	12 hr				19650 (8/10 died)	Cameron et al.
2	Rat CD	4 hr				4740 F (LC50)	Harper et al. 1975
3	Mouse SPF-Of1	6 hr				3907 F (LC50)	Bonnet et al. 1979
4	Mouse NS	12 hr.				19650 (9/10 died)	Cameron et al. 1938
<b>Systemic</b>							
5	Human	5 d 1-7.5 hr/d	Resp		100 F (nose and throat irritation)		Hake et al. 1981
			Cardio	100 F			
			Hemato	100 F			
			Renal	100 F			
			Ocular		100 F (eye irritation)		
6	Human	7 hr	Cardio	100 M			Ogata et al. 1970
7	Rat Sprague- Dawley	4 d 4hr/d	Resp		1000 F (decreased pulmonary microsomal activity)		Patel et al. 1978
8	Rat Sprague- Dawley	4 hr	Resp		1000 F (decreased pulmonary microsomal activity)		Patel et al. 1978
9	Rat NS	1, 3, or 5 d 6hr/d	Resp		300 M (transiently decreased lung surfactant levels)		Silverman and Schatz 1991

TABLE 2-4. Levels of Significant Exposure to *p*-Xylene - Inhalation (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
10	Rat Fischer-344	1 or 3 d 6hr/d	Hepatic	1600 M			Simmons et al. 1991
11	Rat Sprague- Dawley	3 d 6hr/d	Resp		2000 M (decreased cytochrome P-450)		Toftgard and Nilsen 1982
			Renal		2000 M (decreased relative kidney weight)		
12	Rat CFY	7 d 24hr/d Gd 7-14	Hepatic	700 F			Ungvary et al. 1980b
			Bd Wt	700 F			
13	Mouse Balb/C	6 min	Resp		2626 M (transient decrease in respiratory rate)		Korsak et al. 1990
14	Mouse C3H/H3J	4 d 6 hr/d	Hepatic	1208 F			Selgrade et al. 1993
			Bd Wt	1208 F			
15	Rabbit New Zealand	2 d 4hr/d	Resp		1000 M (decreased pulmonary microsomal activity)		Patel et al. 1978
<b>Neurological</b>							
16	Human	5 d 1-7.5 hr/d			100 F (dizziness)		Hake et al. 1981
17	Human	4 hr		69 M			Olson et al. 1985
18	Rat Sprague- Dawley	3 d 6hr/d			2000 M (increased brain levels of catecholamine)		Andersson et al. 1981
19	Rat Long-Evans	4 hr		800 M	1600 M (altered visual evoked potentials)		Dyer et al. 1988

TABLE 2-4. Levels of Significant Exposure to *p*-Xylene - Inhalation (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
20	Rat NS	6 hr				3000 M (impaired rotarod performance)	Korsak et al. 1990
21	Rat NS	4 hr				1940 M (narcosis)	Molnar et al. 1986
22	Rat NS	1,3,8,13 d 5d/wk 6hr/d		400 M		800 M (decreased axonal transport)	Padilla and Lyerly 1989
<b>Developmental</b>							
23	Rat Sprague- Dawley	10 d 6hr/d Gd 7-16		1612 F			Rosen et al. 1986
24	Rat CFY	8 d 24hr/d Gd 7-14			35 (skeletal retardation signs)		Ungvary et al. 1980b
25	Rat CFY	24-48 hr Gd 9 and 10				691 (27% decrease in fetal weight)	Ungvary et al. 1981

TABLE 2-4. Levels of Significant Exposure to *p*-Xylene - Inhalation (continued)

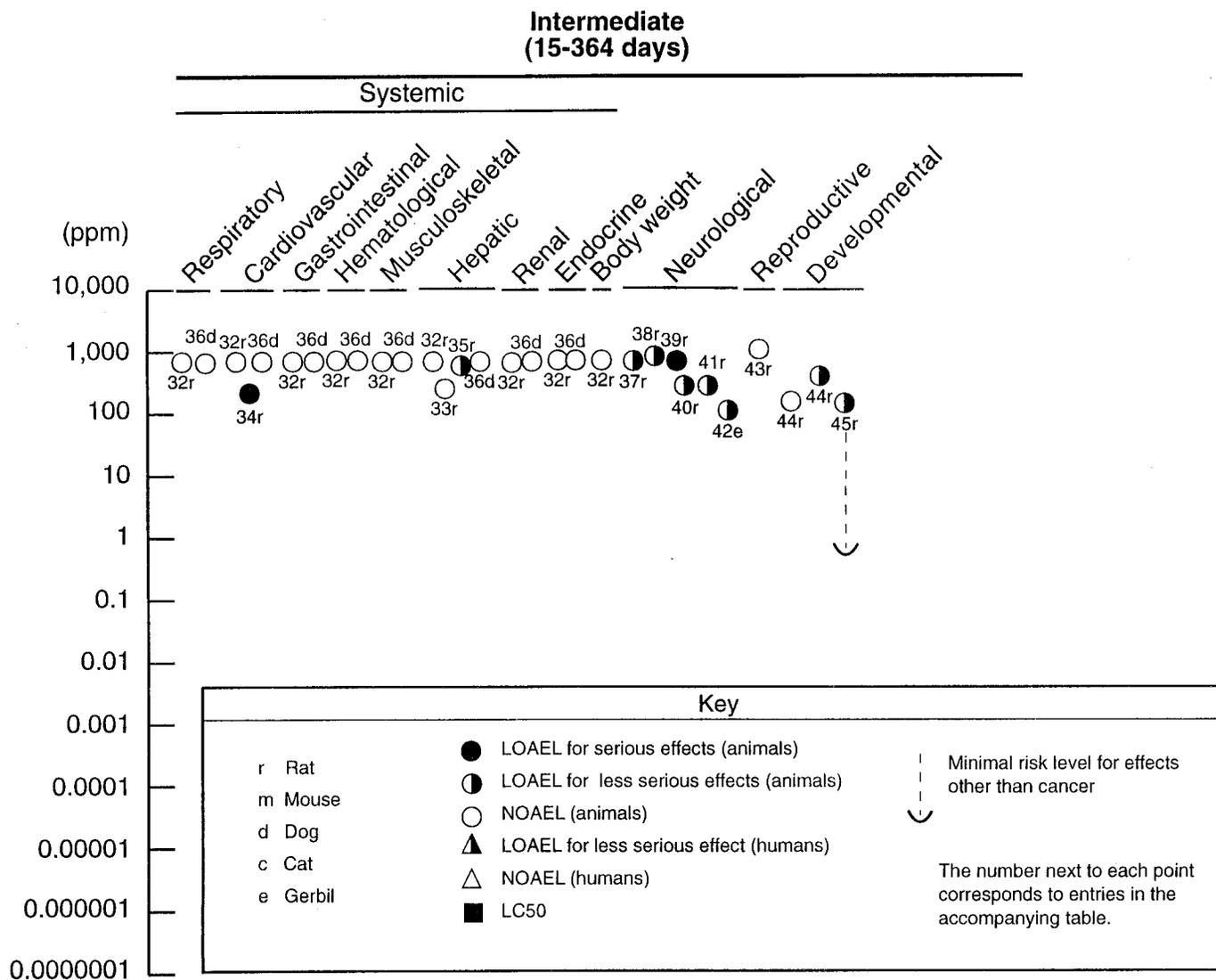
Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
26	Human	4 wk 5d/wk 1-7.5 hr/d	Resp	20 M	100 M (nose and throat irritation)		Hake et al. 1981
			Cardio	150 M			
			Hemato	150 M			
			Renal	150 M			
			Ocular	20 M	100 M (eye irritation)		
<b>Neurological</b>							
27	Human	4 wk 5d/wk 1-7.5 hr/d		150 M			Hake et al. 1981

<sup>a</sup>The number corresponds to entries in Figure 2-4.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = females; Gd = gestation day; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; *p*-xylene = *para*-xylene; Resp = respiratory; wk = week(s)



Figure 2-1. Levels of Significant Exposure to Mixed Xylene – Inhalation (continued)



**Figure 2-1. Levels of Significant Exposure to Mixed Xylene – Inhalation (continued)**

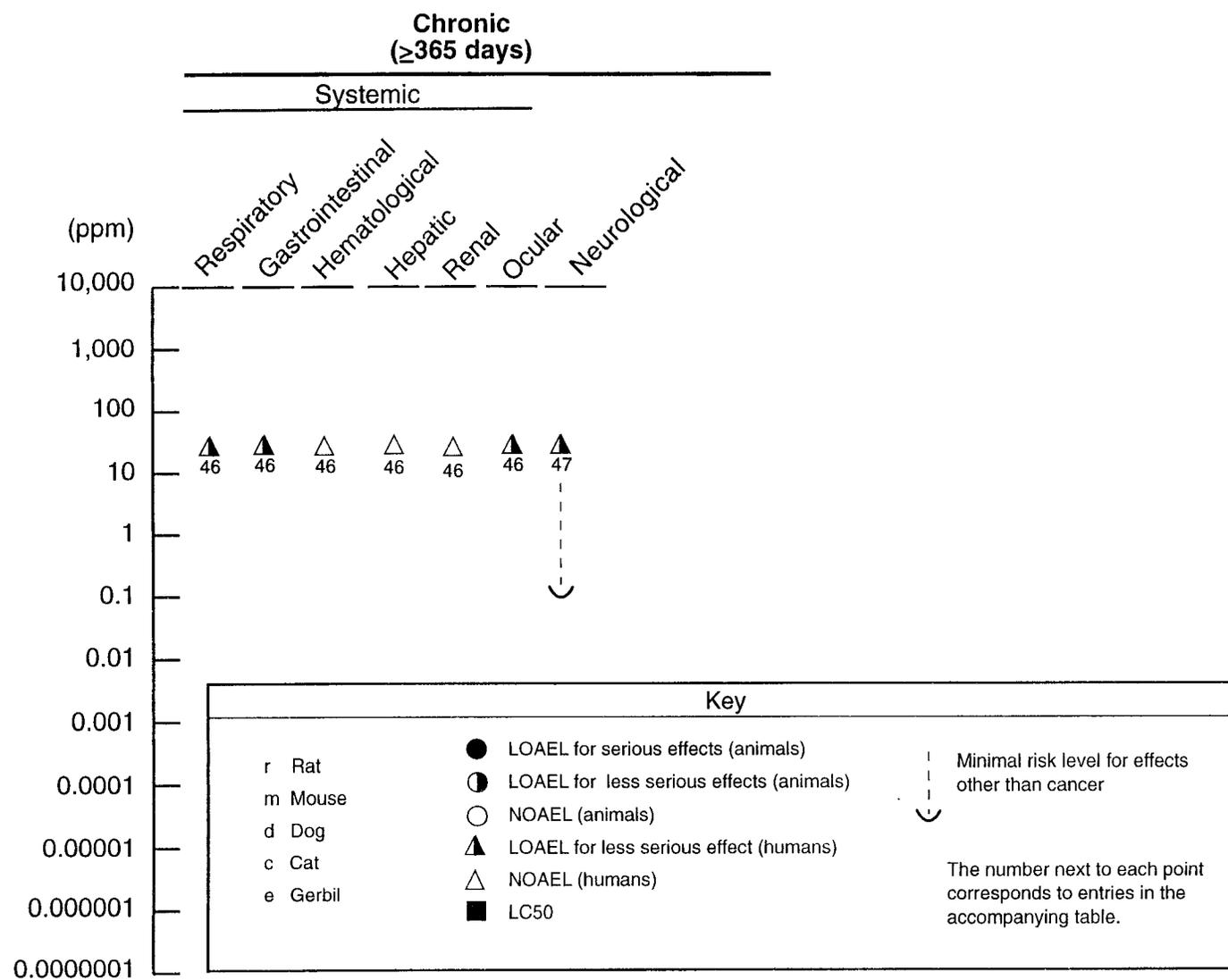
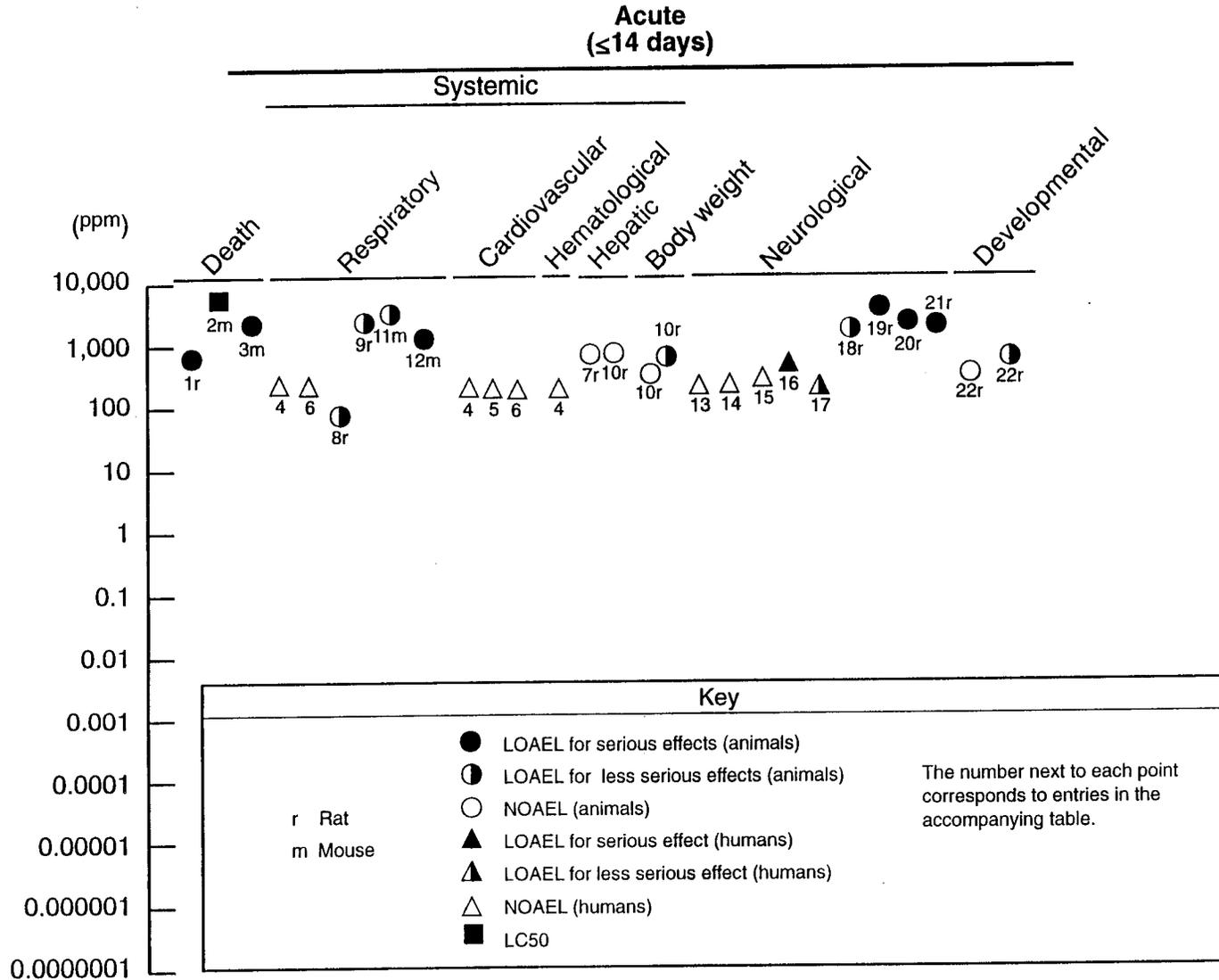
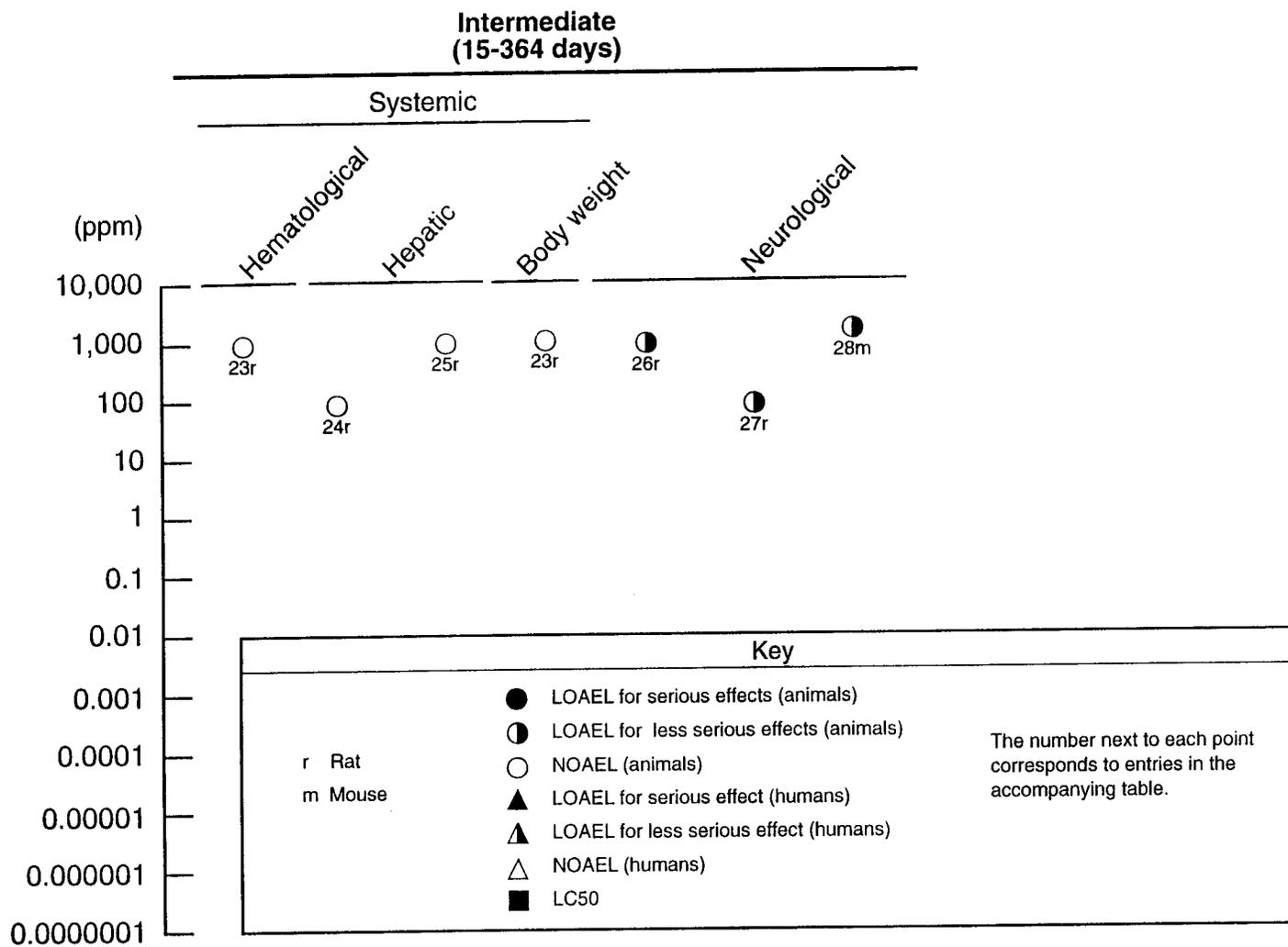


Figure 2-2. Levels of Significant Exposure to *m*-Xylene – Inhalation



**Figure 2-2. Levels of Significant Exposure to *m*-Xylene – Inhalation (continued)**



**Figure 2-3. Levels of Significant Exposure to *o*-Xylene – Inhalation**

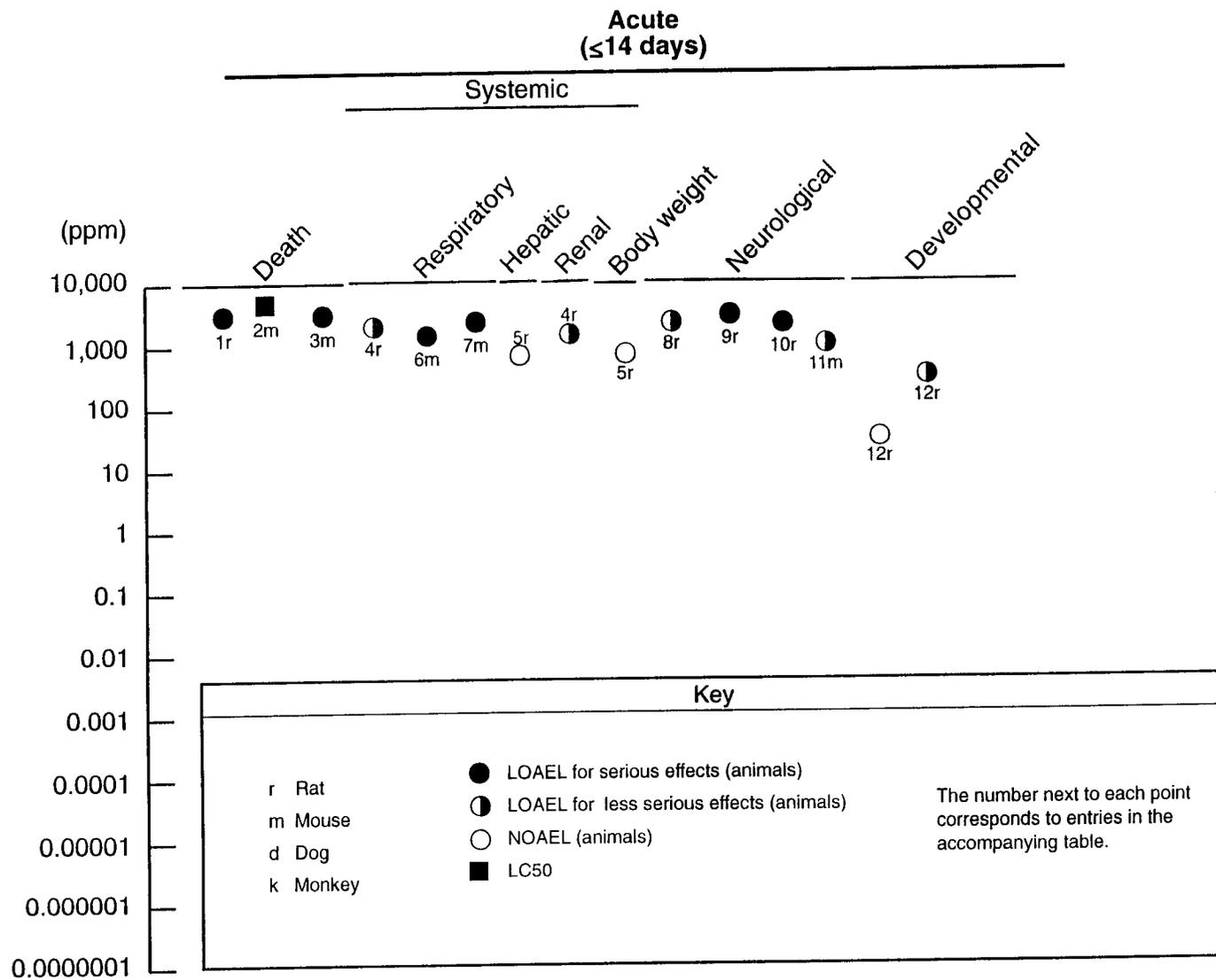


Figure 2-3. Levels of Significant Exposure to o-Xylene – Inhalation (continued)

