Xylenes Category:

m-Xylene (CAS No. 108-38-3), o-Xylene (CAS No. 95-47-6), p-Xylene (CAS No. 106-42-3), Mixed Xylenes (CAS No. 1330-20-7)

Voluntary Children's Chemical Evaluation Program (VCCEP) Tier 1 Pilot Submission

Docket Number OPPTS - 00274D

American Chemistry Council
Benzene, Toluene, and Xylenes VCCEP Consortium

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GLOSSARY OF TERMS

µg	Microgram
ACGIH	American Conference of Governmental Industrial Hygienists
ACH	Air Changes per Hour
AEGL	Acute Exposure Guideline Level
ATSDR	Agency for Toxic Substances and Disease Registry
CAA	Clean Air Act
CARB	California Air Resources Board
CAS	Chemical Abstract Service
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFM	cubic feet per minute
CNS	Central Nervous System
CPSC	Consumer Product Safety Commission
EHC	Environmental Health Criteria
EPA	Environmental Protection Agency
ETS	Environmental Tobacco Smoke
FDA	Food and Drug Administration
FHSA	Federal Hazardous Substances Act
g	Gram
GC/MS	Gas Chromatograph/Mass Spectrometry
GD	Gestation Day
HEC	Human Equivalent Concentration
HI	Hazard Index
High-end exposure	An exposure that was calculated using exposure concentrations representative of a 90th or 95th percentile of the range of values in a given dataset, depending on availability in the published.
HQ	Hazard Quotient
I-O	Indoor-Outdoor (ratio)
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IUR	Inventory Update Rule (TSCA)
kg	Kilogram
kHz	Kilohertz (thousands of cycles per second)
LD	Lactation Day
LOAEL	Lowest observable adverse effect level
m-xylene	Meta-xylene (1,3-dimethylbenzene)
MACT	Maximum Achievable Control Technology
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	Milligram
Mixed Xylenes	A mixture of o-xylene, m-xylene, p-xylene, and ethylbenzene, in varying concentrations. Also referred to as commercial xylene, technical-grade xylene
mL	Milliliter
MSDS	Material Safety Data Sheet
MSHA	Mine Safety and Health Administration
NCEA	National Center for Environmental Assessment
NCOD	National Drinking Water Contaminant Occurrence Database
NESCAUM	Northeast States for Coordinated Air Use Management

NHANES	National Health and Nutrition Examination Survey
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OECD	Organization of Economic Cooperation and Development
OEHHA	Office of Environmental and Human Health Assessment (Cal.)
OPPTS	Office of Pollution Prevention and Toxic Substances (EPA)
OSHA	Occupational Safety and Health Administration
o-xylene	Ortho-xylene (1,2-dimethylbenzene)
NESHAPs	National Emission Standards for Hazardous Air Pollutants
NIOSH	National Institute of Occupational Safety and Health
PAMS	Photochemical Assessment Monitoring Stations
PBPK	Physiologically-Based Pharmacokinetic (models, modeling)
PEL	Permissible Exposure Limit (OSHA)
ppb	Part Per Billion
ppm	Part Per Million
PPPA	Poison Prevention Packaging Act
p-xylene	Para-xylene (1,4-dimethylbenzene)
RCRA	Resource Conservation and Recovery Act
REL	Recommended Exposure Limit
RfC	Inhalation Reference Concentration
RfD	Oral Reference Dose
RFG	Reformulated Gasoline
SARA	Superfund Amendments and Reauthorization Act
SD	Standard Deviation
SDWA	Safe Drinking Water Act
SEM	Standard Error of the Mean
SIAM	SIDS Initial Assessment Meeting
SIAR	Screening Information Assessment Report
SIDS	Screening Information Data Set
STEL	Short-Term Exposure Limit
TEAM	Total Exposure Assessment Method
TLV	Threshold Limit Value
TRI	Toxic Release Inventory
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
Typical Exposure	An exposure that was calculated using the average or median exposure concentrations in a given dataset (depending on availability) and average or median values for exposure parameters.
UF	Uncertainty Factor
USGS	United States Geological Survey
VOC	Volatile Organic Compound
VCCEP	Voluntary Children's Chemical Evaluation Program
WAGM	Weighted Average Geometric Mean
WHO	World Health Organization
Xylene/Xylenes	Referring to any combination of the individual xylene isomers and/or mixed xylenes