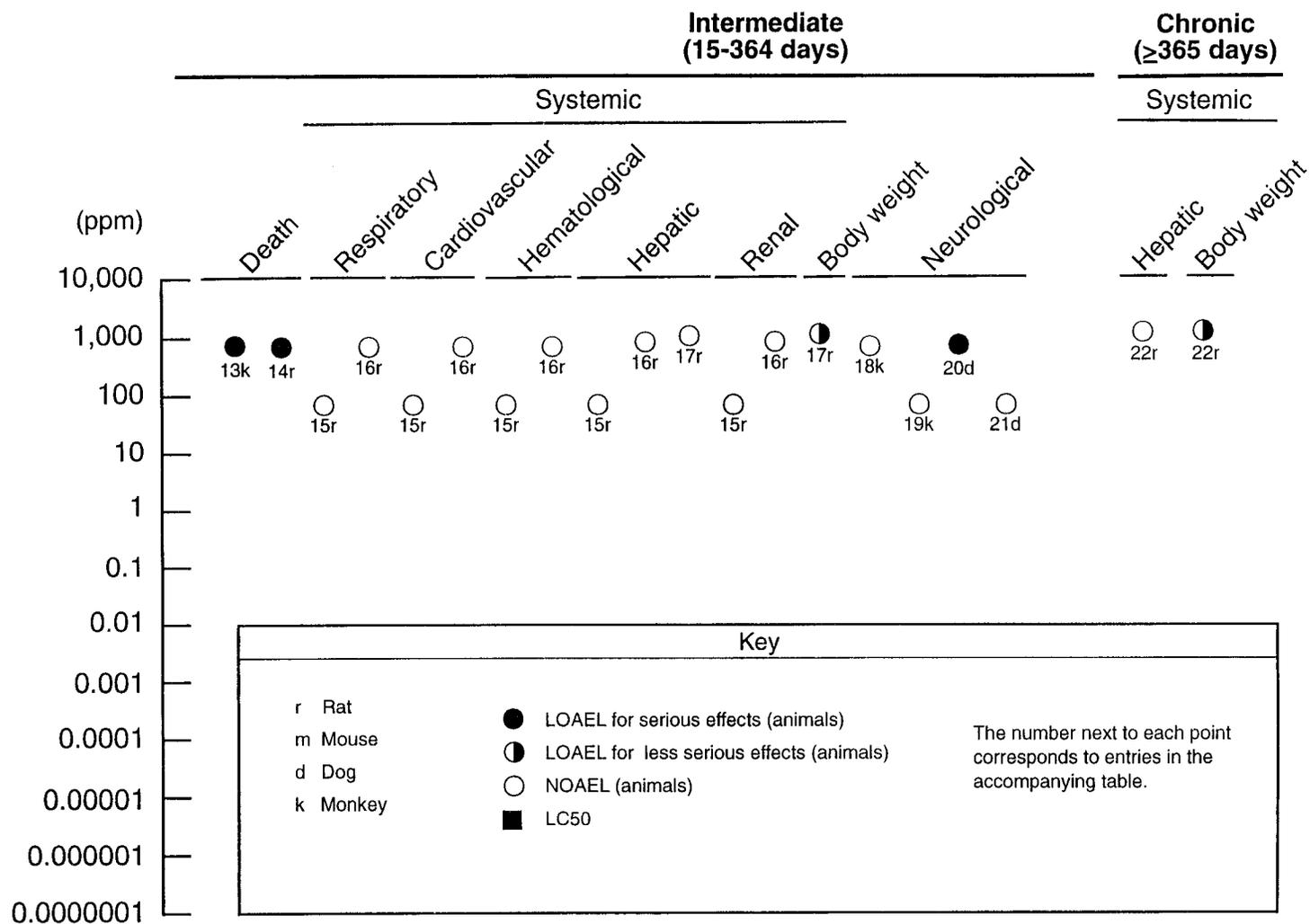
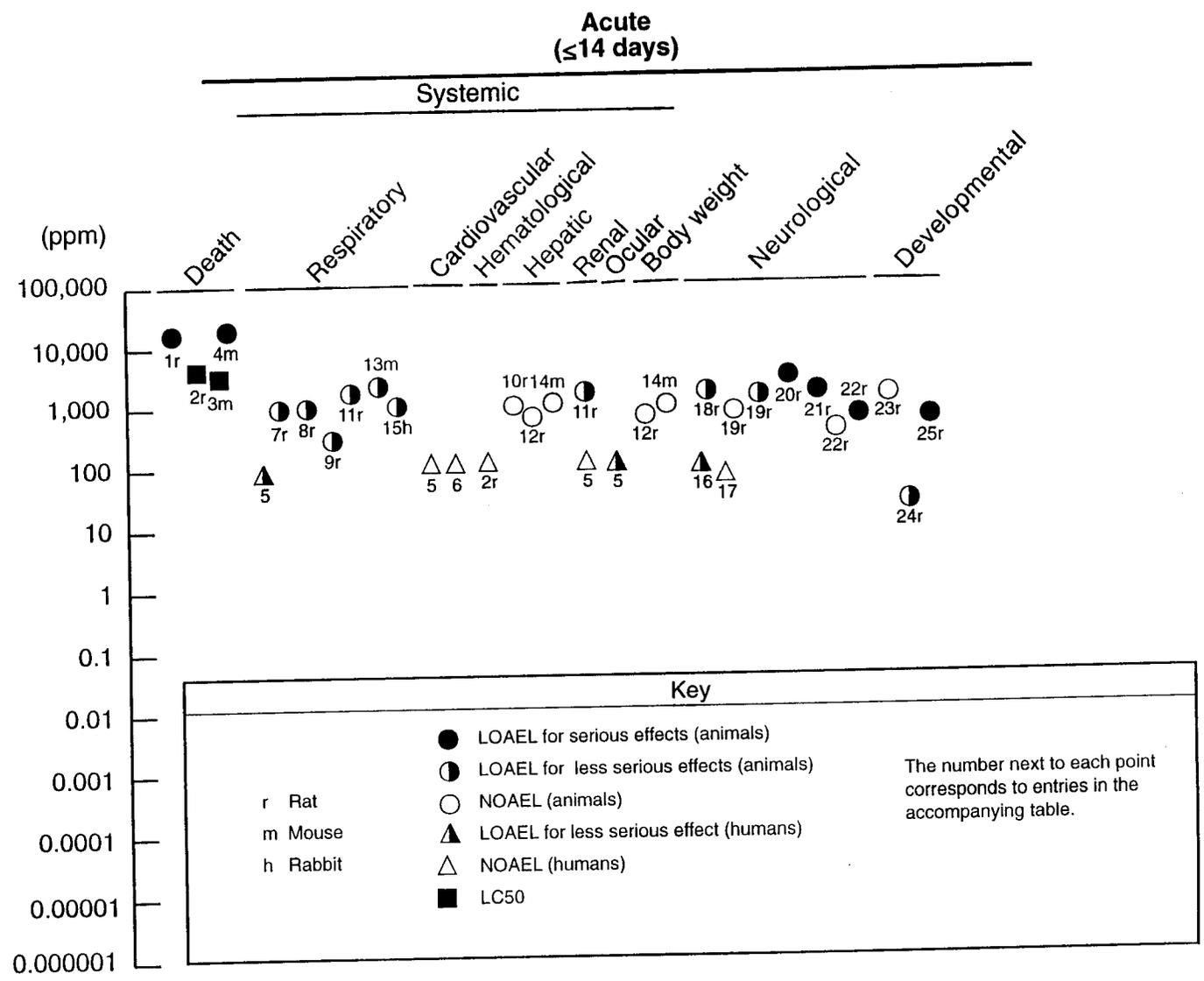
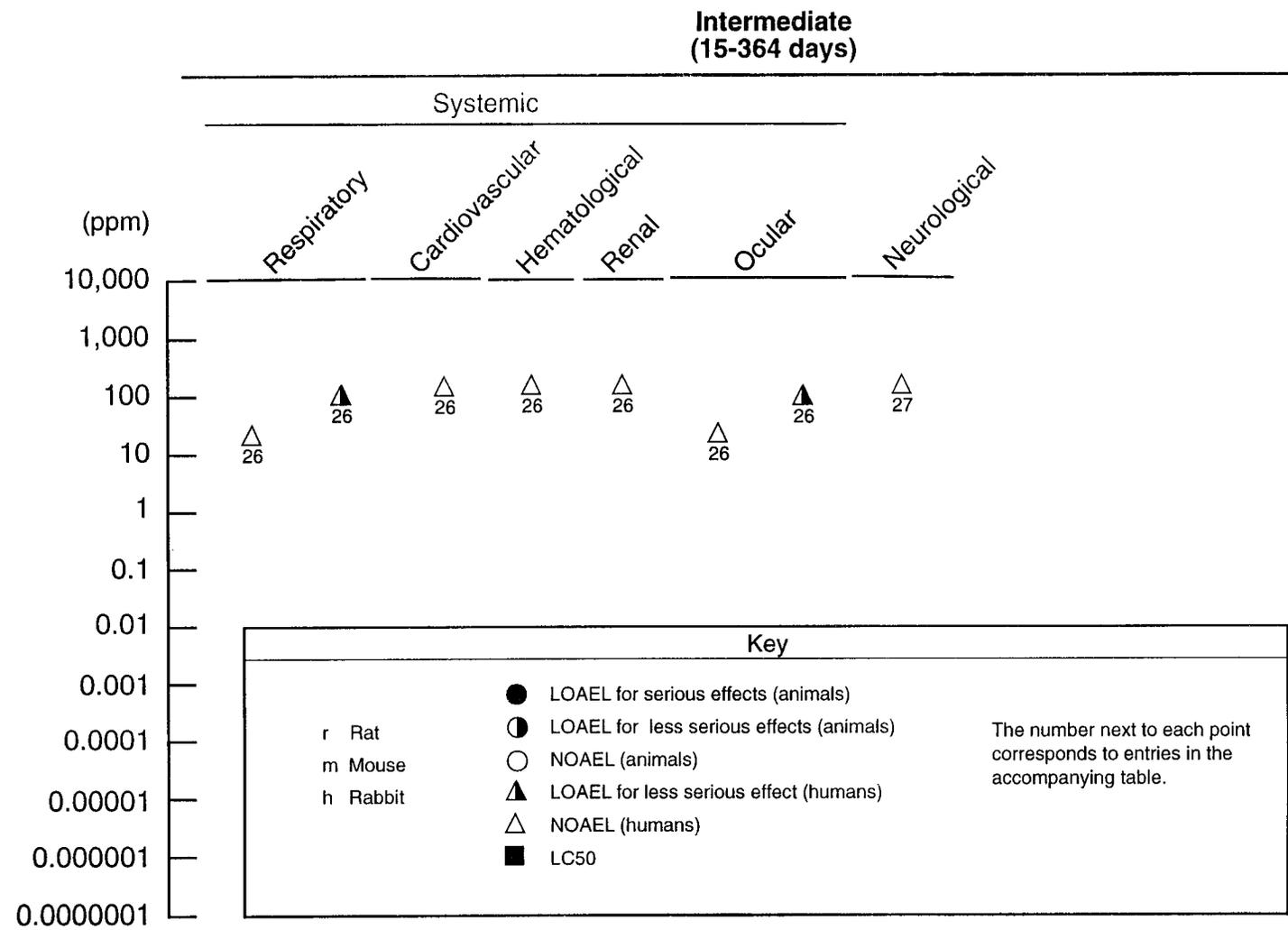


Figure 2-4. Levels of Significant Exposure to *p*-Xylene – Inhalation



**Figure 2-4. Levels of Significant Exposure to p-Xylene – Inhalation (continued)**



## 2. HEALTH EFFECTS

exposed to mixed xylene at a concentration of 396 ppm for 30 minutes (Hastings et al. 1986). Chest X-rays obtained from volunteers exposed to a time-weighted-average concentration of 200 ppm *m*-xylene for 3.67 hours/day for 4 days showed no adverse effects on the lungs (Seppalainen et al. 1989). Also, no effects on pulmonary ventilation volume were observed in volunteers exposed to 150 ppm *p*-xylene for 5 days/week in a multi-week trial (Hake et al. 1981). At much higher concentrations, however, the lung may be adversely affected. 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). Chronic occupational exposure of workers to an unspecified concentration of vapors of mixed xylene has also been associated with labored breathing and impaired pulmonary function (Hipolito 1980; Roberts et al. 1988). A significant ( $p < 0.01$ ) increase in the prevalence of nose and throat irritation was reported by workers chronically exposed to mixed xylene vapors at a geometric mean TWA concentration of 14 ppm (Uchida et al. 1993).

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. 1975a; De Ceaurriz et al. 1981; Furnas and Hine 1958; Korsak et al. 1990). Exposure to concentrations of 2,440 ppm mixed xylene for 6 minutes (Korsak et al. 1988), to 1,467 ppm *o*-xylene for 5 minutes (De Ceaurriz et al. 1981), or to 1,361 ppm *m*-xylene for 6 minutes (Korsak et al. 1993) produced a 50% decrease in respiratory rate in mice. Comparison of the individual xylene isomers showed that the irritant effects of *m*- and *o*-xylene as quantified by measurements of respiratory rate in mice are more pronounced than those of *p*-xylene, with *o*-xylene having the most prolonged effect (Korsak et al. 1990). In rats that died as a result of exposure to 9,900 ppm mixed xylene for 4 hours, atelectasis, hemorrhage, and edema of the lungs were observed (Carpenter et al. 1975a). Biochemical changes detected in the lungs after acuteduration intermittent exposure include transiently decreased lung surfactant levels at 300 ppm *p*-xylene (Silverman and Schatz 1991) and decreased pulmonary microsomal enzyme activities at 2,000 ppm mixed xylene, 75-2,000 ppm *m*-xylene, 2,000 ppm *o*-xylene, or 1,000 ppm or 3,400 ppm *p*-xylene (Day et al. 1992; Elovaara et al. 1980, 1987; Pate1 et al. 1978; Silverman and Schatz 1991; Toftgard and Nilsen 1982). The LOAEL of 75 ppm for *m*-xylene was based on decreased P-450 and 7-ethoxycoumarin *O*-deethylase activities noted in the lungs of rats exposed for 24 hours (Elovaara et al. 1987). The decrease in pulmonary microsomal activity by selective inactivation of enzymes can

## 2. HEALTH EFFECTS

result from damage to lung tissue caused by the toxic metabolite of xylene, a methylbenzaldehyde (Carlone and Fouts 1974; Pate1 et al. 1978; Smith et al. 1982); the selective inactivation of enzymes may also result in anoxia. No histopathological changes in the lungs were evident in rats, dogs, guinea pigs, or monkeys following intermediate exposure for 90-127 days to concentrations of 78 ppm *o*-xylene on a continuous basis (Jenkins et al. 1970) or 13 weeks to 810 ppm mixed or 6 weeks to 780 ppm *o*-xylene, 5 weeks to 300 ppm *m*-xylene, or for 5 days to 300 ppm *p*-xylene on an intermittent basis (Carpenter et al. 1975a; Elovaara et al. 1987; Jenkins et al. 1970; Silverman and Schatz 1991). No animal studies were located that evaluated the respiratory effects of mixed xylene or single xylene isomers following chronic inhalation exposure.

**Cardiovascular Effects.** Limited human data are available regarding the cardiovascular effects of xylene following inhalation exposure. Although tachycardia was reported by one of nine persons exposed to unidentified levels of xylene as a result of its use in a sealant in a heating duct, no effects on heart rate, blood pressure, or cardiac function were noted in humans exposed for an acute duration (of 70 minutes to 7 hours) to up to 299 ppm mixed xylene (Gamberale et al. 1978), 200 ppm *m*-xylene (Ogata et al. 1970; Seppalainen et al. 1989), or 150 ppm *p*-xylene (Hake et al. 1981; Ogata et al. 1970). Furthermore, two survivors exposed to an estimated 10,000 ppm xylene in an industrial accident had normal pulse, blood pressure, and heart sounds upon hospitalization. Chronic occupational exposure to xylene along with other chemical agents has resulted in complaints of heart palpitations, chest pain, and an abnormal electrocardiogram (ECG) (Hipolito 1980; Kilbum et al. 1985). However, the contribution of other chemical exposures to these effects cannot be eliminated.

Data regarding cardiovascular effects in animals are limited. Morphological changes in coronary microvessels (increased wall thickness) was noted in rats exposed to 230 ppm xylene (unspecified composition) for 4 weeks (Morvai et al. 1987). Other effects seen in rats inhaling unspecified (lethal) concentrations of xylene of unknown composition included ventricular repolarization disturbances and occasional arrhythmias; however, the toxicity of unknown components is not known (Morvai et al. 1976). However, no adverse effects on the heart were observed upon histopathological examination of rats and dogs exposed intermittently for 10-13 weeks to mixed xylene at concentrations as high as 810 ppm (Carpenter et al. 1975a) or rats, guinea pigs, dogs, or monkeys exposed to *o*-xylene at 78 ppm on a continuous basis for 90-127 days or 780 ppm on an intermittent basis for 6 weeks (Jenkins et al. 1970). No information was located regarding cardiovascular effects in animals after chronic exposure to mixed xylene or its individual isomers.

## 2. HEALTH EFFECTS

**Gastrointestinal Effects.** Symptoms of nausea, vomiting, and gastric discomfort have been noted in workers exposed to xylene vapors (concentration unspecified) (Goldie 1960; Hipolito 1980; Klaucke et al. 1982; Nersesian et al. 1985; Uchida et al. 1993). These symptoms subsided after cessation of the xylene exposure. Anorexia and vomiting were also observed in a patient admitted to the hospital after sniffing paint containing xylene and other unknown substances over a 2-week period in an effort to become intoxicated (Martinez et al. 1989).

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 13 weeks (Carpenter et al. 1975a). 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 data are limited regarding the effects of xylene on the blood. Hemoglobin content of the blood was unaffected in two workers exposed to an estimated 10,000 ppm of mixed xylene in an industrial accident (Morley et al. 1970). Female volunteers had normal blood counts after exposure to 100 ppm *p*-xylene for 1-7.5 hours/day for 5 days (Hake et al. 1981). Decreased white blood cell counts were observed in two women with chronic occupational exposure to xylene (Hipolito 1980; Moszczynsky and Lisiewicz 1983, 1984a), but exposure to other chemicals cannot be ruled out as an alternative explanation for the effects observed.

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 as well. Because benzene is an agent known to cause leukemia and other blood dyscrasias in humans, these effects cannot be solely attributed to xylene (ECETOC 1986).

An occupational study in which no benzene exposure was involved (Uchida et al. 1993) found no hematological effects (RBC, WBC and platelet counts, and hemoglobin concentrations were unchanged). Workers (175) were exposed to a geometric mean TWA of 14 ppm xylene for an average of 7 years, and mixed xylene exposure accounted for 70% or more of the total exposure (Uchida et al. 1993). This study suggests that occupational exposure to relatively low concentrations of xylenes does not cause hematological effects.

## 2. HEALTH EFFECTS

No effect on erythrocyte fragility was observed in rats exposed to 15,000 ppm mixed xylene for 45 minutes (Carpenter et al. 1975a). No adverse hematological effects have been observed in rats exposed to 2,764 ppm mixed xylene for 5 hours/day for 9 days (Wronska-Nofer et al. 1991). Similarly, no effects on hematological parameters were observed in rats or dogs following intermediate-duration intermittent exposure to concentrations as high as 810 ppm of mixed xylene (Carpenter et al. 1975a) or in guinea pigs exposed to 78 ppm *o*-xylene continuously or 780 ppm *o*-xylene intermittently (Jenkins et al. 1970) for an intermediate duration. Increases in leukocyte count were reported in rats and dogs exposed intermittently to 780 ppm *o*-xylene for 6 weeks (Jenkins et al. 1970), but it is unknown whether these increases were statistically significant.

**Musculoskeletal Effects.** A 1993 occupational study indicates that workers exposed to xylenes (geometric mean TWA 14 ppm) reported reduced grasping power and reduced muscle power in the extremities more frequently than the unexposed controls (Uchida et al. 1993). This effect was a neurological effect rather than a direct effect on the muscles. No additional data were available regarding musculoskeletal effects in humans following inhalation exposure to mixed xylene or its individual isomers. Animal data regarding musculoskeletal effects following xylene inhalation are limited but provide no indication that xylene produces musculoskeletal effects. No lesions were observed in the skeletal muscle of rats and dogs exposed for an intermediate exposure to concentrations as high as 810 ppm mixed xylene (Carpenter et al. 1975a).

**Hepatic Effects.** Human data regarding hepatic effects following inhalation of xyiene are limited to several case and occupational studies that include exposure to other compounds (Dolara et al. 1982; Klaucke et al. 1982; Kurppa and Husman 1982; Morley et al. 1970; Uchida et al. 1993). Two of these studies suggest that acute-duration exposure to high levels of xylene may result in hepatic toxicity. Two painters who survived exposure to an estimated 10,000 ppm of xylene and several workers who were exposed to an estimated 700 ppm of xylene had transiently elevated serum transaminase levels (Klaucke et al. 1982; Morley et al. 1970). The one painter that died had hepatocellular vacuolation following exposure to xylene for 18.5 hours. D-Glucaric acid levels were increased in the urine of workers exposed to toluene, xylene, and pigments (Dolara et al. 1982). Urinary glucaric acid has been correlated with liver cytochrome P-450 and serum gamma-glutamyltranspeptidase activity (Dolara et al. 1982). An occupational study in which workers were exposed an average of 7 years to greater than 70% mixed xylenes (geometric mean TWA 14 ppm) found no changes in serum biochemistry values which reflect liver function (total bilirubin, aspartate aminotransferase, alanine aminotransferase,

## 2. HEALTH EFFECTS

gamma glutamyl transpeptidase, alkaline phosphatase, and leucine aminopeptidase) (Uchida et al. 1993). This study suggests that low-level occupational exposure to xylenes does not result in hepatic effects.

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 increased hepatic cytochrome P-450 content in rats (Elovaara 1982; Elovaara et al. 1980; Pate1 et al. 1979; Savolainen et al. 1978; Selgrade et al. 1993; Toftgard and Nilsen 1981, 1982; Toftgard et al. 1981; Ungvary et al. 1980a). Following acute exposures to mixed xylene (Savolainen et al. 1978; Ungvary 1990; Wisniewska-Knypl et al. 1989), *m*-xylene (Elovaara 1982; Ungvary et al. 1980b), *o*-xylene (Tatrai and Ungvary 1980; Ungvary et al. 1980a), or *p*-xylene (Pate1 et al. 1979; Simmons et al. 1991; Ungvary et al. 1980b), effects have been observed including increased relative liver weight (Simmons et al. 1991; Tatrai and Ungvary 1980; Ungvary et al. 1980a, 1980b), cytochrome P-450 content (Simmons et al. 1991; Ungvary 1990; Ungvary et al. 1980a; Wisniewska-Knypl et al. 1989), microsomal protein (Elovaara 1982), microsomal enzyme activity (Elovaara 1982; Savolainen et al. 1978; Ungvary 1990; Ungvary et al. 1980a; Wisniewska-Knypl et al. 1989), proliferation of the endoplasmic reticulum (Ungvary 1990; Wisniewska-Knypl et al. 1989), and decreased hexobarbital sleep time (Ungvary 1990; Ungvary et al. 1980a). Similar changes were observed in rabbits and mice (Ungvary 1990). Although histopathological examination of livers in most studies showed no adverse effects (Elovaara 1982; Simmons et al. 1991; Ungvary et al. 1980b), minor histopathological changes suggesting mild hepatic toxicity included decreased glycogen content, dilation of the cisterns of the rough endoplasmic reticulum, separation of ribosomes from the membranes, variously shaped mitochondria, and increased autophagous bodies (Tatrai and Ungvary 1980; Ungvary 1990). Also, increased serum transaminases were observed following a 4-hour exposure of rats to 1,000 ppm *p*-xylene (Pate1 et al. 1979).

Many similar hepatic effects appear after intermediate exposure to mixed xylene or *o*-xylene. They include increased absolute and/or relative hepatic weight in rats (Kyrklund et al. 1987; Tatrai and Ungvary 1980; Tatrai et al. 1981; Toftgard et al. 1981; Ungvary 1990; Ungvary et al. 1980a), cytochrome P-450 (Tatrai et al. 1981; Ungvary 1990; Ungvary et al. 1980a); microsomal enzyme activity (Elovaara et al. 1980, 1987; Tatrai et al. 1981; Toftgard et al. 1981; Ungvary 1990; Ungvary et al. 1980a), and proliferation of the smooth and rough endoplasmic reticulum (Rydzynski et al. 1992; Tatrai and Ungvary 1980; Tatrai et al. 1981; Ungvary 1990) and decreased hexobarbital sleeping time (Tatrai et al. 1981; Ungvary 1990; Ungvary et al. 1980a). Similar effects were observed in rabbits and

## 2. HEALTH EFFECTS

mice (Ungvary 1990). As in the acute studies, several intermediate studies in rats, guinea pigs, monkeys, or dogs, reported no effect on serum transaminases (Carpenter et al. 1975a; Tatrai et al. 1981) or hepatic morphology (Carpenter et al. 1975a; Jenkins et al. 1970). Ultrastructural examination of livers showed only minor changes: decreased hepatic glycogen in rats (Tatrai and Ungvary 1980; Ungvary 1990; Ungvary et al. 1980b), ultrastructural changes in hepatic rough endoplasmic reticulum and mitochondria in rats (Tatrai and Ungvary 1980; Ungvary 1990), increased autophagous bodies (Tatrai et al. 1981; Ungvary 1990), and changes in the distribution of hepatocellular nuclei in rats (Tatrai and Ungvary 1980).

Increased liver weight and microsomal enzyme activity were reported in a study in which rats were exposed to 1,096 ppm *o*-xylene for one year (Tatrai et al. 1981). Electron microscopic examination of liver revealed a proliferation of the endoplasmic reticulum and only very minor toxic effects on mitochondria as exemplified by increased numbers of peroxisomes. Therefore, these effects were considered as adaptive changes.

**Renal Effects.** Although urinalyses (using a dip-stick technique) of volunteers exposed to *p*-xylene at 100 ppm for 5 days or up to 150 ppm in a multi-week exposure paradigm showed no adverse effects on the kidneys (Hake et al. 1981), limited data from case reports and occupational studies suggest that inhalation exposure to solvent mixtures containing xylene may be associated with adverse renal effects in humans (Askergren 1981, 1982; Franchini et al. 1983; Martinez et al. 1989; Morley et al. 1970). These effects included increased blood urea (Morley et al. 1970), distal renal tubular acidemia (Martinez et al. 1989), decreased urinary clearance of endogenous creatinine (Morley et al. 1970), increased urinary levels of  $\beta$ -glucuronidase (Franchini et al. 1983), and increased urinary excretion of albumin, erythrocytes, and leukocytes (Askergren 1981, 1982). However, no definitive conclusions can be made from these renal effects from xylene inhalation exposure because of confounding exposures to other solvents.

In an occupational study in which the exposure was predominantly to mixed xylenes (geometric mean TWA 14 ppm) (Uchida et al. 1993), no effects on measures of kidney function (serum creatinine or urinalysis for urobilinogen, sugar, protein, and occult bleeding) were noted. This study suggests that low-level occupational exposure to xylenes does not result in kidney effects.

## 2. HEALTH EFFECTS

The renal effects of mixed xylene and *o*-xylene following inhalation exposure have been evaluated in acute and intermediate studies with rats, guinea pigs, dogs, and monkeys (Carpenter et al. 1975a; 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 13 weeks and 90-127 days, respectively (Carpenter et al. 1975a; Jenkins et al. 1970).

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

**Endocrine Effects.** No human data were available regarding endocrine effects following inhalation exposure to mixed xylene or xylene isomers. Inhalation exposure to 810 ppm mixed xylene for 13 weeks produced no adverse adrenal, thyroid, or parathyroid effects in the dog (Carpenter et al. 1975a).

**Ocular Effects.** Human data indicate that acute inhalation exposures to 460 ppm mixed xylene and 100 ppm *p*-xylene vapors produce mild and transient eye irritation (Carpenter et al. 1975a; Hake et al. 1981; Hastings et al. 1986; Klaucke et al. 1982; Nelson et al. 1943; Nersesian et al. 1985). This effect is probably the result of direct contact of the xylene vapor with the eye and as such is described under Ocular Effects in Section 2.2.3.2.

No animal data were available regarding ocular effects following inhalation exposure to mixed xylenes or xylene isomers.

**Body Weight Effects.** No studies were located regarding body weight effects in humans following inhalation exposure to mixed xylenes or xylene isomers.

A number of intermediate-duration intermittent inhalation studies of xylene have examined body weight effects in animals (Carpenter et al. 1975a; Korsak et al. 1992; Rosengren et al. 1986; Tatrai et

## 2. HEALTH EFFECTS

al. 1981). Except for the study by Tatrai et al. (1981) in which a 12% decrease in body weight was observed in rats exposed to 1,096 ppm, no significant effects on body weight were noted.

**Metabolic Effects.** Metabolic acidosis was reported in a man who sniffed paint containing xylenes (Martinez et al. 1989). However, other components in the paint may have contributed to this metabolic effect. Additional data concerning metabolic effects following inhalation exposure of humans or animals to xylenes were not available.

### 2.2.1.3 Immunological and Lymphoreticular Effects

Limited data were available regarding immunological and lymphoreticular effects of xylene in humans. Decreased lymphocytes (Moszczynsky and Lisiewicz 1983, 1984a) and decreased serum complement (Smolik et al. 1973) have been observed in workers exposed to xylene. However, no determination can be made regarding the association between inhalation of xylene and immunological effects from the available human studies, because workers were concurrently exposed to other chemical agents.

Acute exposure (4 days, 4 hours/day) of mice to 1,208 ppm *p*-xylene had no effect on natural killer cell activity, although mortality from murine cytomegalovirus was increased (Selgrade et al. 1993). The investigators (Selgrade et al. 1993) attributed the enhanced virus susceptibility to increased liver toxicity rather than to an effect on the immune system. Intermittent exposure of rats and dogs to mixed xylenes for 10 or 13 weeks resulted in no effect on spleen weight (Carpenter et al. 1975a). No additional data were located concerning immunological and lymphoreticular effects in animals exposed to xylenes.

### 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 (Carpenter et al. 1975a; Dudek et al. 1990; Gamberale et al. 1978; Riihimaki and Savolainen 1980; Savoianen and Linnavuo 1979; Savolainen and Riihimaki 1981a; Savolainen et al. 1979b, 1984, 1985a).

## 2. HEALTH EFFECTS

Dizziness was reported by the majority of subjects exposed to 690 ppm mixed xylene for 15 minutes, but in only one of six persons exposed at 460 ppm (Carpenter et al. 1975a). Likewise, no impairment in performance tests was observed in sedentary subjects exposed at 299 ppm for 70 minutes (15 men) (Gamberale et al. 1978) or at 396 ppm for 30 minutes (10 men) (Hastings et al. 1986). However, in some cases, decrements in some neuronal functions have been observed at lower concentrations. Thus exposure to 100 ppm mixed xylene for 4 hours resulted in prolonged reaction time (Dudek et al. 1990) and exposure to 299 ppm mixed xylene for 70 minutes during exercise resulted in impaired short-term memory and reaction time (Gamberale et al. 1978). The difference between the effects in the absence and presence of exercise may be due to increased xylene respiratory uptake during exercise. Based on the LOAEL of 100 ppm for prolonged reaction times (Dudek et al. 1990), an acute-duration MRL of 1 ppm has been derived for mixed xylenes as presented in Table 2-1 and Figure 2-1.

Electroencephalograms obtained from 9 men exposed to *m*-xylene at 200 ppm (TWA) for 4 hours showed only minor changes (Seppalainen et al. 1991). These changes were characterized as a slight increase in alpha-wave frequency and percentage early in the exposure period and a decrease in exercise-induced increases in theta and delta waves indicating central nervous system effects. Studies using the *m*-isomer of xylene have also indicated that some tolerance may occur during acute exposures. While exposure to stable concentrations of *m*-xylene for 7 hours or 4 hours, twice a week in the range of up to approximately 280 ppm had no effect on body sway, coordination, or reaction time (Ogata et al. 1970; Savolainen 1980; Savolainen et al. 1980b), exposure for 6 hours or 6-9 days to levels fluctuating between 64 and 400 ppm produced impairment in human body balance and/or reaction time (Savolainen and Linnavuo 1979; Savolainen and Riihimaki 1981a; Savolainen et al. 1979b, 1980a, 1984, 1985a). A 3-hour exposure of nine male volunteers to *m*-xylene at 200 ppm during exercise resulted in a slight but significant ( $p < 0.05$ ) change in the N135 component of a pattern visual evoked potential (Seppalainen et al. 1989). Laine et al. (1993) saw no clear effects on visual reaction times or auditory choice reaction times in nine male volunteers exposed to levels of *m*-xylene fluctuating between 135 and 400 ppm (TWA 200 ppm) with or without exercise. Levels of *m*-xylene fluctuating between 135 and 400 ppm produced a slight decrease in the latency of visual evoked potentials (Seppalainen et al. 1989), but no clear effects on visual reaction times or auditory choice reaction times (Laine et al. 1993).

Objective measures of neurological function (electroencephalography, tests of motor activity and cognitive performance) in humans are not affected by acute or intermediate, intermittent or continuous

## 2. HEALTH EFFECTS

inhalation exposure to *p*-xylene for 4 hours or up to 7 hours for 5 days at concentrations ranging from 69 to 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 variability in results. However, some sex difference in subjective reports of central nervous system effects was observed (Hake et al. 1981). Three women exposed to *p*-xylene at 100 ppm for 1-7.5 hours/day, for 5 days, showed no effects on electroencephalograms, evoked potentials, or cognitive performance, but frequently reported headache and dizziness as a result of exposure (Hake et al. 1981). In contrast, four men exposed at concentrations of up to 150 ppm *p*-xylene under the same exposure conditions reported no increase in headaches or dizziness.

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; however, most studies are difficult to evaluate because the exposure conditions either have not been well characterized or the subjects may have been exposed to other chemicals in addition to xylene. The neurological symptoms observed include headache, nausea, dizziness, difficulty concentrating, impaired memory, slurred speech, ataxia, fatigue, agitation, confusion, tremors, labored breathing, and sensitivity to noise (Arthur and Curnock 1982; Goldie 1960; Gupta et al. 1990; Hipolito 1980; Klaucke et al. 1982; Martinez et al. 1989; Morley et al. 1970; Nersesian et al. 1985; Roberts et al. 1988; Uchida et al. 1993). 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 Cumock 1982; Goldie 1960; Martinez et al. 1989; Morley et al. 1970). Long-term exposure (10-44 years) of 83 spray painters to mixed solvents (predominantly below the TLVs) was associated with an increase ( $p \leq 0.05$ ) in depression and "loss of interest," but no significant effects on psychological performance tests or CAT-scan measures of brain atrophy were found (Triebig et al. 1992a, 1992b). Because other chemicals were present with xylenes in many of these studies, the effects observed cannot be conclusively attributed to xylene exposure.

In the study in which xylene exposure was most well defined (Uchida et al. 1993), 175 workers in a Chinese factory exposed for an average of 7 years reported an increase in subjective symptoms including an increased prevalence of anxiety, forgetfulness, inability to concentrate, and dizziness. Xylene levels, measured with a diffusive sampler, indicated that these workers were exposed to mixed

## 2. HEALTH EFFECTS

xylenes at an average TWA of 21 ppm (14 ppm geometric mean). Xylenes accounted for >70% of the total exposure, with *m*-xylene accounting for 50% of the xylene exposure, followed by *p*- and *o*-xylenes. Toluene and ethylbenzene levels were about 1 and 3 ppm, respectively, with no benzene exposure. Based on the subjective effects (Uchida et al. 1993), a chronic MRL of 0.1 ppm was derived for mixed xylene as presented in Table 2-1 and Figure 2-1.

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, dogs, cats, 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, altered visual evoked potentials, elevated auditory thresholds, hearing loss, and decreased acetylcholine in midbrain and norepinephrine in hypothalamus (suggestive of effect on motor control, sleep, and memory maintenance) (Andersson et al. 1981; Bushnell 1989; Carpenter et al. 1975a; De Ceaurriz et al. 1983; Fumas and Hine 1958; Ghosh et al. 1987; Honma et al. 1983; Korsak et al. 1988, 1990; 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 exposures to concentrations inducing behavioral changes in rats and mice ranged from 114 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 unspecified levels of mixed xylene resulted in respiratory paralysis (Morvai et al. 1976), 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. 1975a). Impaired rotarod performance was observed in rats exposed to mixed xylene and the individual xylene isomers at concentrations of 3,000 ppm and above (Korsak et al. 1990). 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 3 days after exposures had ceased. At 1,600 ppm, however, the decrease in axonal transport persisted for 13 days after exposure. All three xylene isomers produced narcosis in rats after 1-4 hours of 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

## 2. HEALTH EFFECTS

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 in conditioned avoidance test. 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 these catecholamines in the hypothalamus of rats were also increased following inhalation of 2,000 ppm *m*-xylene, *o*-xylene, 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 deoxyribonucleic acid (DNA) and/or astroglial proteins increased in rats (at 300-320 ppm) and gerbils (at 160 ppm) after intermediate continuous exposure of 3-4.5 months to xylene (Rosengren et al. 1986; Savolainen and Seppalainen 1979). In addition, increased levels of brain enzymes, changes in 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 mixed xylene (Pryor et al. 1987). Alterations in neurotransmitter levels were observed in some brain areas at 800 ppm mixed xylene for 30 days (Honma et al. 1983). However, no significant long-term alterations in fatty acid levels were noted in the brains of rats after intermediate exposure of 30 or 90 days to 320 ppm mixed xylene (Kyrklund et al. 1987). At 1,600 ppm *m*-xylene for 7 weeks, decreased  $\alpha$ -adrenergic binding compared to the controls was observed in the hypothalamus of exposed mice (Rank 1985). Rats exposed to 100 ppm *m*-xylene intermittently for 3 months or to 1,000 ppm for 6 months showed decreased rotarod performance and decreased spontaneous activity (Korsak et al. 1992). The effect was greater following the 3-month exposure at 1,000 ppm than the 6-month exposure at 100 ppm suggesting that for effects on motor activity, concentration is more important than duration of exposure. No behavioral signs of xylene intoxication were observed in dogs or monkeys exposed continuously to 78 ppm *o*-xylene for up to 127 days, but dogs exposed to 780 ppm *o*-xylene intermittently for 6 weeks exhibited tremors during exposure (Jenkins et al. 1970).

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

## 2. HEALTH EFFECTS

The highest NOAEL values and all LOAEL values for each reliable study for neurological effects in each species and duration category are recorded in Tables 2-1, 2-2, 2-3, and 2-4 and plotted in Figures 2-1, 2-2, 2-3, and 2-4.

### 2.2.1.5 Reproductive Effects

Spontaneous abortions were increased among 37 women exposed to xylene and formalin in pathology or histology laboratories (Taskinen et al. 1994). The contribution of xylene to this effect cannot be determined. No additional studies were located regarding reproductive effects in humans following inhalation exposure to mixed xylene or to xylene isomers.

Continuous exposure of CFY rats for 8 days on days 7-14 during pregnancy to 775 ppm mixed xylene produced an increased number of resorptions without any maternal toxicity; reduced fertility was also observed (Balogh et al. 1982). However, no adverse reproductive effects were noted following inhalation exposure of male and female CD rats to mixed xylene at concentrations as high as 500 ppm during pre-mating, mating, pregnancy, and lactation (Bio/dynamics 1983). Inhalation exposure of male Sprague-Dawley rats to 1,000 ppm mixed xylene for 61 days produced no alterations in testes, accessory glands or circulating male hormone levels (Nylen et al. 1989). Strain differences may account for the differential response to mixed xylene in these studies. The highest NOAEL and LOAEL values for each reliable study for reproductive effects in rat for each duration category are recorded in Table 2-1 and plotted in Figure 2-1.

### 2.2.1.6 Developmental Effects

Although the human data regarding the developmental effects of xylene suggest a possible relationship between solvent (unspecified) exposure and developmental toxicity (Holmberg and Nurminen 1980; Kucera 1968; Taskinen et al. 1989; Windham et al. 1991), these data are limited for assessing the relationship between inhalation of xylene and developmental effects because the available studies involved concurrent exposure to other solvents in addition to xylene in the workplace (Holmberg and Nurminen 1980; Kucera 1968; Taskinen et al. 1989; Windham et al. 1991) and because of the small number of subjects ranging from 9 to 61 (Taskinen et al. 1989; Windham et al. 1991).

## 2. HEALTH EFFECTS

Both mixed xylene and the individual isomers produce fetotoxic effects in laboratory animals. Effects of mixed xylene observed in rats, mice, and rabbits 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; Hass and Jacobsen 1993; Hudak and Ungvary 1978; Litton Bionetics 1978a; Mirkova et al. 1983; Ungvary 1985; Ungvary and Tatrai 1985). The levels at which these effects were observed depended upon the composition and concentration of mixed xylene, the time of exposure, and on the choice of strain and test species used. In addition, animals in a number of studies were exposed 24 hours/day (Balogh et al. 1982; Hudak and Ungvary 1978; Ungvary 1985; Ungvary and Tatrai 1985), whereas animals in other studies (Bio/dynamics 1983; Hass and Jacobsen 1993; Litton Bionetics 1978a; Mirkova et al. 1983) were exposed 6 hours/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 due to poor animal husbandry. 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) and at 138 ppm in the study by Ungvary (1985); however, no maternal toxicity occurred at exposure levels of 100-400 ppm in the studies by Bio/dynamics (1983), Hass and Jacobsen (1993); 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 1985; 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 observed at 438 and 775 ppm in the study by Balogh et al. (1982). This study suggests that relatively high concentrations of xylenes can limit oxygen delivery to the placenta, which in turn can lead to increased placental weights. Hass and Jakobsen (1993) reported decreased rotarod performance in 1- and 2-day-old rat pups exposed to 200 ppm mixed xylenes 6 hours/day on gestation days 4-20. No maternal toxicity was reported in this study, and it is not clear if the effect on rotarod performance was a permanent deficit or a result of xylenes still present in the offspring. Based on the LOAEL of 200 ppm for decreased rotarod performance (Hass

## 2. HEALTH EFFECTS

and Jakobsen 1993), an intermediate-duration MRL of 0.7 ppm has been derived for mixed xylenes as presented in Table 2-1 and Figure 2-1.

Inhalation of *o*- or *p*-xylene at concentrations similar to those at which mixed xylene caused fetal toxicity, produced decreased fetal weight, skeletal retardation, and post-implantation loss in rats, mice, and rabbits following maternal exposure during gestation days 7-14/15 (Ungvary and Tatrai 1985; Ungvary et al. 1980b, 1981); no maternal toxicity was observed. 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 pattern and duration, etc.). For example, Rosen et al. (1986) exposed animals for 6 hours/day, whereas animals were exposed 24 hours/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 et al. (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). Thus, it is difficult to determine whether mixed xylene are selectively toxic to the fetus or the observed developmental toxicity was secondary to maternal toxicity.

The highest NOAEL value and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Tables 2-1, 2-2, 2-3, and 2-4 and plotted in Figures 2-1, 2-2, 2-3, and 2-4.

### 2.2.1.7 Genotoxic Effects

Limited human data are available regarding the genotoxic effects of mixed xylene following inhalation exposure. No inhalation studies were located regarding the genotoxicity of *m*-xylene, *o*-xylene, or *p*-xylene in humans and animals. Results of studies by Pap and Varga (1987) and Richer et al. (1993) suggest 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

## 2. HEALTH EFFECTS

isomeric composition of the xylene in these studies was not reported (Haglund et al. 1980; Zhong et al. 1980); therefore, it is difficult to assess the contribution of the individual isomers of xylene. The rat study was limited by the lack of details regarding exposure concentrations and duration of exposure. A possible exposure to other solvents in human studies can not be ruled out. 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).

Other genotoxicity studies are discussed in 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 and suggest a possible relationship between coal-based xylene exposure and leukemia (Arp et al. 1983; Wilcosky et al. 1984). Both contain limitations (e.g., small number of subjects ranging from 9 to 85 male workers, 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

### 2.2.2.1 Death

Death in humans following accidental or intentional ingestion of xylene was reported by Abu Al Ragheb et al. (1986). 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. Death was attributed to respiratory failure secondary to depression of the respiratory center in the brain.

Mortality was observed in laboratory animals following the ingestion of mixed xylene and isomers of xylene. Acute oral LD<sub>50</sub>s have been determined for mixed xylene (Hine and Zuidema 1970; NTP 1986) and *m*-xylene (Smyth et al. 1962) in rats and mice. Reported acute oral LD<sub>50</sub> values in rats for

## 2. HEALTH EFFECTS

mixed xylene range from 3,523 mg/kg when administered in corn oil (NTP 1986) to 8,600 mg/kg when administered undiluted (Hine and Zuidema 1970). It appears that the absorption of xylene was enhanced by corn oil due to its greater lipophilicity. The acute oral LD<sub>50</sub> for mixed xylene in male and female mice was 5,627 mg/kg and 5,251 mg/kg, respectively (NTP 1986). Eight of 10 rats given daily gavage doses of 2,000 mg/kg mixed xylene and 10 of 10 mice given daily oral doses of 4,000 mg/kg mixed xylene in corn oil for 14 days died (NTP 1986). The LD<sub>50</sub> for *m*-xylene in rats was 6,661 mg/kg (Smyth et al. 1962). The wide range of LD<sub>50</sub> values in rats may be due to differences in xylene composition, strain, sex, nutritional status (fasted or nonfasted), and/or variation in vehicle. According to the toxicity classification system of Hodge and Sterner (1949), these LD<sub>50</sub> values indicate that mixed xylene and *m*-xylene are slightly toxic by acute oral exposure.

According to a study by Gerarde (1959), *m*-xylene may be slightly less toxic than the other two isomers. A single oral dose of 4,320 mg/kg of *m*-xylene resulted in death in 3/10 rats, whereas a single oral dose of 4,400 mg/kg of *o*-xylene or 4,305 mg/kg of *p*-xylene produced death in 7/10 and 6/10 rats, respectively. In another study, two females died from a group of 10 male and 10 female rats that received 2,000 mg/kg/day *p*-xylene for 10 days (Condie et al. 1988).

No deaths were observed following intermediate-duration oral administration of mixed xylene doses as high as 1,000 mg/kg/day in rats and 2,000 mg/kg/day in mice for 14 days (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 appeared to be dose related in the treated rats, many of the early deaths were related to an error in gavage methodology. 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).

All LD<sub>50</sub> values and LOAEL values from each reliable study for death in each species and 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.

#### 2.2.2.2 Systemic Effects

The systemic effects observed after oral exposure to xylene are discussed below. The highest NOAEL value and all LOAEL values from each reliable study for systemic effects in each species and 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.

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

Key to figure <sup>a</sup>	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat Long-Evans	once (G)				8640 M (LD50)	Hine and Zuidema 1970
2	Rat Albino-Wistar CFT	once (GO)				5950 F (4/6 died)	Muralidhara and Krishnakumari 1980
3	Rat F344/N	14 d 1x/d (GO)				2000 (8/10 died)	NTP 1986
4	Rat F344/N	once (GO)				3523 M (LD50)	NTP 1986
5	Mouse B6C3F1	once (GO)				5627 M (LD50) 5251 F (LD50)	NTP 1986
6	Mouse B6C3F1	14 d 1x/d (GO)				4000 (10/10 died)	NTP 1986
<b>Systemic</b>							
7	Rat F344/N	14 d 1x/d (GO)	Resp	1000		2000 (shallow and labored breathing)	NTP 1986
			Bd Wt	500	1000M (18% decrease in body weight gain in males)		

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

Key to figure <sup>a</sup>	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
8	Mouse B6C3F1	14 d 1x/d (GO)	Resp	1000		2000 (shallow breathing)	NTP 1986
			Bd Wt	1000	2000 M (89% decrease in body weight gain)		
<b>Neurological</b>							
9	Rat Albino- Wistar	once (GO)				5950 F (coma)	Muralidhara and Krishnakumari 1980
10	Rat F344/N	once (GO)				4000 (decreased hindleg movement, incoordination, prostration)	NTP 1986
11	Mouse B6C3F1	1x/d 5d/wk 13 wk  (GO)				2000 (weakness, lethargy, unsteadiness, tremors, & partial paralysis)	NTP 1986
<b>Developmental</b>							
12	Mouse CD-1	10 d Gd 6-15 3x/d (GO)		1030 F		2060 F (cleft palate)	Marks et al. 1982

**TABLE 2-5. Levels of Significant Exposure to Mixed Xylene - Oral (continued)**

Key to figure <sup>a</sup>	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
13	Rat Sprague-Dawley	90 d 1x/d (GO)	Hemato	750 F	1500 F (mild polycythemia and leukocytosis; increased spleen weight)		Condie et al. 1988
			Hepatic	150 F	750 F (increased serum transaminases)		
			Renal		150 <sup>b</sup> F (early chronic nephropathy)		
14	Rat F344/N	13 wk 5d/wk 1x/d (GO)	Resp	1000			NTP 1986
			Cardio	1000			
			Gastro	1000			
			Hemato	1000			
			Musc/skel	1000			
			Hepatic	1000			
			Renal	1000			
			Ocular	1000			
			Bd Wt	500 M	1000M (15% decrease in body weight)		

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

Key to <sup>a</sup> figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
15	Mouse B6C3F1	13 wk 5d/wk 1x/d (GO)	Cardio	2000			NTP 1986
			Gastro	2000			
			Hemato	2000			
			Musc/skel	2000			
			Hepatic	2000			
			Renal	2000			
			Ocular	2000			
			Bd Wt	1000	2000 F (16% decrease in body weight gain)		
<b>Neurological</b>							
16	Rat Sprague- Dawley	90 d 1x/d (GO)		750 M	1500M (increased aggressiveness)	Condie et al. 1988	
17	Rat F344/N	13 wk 5d/wk 1x/d (GO)		1000		NTP 1986	
18	Mouse B6C3F1	103 wks 5d/wk 1x/d (GO)		500	1000 (hyperactivity)	NTP 1986	
<b>Reproductive</b>							
19	Rat F344/N	13 wk 5d/wk 1x/d (GO)		1000		NTP 1986	

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

Key to figure <sup>a</sup>	Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
20	Mouse B6C3F1	13 wk 5d/wk 1x/d (GO)		2000			NTP 1986
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
21	Rat F344/N	103 wk 5d/wk 1x/d (GO)	Resp	500			NTP 1986
			Cardio	500			
			Gastro	500			
			Hemato	500			
			Musc/skel	500			
			Hepatic	500			
			Renal	500			
			Dermal	500			
			Ocular	500			
			Bd Wt	500			
22	Mouse B6C3F1	103 wk 5d/wk 1x/d (GO)	Resp	1000			NTP 1986
			Cardio	1000			
			Gastro	1000			
			Hemato	1000			
			Musc/skel	1000			
			Hepatic	1000			
			Renal	1000			
			Dermal	1000			
			Ocular	1000			
			Bd Wt	1000			

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

Key to figure <sup>a</sup>	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
<b>Neurological</b>						
23	Rat F344/N	103 wk 5d/wk 1x/d (GO)		500		NTP 1986
<b>Reproductive</b>						
24	Rat F344/N	103 wk 5d/wk 1x/d (GO)		500		NTP 1986
25	Mouse B6C3F1	103 wk 5d/wk 1x/d (GO)		1000		NTP 1986

<sup>a</sup>The number corresponds to entries in Figure 2-2.

<sup>b</sup>Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.2 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability)

Bd wt = body weight; Cardio = cardiovascular; d = day(s); F = females; (G) = gavage, not specified; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill, LOAEL = lowest-observed-adverse-effect level; M = males; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x=time(s)

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat NS	once (GO)				4320 (3/10 died)	Gerarde 1959
2	Rat Carworth- Wistar	once (G)				6661 M (LD50)	Smyth et al. 1962
<b>Systemic</b>							
3	Rat Sprague- Dawley	10 d 1x/d (GO)	Hemato	2000			Condie et al. 1988
			Renal Bd Wt	2000 2000			
<b>Developmental</b>							
4	Mouse ICR/SIM	5 d 1x/d Gd 8-12 (GO)		2000 F			Seidenberg et al. 1986
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
5	Rat NS	3.5 wk 5d/wk 1x/d (GO)	Resp		800 M (decreased cytochrome P-450)		Elovaara et al. 1989
			Hepatic		800 <sup>b</sup> M (increased plasma SGPT and plasma membrane damage)		

TABLE 2-6. Levels of Significant Exposure to *m*-Xylene - Oral (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency/ (specific route)	System	LOAEL		Reference	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
6	Rat Sprague- Dawley	13 wk 7d/wk 1x/d (GO)	Resp	800			Wolfe 1988a
			Cardio	800			
			Gastro	800			
			Hemato	800			
			Musc/skel	800			
			Hepatic	800			
			Renal	800			
			Dermal	800			
			Ocular	800			
<b>Neurological</b>							
7	Rat Sprague- Dawley	13 wk 7d/wk 1x/d (GO)		800			Wolfe 1988a
<b>Reproductive</b>							
8	Rat Sprague- Dawley	13 wk 7d/wk 1x/d (GO)		800			Wolfe 1988a

<sup>a</sup>The number corresponds to entries in Figure 2-6.

<sup>b</sup>Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.6 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability)

Bd wt = body weight; Cardio = cardiovascular; d = day(s); F = female; (G) = gavage, not specified; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; *m*-xylene = *meta*-xylene; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x=time(s)

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat NS	once (GO)				4400 (7/10 died)	Gerarde 1959
<b>Systemic</b>							
2	Rat Sprague- Dawley	10 d 1x/d (GO)	Hemato	2000			Condie et al. 1988
			Renal	2000			
			Bd Wt	1000	2000M (14% decrease in body weight)		

<sup>a</sup>The number corresponds to entries in Figure 2-7.

Bd Wt = body weight; d = day(s); (GO) = gavage in oil; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; *o*-xylene = *ortho*-xylene; x=time(s)

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

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat Sprague-Dawley	10 d 1x/d (GO)				2000 F (2/20 died)	Condie et al. 1988
2	Rat NS	once (GO)				4305 (6/10 rats died)	Gerarde 1959
<b>Systemic</b>							
3	Rat Sprague-Dawley	10 1x/d (GO)	Hemato	2000			Condie et al. 1988
			Renal	2000			
			Bd Wt	1000	2000M (13% decrease in body weight)		
4	Rat Long-Evans	once (GO)	Other	1000 M	2000M (mild hypothermia)		Dyer et al. 1988
5	Rat Sprague-Dawley	once (GO)	Resp		1000 F (decreased pulmonary microsomal activity)		Patel et al. 1978
<b>Immuno/Lymphoret</b>							
6	Rat Sprague-Dawley	10 d 1x/d (GO)		1000	2000 (11% decrease in relative thymus weight)		Condie et al. 1988
<b>Neurological</b>							
7	Rat Long-Evans	once (GO)		125 <sup>b</sup> M	250M (altered visual evoked potentials)		Dyer et al. 1988

TABLE 2-8. Levels of Significant Exposure to *p*-Xylene - Oral (continued)

Key to figure <sup>a</sup>	Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	LOAEL		Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
<b>INTERMEDIATE EXPOSURE</b>						
<b>Systemic</b>						
8	Rat Sprague- Dawley	13 wk 7d/wk 1x/d (GO)	Resp	800		Wolfe 1988b
			Cardio	800		
			Gastro	800		
			Hemato	800		
			Musc/skel	800		
			Hepatic	800		
			Renal	800		
			Dermal	800		
			Ocular	800		
<b>Neurological</b>						
9	Rat Sprague- Dawley	13 wk 7d/wk 1x/d (GO)		800		Wolfe 1988b
<b>Reproductive</b>						
10	Rat Sprague- Dawley	13 wk 7d/wk 1x/d (GO)		800		Wolfe 1988b

<sup>a</sup>The number corresponds to entries in Figure 2-8.