1 Executive Summary

This submission by the American Chemistry Council Benzene, Toluene & Xylene VCCEP Consortium (the "Consortium") covers the Tier 1 review of the xylenes category – meta (m)-xylene (CAS No. 108-38-3), ortho (o)-xylene (CAS No. 95-47-6), para (p)-xylene (CAS No. 106-42-3), and mixed xylenes (CAS No. 1330-20-8) - under the VCCEP Pilot Program. Meta-xylene and ortho-xylene were included in the VCCEP Pilot Program because they were included in several biomonitoring and environmental monitoring databases that the EPA used to identify chemicals that may have the potential for children's exposure. The Consortium has chosen to include p-xylene and mixed xylenes (a complex product of C8 aromatic hydrocarbons) in this assessment in order to present the full xylenes category that was reviewed under the OECD SIDS program and other assessments (EPA, 2003A, AEGL, etc). The treatment of the individual xylene isomers and mixed xylenes as a single category is common throughout most of the previous xylenes assessments and is well supported by their similar physical and chemical properties, hazard properties, potential health effects, and exposure sources. In this VCCEP assessment, the terms "xylenes" or "xylene" refer to the category as a whole.

Production and Use

Mixed xylenes, generally manufactured in petroleum refining processes, are produced in the range of 6-7 million metric tonnes a year. The vast majority of the mixed xylenes production, approximately 94%, is used in the manufacture of the o-, m-, and p-xylene isomers, with p-xylene accounting for a large majority (approximately 88%) of isomer production. The xylene isomers are used as intermediate feedstocks in the production of polyester fibers and resins used in such products as fabric, molded plastic, films and beverage bottles. Some mixed xylenes production, approximately 4%, is used in solvent applications such as paints and coatings. Most of the small remaining portion of mixed xylenes production is added to gasoline to improve octane ratings.

Hazard Assessment

A large number of toxicology studies have been conducted on xylenes, including studies that address the endpoints considered in the VCCEP program.

Results from acute oral, dermal or inhalation toxicity studies in rats and mice indicate that the acute toxicity of xylene isomers and mixed xylenes is very low. Acute toxicity was typically characterized by central nervous system depression at high doses. Mixed xylenes and xylene isomers are irritating to the skin and eyes.

The predominant effects of repeat exposures to xylenes administered by inhalation or orally were mild hepatic alterations that were considered adaptive responses to hydrocarbon exposure. NOAELs and LOAELs were determined primarily on decreases in body weight and increased liver weight and liver enzyme changes. Inhalation studies performed by different investigators and single dose levels over durations of exposure of 6 weeks to 6 months demonstrated NOAELs in the range of 800-1000 ppm. Oral administration of mixed xylenes for 13 weeks (5 days/week) to rats or mice resulted in LOAELs of 1000 mg/kg/day [rats] or 2000 [mice].

Xylenes do not induce gene mutation or DNA damage in bacteria, or gene mutation or cytogenetic damage to mammalian cells in culture. No chromosome aberrations or increased incidence of sister chromatid exchanges were seen in animal or human subjects. Xylenes are not genotoxic.

Reproduction parameters in rats were not adversely affected by exposure to mixed xylenes in a 1-generation study at concentrations up to 500 ppm or in two dominant lethal studies in which male rats and mice were treated by injection and mated with untreated females, weekly throughout the spermatogenic cycle. No adverse effects on testes, accessory sex glands, or circulating male hormones were observed in rats exposed to 1000 ppm mixed xylenes for 61 days. Extremely high anesthetizing doses of xylene, administered daily for 7 days did affect testes weight, testosterone levels, and spermatozoa counts in Wistar rats.