<sup>b</sup>Used to derive an acute oral Minimal Risk Level (MRL) of 1 mg/kg; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability)

Bd wt = body weight; Cardio = cardiovascular; d = day(s); F = female; Gastro = gastrointestinal; (GO) = gavage in oil; Hemato = hematological; Immuno/lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; *p*-xylene = *para*-xylene; Resp = respiratory; wk = week(s); x=time(s)

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

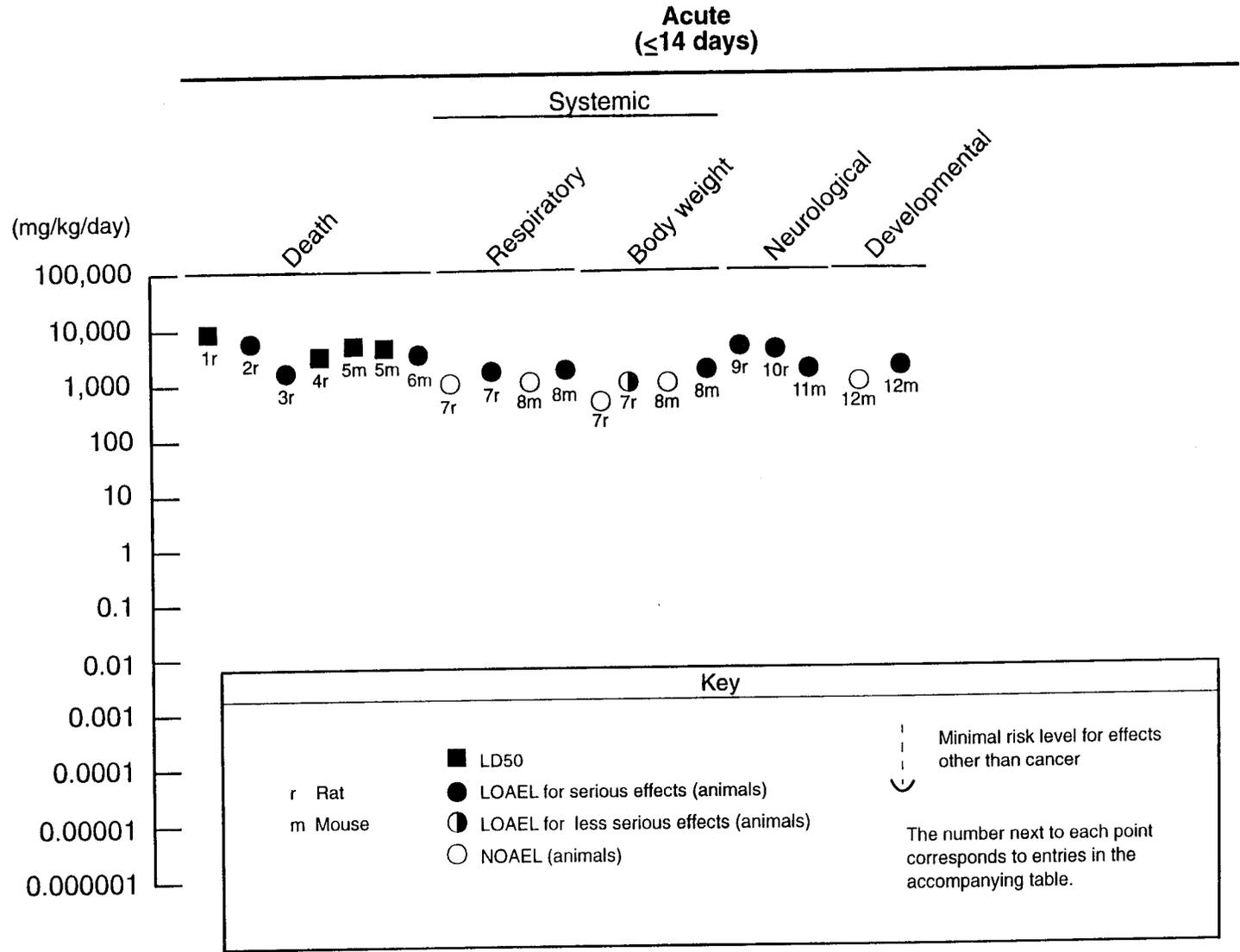


Figure 2-5. Levels of Significant Exposure to Mixed Xylene – Oral (continued)

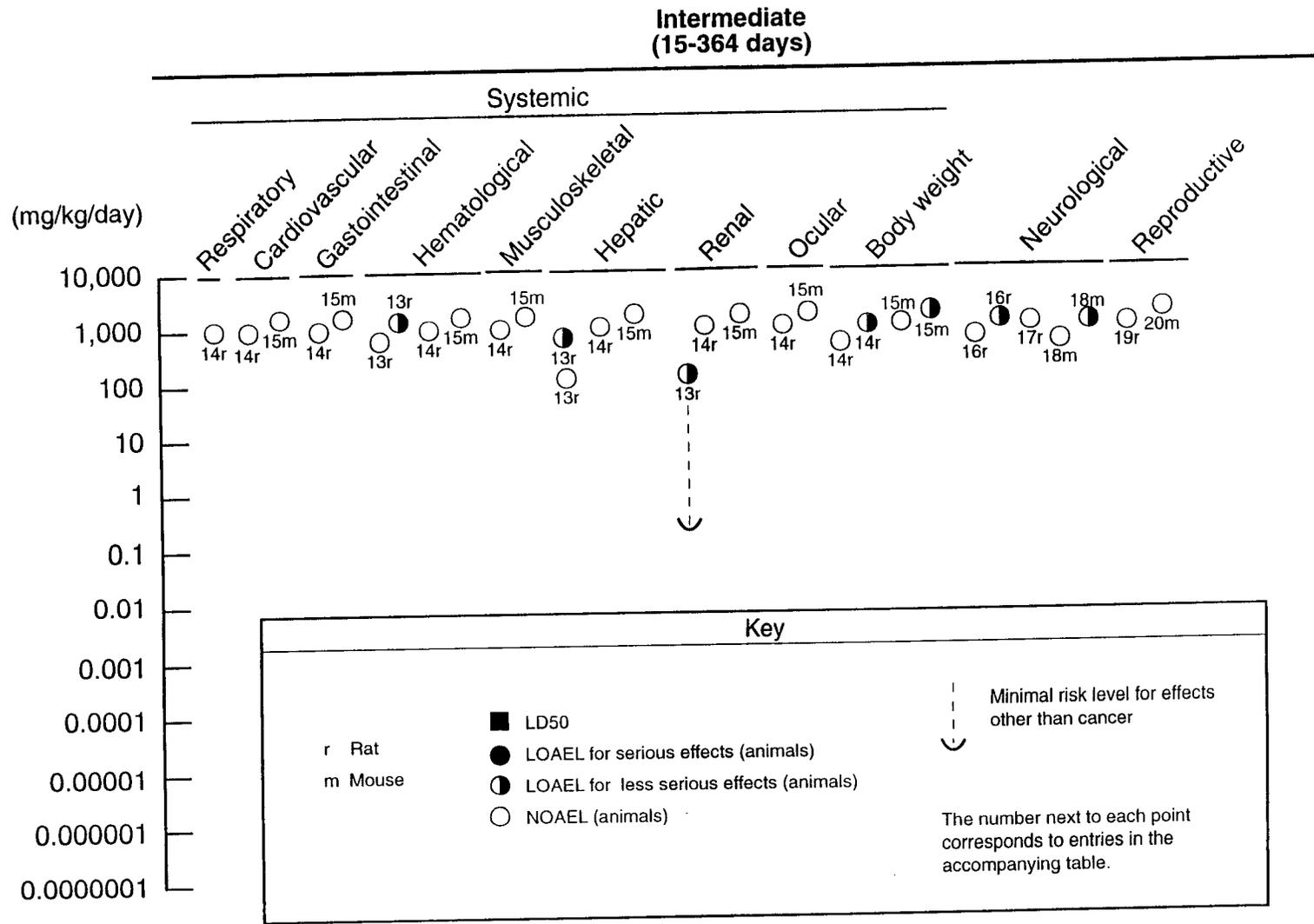


Figure 2-5. Levels of Significant Exposure to Mixed Xylene – Oral (continued)

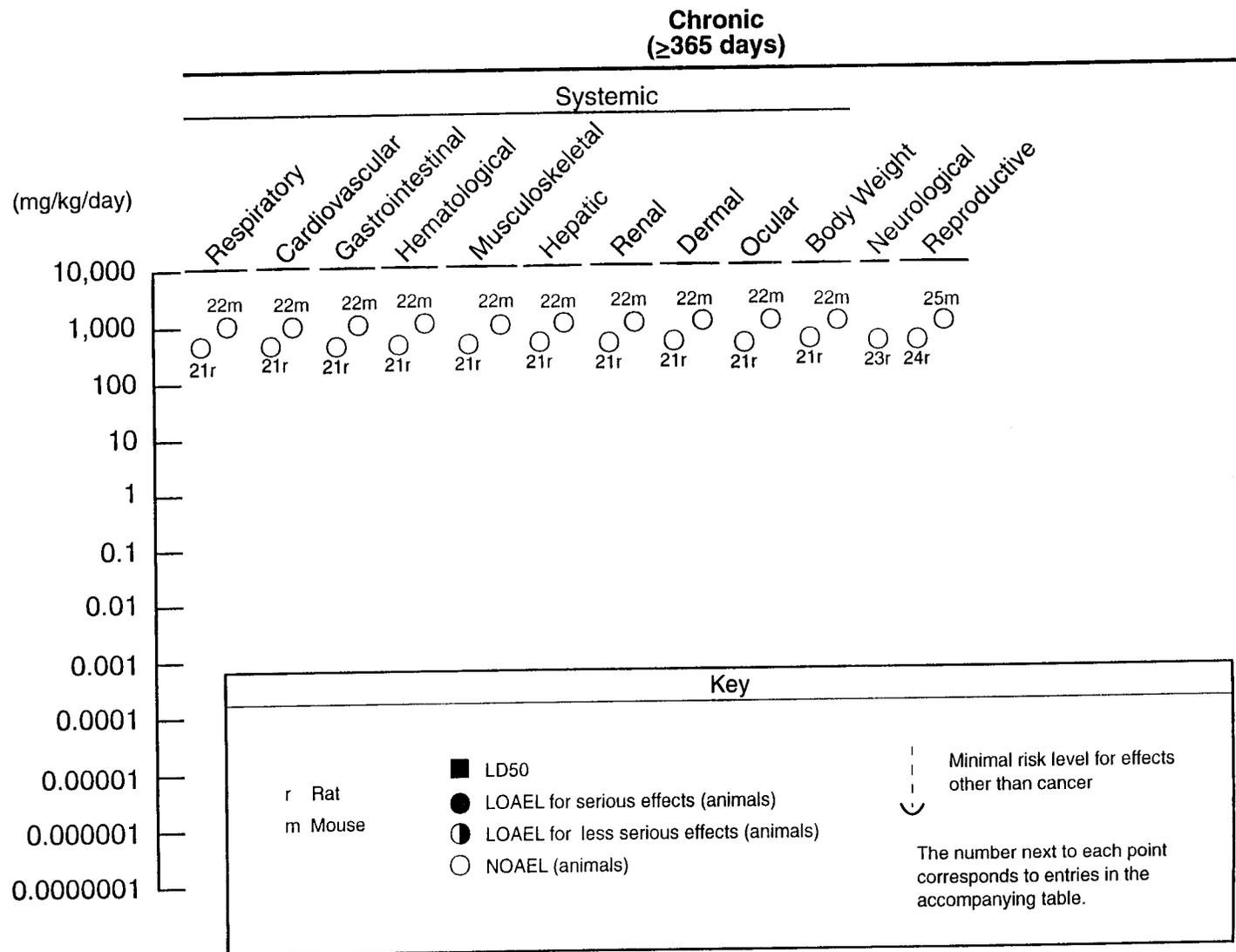
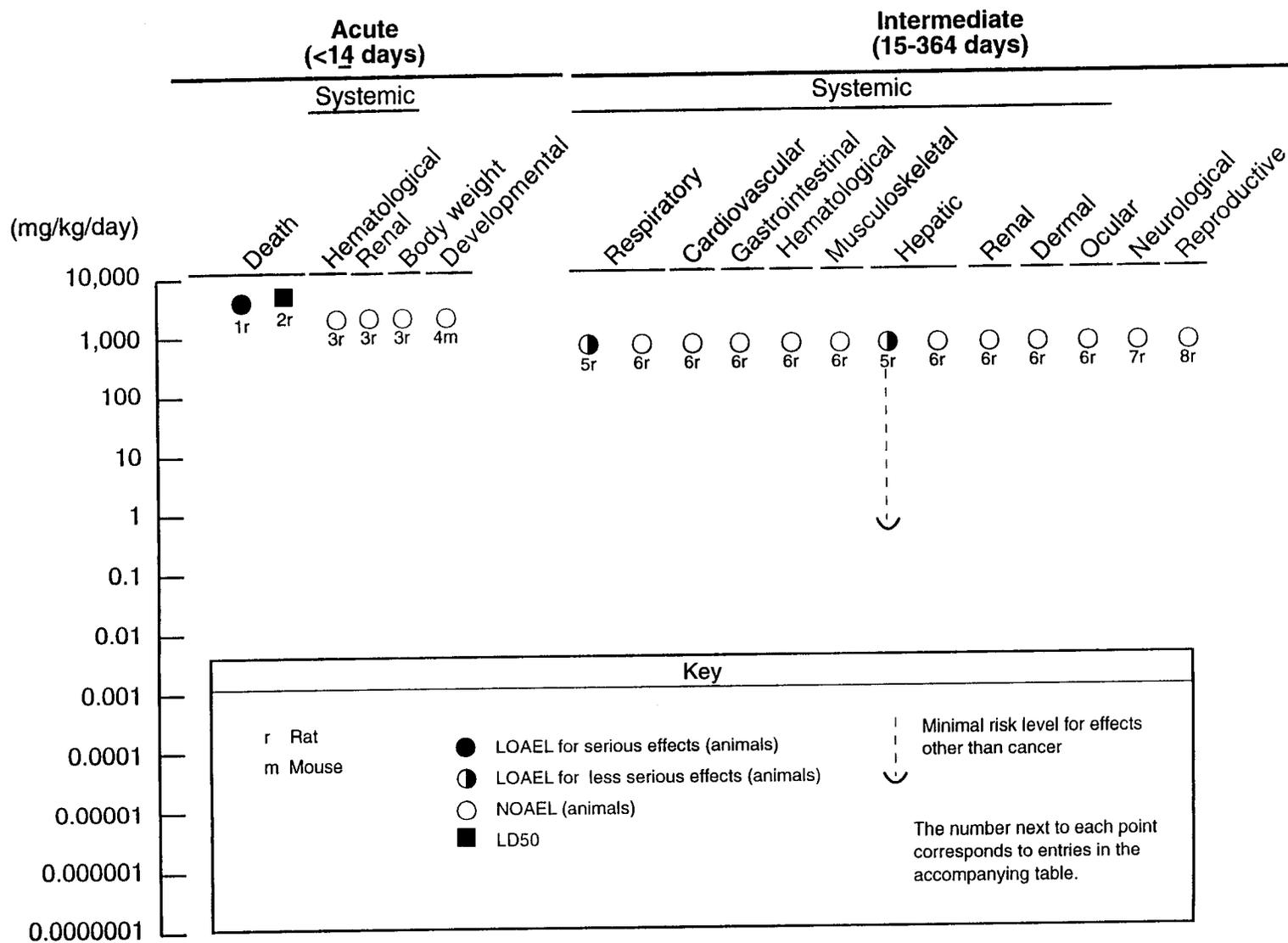


Figure 2-6. Levels of Significant Exposure to *m*-Xylene – Oral



**Figure 2-7. Levels of Significant Exposure to o-Xylene – Oral**

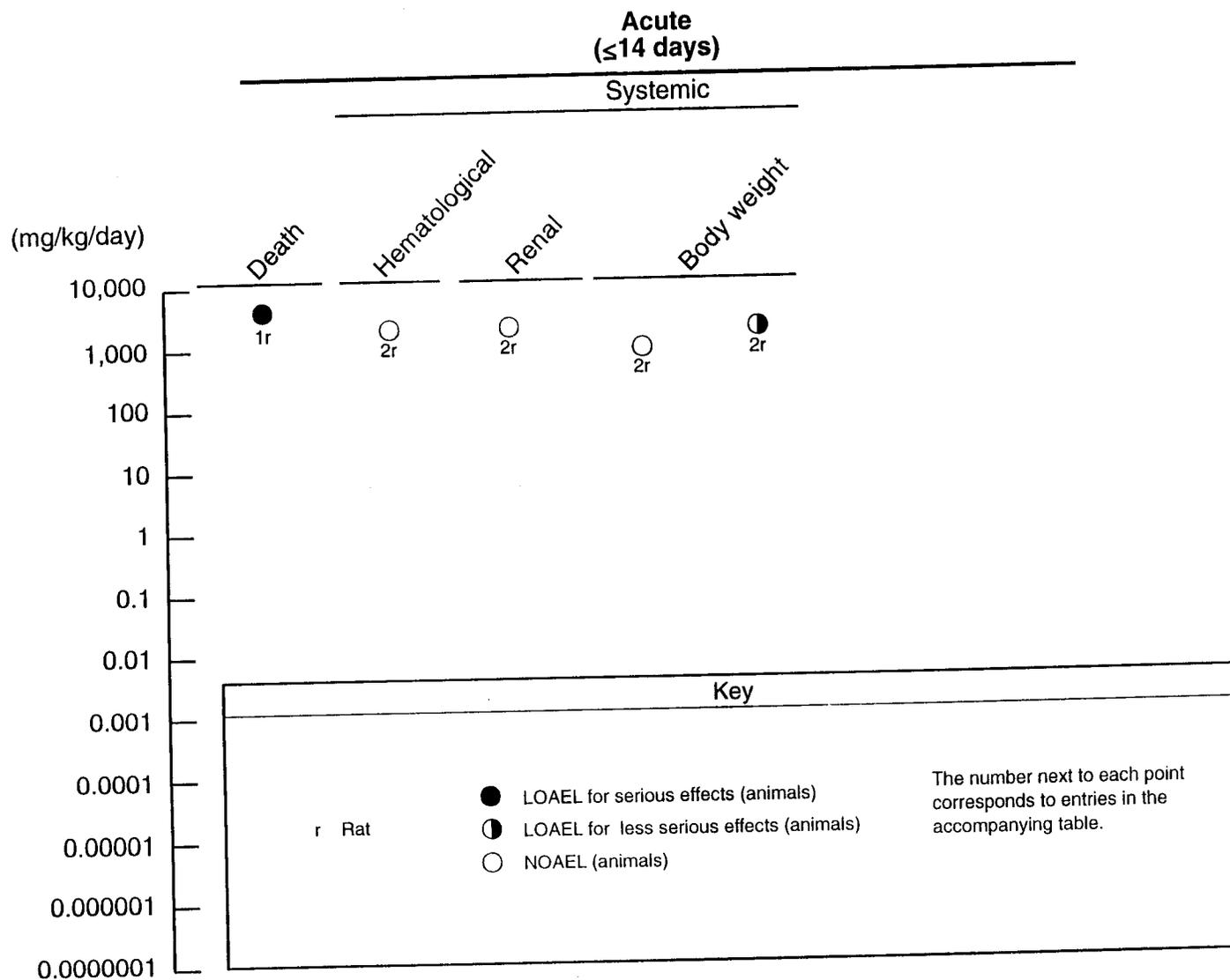


Figure 2-8. Levels of Significant Exposure to *p*-Xylene – Oral

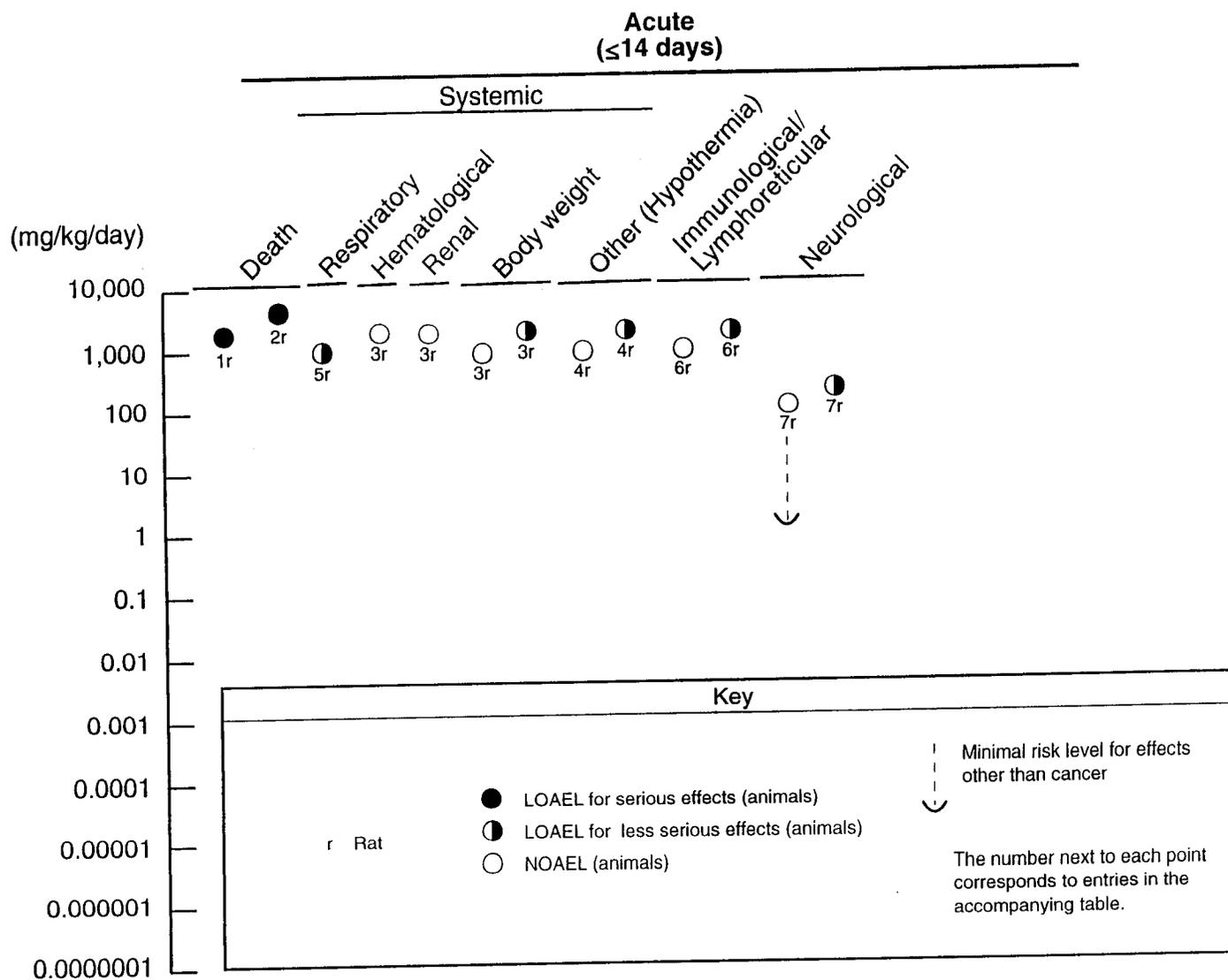
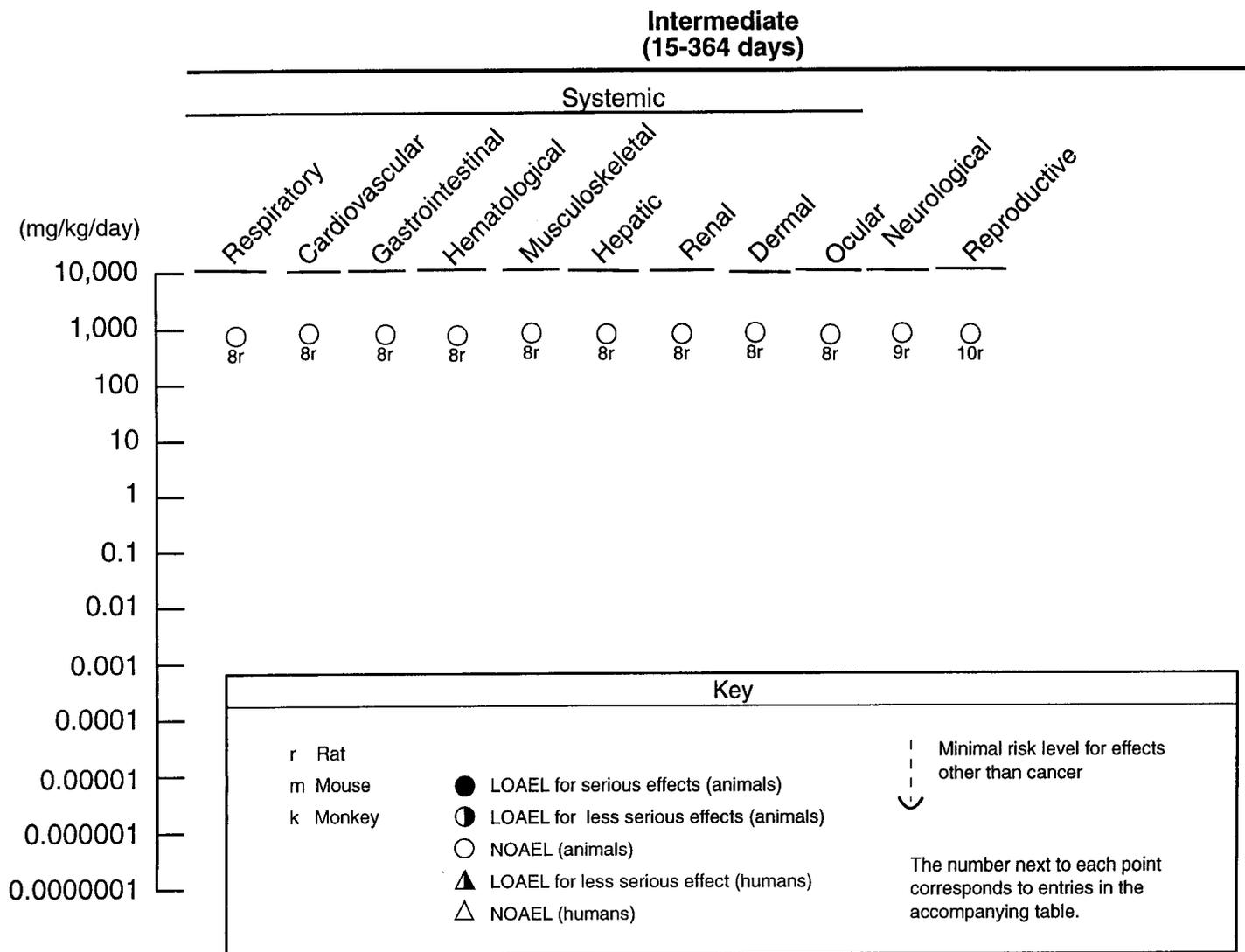


Figure 2-8. Levels of Significant Exposure to p-Xylene – Oral (continued)



## 2. HEALTH EFFECTS

**Respiratory Effects.** Limited information was located regarding respiratory effects in humans following oral exposure to mixed xylene or xylene isomers. Postmortem examination of a man who committed suicide by ingesting xylene showed pulmonary congestion and edema (Abu Al Ragheb et al. 1986). Death resulted from centrally mediated respiratory depression.

A single oral dose of 4,000 mg/kg in mice or daily oral dosing of rats and mice by gavage with mixed xylene for 14 days at 2,000 mg/kg/day resulted in shallow and labored breathing immediately after dosing, but no compound-related effects were observed in the lungs at necropsy (NTP 1986). Mice given daily oral doses of 2,000 mg/kg/day, 5 days/week, for 13 weeks exhibited similar effects 15-60 minutes after dosing (NTP 1986). Histopathological examination of the lungs and mainstem bronchi of rats and mice administered mixed xylene at doses as high as 1,000 mg/kg/day in rats and 2,000 mg/kg/day in mice for 13 weeks or 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 (Wolfe 1988a, 1988b).

Decreased pulmonary microsomal enzyme activity was observed in rats after a single oral dose of 1,000 mg/kg of *p*-xylene (Pate1 et al. 1978) and decreased pulmonary cytochrome P-450 content were observed in rats after gavage dosing with 800 mg/kg/day, 5 days/week, for 3 weeks (Elovaara et al. 1989), suggesting some direct toxicity of xylene in the lungs. Selective inactivation of enzymes can result in damage to tissue caused by the toxic metabolite of xylene, a methylbenzaldehyde (Carlone and Fouts 1974; Pate1 et al. 1978; Smith et al. 1982). The formation of the methylbenzaldehydes has not been confirmed in humans.

**Cardiovascular Effects.** Limited information was located regarding cardiovascular effects in humans following oral exposure to mixed xylene or its isomers. Postmortem examination showed no adverse effects on the heart or coronary arteries of a man who committed suicide by ingesting a large but unknown quantity of xylene (Abu Al Ragheb et al. 1986). No adverse cardiovascular effects were noted following histopathological examination of the heart in rats and mice exposed to mixed xylene at  $\approx$ 63-2,000 mg/kg/day 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 800 mg/kg/day for 13 weeks (Wolfe 1988a, 1988b).

## 2. HEALTH EFFECTS

**Gastrointestinal Effects.** No superficial erosions, deep ulcerations, or other lesions were observed during postmortem examination of the gastric mucosa of a person who died 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 13 weeks or in rats and mice administered doses as high as 500 and 1,000 mg/kg/day, respectively, for 2 years revealed no adverse effects on the stomach, small intestine, or colon (NTP 1986). Administration of *p*-xylene up to 800 mg/kg/day for 13 weeks also had no significant effect on gastrointestinal organs of rats (Wolfe 1988a, 1988b).

**Hematological Effects.** No studies were located regarding hematological effects in humans following oral exposure to mixed xylene or xylene isomers. Exposure of rats to 2,000 mg/kg/day *p*-xylene for 10 days resulted in no effects detectable in routine hematological analysis (Condie et al. 1988). Exposure to *o*- and *m*-xylene at 2,000 mg/kg/day for 10 days produced a decrease in the spleen weight of male rats (Condie et al. 1988); however, hematological analyses in these rats were normal. 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). No effects were observed upon histopathological examination of the bone marrow following exposure to 800 mg/kg/day of *p*-xylene in rats and mice (Wolfe 1988a), 1,000 mg/kg/day mixed xylene in rats for 13 weeks (NTP 1986), 2,000 mg/kg/day mixed xylene in mice for 13 weeks (NTP 1986), or 500 mg/kg/day mixed xylene in rats and 1,000 mg/kg/day in mice for 2 years (NTP 1986).

**Musculoskeletal Effects.** No studies were located regarding musculoskeletal effects in humans 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, sternbrae, or vertebrae following intermediate or chronic exposure to mixed xylene up to 2,000 mg/kg/day for mice and 1,000 mg/kg/day for rats for 13 weeks and 1,000 mg/kg/day for mice or 500 mg/kg/day for rats for 103 weeks (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 up to 800 mg/kg/day for 13 weeks (Wolfe 1988a, 1988b).

## 2. HEALTH EFFECTS

**Hepatic Effects.** No studies were located regarding hepatic effects in humans following oral exposure to mixed xylene or xylene isomers. In general, studies in animals have shown mostly adaptive changes in response to oral exposure to mixed xylene. These studies revealed increased activity of liver enzymes without any histopathological changes in the liver tissue. Therefore, the NOAEL for hepatotoxicity can not be determined. In acute and intermediate studies with rats, oral exposure to mixed xylene (Condie et al. 1988; Ungvary 1990), and its isomers (Condie et al. 1988; Elovaara et al. 1989; Pyykko 1980) has been associated with hepatic enzyme induction and increased hepatic weight. In the study by Condie et al. (1988), acute exposure to *p*-xylene at 250 mg/kg/day and *m*- and *o*-xylene at 1,000 mg/kg/day for 10 days caused increases in liver weight. An intermediate oral MRL of 0.6 mg/kg/day (Elovaara et al. 1989) was calculated for *m*-xylene as described in the footnote in Table 2-6. Administration of doses of 1,060 mg/kg/day of all three xylene isomers for 3 days also produced increased cytochrome b<sub>5</sub> content and increased activities of liver enzymes in rats (Pyykko 1980), with the different isomers showing different enzyme induction potencies. Increased liver weight was observed with *m*- and *o*-xylene, but not *p*-xylene, and increased cytochrome P-450 was observed only with *m*-xylene. Administration of mixed xylene 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 the liver. However, mild increases in serum transaminases were observed at 750 mg/kg/day. Similar increases in serum alanine aminotransferase were observed following ingestion of 800 mg/kg/day of *m*-xylene for 3 weeks (Elovaara et al. 1989). No effects were noted upon histopathological examination of the liver of rats and mice, that were administered mixed xylene for a chronic or intermediate period of time with doses as high as 2,000 mg/kg/day for mice; 1,000 mg/kg/day for rats for 13 weeks; and 1,000 mg/kg/day for mice and 500 mg/kg/day for rats for 103 weeks (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 (Wolfe 1988a, 1988b).

**Renal Effects.** No studies were located regarding renal effects in humans following oral exposure to mixed xylene or xylene isomers. No animal studies were located regarding the effects of acute-duration exposure to mixed xylene, but studies using the individual xylene isomers indicated that only adaptive changes in response to xylene exposure occurred (Condie et al. 1988; Pyykko 1980). At 1,060 mg/kg/day for 3 days, increases in kidney weight were observed with *m*-xylene and increases in microsomal enzyme content and activity were observed with all three isomers (Pyykko 1980). No effects on urine parameters were noted after a 10 day exposure to 2,000 mg/kg/day of any of the

## 2. HEALTH EFFECTS

isomers (Condie et al. 1988). The majority of studies using mixed xylene or its isomers for intermediate or chronic durations also showed no adverse effects on the kidneys. The only toxic change observed was increased hyaline droplet change in males and increased early chronic nephropathy in females at 150 mg/kg/day mixed xylene for 90 days. Although urine from these rats were normal (Condie et al. 1988), continued hyalin droplet accumulation can result in cell damage. Increased relative kidney weight was also observed in male rats given mixed xylene at 750 mg/kg/day and in female rats at 1,500 mg/kg/day for 90 days (Condie et al. 1988). Similarly, increased kidney weight and microsomal enzyme activity were observed in rats exposed to 800 mg/kg/day of *m*-xylene, 5 days/week, for 3 weeks (Elovaara et al. 1989). Increased relative kidney weight was also observed in male rats administered 800 mg *m*-xylene/kg/day for 13 weeks (Wolfe 1988a, 1988b). Histopathology of the kidneys and urinary bladder were normal. Also, no adverse effects were noted upon histopathological examination of the kidneys 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). The apparent differences noted between a 90-day study and a 103-week study were caused by the different strains of rats used. An intermediate oral MRL of 0.2 mg/kg/day (Condie et al. 1988) was calculated for mixed xylene as described in the footnote in Table 2-5.

**Dermal Effects.** No studies were located regarding dermal effects in humans following oral exposure to mixed xylene or xylene isomers. Limited information was located regarding dermal effects in animals. No adverse effects were noted during microscopic examination of the skin of rats and mice administered mixed xylene at doses as high as 2,000 mg/kg/day in mice and 1,000 mg/kg/day for rats for an intermediate (13 weeks) period of time or as high as 1,000 mg/kg/day for mice and 500 mg/kg/day for rats for a chronic (103 weeks) period of time (NTP 1986). The skin of rats administered doses as high as 800 mg/kg/day of *m*- or *p*-xylene for 13 weeks appeared normal upon histopathological examination (Wolfe 1988a, 1988b).

**Ocular Effects.** No studies were located regarding ocular effects in humans following oral exposure to mixed xylenes or xylene isomers. Histopathological examination of the eyes of rats and mice orally exposed to mixed xylenes (NTP 1986) or to *m*- or *p*-xylene (Wolfe 1988a, 1988b) for 13 or 103 weeks showed no effects. No additional data regarding ocular effects in animals following oral exposure to xylenes were available.

## 2. HEALTH EFFECTS

**Body Weight Effects.** Effects on body weight were observed in several acute studies of the effects of mixed xylene and its isomers (Condie et al. 1988; NTP 1986; Pyykko 1980). A 14-day exposure of rats and mice to mixed xylene resulted in an 18% decrease in body weight gain in male rats at 1000 mg/kg/day and an 89% decrease in bodyweight gain in male mice at 2,000 mg/kg/day (NTP 1986). Body weights of male rats given 2,000 mg/kg/day *o*- or *p*-xylene, but not *m*-xylene, for 10 days showed 14% and 13% decreases, respectively, relative to controls (Condie et al. 1988); in female mice, a 16% decrease was noted following 13 weeks of exposure to 2000 mg/kg/day mixed xylene (NTP 1986). Exposure to *m*-, *o*-, and *p*-xylene for 3 days resulted in weight losses of between 2.5 and 3 times that observed in control rats (Pyykko 1980). Food consumption and body weight gain were decreased during intermediate exposure at 200 mg *m*-xylene/kg/day in males for 13 weeks (Wolfe 1988a). Body weight in male rats at 1,000 mg/kg/day and in female mice at 2,000 mg/kg/day mixed xylene were decreased 15% and 16%, respectively, in a 13-week study but were comparable to those of controls in a similar chronic study (NTP 1986).

### 2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to mixed xylene or xylene isomers. The only information suggesting a possible toxic effect of mixed xylene or its isomers on the immune system was a decrease in spleen and thymus weight observed in rats exposed for 10 days to 2,000 mg/kg/day *p*-xylene (Condie et al. 1988). Organ weight changes were not accompanied by histopathological changes.

The NOAEL and LOAEL values for immunological effects of *p*-xylene in rats are recorded in Table 2-8 and plotted in Figure 2-8.

### 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 an unknown amount (Recchia et al. 1985). The composition of the xylene was also unknown.

Clinical signs consistent with central nervous system toxicity have been observed in rats and mice following oral exposure to mixed xylene. A single oral dose of 4,000 mg/kg caused incoordination,

## 2. HEALTH EFFECTS

prostration, decreased hindleg movement, and hunched posture in rats and tremors, prostration, and/or slowed breathing in mice (NTP 1986). Mild sedation at 2,000 mg/kg and increases in latency of several peaks in flash-evoked potentials at doses of 250 mg/kg and higher were observed following single doses of *p*-xylene; no effect was seen at 125 mg/kg/day (Dyer et al. 1988). This NOAEL was used to derive an MRL of 1 mg/kg/day for acute oral exposure to *p*-xylene. 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 13 weeks revealed no adverse effects (NTP 1986). However, mice at 2,000 mg/kg/day displayed weakness, lethargy, unsteadiness, tremors, and partial paralysis of the hindlimbs for up to 60 minutes after dosing. Following gavage of 1,000 mg/kg/day in the chronic bioassay, hyperactivity was noted for 5-30 minutes in weeks 4-13 of study in both male and female mice (NTP 1986). No adverse effects were noted in the histopathology of spinal cord and brain of rats administered doses of *m*- or *p*-xylene as high as 800 mg/kg/day for 13 weeks (Wolfe 1988a, 1988b); although the brain-to-body weight ratio was increased in males dosed with 800 mg/kg/day of *m*-xylene, no histopathological changes were seen. Clinical signs included hyperactivity, convulsions, salivation, and epistaxis. Increased aggressiveness was also observed in rats given 1,500 mg/kg/day mixed xylene for 90 days (Condie et al. 1988). In chronic studies, no histopathological changes were noted in the brain of rats or mice receiving 500 or 1,000 mg/kg/day mixed xylene for 103 weeks, respectively; however, mice at 1,000 mg/kg/day showed hyperactivity from week 4 to the end of the study (NTP 1986). An acute oral MRL of 1 mg/kg/day (Dyer et al. 1988; NTP 1986) was calculated for *p*-xylene as described in the footnote in Table 2-8.

The highest NOAEL value and all LOAEL values from each reliable study 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 Reproductive Effects**

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

No studies in animals directly examining reproductive function following oral administration of mixed xylene or its isomers were located; however, histological examination of rats and mice administered mixed xylene at doses as high as 1,000 mg/kg/day in rats and 2,000 mg/kg/day in mice for 13 weeks

## 2. HEALTH EFFECTS

revealed no adverse effects on 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 (Wolfe 1988a, 1988b). In chronic studies, no adverse histopathological changes were observed in the reproductive organs in rats at doses as high as 500 mg/kg/day and in mice at doses as high as 1,000 mg/kg/day for 103 weeks (NTP 1986). The highest NOAEL value from each reliable study 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.

### 2.2.2.6 Developmental Effects

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

Significantly increased incidences of cleft palate and decreased fetal body weight were reported following maternal oral exposure during gestation days 6-15 to doses of 2,060 mg/kg/day mixed xylene in mice (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 maternal toxicity or a predisposition of mice under stress to give birth to offspring with this birth defect. In a teratology screening study, 2,000 mg/kg/day of *m*-xylene produced no evidence of fetal toxicity in mice (Seidenberg et al. 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 all LOAEL values from each reliable study for developmental effects are recorded in Tables 2-5 and 2-6 and plotted in Figures 2-5 and 2-6.

### 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 1,000 mg/kg within a 24-hour period (Feldt 1986).

Other genotoxicity studies are discussed in Section 2.4.

## 2. HEALTH EFFECTS

**2.2.2.8 Cancer**

No data were located regarding 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). In a chronic bioassay, rats and mice of both sexes received mixed xylene by gavage at 0, 250, or 500 mg/kg/day and 0, 500, or 1,000 mg/kg/day, respectively, for 103 weeks. 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. In the other chronic study (Maltoni et al. 1983, 1985), male and female rats were fed xylene (unspecified) by gavage at 0 or 500 mg/kg/day, 4-5 days a week for 104 weeks. 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.

**2.2.3 Dermal Exposure**

In addition to studies that have directly examined the health effects of dermal exposure to xylene, a number of reports of health effects resulting from occupational exposure to xylene have been included in this section. Dermal contact with xylene is likely in many occupational situations, and absorption of xylene has been demonstrated in humans (Engstrom et al. 1977; Riihimaki 1979b; Riihimaki and Pfaffli 1978). The results of the occupational studies must be interpreted with caution, however, because of coexposure to other compounds.

**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; Smyth et al. 1962). The acute dermal LD<sub>50</sub> in rabbits has been determined to be

## 2. HEALTH EFFECTS

3,228 mg/kg/day for *m*-xylene and greater than 114 mg/kg/day for mixed xylene for 4 hours or more (Hine and Zuidema 1970; Smyth et al. 1962).

The LD<sub>50</sub> value for death in rabbits as a result of acute-duration exposure to *m*-xylene is recorded in Table 2-10.

**2.2.3.2 Systemic Effects**

No studies were located regarding musculoskeletal effects in humans or animals following dermal exposure to mixed xylenes or xylene isomers. The systemic effects that were observed after dermal exposure to xylene are discussed below. All LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 2-9 and 2-10.

**Respiratory Effects.** Case reports of dryness of the throat (Goldie 1960) in painters and decreased pulmonary function and dyspnea in histology technicians with chronic exposure to xylene (Hipolito 1980) have been published. It is likely that these effects represent direct effects of xylene or other solvents on the respiratory tissues and they are discussed in more detail in Section 2.2.1.2. No studies were located regarding respiratory effects in animals following dermal exposure to mixed xylene or xylene isomers, although some of the inhalation studies also involved exposure via dermal route as well.

**Cardiovascular Effects.** Cases of flushing, chest pains, and palpitations in histology technicians have been reported (Hipolito 1980). These studies also involved exposure via inhalation route. It is unclear whether these effects are directly attributable to xylene exposure because of possible exposure to other chemicals. No studies were located regarding cardiovascular effects in animals after dermal exposure to mixed xylene or xylene isomers.

**Gastrointestinal Effects.** Gastric discomfort in painters (Goldie 1960) and nausea in histology technicians (1980) have been reported; these studies also involved exposure via inhalation route. However, other chemicals in the workplace may have contributed to these effects. No studies were located regarding gastrointestinal effects in animals following dermal exposure to mixed xylene or xylene isomers.

TABLE 2-9. Levels of Significant Exposure to Mixed Xylene - Dermal

Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>						
<b>Death</b>						
Mouse Hall	once				57 (8/120 died)	Pound and Withers 1963
<b>Systemic</b>						
Mouse Hall	once	Dermal		57 (edema, irritation, scaliness of skin)		Pound and Withers 1963
Rabbit NS	once	Ocular		23 (mild irritation of eyes)		Consumer Product Testing 1976
Rabbit New Zealand white	once	Dermal		23 M (moderately irritating to the conjunctiva)	114 M (moderate to severe skin irritation)	Hine and Zuidema 1970
Rabbit New Zealand white	once	Ocular		23 M (eye irritation)		Hine and Zuidema 1970
Gn pig Dunkin Hartley	3 d 3x/d	Dermal		2.3 F (skin irritation)		Anderson et al. 1986

d = day (s); F = female; Gn pig = Guinea pig; LOAEL = lowest-observed -adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not stated; x = times

TABLE 2-10. Levels of Significant Exposure to *m*-Xylene - Dermal

Species/ (strain)	Exposure/ duration/ frequency (specific route)	System	NOAEL		LOAEL		Reference
			NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
Rabbit Albino New Zealand	24 hr					3228 M (LD50)	Smyth et al. 1962
<b>Systemic</b>							
Rabbit New Zealand albino	once	Ocular		114 (eye irritation)			Smyth et al. 1962
Rabbit Albino	once	Dermal		2.3 (skin irritation)			Smyth et al. 1962

hr = hour(s); LD50 = lethal dose, 50% dead; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level

## 2. HEALTH EFFECTS

**Hematological Effects.** Decreased white blood cell count has been observed in histology technicians (Hipolito 1980) and in workers with occupational exposure to benzene, toluene, and xylene (Moszczyński and Lisiewicz 1983, 1984a); these studies also involved exposure via inhalation route. However, chemicals other than xylene may have caused these decreases. No studies were located regarding hematological effects in animals following dermal exposure to mixed xylene or xylene isomers.

**Hepatic Effects.** When compared with unexposed controls, workers with occupational exposure via dermal and inhalation routes to toluene, xylene, and pigments had significantly increased urinary D-glucaric acid content in the urine indicating hepatic microsomal enzyme induction (Dolara et al. 1982). Serum antipyrine half-life was increased, suggesting possible hepatotoxicity. No effect on serum aminotransferases was observed in workers exposed to a mixture of solvents (Kurppa and Husman 1982). These studies also involved exposure via inhalation route. These studies are limited in that multiple chemical exposures occurred and the effects observed cannot be directly attributed to xylene. No studies were located regarding hepatic effects in animals following dermal exposure to mixed xylene or xylene isomers.

**Renal Effects.** Occupational exposure to a mixture of mainly xylene and toluene resulted in elevated albumin, erythrocytes, and leukocytes in the urine (Askergren 1981, 1982). In addition, increased  $\beta$ -glucuronidase was observed in the urine of painters (Franchini et al. 1983). However, these studies are limited in that the effects observed may also be attributable to exposure to other chemicals in the workplace and that inhalation as well as dermal exposure could have occurred. No studies were located regarding renal effects in animals following dermal exposure to mixed xylene or xylene isomers.

**Dermal Effects.** Acute dermal exposure of human subjects to undiluted *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; Riihimäki 1979b). Urticaria was reported in a female cytology worker exposed predominantly to xylene vapors (Palmer and Rycroft 1993). Because this response probably had an immunological component, it is discussed further in the Immunological and Lymphoreticular Effects section.

## 2. HEALTH EFFECTS

Mild-to-severe skin irritation was noted in rabbits, guinea pigs, and mice treated topically with mixed xylene (2.3-14 mg/kg/day) in acute studies (Anderson et al. 1986; Consumer Product Testing 1976; Food and Drug Research Labs 1976; Hine and Zuidema 1970; Pound and Withers 1963). The extent of the irritation appeared to increase with duration of exposure; the most severe dermal irritation ratings were obtained in the longest exposures of 10-days (Hine and Zuidema 1970). Skin irritation of an unspecified severity was also observed following application of 0.01 mL (2.3 mg/kg, 24 hours) of *m*-xylene to the skin of rabbits (Smyth et al. 1962). Moderate-to-marked irritation and moderate necrosis were observed in rabbits with a 2-4 week dermal exposure to undiluted xylene (Wolf et al. 1956). No chronic animal studies evaluating the dermal effects of xylene were located.

**Ocular Effects.** There are no reports of the effects of direct contact of the eye with liquid xylene in humans, but several case reports and experimental exposures of humans to mixed xylene and *p*-xylene vapors have resulted in transient eye irritation (Carpenter et al. 1975a; Hake et al. 1981; Hastings et al. 1986; Klaucke et al. 1982; Nelson et al. 1943; Nersesian et al. 1985). In the experimental exposure situations, eye irritation was reported at concentrations of mixed xylene as low as 200 ppm for 3-5 minutes (Nelson et al. 1943) and of *p*-xylene as low as 100 ppm for 1-7.5 hours/day for 5 days (Hake et al. 1981). Eye irritation was more frequently reported by workers exposed to mixed xylene (geometric mean TWA 14 ppm) than by the controls (Uchida et al. 1993).

Instillation of 0.1 mL (23 mg/kg/day) of mixed xylene into the eyes of rabbits resulted in slight-to-moderate eye irritation (Consumer Product Testing 1976; Hine and Zuidema 1970). Eye irritation was also observed following a single instillation of 0.5 mL of *m*-xylene (concentration not reported) into the eyes of rabbits (Smyth et al. 1962).

### 2.2.3.3 Immunological and Lymphoreticular Effects

Limited data were located regarding immunological and lymphoreticular effects in humans following dermal exposure to xylene. Occupational exposure to benzene, toluene, and xylene resulted in decreased serum complement (Smolik et al. 1973) and in decreased lymphocytes, but there was no effect on lymphocyte reactions when stimulated with phytohemagglutinin (Moszczynsky and Lisiewicz 1983, 1984a). Interpretation of these studies is limited in that chemicals other than xylene may have accounted for the effects observed. Also exposures via inhalation and dermal routes may have occurred. Contact urticaria was reported in a female cytology worker exposed predominantly to

## 2. HEALTH EFFECTS

xylene vapors (Palmer and Rycroft 1993). A closed patch test resulting in severe erythema and wealing provides evidence that the effect was a result of direct contact of xylene vapor with the skin and suggests that the reaction was immunological.

No studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to mixed xylene or xylene isomers.

### **2.2.3.4 Neurological Effects**

Occupational exposure to xylene has been reported to result in headache, dizziness, malaise, a feeling of drunkenness, irritability, fine tremor, dysphasia, hyperreflexia, and/or impaired concentration and memory (Goldie 1960; Hipolito 1980; Kilburn et al. 1985; Roberts et al. 1988). These studies are limited, however, because other chemical exposures in the workplace may have been responsible for the effects observed and that exposures via inhalation and dermal routes may have occurred. No studies were located regarding neurological effects in animals after dermal exposure to mixed xylene or xylene isomers.

### **2.2.3.5 Reproductive Effects**

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

### **2.2.3.6 Developmental Effects**

The human data regarding the developmental effects of xylene suggest a possible relationship between occupational solvent exposure and developmental toxicity (Holmberg and Nurminen 1980; Kucera 1968; Taskinen et al. 1989; Windham et al. 1991). However, these data are limited for assessing the relationship between dermal exposure to 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; Windham et al. 1991), because few subjects were tested (Taskinen et al. 1989; Windham et al. 1991), and because it is extremely difficult to have a pure dermal exposure since such exposure in the absence of respiratory protection is accompanied by inhalation exposure.

## 2. HEALTH EFFECTS

Dermal exposure of pregnant rats to doses as low as 200 mg/kg/day of xylene (unspecified concentration and isomer) throughout gestation produced decreases in enzyme activity (cholinesterase, cytochrome) in fetal and maternal brain tissue (Mirkova et al. 1979). Pregnant dams exposed to xylene at 2,000 mg/kg/day showed impaired motor activity in behavioral tests suggesting a neurotoxic effect of xylene.

### **2.2.3.7 Genotoxic Effects**

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

Genotoxicity studies are discussed in Section 2.4.

### **2.2.3.8 Cancer**

Studies of workers occupationally exposed to solvents have examined the cancer and leukemia risks and suggest a possible relationship between coal-based xylene exposure and leukemia (Arp et al. 1983; Wilcosky et al. 1984). Both contain limitations (e.g., small number of subjects, no exposure concentrations, unknown composition of xylene and possible exposure to benzene and other chemicals) that preclude a definitive conclusion regarding dermal exposure to xylene and cancer; development of these studies probably also involved exposure via inhalation.

Limited information was located regarding the carcinogenicity of dermal exposure to xylene in animals (Berenblum 1941; Pound 1970; Pound and Withers 1963). Application of xylene (concentration, purity, and amount unspecified) to the skin for 25 weeks resulted in no increase in skin tumors, and did not potentiate the number of skin tumors produced by benz[a]pyrene (Berenblum 1941). However, two studies showed that a single xylene pretreatment enhanced the number of tumors produced by a combination of ultraviolet light irradiation (initiation) and croton oil (promotion) (Pound 1970) or urethane (initiation) and croton oil (promotion) (Pound and Withers 1963). These findings suggest that xylene may be a promoter for skin cancer and might also act as initiator or cocarcinogen. These studies are limited in that tumors other than skin tumors were not assessed and untreated controls were not used.

## 2. HEALTH EFFECTS

**2.3 TOXICOKINETICS**

Studies in humans and animals have shown that xylenes are well absorbed by the inhalation and oral routes. Approximately 60% of inspired xylene is retained and approximately 90% of ingested xylene is absorbed. Absorption of xylene also occurs by the dermal route, but to a much lesser extent than by the inhalation and oral routes especially following exposure to xylene vapor. Following absorption, xylene is rapidly distributed throughout the body by way of the systemic circulation. In the blood, xylene is primarily bound to serum proteins. Xylene accumulates primarily in adipose tissue. Xylene is primarily metabolized by oxidation of a methyl group and conjugation with glycine to yield the methylhippuric acid. All three isomers of xylene are metabolized in this way. In humans exposed to xylene, greater than 90% of xylene is excreted in the urine as the methylhippuric acid. Aromatic hydroxylation of xylene to xylenol occurs to only a limited extent in humans. Less than 2% of an absorbed dose is excreted in the urine as xylenol. Other minor metabolites found in urine include methylbenzyl alcohol and glucuronic acid conjugates of the oxidized xylene. Metabolism in animals is qualitatively similar, but glucuronide conjugates make up a larger proportion of the urinary excretion products (see Figures 2-9 and 2-10). In addition, methylbenzaldehyde (the product of the action of alcohol dehydrogenase on methylbenzyl alcohol) has been detected in animals but has not been confirmed in humans. In humans, about 95% of the absorbed xylene is excreted in the urine, with about 5% excreted unchanged in the exhaled air. Elimination from most tissue compartments is rapid, with slower elimination from muscle and adipose tissue. Some authors have suggested that methylbenzaldehyde may be responsible for the toxic effects of xylene.

**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 urine metabolites increase in proportion to exposure (Inoue et al. 1993; Jonai and Sato 1988; Kawai et al. 1991; Ogata et al. 1970; Riihimaki and Pfaffli 1978; Riihimaki et al. 1979b; Sedivec and Flek 1976b; Senczuk and Orłowski 1978; Wallen et al. 1985) and in proportion to increased ventilatory rates during exercise (Astrand 1982; Astrand et al. 1978; Bergert and Nestler 1991; Engstrom and Bjurstrom 1978; Riihimaki and Savolainen 1980; Riihimaki et al. 1979b). Absorption of the retained isomers appears to be similar, regardless of exposure duration or dose.

## 2. HEALTH EFFECTS

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 ( $\approx$ 1 hour) and represents the establishment of an equilibrium between the inhaled xylene and blood. Alveolar air concentrations of xylenes in male volunteers exposed to 100 or 299 ppm mixed xylenes for 70 minutes reached equilibration within 10 minutes (Gamberale et al. 1978).

Many authors have measured the retention of xylene in the lungs 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; Wallen et al. 1985). Pulmonary retention does not appear to differ on the basis of sex (Senczuk and Orłowski 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 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. 1979). However, absorption was not quantified.

Based on urinary excretion in animals, it appears that xylene is absorbed following oral exposure. Almost complete absorption (87-92%) occurred following ingestion of a dose of 1.8 grams *m*-xylene,

## 2. HEALTH EFFECTS

or of 1.74 grams *o*- or *p*-xylene (Bray et al. 1949). Xylene absorption was also rapid following oral exposure. Peak blood levels of *m*-xylene were observed within 20 minutes after a bolus dose of 0.27 mg/kg/day (Turkall et al. 1992). Absorption in females was significantly more rapid than in males possibly due to availability of more adipose tissue. If *m*-xylene was ingested in the form of xylene adsorbed on sandy or clay soil, the absorption rate was decreased in female rats but unaffected in males (Turkall et al. 1992). If the xylene was adsorbed on sandy soil, the amount absorbed increased both the peak blood levels of *m*-xylene and the total amount of xylene in female versus male rats.

**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 1979b; Riihimaki and Pfaffli 1978). Dermal absorption may occur via exposure to *m*-xylene vapors, as well as through direct dermal contact with the solvent (Dutkiewicz and Tyras 1968; Engstrom et al. 1977; Riihimaki 1979b; Riihimaki and Pfaffli 1978). Absorption of *m*-xylene vapor through the skin was approximately 0.1-2% that via inhalation exposure (Riihimaki and Pfaffli 1978). In humans, the estimated absorption rate following immersion of both hands in *m*-xylene for 15 minutes was approximately 2  $\mu\text{g}/\text{cm}^2/\text{minute}$  (Engstrom et al. 1977). Another study suggested that the rate of absorption was 75-160  $\mu\text{g}/\text{cm}^2/\text{minute}$  (Dutkiewicz and Tyras 1968). The variability in the concentration of test chemicals and purity may account for differences in the results; however, no details were provided. 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).