Multiple studies have examined standard developmental toxicity endpoints in offspring of animals exposed to mixed xylenes or individual xylene isomers. Developmental effects in offspring of pregnant animals exposed to xylenes have been observed although generally at dose levels high enough to induce maternal stress and toxicity. Saillenfait et al. (2003) conducted the most comprehensive developmental studies of xylenes in rats, evaluating all three individual isomers (o-, *m*-, and *p*-xylene), and mixed xylenes under the same laboratory conditions at concentrations of 0, 100, 500, 1000, or 2000 ppm, 6 hours/day during gestation days (GD) 6-20, in accordance with OECD protocol 414 (2001) and EPA OPPTS 870.3700 (1998) testing guideline. All materials caused maternal toxicity (reduction in maternal body weight gain) at 1000 and 2000 ppm. Decreased corrected maternal weight gain (without gravid uterus) and food consumption were observed at 1000 and 2000 ppm *o*-, *m*-, and *p*-xylene and at 2000 ppm of mixed xylenes. No fetal malformations were induced by any test material. Decreased fetal body weight occurred at the maternally toxic doses of 1000 and 2000 ppm for all materials, and also at 500 ppm and greater for *o*-xylene and mixed xylenes. Significant increase in mean percent fetuses with skeletal variations of all types/litter was seen at 2000 ppm concentrations of *o*- and *p*-xylene. No single skeletal variation occurred at an incidence significantly higher than that in controls.

Xylenes do not appear to affect the immune system in animals and limited human data does not demonstrate diminished immunological reactivity. Mice exposed by inhalation to para-xylene at concentrations up to 1200 ppm did not exhibit adverse effects on natural killer [NK] cells. Repeated oral exposure to meta-, para-, or ortho-isomers for 10 days at oral doses up to 2000 mg/kg/day increased liver weight but slight decreases in thymus or spleen weight were only seen with *p*-xylene exposure. Mixed xylenes did not induce any organ weight changes.

Exposure to xylenes by the oral or inhalation routes can result in nervous system effects such as tremors, incoordination, muscle spasms, respiratory distress, hearing loss or elevated auditory thresholds, lethargy, hyperactivity, and changes in brain enzyme activity and levels of brain protein. Auditory impairment in rats induced by xylenes exposure at high inhalation concentrations (800-1800 ppm) for 5 days to 6 weeks have been reported. Korsak et al. (1992, 1994) demonstrated that exposure to *m*-xylene for 3 months decreased rotarod performance at 100 ppm in trained male rats beginning after 1 month of exposure and continuing at the same level throughout the exposure period without altering body weight, organ weight or clinical chemistry parameters; no effect was observed at 50 ppm m-xylene. Xylenes are known to induce narcosis at high doses in humans and a range of CNS effects at lower doses. Human experimental trials indicate acute effects on sensory-motor

and information processing functions with slight impairment at 100-200 ppm, and adaptation at 200 ppm exposure over several days.

There are several studies that have assessed developmental neurotoxicity in xylenes. The available studies have some limitations including the absence of dose response data, the lack of definitive NOAEL levels, and the lack of consistency in results of some of the test batteries. However, the study by Hass et. al. (1995, 1997), while only conducted at a single dose of 500 ppm, was a well-conducted sophisticated evaluation of the postnatal development and behavior of rats exposed prenatally to mixed xylenes. There were some slight effects of performance on Morris Water Maze measured in female offspring that were not measured in males or in females with various toys in their cages. In a study on p-xylene in rats, there were no neurobehavioral effects on motor activity (figure-8 maze) or on acoustic startle response in the offspring of dams exposed to 800 and 1600 ppm prenatally (Rosen 1986). EPA concluded in the xylenes IRIS database that the LOAEL for developmental neurobehavioral effects is 500 ppm, based primarily on the Hass 1995 study, and that the developing organism is not more sensitive than the adult to xylene exposure.

Chronic oral toxicity/carcinogenicity studies have been performed in rats and mice. Studies of 103 weeks duration completed by the National Toxicology Program (NTP) did not result in significant toxicological changes beyond increased levels of hyperactivity after dosing in high dose rats and mice and slightly lower body weight in high dose male rats exposed to 500 mg/kg mixed xylenes (top dose). Increased mortality in rats at the 500 mg/kg dose was attributed to dosing errors but still was used as the basis for the establishing a tentative LOAEL of 500 mg/kg and a NOAEL of 250 mg/kg. In mice, the LOAEL was set at the maximum dose of 1000 mg/kg and the NOAEL was 500 mg/kg.