Limited information is available regarding the absorption of xylene following dermal exposure in animals. Dermal absorption has been shown to occur, since elevated blood levels of *m*-xylene were observed following topical application (Morgan et al. 1991; Skowronski et al. 1990). Permeability of rat skin to *m*-xylene was estimated from blood levels obtained during dermal exposure to liquid *m*-xylene (Skowronski et al. 1990) or *m*-xylene vapors (McDougal et al. 1990). Permeability constants were calculated and were found to be greater than those calculated for humans. *m*-Xylene adsorbed on sandy soil or clay soils showed lower peak absorption than for *m*-xylene alone and clay soil significantly prolonged the absorption half-life, but the total amount absorbed over an unspecified

## 2. HEALTH EFFECTS

period was unchanged (Abdel-Rahman et al. 1993; Skowronski et al. 1990). Also, the absorption of *o*-xylene was examined using excised abdominal skin from rats (Tsuruta 1982). As the time of contact with *o*-xylene increased, the amount of *o*-xylene that penetrated the excised skin increased. The penetration rate was estimated to be 0.967 nmol/cm<sup>2</sup>/minute (Tsuruta 1982). The skin partition coefficient for *m*-xylene was found to be 50.4 ± 1.7 using rat skin *in vitro* (Mattie et al. 1994). *m*-Xylene equilibrated with the skin in 2 hours. Skin partition values for a series of solvents including *m*-xylene correlated well with permeability constants (McDougal et al. 1990), but not with octanol water partition coefficients. 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 the xylene in blood is bound to serum proteins and about 10-15% of the original content is associated with protein-free 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 *m*-xylene or *p*-xylene and their metabolites 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.

## 2. HEALTH EFFECTS

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 possibly by inducing its own metabolism (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 and *o*-xylene have been shown to readily cross the placenta and were distributed in amniotic fluid and embryonic and fetal tissues (Ghantous and Danielsson 1986; Ungvary et al. 1980b). The level detected in fetal tissues (brain, liver, lung, and kidney), 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). Also, higher levels were detected in fetal tissues than in amniotic fluid (Ungvary et al. 1980b).

### 2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans following oral exposure to mixed xylene or xylene isomers. In rats administered *m*-xylene by gavage, fat contained the highest tissue concentration of radioactivity; approximately 0.3% of the dose was found in fat in females and 0.1% in fat in males (Turkall et al. 1992).

### 2.3.2.3 Dermal Exposure

No studies were located regarding distribution of xylene in humans following dermal exposure to mixed xylene or individual isomers. Extremely limited information was located regarding distribution in animals following dermal absorption. One study showed that only 0.01% of the administered dose of xylene could be found bound to the skin at the application site 48 hours after topical application (Skowronski et al. 1990). This amount was doubled if the xylene applied was adsorbed onto clay or sandy soils. The clay soil matrix also increased the amount of *m*-xylene found in fat.

### 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 toluic acids (methylhippuric acids) that are excreted into the urine (Astrand et al. 1978; Norstrom et al. 1989; Ogata et al. 1970,

## 2. HEALTH EFFECTS

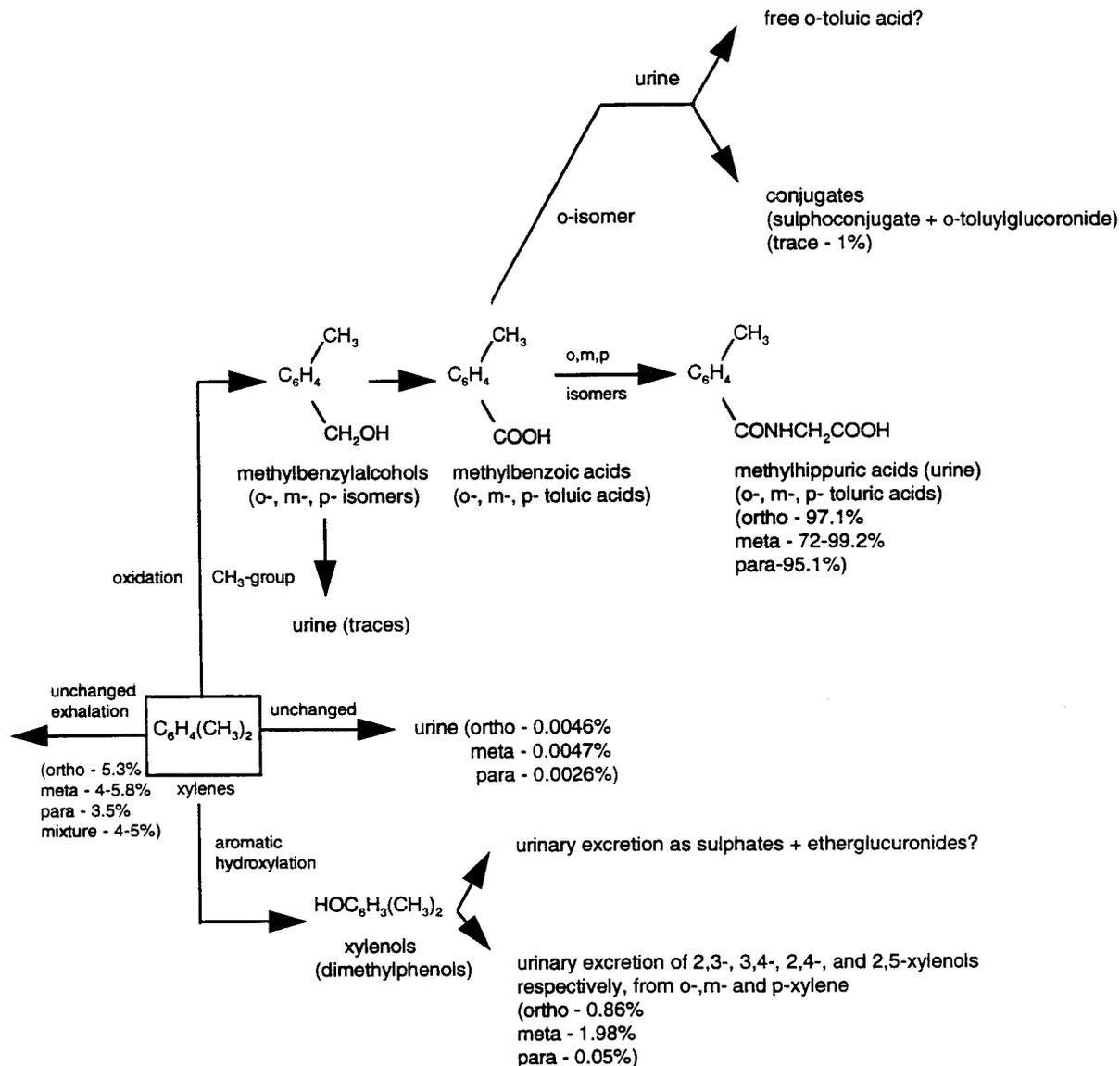
1979; Riihimaki et al. 1979a; Sedivec and Flek 1976b; Senczuk and Orłowski 1978). This metabolic pathway accounts for almost all of the absorbed dose of xylene, regardless of the isomer, the route of administration, the administered dose, or the duration of exposure. Minor metabolic pathways that account 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), xylene mercapturic acid (Norstrom et al. 1988), and 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. 1979; 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 intraperitoneal injection, 10-56.6% 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 was metabolized to the appropriate toluylglucuronide (Ogata et al. 1979; van Doorn et al. 1980). The amounts of *m*-methylhippuric acid and *p*-methylhippuric acid excreted in the urine accounted for 49-63% and 64-75% of the administered dose, respectively (Ogata et al. 1979; Sugihara and Ogata 1978). Similar results were seen in rats administered *m*-xylene by gavage (Turkall et al. 1992). In studies with rabbits, 60% of an administered *o*-xylene dose, 81% of an *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 (Ogata et al. 1979; Turkall et al. 1992; van Doorn et al. 1980). In rats administered *m*-xylene by the dermal route, the major metabolite in the urine over a 24-hour period was identified as methylhippuric acid (82.3%), with xylenol comprising 7.2% and unchanged *m*-xylene comprising 3.8% of the urinary products (Skowronski et al. 1990). In rats given *m*-xylene adsorbed onto sandy soil, the proportion of xylenol present in the urine at over the first 12 hours of excretion was significantly increased.

Studies in animals have also shown that the metabolism of xylene may be influenced by prior exposures to xylene (Elovaara et al. 1989). Pretreatment of rats with *m*-xylene increased the percentage of methylhippuric acid and thioethers in the urine by approximately 10%.

2. HEALTH EFFECTS

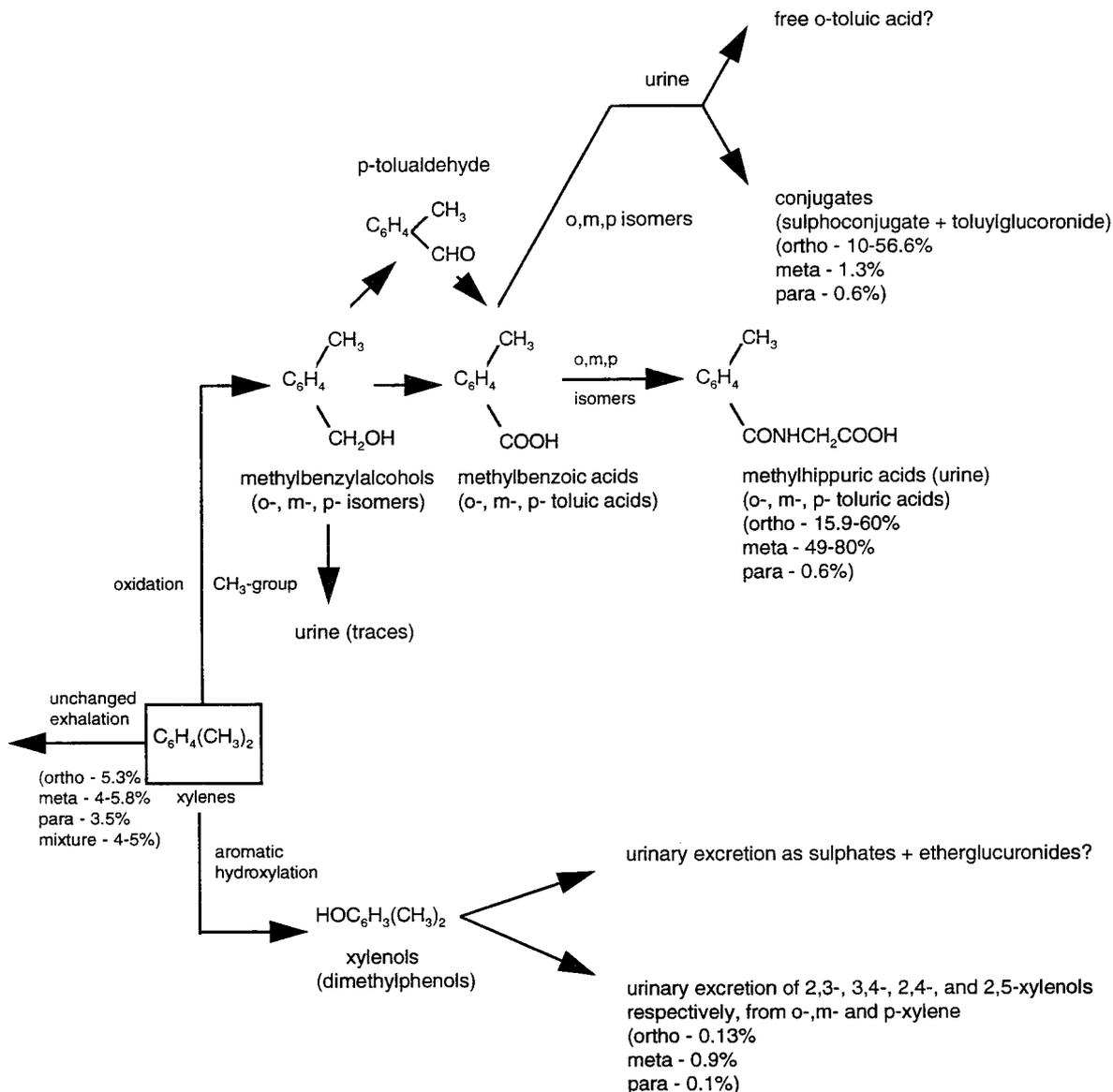
Figure 2-9. Metabolic Scheme For Xylenes - Humans \*



\* Derived from Astrand et al. 1978; Ogata et al. 1980; Riihimaki et al. 1979a, 1979b; Sedivec and Flek 1976b; Senczuk and Orlowski 1978; Toftgard and Gustafsson 1980

2. HEALTH EFFECTS

Figure 2-10. Metabolic Scheme For Xylenes - Animals \*



\* Derived from 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.

## 2. HEALTH EFFECTS

A toxic metabolite of xylene in rats and rabbits appears to be methylbenzaldehyde (tolualdehyde) (Carlone and Fouts 1974; Pate1 et al. 1978; Smith et al. 1982). It is formed by the action of alcohol dehydrogenase on methylbenzyl alcohol in lung and liver tissues. The presence of 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).

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. 1979; 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. 1979; 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  $\mu\text{mol}/\text{minute}$  (Riihimaki et al. 1979a, 1979b). If this limit is approached, other elimination pathways may be activated, such as conjugation with glucuronic acid or aromatic hydroxylation to form xlenols. 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. 1979; Pellizzari et al. 1992; Riihimaki et al. 1979b; Sedivec and Flek 1976b; Senczuk and Orłowski 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 xlenols (Sedivec and Flek 1976b). The excretion of methylhippuric acids is rapid and a significant amount is detected in

## 2. HEALTH EFFECTS

the urine within 2 hours of exposure. The amount of methylhippuric acid increases with time. 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 (half-life: 1 hour) and a slower one (half-life: 20 hours). 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). Physiologically based pharmacokinetic modeling suggests that the urinary excretion of *m*-methylhippuric acid following *m*-xylene exposure of humans is linear at concentrations up to 500 ppm, and that elimination of *m*-methylhippuric acid is slower in individuals with a greater percentage of body fat, e.g., women (Kaneko et al. 1991a, 1991b).

Human volunteers acutely exposed by inhalation to 100 or 200 ppm *m*-xylene for 7 hours 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 acid was detected 24 hours later (Senczuk and Orłowski 1978).

Exercise increased the amount of xylene absorbed and thus increased the amount of *m*-methylhippuric acid and 2,4-xyleneol eliminated in the urine of men exposed to *m*-xylene (Riihimaki et al. 1979b). No saturation of metabolism of xylene occurred. 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). Urinary excretion of methylhippuric acid correlates well with exposure (Kawai et al. 1992; Lapare et al. 1993; Skender et al. 1993), and based on a study of workers occupationally exposed to mixed xylenes (geometric mean TWA 14 ppm), Inoue et al. (1993) estimated a slope of 13 mg methylhippuric acid/L/ppm (11.1 mg/g

## 2. HEALTH EFFECTS

creatinine/ppm) for all three isomers. A sex-related difference in the urinary excretion of methylhippuric acids was not observed (Inoue et al. 1993).

Limited information was located on the elimination of the metabolites of xylene following inhalation exposure of experimental animals. *m*-Methylhippuric acid was also 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 an unspecified number of male volunteers given oral doses of 40 mg/kg/day of *o*-xylene or *m*-xylene, the molar (mol) 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. 1979). More of the *m*-xylene is eliminated as methylhippuric acid than the ortho derivative for *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*-toluic 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. 1979). 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 higher doses, this minor pathway would be used to a greater degree as the major pathway becomes saturated.

Excretion of radioactivity by rats following an oral dose of *m*-xylene showed most excretion occurred in the urine during the first 12 hours after dosing (50-59%) with excretion in exhaled air secondary (8-22%) (Turkall et al. 1992). *m*-Methylhippuric acid comprised 67-75% of the urinary radioactivity, with xylenol comprising 2-18%, and unchanged xylene comprising approximately 1%. The excretion in exhaled air was significantly greater in females (22%) than in males (8%). This suggests a higher metabolic capacity in male than in female rats. When *m*-xylene adsorbed onto sandy soil matrix was administered, the excretion of radioactivity in urine and exhaled air in female rats was significantly decreased compared to *p*-xylene during the first 12 hours (Turkall et al. 1992). Whereas in males, xylene in a sandy or clay soil matrix increased the excretion of radioactivity in exhaled air during the

## 2. HEALTH EFFECTS

first 12 hours. 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-xynenol and 0.03% as 2,3-xynenol, 0.9% of a dose of *m*-xylene as 2,4-xynenol, and 1% of a dose of *p*-xylene as 2,5-xynenol. A trace of the 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 two-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  $\mu\text{mol}/\text{hour}$  at 2 hours following immersion of both hands in *m*-xylene for 15 minutes (Riihimaki 1979b). It decreased to approximately 2 nmol/L at the 5th postexposure hour. These results indicate that although absorption was delayed, it was gradual and protracted.

The major route of excretion in rats following dermal application of *m*-xylene was in expired air (62% of the initial dose) with 43% excretion in the urine (Skowronski et al. 1990). The majority of the excretion in expired air occurred within the first 12 hours, with excretion in the urine occurring primarily during the first 24 hours. The amount excreted in the feces was less than 0.5%. If the *m*-xylene was applied to the skin in the form of a sandy soil matrix, the excretion was similar to that seen with *m*-xylene alone, but if the *m*-xylene was applied adsorbed onto clay soil matrix, approximately equal amounts were excreted in exhaled air and in the urine (46% and 53%, respectively).

**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. 1979; 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 the various metabolites differ. Elimination of xylene isomers is related more to absorption than it is with

## 2. HEALTH EFFECTS

dose or duration of exposure. In rats, 49-62.6% of various doses of *m*-xylene or 64-75% of various doses of *p*-xylene were excreted in the urine as *m*-methylhippuric acid or *p*-methylhippuric acid, respectively (Sugihara and Ogata 1978). Urinary excretion of *o*-toluic acid glucuronide and *o*-methylhippuric acid accounted for 57% and 16% of single intraperitoneal dose of 1,240 mg *o*-xylene/kg given to rats (Ogata et al. 1979). The amount of *o*-toluic acid glucuronide and *o*-methylhippuric acid excreted reached a maximum 8-24 hours after dosing. Mercapturic acid derivatives were present in the urine of rats following an intraperitoneal dose of *m*-, *o*-, or *p*-xylene (Tanaka et al. 1990; van Doorn et al. 1980). The percentages ranged from 0.6% (*p*-xylene) to 10-29% (*o*-xylene).

**2.3.5 Mechanisms of Action**

Although the mechanisms by which xylene exerts its toxic effects on the nervous system, lung, kidney, and developing fetus are not completely understood, a number of theories exist.

The central nervous system toxicity observed during exposure to high concentrations of xylene has been attributed to the liposolubility of xylene in the neuronal membrane (Desi et al. 1967; EPA 1985a; Gerarde 1959; Savolainen and Pfaffli 1980; Tahti 1992). It has been suggested that xylene disturbs the action of proteins essential to normal neuronal function. This is similar to the way general anesthetic agents work, i.e., either by a disruption of the lipid environment in which membrane proteins function or by direct interaction with the hydrophobic/hydrophilic conformation of proteins in the membranes. Changes in levels of various neurotransmitters and lipid composition have been observed in several brain areas following acute- and intermediate-duration exposure to xylene (Andersson et al. 1981; Honma et al. 1983; Savolainen and Seppalainen 1979). It is unclear whether these represent direct effects of xylene or are secondary changes resulting from nonspecific central nervous system depression. 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).

Inhibition of pulmonary microsomal enzymes has been observed by several investigators (Elovaara et al. 1987; Patel et al. 1978; Silverman and Schatz 1991; Smith et al. 1982; Stickney et al. 1989). The exact mechanism of the enzyme inhibition is unknown but has been attributed to the formation of a

## 2. HEALTH EFFECTS

toxic reactive metabolite (such as methylbenzaldehyde) that binds directly to microsomal protein and inactivates the microsomal enzymes (Pate1 et al. 1978; Smith et al. 1982). Direct effects on microsomal membrane fluidity and/or lipid content do not appear to be involved (Stickney et al. 1989). The mechanism for xylene's toxic effects on the kidneys is also unknown, but may be related to formation of reactive metabolites and subsequent irritation or direct membrane fluidization (EPA 1985a). In humans exposed to solvent mixtures containing xylene, the increased urinary levels of  $\beta$ -glucuronidase have been proposed to be due to a faster cellular turnover in the renal tubular epithelium because of a mild toxicity (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 also indicates potential toxic injury to the kidney (Askergren 1982).

The exact mechanism by which mixed xylene or its 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 decreased levels of these hormones may have been due to increased microsomal enzyme activity and increased hormone catabolism.

### 2.4 RELEVANCE TO PUBLIC HEALTH

People 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. Xylene volatilizes rapidly from surface water and soil; therefore, inhalation is the most likely route of exposure to xylene at these sites. The human health effects of xylene 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. Ingestion of xylene may be of concern because of the potential for xylene to contaminate sources of drinking water. Dermal exposure is also of concern because of potential workplace exposure and also general population exposure from use of household products containing xylene. 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. Available case reports, occupational studies, and studies on human volunteers suggest that both short- and long-term xylene exposures

## 2. HEALTH EFFECTS

result in a variety of adverse nervous system effects that include headache, mental confusion, narcosis, alterations in body balance, impaired short-term memory, dizziness, and tremors. Eye and respiratory tract irritation can occur, and pulmonary function may also be affected. The liver and kidney may also be targets of xylene toxicity in humans, although in healthy individuals liver and kidney effects are unlikely to occur at concentrations below those which cause neurological effects and eye and respiratory tract irritation. Additional data are needed to further assess this relationship. Genotoxic and carcinogenic effects of xylene have not been reported in humans or animals. In animals, xylene also produces nervous system and respiratory effects. Animal studies also suggest that the developing fetus may be sensitive to xylene exposure. Higher doses of xylene have produced unconsciousness and death in both humans and animals. Humans can be exposed to mixed xylene and/or its isomers in the industrial environment, in communities surrounding those areas, and in and around hazardous waste sites. 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 xylene could be useful because potentially high levels may be present at hazardous waste sites. Furthermore, studies involving occupational exposure to xylene suggest that it has the potential for bioaccumulation in human adipose tissue. Subgroups of the population may be extremely sensitive, and effects seen at high levels in animals may be predictive of effects in these subgroups at much lower levels.

### **Minimal Risk Levels for Xylene**

#### ***Inhalation MRLs***

- An MRL of 1 ppm has been derived for an acute-duration inhalation exposure (14 days or less) to mixed xylene. This MRL is based on increased reaction times that were observed in 10 male volunteers exposed to xylenes (composition not stated) at 100 ppm for 4 hours (Dudek et al. 1990). That 100 ppm is near the threshold for adverse effects is supported by a study by Gamberale et al. (1978). In this study, no effects on reaction times were observed in 15 male volunteers exposed to xylenes at 100 or 299 ppm (12.8% *p*-, 12.1% *o*-, 54.4% *m*-xylene, 20.7% ethylbenzene) through a breathing valve for 70 minutes (Gamberale et al. 1978). In eight men that exercised during the first 30 minutes of a 70-minute exposure at 299 ppm xylene, reaction time was increased and short-term memory was impaired (Gamberale et al. 1978). Effects of exposure at 100 ppm with exercise were not studied.

## 2. HEALTH EFFECTS

- An MRL of 0.7 ppm has been derived for intermediate-duration inhalation exposure (15 to 364 days) to mixed xylene. This MRL is based on the observation of reduced rotarod performance of offspring (measured on the first 3 days after birth) from rats exposed to 200 ppm technical grade xylene 6 hours/day on gestation days 4-20 (Hass and Jakobsen 1993). No maternal toxicity (body weight, clinical signs) or effects on reproduction and litter end points (e.g., implantations, resorptions, fetal body weight) were observed. A study by Rosengren et al. (1986) in which male and female gerbils were exposed to analytical grade xylene at 0, 160, or 320 ppm continuously for 3 months followed by a 4-month exposure-free period provides further evidence that the nervous system is a target of xylene. Total glial fibrillary acid protein (GFA), a marker of astroglial proliferation, was increased at 320 ppm. At 160 ppm, GFA was increased in the anterior cerebellar vermis, and DNA was increased in the posterior cerebellar vermis. S-100, also an astroglial marker, was not altered at 160 ppm, but was increased in the frontal cerebral cortex at 320 ppm.
- An MRL of 0.1 ppm has been derived for chronic exposure to mixed xylenes. This MRL is based on an increase of subjective symptoms including anxiety, forgetfulness, inability to concentrate, eye and nasal irritation, dizziness, and sore throats reported by workers exposed to xylenes for an average of 7 years at a geometric mean TWA concentration of 14 ppm (Uchida et al. 1993). Hematology, serum biochemistry (total protein, albumin, SCOT, SGPT, alkaline phosphatase, lactate dehydrogenase, leucine aminopeptidase, amylase, BUN, creatinine), and urinalysis measures did not show any effects.

***Oral MRLs***

- An MRL of 1 mg/kg/day has been derived for acute oral exposure (14 days or less) to *p*-xylene. This MRL is based on a NOAEL value for alteration in visual evoked potentials in rats exposed to *p*-xylene (Dyer et al. 1988). The use of a neurological end point for derivation of the MRL is supported by the large number of inhalation and oral studies with xylene that have demonstrated that this is a sensitive end point.
- An MRL of 0.2 mg/kg/day has been derived for intermediate oral exposure (15-364 days) to mixed xylene. This MRL is based on a LOAEL for renal toxicity particularly in female in rats exposed to mixed xylene for 90 days (Condie et al. 1988). Gross necropsy and histopathology

## 2. HEALTH EFFECTS

indicated that females had a dose-related increase in early chronic nephropathy, while males had only slight-to-mild hyaline droplet change. Occupational exposure studies (Askergren 1981, 1982; Askergren et al. 1981b, 1981c; Franchini et al. 1983) suggest that the kidney may be a susceptible target organ in humans.

- An MRL of 0.6 mg/kg/day has been derived for intermediate oral exposure (15-364 days) to *m*-xylene. This MRL is based on a LOAEL for hepatotoxicity (increased plasma alanine aminotransferase and plasma membrane damage) in rats exposed to *m*-xylene for 3.5 weeks (Elovaara et al. 1989).

Data are insufficient for the derivation of oral MRLs for *o*-xylene for any duration period. In addition, no chronic oral MRLs were derived because a chronic LOAEL for a nonserious effect has not been identified. The lowest LOAEL is decreased survival in mice (NTP 1986), a serious effect, from which ATSDR does not derive MRLs.

Because of the extremely complex nature of dermal exposure, ATSDR has not yet established a methodology for deriving dermal MRLs.

The following summary concerning the effects of xylenes does not consider interactions with other chemicals. Studies of interactions of xylene with other chemicals are discussed in Section 2.6.

**Death.** Xylene can be fatal to both humans and animals following inhalation and oral exposure to very high amounts. Death has been observed in animals following dermal exposure to 3,228 mg/kg/day of mixed xylene (Smyth et al. 1962), but no cases regarding death from dermal exposure have been reported in humans. Death in humans and animals appears to be caused by either respiratory failure or ventricular fibrillation after inhalation and/or oral exposure. The amount of xylene necessary to cause death is relatively large in both animals and humans, and reports of death in humans following inhalation exposure to 10,000 ppm xylene occurred in areas of poor ventilation (Morley et al. 1970). 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. Similarly, dermal exposure to small amounts of xylene found in soil is extremely unlikely to result in death.

## 2. HEALTH EFFECTS

**Systemic Effects**

***Respiratory Effects.*** In humans, acute inhalation of 200 ppm mixed xylene for 3-5 minutes produced nose and throat irritation (Nelson et al. 1943). Severe lung congestion with pulmonary hemorrhages and edema was noted in a worker who died following acute inhalation of paint fumes containing about 10,000 ppm xylene (Morley et al. 1970). In addition, chronic occupational exposure to xylene vapors (concentration unspecified) 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 metabolic capacity of the lungs, decreased respiratory rate, labored breathing, irritation of the respiratory tract, pulmonary edema, and pulmonary inflammation (Carpenter et al. 1975a; De Ceaurriz et al. 1981; Elovaara et al. 1987, 1989; Fumas and Hine 1958; Korsak et al. 1988, 1990; Patel et al. 1978; Silverman and Schatz 1991; Toftgard and Nilsen 1982). Therefore it is possible that persons exposed to xylene vapors at hazardous waste sites may experience some nose and throat irritation. Insufficient evidence is available to conclude whether chronic low-level exposure may result in impaired pulmonary function.

***Cardiovascular Effects.*** In some reports, chronic occupational exposure of workers to xylene (concentration unspecified) by inhalation has been associated with increased heart palpitation and abnormal ECGs (Hipolito 1980; Kilbum et al. 1985). However, these 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 (Morvai et al. 1976, 1987) 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 very high levels (unspecified) of xylene have included ventricular repolarization disturbances, atrial fibrillation, arrhythmias, occasional cardiac arrest, and changes in ECG (Morvai et al. 1976). Morphological changes in coronary microvessels have also been observed in rats exposed to 230 ppm xylene (composition unspecified) (Morvai et al. 1987). However, histopathologic lesions of the heart have not been observed in other studies (Carpenter et al. 1975a; Jenkins et al. 1970; NTP 1986; Wolfe 1988a, 1988b). Except during activities such as cleanup activities, it is unlikely that sufficiently high levels

## 2. HEALTH EFFECTS

of exposure would occur acutely at hazardous waste sites to induce disturbances in cardiac rhythms. Data are inconclusive as to whether chronic low-level exposures could result in such changes.

***Gastrointestinal Effects.*** Nausea, vomiting, and gastric discomfort have been noted in workers following inhalation of high concentration of xylene (Goldie 1960; Hipolito 1980; Kilburn et al. 1985; Klaucke et al. 1982; Nersesian et al. 1985); however, these studies did not report the exposure concentrations 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). If sufficiently high levels of exposure occur at hazardous waste sites, some degree of nausea may occur.

***Hematological Effects.*** 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 causes leukemia and other blood dyscrasias in humans, these effects cannot be attributed solely to xylene. An occupational study in which no benzene exposure was involved (Uchida et al. 1993) found no hematological effects. Hematological effects have not been observed in rats, dogs, or guinea pigs exposed by inhalation to 810 ppm mixed xylene or 780 ppm *o*-xylene for an intermediate period (Carpenter et al. 1975a; 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.

***Musculoskeletal Effects.*** Workers occupationally exposed to relatively low concentrations of mixed xylene reported reduced grasping power and reduced muscle power in the extremities more frequently than unexposed controls (Uchida et al. 1993). Animal data regarding musculoskeletal effects following xylene exposure are limited. Microscopic examination of skeletal muscle of rats exposed for an intermediate period of time to 810 ppm mixed xylene, 800 ppm *m*-xylene, or 800 ppm *p*-xylene revealed no treatment-related lesions (Carpenter et al. 1975a; NTP 1986; Wolfe 1988a, 1988b). Thus, effects on the musculoskeletal system appear to be unlikely to result from exposures to xylene at hazardous waste sites.

## 2. HEALTH EFFECTS

***Hepatic Effects.*** Human data regarding the hepatic effects following inhalation of xylene are limited to several case and occupational studies (Dolara et al. 1982; Klaucke et al. 1982; Kurppa and Husman 1982; Morley et al. 1970; Uchida et al. 1993). 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 acute exposure to 2,000 ppm and intermediate exposure to 345 or 800 ppm mixed xylene and/or individual isomers produce a variety of mild hepatic effects (Elovaara 1982; Elovaara et al. 1980; Patel et al. 1979; Savolainen et al. 1978; Toftgard and Nilsen 1981, 1982; Toftgard et al. 1981; Ungvary 1980a, 1980b; 1990), and they provide evidence that humans might be at increased risk of developing such effects following xylene exposure to high concentrations. Effects seen in animals include: increased hepatic cytochrome P-450 and b5 content, increased hepatic weight, increased liver-to-body weight ratios, decreased hepatic glycogen, proliferation of 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; 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 were probably caused by an increased rate of metabolism by the liver and were not necessarily adverse effects (EPA 1985a; Tatrai et al. 1981). Thus, it is unlikely that hepatotoxicity would result from exposures at hazardous waste sites.

***Renal Effects.*** The available human studies that investigated 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 at high concentrations (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  $\beta$ -glucuronidase, and increased urinary excretion of albumin, erythrocytes, and leukocytes (Askergren 1982; Franchini et al. 1983; Morley et al. 1970). No renal effects were observed following occupational exposure at low concentrations (Uchida et al. 1993). 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

## 2. HEALTH EFFECTS

noted in studies with rats, guinea pigs, dogs, and monkeys exposed at xylene concentrations of 50-2,000 ppm 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, atrophy and increased amounts of hyaline droplets consistent with early chronic nephropathy were observed, although in studies by Carpenter et al. (1975a) and Jenkins et al. (1970) the biochemical changes were not associated with any histopathologic lesions of the kidney.

***Endocrine Effects.*** Potential endocrine effects of xylenes have not been well studied. There are no available data regarding endocrine effects in humans. Inhalation exposure of dogs to 810 ppm mixed xylene for 13 weeks produced no adverse adrenal, thyroid, or parathyroid effects (Carpenter et al. 1975a).

***Dermal Effects.*** Dermal exposure of humans to xylene causes skin irritation, dryness and scaling of the skin, and vasodilation (Engstrom et al. 1977; Riihimaki 1979b). In addition, contact urticaria can develop after occupational exposure to xylene vapors (Palmer and Rycroft 1993). Animal data provide additional evidence that dermal exposure to xylene produces dermal effects. These included skin erythema and edema, eschar formation in some animals, and epidermal thickening (Hine and Zuidema 1970). Thus, skin irritation may result from exposure to high levels of xylene at hazardous waste sites.

***Ocular Effects.*** Exposure of humans to 460 ppm xylene vapors causes ocular irritation (Carpenter et al. 1975a; Hake et al. 1981; Klaucke et al. 1982; Nelson et al. 1943; Nersesian et al. 1985). Direct instillation of xylene into the eyes of rabbits results in slight-to-moderate eye irritation (Consumer Product Testing 1976; Hine and Zuidema 1970; Smyth et al. 1962). Therefore, exposure to high concentrations of xylene at hazardous waste sites may result in eye irritation.

***Body Weight Effects.*** Body weight changes have been reported in animals exposed to xylenes at 1,096 ppm by inhalation (Tatrai et al. 1981) and following oral exposure at doses >200 mg/kg/day (Condie et al. 1988; NTP 1986; Pyyko 1980; Wolfe 1988a). Body weight changes in animals have not been examined following dermal exposure to xylenes. The significance of the limited animal data to human health is not known.

## 2. HEALTH EFFECTS

**Metabolic Effects.** A single report of metabolic acidosis in a man who sniffed paint containing xylenes suggests that xylene may have the potential to cause metabolic effects (Martinez et al. 1989). Animal studies showing metabolic effects of xylenes were not available.

**Immunological and Lymphoreticular Effects.** Very few human and animal data are available to evaluate the immunological and lymphoreticular effects of xylene. Decreased lymphocyte count (Moszczynsky and Lisiewicz 1983, 1984a) and decreased serum complement (Smolik et al. 1973) were reported in workers exposed to 0.13 ppm xylene and other solvents for 0.25-18 years. Immunological contact urticaria has been reported in a worker exposed to xylene vapor (Palmer and Rycroft 1993). In mice exposed acutely to xylene, no effect on natural killer cell activity was observed (Selgrade et al. 1993). Repeated oral exposure of rats to 2,000 mg/kg/day *p*-xylene caused decrease in thymus and spleen weights (Condie et al. 1988); however, no histopathological changes in the thymus or spleen were found. Therefore, the relevance of these findings to public health is not precisely known, although reduced immune function may be an inferred probability because of xylene's effects on both lymphocytes (human) and thymus (animals).

**Neurological Effects.** Neurological effects in humans following oral or dermal exposure to xylene have not been studied. Results of experimental studies with humans indicate that acute inhalation exposure to 100 ppm mixed xylene or 200 ppm *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 Linnavuo 1979; Savolainen and Riihimaki 1981 a; Savolainen et al. 1979b, 1980a, 1984; 1985a). 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 Cumock 1982; Goldie 1960; Hipolito 1980; Klaucke et al. 1982; Morley et al. 1970; Nersesian et al. 1985; Roberts et al. 1988; Uchida et al. 1993). In several case reports, isolated instances of unconsciousness, amnesia, brain hemorrhage, and seizures have been associated in a limited number of individuals with acute inhalation exposure to solvent mixtures containing xylene (Arthur and Cumock 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 at concentrations ranging from 160 to 2,000 ppm. Signs of neurotoxicity observed in rats, mice, and gerbils following acute and

## 2. HEALTH EFFECTS

intermediate inhalation exposure to the various xylene isomers have included narcosis, prostration, incoordination, tremors, muscular spasms, labored respiration, 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. 1975a; De Ceaurriz et al. 1983; Fumas 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, 1979a; Wimolwattanapun et al. 1987). Studies in animals also show that oral exposure to xylene may result in nervous system effects such as tremors, respiratory depression, weakness, lethargy, unsteadiness, and hyperactivity (Condie et al. 1988; NTP 1986). If persons are exposed to high concentrations of xylene by the inhalation or oral routes, they may experience adverse effects on the nervous system.

**Reproductive Effects.** The relevance to public health regarding xylene exposure and adverse reproductive effects is not known because of the limited 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 500 ppm 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 at 800 and 1,000 mg/kg/day of xylene, respectively (NTP 1986; Wolfe 1988a, 1988b). No other studies were located regarding reproductive effects in animals following inhalation or dermal exposure to xylene or its isomers. Therefore, the relevance of the findings in available animal studies to public health is not known.

**Developmental Effects.** 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 offspring of women exposed to very high levels of xylene or its isomers during pregnancy. Results of studies with rats and mice indicate that inhalation exposure to 500 ppm mixed xylene or 700 ppm *m*-xylene, 350 ppm *o*-xylene, or 691 ppm *p*-xylene may induce increased fetal death, decreased fetal weight, delayed skeletal development, skeletal anomalies, enzymatic changes in fetal organs, and maternal toxicity (Bio/dynamics 1983; Hudak and Ungvary 1978; Marks et al. 1982;

## 2. HEALTH EFFECTS

Mirkova et al. 1983; Ungvary et al. 1980b, 1981). Decreased rotarod performance was observed in 1- and 2-day-old rat pups exposed to 200 ppm mixed xylenes on gestation days 4-20 (Hass and Jakobsen 1993). Oral exposure to 2,060 mg/kg/day 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 maternal toxicity but no developmental effects in rats (Rosen et al. 1986). These studies were generally limited but, taken together, suggest fetotoxic effects, although most of these are secondary to maternal toxicity. The possibility that offspring of women exposed to xylene may be adversely affected cannot be eliminated.

**Genotoxic Effects.** Mixed xylene, and the individual xylene isomers, have 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 2-1 1 and 2-12) following *in vitro* exposure (Anderson et al. 1990; Bos et al. 1981; Connor et al. 1985; DeMarini et al. 1991; Florin et al. 1980; Haworth et al. 1983; Litton Bionetics 1978b; McCarroll et al. 1981a, 1981b; NTP 1986; Richer et al. 1993; 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 (Mohtashampur 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; Richer et al. 1993). All human studies involved occupational exposure to other chemicals in addition to xylene. As summarized in Table 2-12, 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. *Salmonella 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; Hejtmanikova 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 *Escherichia coli* strain Sd-4-73 (Szybalski 1958).

TABLE 2-11. Genotoxicity of Xylene *In Vitro*

Species (test system)	End point	Results		Reference	Isomer
		With activation	Without activation		
Prokaryotic organisms:					
<i>Salmonella typhimurium</i> TA97, TA98, TA100, TA1535/plate incorporation assay	Mutation	—	—	NTP 1986	Mixed xylene
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537/plate incorporation assay	Mutation	—	—	Haworth et al. 1983	<i>m</i> -Xylene <i>o</i> -Xylene <i>p</i> -Xylene
<i>S. typhimurium</i> TA98, TA100, UTH8414, UTH8413/plate incorporation assay	Mutation	— — —	— — —	Connor et al. 1985	<i>m</i> -Xylene <i>o</i> -Xylene <i>p</i> -Xylene
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538/plate incorporation assay	Mutation	— — —	— — —	Bos et al. 1981	<i>m</i> -Xylene <i>o</i> -Xylene <i>p</i> -Xylene
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537/spot and plate incorporation assays	Mutation	— —	— —	Florin et al. 1980	<i>m</i> -Xylene <i>p</i> -Xylene
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538/suspension and plate incorporation assays	Mutation	—	—	Litton Bionetics 1978b	Mixed xylene

TABLE 2-11. Genotoxicity of Xylene *In Vitro* (continued)

Species (test system)	End point	Results		Reference	Isomer
		With activation	Without activation		
<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538/plate incorporation assay	Mutation	—	—	Shimizu et al. 1985	<i>p</i> -Xylene
<i>Escherichia coli</i> WP2uvrA/plate incorporation assay	Mutation	—	—	Shimizu et al. 1985	<i>p</i> -Xylene
<i>E. coli</i> WP2 ( $\lambda$ ) (Ionii, sulA1, trpE65, uvrA155, lamB <sup>+</sup> ), microscreen prophage-induction assay	Mutation	—	—	DeMarini et al. 1991	Mixed xylene
<i>E. coli</i> WP2, WP2uvrA, WP67, CM611, WP100, W3110polA <sup>+</sup> , p3478pola <sup>-</sup> /DNA repair microsuspension assay	DNA damage	—	—	McCarroll et al. 1981b	Not reported (technical grade)
<i>Bacillus subtilis</i> H17, M45/modified rec assay	DNA damage	—	—	McCarroll et al. 1981a	Not reported (technical grade)
Eukaryotic organisms:					
<i>Saccharomyces cerevisiae</i> D4/suspension and plate incorporation assays	Mitotic gene conversion	—	—	Litton Bionetics 1978b	Mixed xylene

TABLE 2-11. Genotoxicity of Xylene *In Vitro* (continued)

Species (test system)	End point	Results		Reference	Isomer
		With activation	Without activation		
Mammalian cells:					
Cultured mouse lymphoma cells (L5178Y, TK+/-)/forward mutation assay	Mutation	-	-	Litton Bionetics 1978b	Mixed xylene
Cultured human lymphocytes	Sister chromatid exchange and chromosomal aberrations	Not tested	-	Gerner-Smidt and Friedrich 1978	Not reported
Cultured human lymphocytes	Sister chromatid exchange	Not tested	-	Richer et al. 1993	Mixed xylene
Cultured Chinese Hamster ovary cells	Sister chromatid exchange and chromosomal aberrations	-	-	Anderson et al. 1990	Mixed xylene
Cultured Chinese Hamster ovary cells	Chromosomal aberrations	-	-	Anderson et al. 1990	Mixed xylene

- = negative result

TABLE 2-12. Genotoxicity of Xylene *In Vivo*

Species (test system)	End point	Exposure route	Results	Reference	Isomer
Mammalian cells:					
Human peripheral lymphocytes	Sister chromatid exchange and chromosomal aberrations	Inhalation (occupational exposure)	—	Haglund et al. 1980	Not reported
Human peripheral lymphocytes	Sister chromatid exchange	Inhalation (occupational exposure)	—	Pap and Varga 1987	Mixed xylene
Human peripheral lymphocytes	Sister chromatid exchange	Inhalation (three exposures)	—	Richer et al. 1993	Mixed xylene
Rat bone marrow aberrations	Chromosomal (single exposure)	Intraperitoneal	—	Litton Bionetics 1978b	Mixed xylene (11.4% <i>o</i> -xylene, 0.3% <i>p</i> -xylene, 36.1% ethylbenzene)
Rat bone marrow aberrations	Chromosomal (five exposures)	Intraperitoneal	—	Litton Bionetics 1978b	Mixed xylene (0.3% <i>p</i> -xylene, 36.1% ethylbenzene)
Mouse bone marrow polychromatic-erythrocyte assay (micronucleus test)	Micronuclei formation	Intraperitoneal (two exposures)	— — —	Mohtashami-pur et al. 1985	<i>m</i> -Xylene, <i>o</i> -Xylene, <i>p</i> -Xylene
Rat sperm-head morphology assay	Sperm-head abnormalities	Intraperitoneal	—	Washington et al. 1983	<i>o</i> -Xylene

— = negative result

## 2. HEALTH EFFECTS

Ethylbenzene, a common component of many technical grades of mixed xylene, also demonstrated no mutagenic effects in the gene reversion assay with *Saccharomyces 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. 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). Thus, 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 suggests that xylene metabolites, specifically *m*-xylenol, *p*-xylenol, 2,4-dimethylphenol, and *o*-methylbenzyl alcohol, are also nonmutagenic.

**Cancer.** Very limited data were available regarding the development of cancer in humans following inhalation, oral, or dermal exposure to mixed xylene or individual isomers (Arp et al. 1983; Wilcosky et al. 1984). Animal carcinogenicity data for the xylenes are limited to equivocal oral studies with 500 or 1,000 mg/kg/day mixed xylene (Maltoni et al. 1983, 1985; NTP 1986) and dermal initiation/promotion study (Berenblum 1941; Pound 1970; Pound and Withers 1963). Xylene did not promote benz[a]pyrene skin tumors (Berenblum 1941), but did increase the number of skin tumors resulting from an initiating exposure to ultraviolet light or urethane followed by croton oil treatment (promotion) (Pound 1970; Pound and Withers 1963). No animal carcinogenicity data for xylene 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. The NTP has not classified xylene as to its carcinogenicity. Also, both IARC (1989) and EPA have determined that xylene is not classifiable as to its carcinogenicity in humans (IRIS 1994).

## 2. HEALTH EFFECTS

**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(s) or cell(s) 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(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (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 samples can be taken. It may be 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 not often 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 substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed

## 2. HEALTH EFFECTS

dose, a decrease in the biologically effective dose, or a 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 Xylene**

Xylene levels in the blood and levels of its metabolite, methylhippuric acid, in the urine are the primary markers used to detect exposure to xylene. 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. Moreover, there is no data on background concentrations of xylene in blood or urine. Xylenes are metabolized almost exclusively to methylhippuric acids in humans. Detection of methylhippuric acid in the urine is the most widely used indicator of xylene exposure (ACGIH 1986). A strong association has been shown between urinary methylhippuric acid concentrations and exposure to xylene (Daniel 1 et al. 1992; Jonai and Sato 1988; Kawai et al. 1991); during an 8-hour workshift, a concentration of 57.8 mg/L of methylhippuric acid isomers (i.e., all isomers combined) was found to correlate with exposure to 3.8 ppm (geometric mean concentration) of total xylenes (Kawai et al. 1991). In a study of Chinese men and women occupationally exposed to mixed xylenes, Inoue et al. (1993) estimated that 13 mg of methylhippuric acid would be excreted in a liter of urine for each ppm of xylene exposure (or 11.1 mg/g creatinine/ppm). This relationship was true for both men and women as well as for mixed and individual isomers. 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 1 or 2 days of exposure to xylene, 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). Since the methylhippuric acid background levels in persons not exposed to xylenes are very low, methylhippuric acids are specific markers for xylenes, except for exposure to alkyl toluenes in which the number of carbon atoms in the alkyl group is odd. A minor metabolite of xylene, *N*-acetyl-*S*-xylyl cysteine (a trioether), may also be detected in the urine (Tanaka et al. 1990; van Doorn et al. 1980); however, it is at such low levels in the urine during experimental exposures that it is ineffective as a biomarker (Norstrom et al. 1988). For additional information on the kinetics of xylene absorption, distribution, metabolism, or excretion, see Section 2.3.

## 2. HEALTH EFFECTS

**2.5.2 Biomarkers Used to Characterize Effects Caused by Xylene**

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; Pate1 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 1981a; 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 SUBSTANCES**

The interaction of xylene with alcohol, drugs (aspirin, phenobarbital), and various solvents (1,1,1-trichloroethane, benzene, toluene, ethylbenzene, methyl ethyl ketone) has been evaluated in experimental studies with humans and animals. Xylene has a high potential to interact with numerous substances because the isomers induce microsomal enzymes in the liver (Blanchard and Morris 1994; Liira et al. 1991), while microsomal enzymes in the lungs are inhibited by xylene exposure (Blanchard and Morris 1994; Elovaara et al. 1987; Pate1 et al. 1978; Silverman and Schatz 1991; Toftgard and Nilsen 1982). Which enzymes will be affected is isomer dependent. For example, *m*-xylene is a more potent inducer of P-450 2B enzymes than *p*-xylene (Backes et al. 1993). The isomer differences, as well as organ differences in effects on xenobiotic metabolizing enzymes, make it difficult to predict the interaction of xylene with other substances.

The effects from combined exposure to xylene and ethanol have been studied most extensively because of the reasonable expectancy that some workers will consume alcoholic beverages and subsequently

## 2. HEALTH EFFECTS

might 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, resulting in elevated blood levels of xylene and decreased excretion of methylhippuric acid (Elovaara et al. 1980; Riihimaki et al. 1982a, 1982b; Romer et al. 1986; Savolainen 1980; Savolainen et al. 1978, 1979b, 1980b). A kinetic study in rats (Kaneko et al. 1993) suggests that ethanol inhibition of xylene metabolism occurs only at high concentrations (500 ppm). Paradoxically, ethanol pretreatment causes additive effects with xylene in inducing microsomal enzymes in the liver (Wisniewska-Knypl et al. 1989). This would enhance the metabolic capacity of the liver and modify biological effects of other chemicals that are either detoxified or converted to toxic metabolites by the microsomal enzymes. In summary, it cannot be stated with certainty whether alcohol and xylene would interact to produce synergistic or antagonistic effects in humans and animals because there are reasons why both would occur.

Combined exposure to ethanol and xylene results in macrocytosis and decreased erythrocyte membrane fluidity (Wronska-Nofer et al. 1991). These effects were not observed when either chemical was administered alone. It is unclear whether this interaction is pharmacological or pharmacokinetic in nature.

Acute inhalation exposure to a mixture of toluene and xylene resulted in more than additive respiratory and central nervous system toxicity (Korsak et al. 1988, 1992). Elevated blood levels of xylene and toluene and decreased excretion of the major metabolites of xylene and toluene in the urine (Tardif et al. 1992) suggest mutual metabolic inhibition. However, simultaneous exposures in humans indicate that a threshold exists for this interaction (Tardif et al. 1991). No increase in blood levels of these substances was observed during combined exposures to 50 ppm toluene and 40 ppm xylene over 3 consecutive days, whereas increases in blood levels and levels in exhaled air were observed during a combined 4-hour exposure to 95 ppm toluene and 80 ppm xylene. Thus, combined exposures at below threshold level are unlikely to produce greater than additive toxicity (Tardif et al. 1991). A physiologically based toxicokinetic modeling study using rat data suggests that the interaction between toluene and xylene is competitive, with toluene a more potent inhibitor of xylene metabolism than xylene is of toluene metabolism (Tardif et al. 1993a, 1993b).

Exposure to xylene combined with benzene or ethylbenzene may also produce mutual inhibition of the metabolism of both solvents (Engstrom et al. 1984; Nakajima and Sato 1979b). Ethylbenzene is found

## 2. HEALTH EFFECTS

in commercial xylene. In contrast, ethyl acetate exposure in combination with exposure to *m*-xylene caused a reduction in blood xylene levels (Freundt et al. 1989).

Combined exposures to *m*-xylene and methyl ethyl ketone (2-butanone) produced a synergistic induction of microsomal enzymes (Liira et al. 1991), but the metabolism of *m*-xylene to methylhippuric acid in humans was inhibited with corresponding increases in levels of xylene in blood and fat (Liira et al. 1988, 1991). While the side-chain oxidation of xylene to methylhippuric acid was inhibited, an increase in ring oxidation (xylenol production) was observed (Liira et al. 1991), indicating that the inhibition was specific to a particular oxidation reaction. Thus, it is not known as to whether 2-butanone and *m*-xylene would interact to produce additive or antagonist effects in humans and animals.

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 and peripheral nerve effects were observed when rats were exposed to *n*-hexane and xylene simultaneously (Nylén et al. 1989, 1994), although combined exposure to xylene and *n*-hexane increased loss of auditory sensitivity (Nylén et al. 1994). Bromobenzene, which requires metabolic activation, showed greater toxicity to the liver in *p*-xylene exposed rats, while lung toxicity was not affected (Day et al. 1992).

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 during inhalation exposure to xylene caused greater than additive potentiation of maternal and fetal toxic effects (Ungvary 1985). This was postulated to be due to the interference with metabolism of aspirin by xylene and vice versa.

## 2. HEALTH EFFECTS

Exposure to xylene has been shown to inhibit several microsomal enzymes in the lung (Blanchard and Morris 1994; Elovaara et al. 1987; Patel et al. 1978; Silverman and Schatz 1991; Toftgard and Nilsen 1982). Intraperitoneal administration of *m*-xylene to rats has been shown to alter the pulmonary microsomal metabolism of benzo[a]pyrene resulting in inhibition of its detoxification and increased production of toxic, mutagenic metabolites (bay region diols) (Stickney et al. 1991). Xylene acts as a promotor or cocarcinogen for the induction of skin tumors in mice (Pound 1970). The findings could be relevant in combined human exposures to xylene and polyaromatic hydrocarbons present in cigarette smoke and combustion emissions and especially to petrochemical workers who could be exposed to xylene, crude oils (promotor), and ultraviolet light (initiator).

In addition to interacting with other chemicals, exposure to xylene at high concentrations has also been shown to increase the effects of a virus. Acute exposure of mice to 1,208 ppm (but not 595 ppm) *p*-xylene (4 days, 4 hours/day) increased the mortality resulting from the murine cytomegalovirus (Selgrade et al. 1993). This effect was a result of potentiation of the liver damage caused by the virus rather than an immunological effect.

### 2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to xylene than will most persons exposed to the same level of xylene in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as nutritional deficiencies), and substance exposure history (including smoking). These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects on clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

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;

## 2. HEALTH EFFECTS

Holmberg and Nurminen 1980; Hudak and Ungvary 1978; Kucera 1968; Marks et al. 1982; Mirkova et al. 1983; Ungvary et al. 1980b, 1981). Although no human studies were located indicating maternal or fetal toxicity following mixed xylene exposure, animal studies that involved exposure to *m*-xylene and aspirin or xylene alone suggest there may be a relationship between exposure to the agents and developmental effects (Hudak and Ungvary 1978; Marks et al. 1982; Ungvary 1985; Ungvary et al. 1980b, 1981). In summary, although it is not clear how toxic xylene might be to fetuses and infants, for safety's sake caution is urged. 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). Thus, for pregnant women exposed to xylene, ingestion of aspirin is likely to potentiate adverse effects of xylene in both the mother and the offspring.

People with subclinical and clinical epilepsy are at increased risk of seizures if exposed to xylene because of its excitatory central nervous system effects (Arthur and Cumock 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, 1980b) 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. 1980b).

People with clinical or subclinical renal, hepatic, or cardiac disease may be more susceptible to the effects of xylene. Evidence from occupational and case studies indicates that exposure to high levels of 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; 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 with regard to the adverse effects of xylene following inhalation exposure (Hipolito 1980; Morley et al. 1970).

Data from toxicokinetic studies regarding xylene adsorbed to soils have shown that the bioavailability of xylene in females that have ingested xylene adsorbed to soil is greater than when xylene is ingested alone (Turkall et al. 1992). Thus, females (e.g., female toddlers) that ingest xylene adsorbed to soil

## 2. HEALTH EFFECTS

particles may have an increased risk of adverse health effects. Also, the bioavailability of dermally absorbed xylene adsorbed to clay soils is greater than the bioavailability of dermally absorbed pure xylene (Skowronski et al. 1990). Although the complexities of exposure to xylene-contaminated soil are not well characterized, it seems reasonable to assume that it would require excessive dermal contact with or oral ingestion of heavily contaminated soil to receive a toxic dose through such a route alone.

### 2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to xylene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to xylene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

#### 2.8.1 Reducing Peak Absorption Following Exposure

General recommendations reported for reducing absorption following acute high-dose exposure to xylene include removal of the patient from the source of exposure to fresh air and decontamination of the skin with mild soap and water (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; HSDB 1992; Stutz and Janusz 1988). When the eyes have been involved, copious rinsing with tepid water or normal saline has been used for decontamination (Bronstein and Currance 1988; HSDB 1992; Stutz and Janusz 1988).

The use of emetics and gastric lavage to reduce xylene absorption following ingestion has been recommended only under certain conditions. Xylene causes severe aspiration pneumonitis (Ellenhorn and Barceloux 1988); therefore, it has been recommended that measures used to remove xylene from the gastrointestinal tract limit the possibility of aspiration. Emesis with syrup of ipecac has been suggested only when very large quantities have been ingested (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; HSDB 1992) or another highly toxic substance has been ingested together with xylene (Goldfrank et al. 1990). Emesis has been contraindicated if unprovoked emesis has already occurred or if the patient is not alert or has an impaired gag reflex (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; HSDB 1992). Gastric lavage has been used to empty the stomach contents

## 2. HEALTH EFFECTS

when emesis is contraindicated, but provisions such as the use of a cuffed endotracheal tube have been recommended to limit the possibility of aspiration (Goldfrank et al. 1990; HSDB 1992). In summary, emesis or gastric lavage is recommended to reduce xylene absorption from the gastrointestinal tract only when one is certain that aspiration is not likely to occur.

Although the use of activated charcoal and/or cathartics to limit intestinal absorption are recommended in some treatment protocols (HSDB 1992; Stutz and Janusz 1988), their use has been reported to be equivocal (Ellenhorn and Barceloux 1988). No studies have shown that activated charcoal is effective in adsorbing petroleum distillates or that cathartics are effective in speeding excretion (Goldfrank et al. 1990). Furthermore, because of low viscosity, oil-based cathartics may increase aspiration pneumonitis and absorption (Goldfrank et al. 1990).

### 2.8.2 Reducing Body Burden

In acute exposure situations, most xylene absorbed by the body is excreted in the urine or exhaled air within a day after exposure (see Section 2.3.4). However, charcoal hemoperfusion has been used to speed the removal of xylene from the body and to reverse its acute toxicity (Recchia et al. 1985). Sevcik et al. (1992) also used hemoperfusion and hemodialysis in an attempt to speed removal of xylene. Whether the relative gain from these treatment methods is worth the body burden and other potential risks remains to be established. A small percentage of absorbed xylene is retained in body fat. It has been suggested that over a prolonged period of exposure, significant amounts of xylene could accumulate in adipose tissue (Astrand 1982; Engstrom and Bjurstrom 1978). However, xylene has been shown to induce its own metabolism with the result that greater amounts of metabolites are excreted and less is available for storage (Elovaara et al. 1989; Savolainen et al. 1979a). No information was located regarding methods for reducing adipose stores of xylene. Use of agents known to induce microsomal enzyme activity is a possible experimental method for enhancing excretion of xylene released from adipose stores.

### 2.8.3 Interfering with the Mechanism of Action for Toxic Effects

No information was located on established therapies designed to interfere with the mechanism of action of xylene. However, some speculation is possible regarding areas for future research in this regard. For example, the central nervous system toxicity of xylene is believed to be similar to that

## 2. HEALTH EFFECTS

produced by other nonspecific central nervous system depressants (Desi et al. 1967; EPA 1985a; Gerarde 1959; Savolainen and Pfaffli 1980; Tahti 1992). If circulating xylene levels could be reduced, then the central nervous system toxicity may likewise be reduced (see Section 2.8.2).

Since the exact metabolite responsible for the pulmonary toxicity of xylene has not been identified, it is difficult to speculate on steps to avert its synthesis or speed its excretion. In animals, selective inactivation of enzymes can result in damage to tissue caused by the toxic metabolite of xylene, methylbenzaldehyde. This effect has not been confirmed in humans. Decreased pulmonary microsomal enzyme activity was seen in rats administered a single dose or repeated doses of *p*-xylene for 3 weeks (Elovaara et al. 1989; Patel et al. 1978). However, the inhibition of pulmonary microsomal enzymes decreases to some extent with continued exposure to xylene (Silverman and Schatz 1991); this may indicate that xylene-induced activation of metabolizing enzymes and thereby acceleration of its own metabolism (Elovaara et al. 1989) may be limiting the production of the toxic metabolite. Exposure to other agents known to induce microsomal enzyme activity may also limit the production of an unidentified toxic metabolite.

The available information on the mechanisms of renal and fetotoxicity is insufficient to allow speculation on potential means for blocking these effects.

### 2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, 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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

## 2. HEALTH EFFECTS

**2.9.1 Existing Information on Health Effects of Xylene**

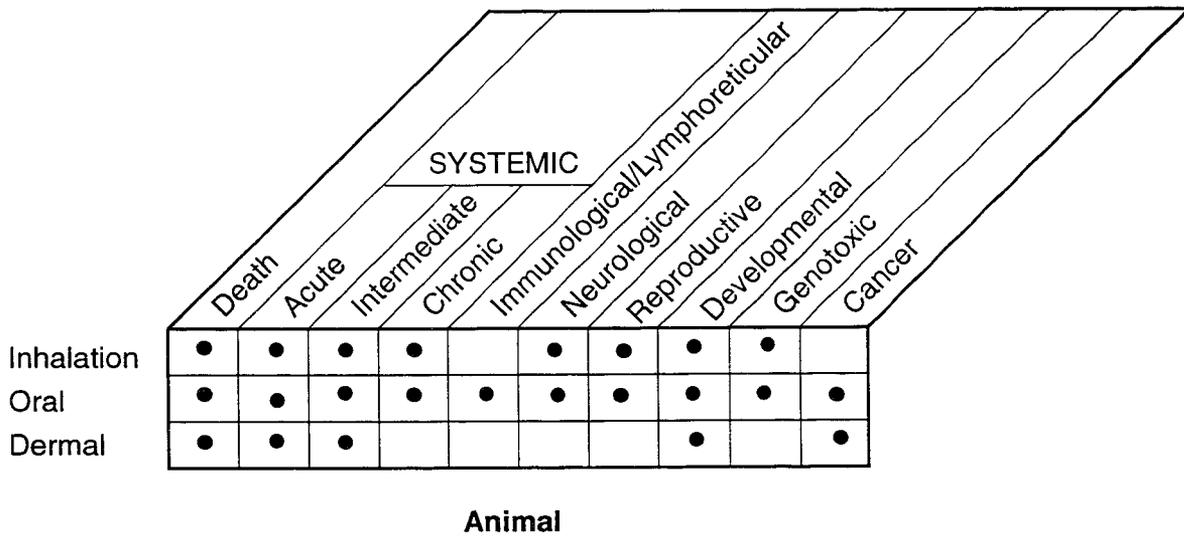
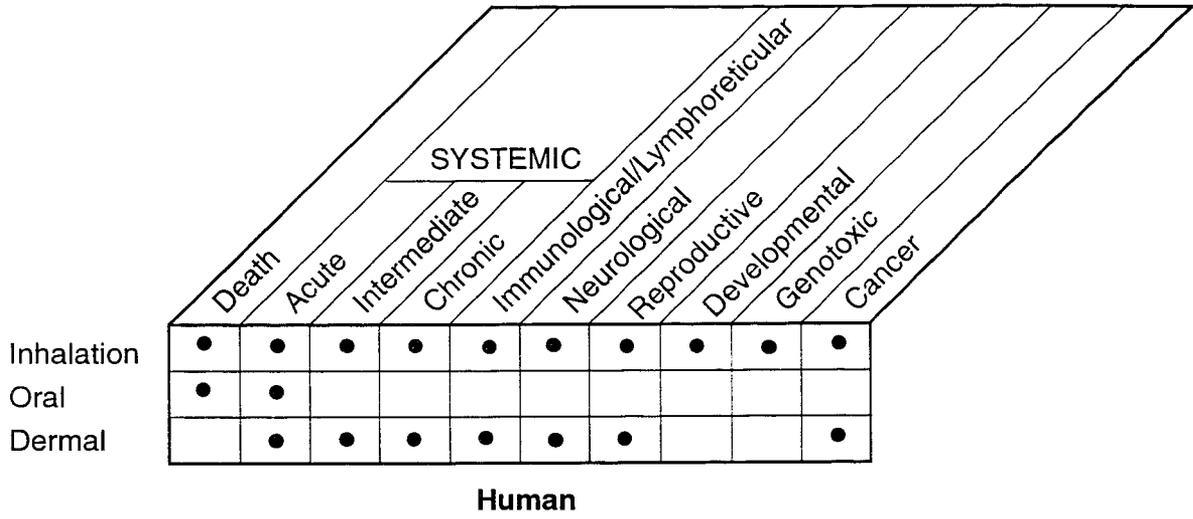
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to xylene are summarized in Figure 2-1 1. The purpose of this figure is to illustrate the existing information concerning the health effects of xylene. Each dot in the figure indicates that one or more 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.” A data need, as defined in ATSDR’s Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

People 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 xylene from surface water and soil occurs rapidly; therefore, inhalation is the most likely route of exposure to xylene at these sites. The human health effects of xylene 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. The bulk of the information on health effects in humans associated with dermal exposure comes from reports of occupational exposures, which are likely to be combined inhalation and dermal exposures. As noted above, ingestion of xylene may be of concern because of the potential for xylene to contaminate sources of drinking water (groundwater) and certain soils. 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 inhalation exposure of humans to xylene has resulted in hepatic and cardiovascular effects as well as neurologic effects. Very limited data regarding the systemic health effects of intermediate-duration human exposure to xylene were located in the literature. Also, very limited 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

2. HEALTH EFFECTS

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



● Existing Studies

## 2. HEALTH EFFECTS

inhaled xylene vapor is difficult because of study design limitations, such as 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.

### 2.9.2 Identification of Data Needs

**Acute-Duration Exposure.** There are acute exposure data in humans and/or animals that indicate that the central nervous system (Andersson et al. 1981; Arthur and Curnock 1982; Bushnell 1989; Carpenter et al. 1975a; De Ceaurriz et al. 1983; Dudek et al. 1990; Dyer et al. 1988; Fumas and Hine 1958; Gamberale et al. 1978; Ghosh et al. 1987; Hake et al. 1981; Klaucke et al. 1982; Korsak et al. 1988; Martinez et al. 1989; Molnar et al. 1986; Morley et al. 1970; Muralidhara and Krishnakumari 1980; Nersesian et al. 1985; NTP 1986; Padilla and Lyerly 1989; Pryor et al. 1987; Savolainen and Linnavuo 1979; Savolainen et al. 1978, 1979b, 1984, 1985a; Seppalainen et al. 1989; Wimolwattanapun et al. 1987) and possibly the developing fetus (Balogh et al. 1982; Hudak and Ungvary 1978; Marks et al. 1982; Ungvary 1985; Ungvary and Tatrai 1985; Ungvary et al. 1980b, 1981) are the major targets of acute xylene toxicity by the inhalation and oral routes. Limited information is available on the nervous system effects of dermal exposure to xylenes (Goldie 1960; Hipolito 1980; Kilburn et al. 1985; Roberts et al. 1988). 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 (Abu Al Ragheb et al. 1986; Bonnet et al. 1979; Cameron et al. 1938; Carpenter et al. 1975a; Condie et al. 1988; Dyer et al. 1988; Fumas and Hine 1958; Gerarde 1959; Harper et al. 1975; Hine and Zuidema 1970; Morley et al. 1970; Muralidhara and Krishnakumari 1980; NTP 1986; Pound and Withers 1963; Smyth et al. 1962; Ungvary et al. 1980b; Wolf et al. 1956). Acute studies have demonstrated that xylene is irritating to the skin and eyes (Anderson et al. 1986; Carpenter et al. 1975a; Consumer Product Testing 1976; De Ceaurriz et al. 1981; Engstrom et al. 1977; Food and Drug Research Labs 1976; Hake et al. 1981; Hine and Zuidema 1970; Klaucke et al. 1982; Nelson et al. 1943; Nersesian et al. 1985; Pound and Withers 1963; Riihimaki 1979b; Smyth et al. 1962; Wolf et

## 2. HEALTH EFFECTS

al. 1956). Inhalation of xylenes has also been shown to cause irritation of the respiratory tract and dyspnea (Carpenter et al. 1975a; De Ceaurriz et al. 1981; Furnas and Hine 1958; Hake et al. 1981; Klaucke et al. 1982; Korsak et al. 1988; Morvai et al. 1976; Nelson et al. 1943; Nersesian et al. 1985). Data were sufficient to determine an acute-duration inhalation MRL for mixed xylenes based on increased reaction times in humans (Dudek et al. 1991). The oral MRL for *p*-xylene was based on a NOAEL for neurological effects in animals. 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 xylene is absorbed through the skin (Dutkiewicz and Tyras 1968; Engstrom et al. 1977; McDougal et al. 1990; Morgan et al. 1991; Riihimaki 1979b; Riihimaki and Pfaffli 1978; Skowronski et al. 1990), although the relative absorption by this route is difficult to ascertain because of the rapid evaporation of xylenes from the skin. Additional acute-duration inhalation and oral studies clarifying which nervous system effects are the most sensitive could help provide critical, reliable guidance values for acute exposure.

**Intermediate-Duration Exposure.** Intermediate-duration inhalation, oral, and dermal studies have identified the central nervous system (Condie et al. 1988; Goldie 1960; Honma et al. 1983; Jenkins et al. 1970; NTP 1986; Pryor et al. 1987; Rank 1985; Savolainen and Seppalainen 1979; Savolainen et al. 1979a), liver (Elovaara et al. 1989; Ungvary 1990), kidneys (Condie et al. 1988), and possibly the developing fetus (Bio/dynamics 1983; Mirkova et al. 1979, 1983; Taskinen et al. 1989) as the primary targets of intermediate-duration xylene exposure. Very few studies were located that examined the effects associated with intermediate-duration dermal exposure to xylenes (Mirkova et al. 1979; Wolf et al. 1956). 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 xylene 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.

An intermediate-duration inhalation MRL was derived based on decreased rotarod performance in offspring from rats exposed on gestation days 4-20 and tested on the first 3 days after birth. Data were sufficient to determine an intermediate-duration oral MRL for mixed xylenes based on renal

## 2. HEALTH EFFECTS

effects in animals and an intermediate-duration oral MRL for *m*-xylene based on hepatic effects in animals. However, these MRLs were based on LOAELs, and a no-effect level in animals would be more suitable for MRL derivation. Additional intermediate-duration inhalation and oral studies that identify NOAELs and LOAELs could provide critical, reliable guidance values for intermediate-duration exposure.

**Chronic-Duration Exposure and Cancer.** Few human (Arp et al. 1983; Askergren 1981, 1982; Askergren et al. 1981b, 1981c; Brasington and Thorpe-Swenson 1991; Dolara et al. 1982; Franchini et al. 1983; Gupta et al. 1990; Hipolito 1980; Holmberg and Nurminen 1980; Kilburn et al. 1985; Kucera 1968; Kurppa and Husman 1982; Moszczynsky and Lisiewicz 1983, 1984a; Roberts et al. 1988; Smolik et al. 1973; Triebig et al. 1992a, 1992b; Uchida et al. 1993; Wilcosky et al. 1984) or animal studies (Tatrai et al. 1981; Maltoni et al. 1983, 1985; NTP 1986) were available regarding the health effects associated with chronic exposure to xylenes. The central nervous system (Gupta et al. 1990; Hipolito 1980; NTP 1986; Roberts et al. 1988) and the kidney (Askergren 1981, 1982; Askergren et al. 1981b, 1981c; Franchini et al. 1983) appear to be the primary targets of chronic xylene exposure.

However, the study by Uchida et al. (1993) suggests that in healthy individuals kidney effects are unlikely to occur at concentrations below those which cause neurological effects and eye and respiratory tract irritation. A chronic-duration inhalation MRL was derived based on the subjective effects noted in the Uchida et al. (1993) study. It is not clear if the effects noted in this study were a result of exposure at the TWA (14 ppm) or a result of short-term exposure at higher concentrations. Studies that focus on neurological effects with different exposure scenarios resulting in the same TWA may help to distinguish between effects caused by transient exposure to higher concentrations and those caused by stable low-level exposure. Data were insufficient for the derivation of a chronic oral MRL, and no chronic dermal studies of xylenes were identified. Since the inhalation and oral routes of exposure are the most important for individuals living near hazardous waste sites or in occupational settings, additional inhalation and oral studies could help provide critical, reliable guidance values for chronic exposure to xylenes.

Few epidemiological studies were available regarding the development of cancer in humans following inhalation, oral, or dermal exposure to mixed xylene or xylene isomers (Arp et al. 1983; Wilcosky et al. 1984). Several oral carcinogenicity bioassays involving lifetime exposure have been conducted with mixed xylene in rats and mice (Maltoni et al. 1983, 1985; NTP 1986); however, all of these bioassays contained limitations that preclude a definitive conclusion regarding the carcinogenicity of

## 2. HEALTH EFFECTS

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 (Berenblum 1941; Pound 1970; Pound and Withers 1963); 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 exposure to low levels would be helpful because chronic exposure by this route may be encountered in the workplace, home, or in the vicinity of hazardous waste sites.

**Genotoxicity.** Limited data are available regarding the genotoxicity of inhalation of xylenes in humans (Haglund et al. 1980; Pap and Varga 1987; Richer et al. 1993). No data are available regarding the potential genotoxicity of xylenes in humans following oral or dermal exposure. Animal studies examining the genotoxicity of inhalation (Zhong et al. 1980) or oral (Feldt 1986) exposure to xylenes have been uniformly negative. Also, a variety of *in vitro* assays (Anderson et al. 1990; Bos et al. 1981; Connor et al. 1985; DeMarini et al. 1991; Epler et al. 1979; Florin et al. 1980; Gemer-Smith and Friedrich 1978; Haworth et al. 1983; Hejtmankova et al. 1979; Litton Bionetics 1978b; McCarroll et al. 1981a, 1981b; NTP 1986; Pool and Lin 1982; Richer et al. 1993; Shimizu et al. 1985) produced 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 needed.

**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 studies of reproductive function 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 (NTP 1986; Wolfe 1988a, 1988b) and chronic (NTP 1986) 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 (Ghantous and Danielsson 1986; Ungvary et al. 1980b), additional studies in animals and epidemiological studies in humans would be useful to assess more fully the reproductive toxicity of xylene and its isomers.

## 2. HEALTH EFFECTS

**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 (Balogh et al. 1982; Bio/dynamics 1983; Hudak and Ungvary 1978; Litton Bionetics 1978a; Marks et al. 1982; Mirkova et al. 1979, 1983; Rosen et al. 1986; Seidenberg et al. 1986; Ungvary 1985; Ungvary and Tatrai 1985; Ungvary et al. 1980b, 1981); however, the quality of many of these studies precludes drawing conclusions. Ingestion of aspirin by pregnant rats exposed to xylene have been shown to potentiate adverse maternal and fetal effects (Ungvary 1985). Additional developmental studies of xylenes in animals would clarify the potential developmental effects of xylenes. Because the nervous system is sensitive to xylenes, animal studies focusing on the development of the nervous system may help identify the LOAEL. Such studies would also be useful because solvent exposure is a common occupational exposure reported by pregnant women (Bentur and Koren 1991). 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 (Moszczynsky and Lisiewicz 1983, 1984a; Smolik et al. 1973); 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 to examine directly the immunotoxicity of mixed xylene or the xylene isomers, although a decrease in thymus weight was observed in one oral study (Condie et al. 1988). Inhalation exposure studies in animals employing only xylene or its isomers may remove uncertainties about the immunotoxicity potential of xylene. One case report indicates that dermal sensitization to xylene is possible (Palmer and Rycroft 1993). Dermal sensitization tests would provide additional 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 inhalation, oral, and dermal exposures to xylene (Andersson et al. 1981; Carpenter et al. 1975a; Condie et al. 1988; Dyer et al. 1988; Hake et al. 1981; Klaucke et al. 1982; Morley et al. 1970; NTP 1986; Ogata et al. 1970; Savolainen et al. 1984, 1985a; Wolfe 1988a, 1988b) (see Sections 2.2.1.4 and 2.2.2.4 for additional data). Data from such studies indicate that xylene adversely affects

## 2. HEALTH EFFECTS

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 high concentrations of xylenes. An occupational study of workers exposed to low concentrations of mixed solvents including xylenes for 10-44 years found no significant effects on CAT-scan measures of brain atrophy (Triebig et al. 1992a). Additional well-conducted studies in animals on the histopathologic changes of the central nervous system following intermediate or chronic exposure may provide useful information on permanent structural alterations induced by xylene.

**Epidemiological and Human Dosimetry Studies.** Limited epidemiological studies (Arp et al. 1983; Askergrén 1981, 1982; Askergrén et al. 1981b, 1981c; Dolara et al. 1982; Franchini et al. 1983; Gupta et al. 1990; Holmberg and Nurminen 1980; Kilburn et al. 1985; Kucera 1968; Kurppa and Husman 1982; Moszczynsky and Lisiewicz 1983, 1984a; Smolik et al. 1973; Taskinen et al. 1989; Uchida et al. 1993; Wilkosky et al. 1984) 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 (Abu Al Ragheb et al. 1986; Arthur and Cumock 1982; Brasington and Thorpe-Swenson 1991; Goldie 1960; Hipolito 1980; Klaucke et al. 1982; Martinez et al. 1989; Morley et al. 1970; Nersesian et al. 1985; Roberts et al. 1988) and occupational studies in which subjects were exposed to other chemical agents in addition to xylene (Arp et al. 1983; Askergrén 1981, 1982; Askergrén et al. 1981b, 1981c; Dolara et al. 1982; Franchini et al. 1983; Gupta et al. 1990; Holmberg and Nurminen 1980; Kilburn et al. 1985; Kucera 1968; Kurppa and Husman 1982; Moszczynsky and Lisiewicz 1983, 1984a; Smolik et al. 1973; Taskinen et al. 1989; Uchida et al. 1993; Wilkosky et al. 1984). Many of the case reports and occupational studies were also limited because exposure conditions were not well characterized. Additional 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, reproductive outcome, and renal effects associated with xylene exposure would be particularly useful since these have been shown to be sensitive end points.

**Biomarkers of Exposure and Effect**

**Exposure.** Methods are available for determining xylene and its metabolite, methylhippuric acid, in biological tissues and fluids (Daniel 1 et al. 1992; Jonai and Sato 1988; Kawai et al. 1991; Sedivec and

## 2. HEALTH EFFECTS

Flek 1976b). 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 intermediate- and chronic-duration exposures. It would be useful to determine if a biomarker of longer-term exposure could be derived, although it is not known whether one could be found.

**Effect.** 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 depression (Gamberale et al. 1978; Riihimaki and Savolainen 1980; Savolainen and Linnavuo 1979; Savolainen and Riihimaki 1981b; Savolainen et al. 1979b, 1984, 1985a). 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 high levels of 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, oral, and dermal exposures in humans and/or animals have been well characterized (Astrand 1982; Engstrom et al 1977; Inoue et al. 1993; Jonai and Sato 1988; Kawai et al. 1991; Ogata et al. 1970, 1979; Riihimaki 1978, 1979b; Riihimaki et al. 1979a, 1979b; Skowronski et al. 1990). The distribution of xylene has been well characterized in animals and identified to a small extent in humans. The database for absorption, distribution, and excretion of xylene isomers in humans and/or animals after inhalation exposure is most extensive. The database for oral and dermal exposures is not as extensive but has been well described. Differences in the rate of metabolism of xylenes after short-term or chronic exposure have been identified. Differences in the

## 2. HEALTH EFFECTS

toxicokinetics of xylene seen when exposure occurs with xylene adsorbed to sandy or clay soil have also been examined. Dermal penetration and resulting doses of xylene could be better characterized.

**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 (Astrand et al. 1978; Bakke and Scheline 1970; Bray et al. 1949; Ogata et al. 1979; Patel et al. 1978; Smith et al. 1982; Sugihara and Ogata 1978; van Doorn et al. 1980). 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 in the metabolism of *o*-xylene in rats and in humans exists. Whereas *o*-xylene is almost exclusively metabolized to *o*-methylbiphenyl acid in humans, 10-56% of *o*-xylene is also conjugated by glucuronide and glutathione in rats. Toxic metabolic intermediates of xylene such as benzaldehyde found in rats has not been found in humans. Additional studies would be helpful for determining whether other differences exist in the metabolism of xylenes among species. Although Inoue et al. (1993) did not observe a sex-related difference in excretion in men and women occupationally exposed to xylenes, sex-related differences in the toxicokinetics of xylene have been identified in animals. Additional studies concerning sex/genetic factors controlling xylene metabolism in humans might be useful.

**Methods for Reducing Toxic Effects.** Current methods used for reducing toxic effects of xylenes after acute exposures concentrate on decreasing absorption (HSDB 1992). Additional research on speeding excretion of xylene and reducing its concentration at its target organs would be valuable. As research identifies the mechanisms underlying the toxic effects of xylenes, additional methods may be developed for combating the effects of xylene at the molecular level. However, at the current time, insufficient information on mechanisms is available to develop such therapies.

### 2.9.3 On-going Studies

David Kalman of the University of Washington is investigating the quantitative relationship between biomarkers of exposure and toxicant dose in humans exposed to alkylated aromatic vapors. The research, sponsored by the National Institute of Environmental Health Sciences (NIEHS), employs a physiologically based pharmacokinetic model (FEDRIP 1994). The research will involve (1) measurement of environmental levels of alkylated aromatic vapors, (2) biological monitoring of

## 2. HEALTH EFFECTS

subjects' levels in breath, blood, and urine, and (3) field administration of a controlled exposure to deuterated alkylbenzene tracer compounds.