Xylenes are rapidly absorbed by the respiratory tract with uptake increased by physical exercise. Absorption is also positively correlated with the amount of body fat. Liquid *m*-xylene is well absorbed through the skin, but *m*-xylene vapor (up to 600 ppm) does not appear to be appreciably dermally absorbed. Xylenes are highly soluble in blood and are taken up primarily in lipid-rich tissues (e.g., fat, brain) and in organs highly perfused with blood (e.g., liver, kidney). Small amounts of *p*-xylene and *o*-xylene have been reported to cross the placenta and distribute in amnionic fluid and fetal tissue. Xylenes undergo extensive metabolism, primarily side-chain oxidation and conjugation with glycine and glucuronic acid for *m*- and *p*-xylenes and by glucuronide formation with a small amount of sulfate conjugates for *o*-xylene. Metabolites are primarily excreted in urine with small amounts of xylene released unchanged in expired air. About 90% of the absorbed dose is excreted in the urine as methylhippuric acid, the glycine conjugate of methylbenzoic acid, following inhalation or dermal (liquid) exposure.

Neurobehavioral effects are considered the critical endpoint to assess xylene toxicity and assays for these effects are used by regulatory agencies to set acceptable levels for human exposure. The work of Korsak et al. (1994) with *m*-xylene was used to establish the IRIS RfC of 0.1 mg/m^3 (EPA 2003a) and to derive the chronic inhalation health benchmark in this VCCEP Risk Assessment of 0.66 mg/m^3 (see Section 8.1).

Exposure Assessment

Information on releases and concentrations of xylenes in the environment indicates that releases have been steadily decreasing since the mid 1980s. This trend can be seen with

the Toxic Release Inventory (TRI) data, as well as ambient air monitoring data from locations throughout the U.S. A child-centered approach was used to define exposure scenarios for children's interaction with xylenes exposure sources including environmental (ambient) sources and use of consumer products. Both typical and high-end estimates of exposure were made. The environmental background/ambient sources of exposure include indoor air, outdoor air, diet, and water. In addition to these ubiquitous sources, certain subpopulations of children may be exposed to xylenes in microenvironments from specific activities such as transportation via gasoline powered vehicles, use of consumer products containing xylenes, or living in a home where tobacco smoking occurs (either used by parents or teenage children). Occupational exposure sources were also considered for mothers to address the potential for exposure to a nursing infant. Xylenes exposure scenarios were developed for different age groups to account for the potential differences in the ways individual exposures vary with age. Five age groups have been chosen to generally correspond with the infant, pre-school, school-age, teenager, and adult stages of life, see Table 1.1.

The exposure assessment indicated that the inhalation pathway is the primary route of exposure with systemic (absorbed) doses at least one order of magnitude higher than those received via oral ingestion or dermal pathways, except for infant ingestion of human milk from an occupationally exposed mother.

Of the inhalation sources of exposures, indoor air contributes the most to overall inhalation doses. Representative indoor air concentrations of xylenes used in this assessment ranged from 7.6 to 9.1 $\mu g/m^3$ for typical exposures and 32 to 36 $\mu g/m^3$ for high end exposures. The impact of smoking on indoor air concentrations of xylenes was also assessed and it was found that environmental tobacco smoke contributes less than 1 $\mu g/m^3$ to the indoor air load for smoking households.

Oral intake of xylenes from diet and tap water ingestion ranged from 4.6×10^{-5} to 2.1×10^{-4} mg/kg/day for typical exposures and from 8.8×10^{-5} to 3.7×10^{-4} mg/kg/day for high end exposures. For infants of occupationally exposed mothers, oral intake of xylenes from ingestion of breast milk was predicted to range from 5.6×10^{-5} mg/kg/day to 2.7×10^{-2} mg/kg/day.

Infrequent exposures to xylene were assessed in spray painting and metals parts degreasing scenarios. Indoor air modeling estimates indicated that the highest 1-hr air concentrations were 9.5 ppm and 30 ppm for typical and high end exposures respectively, during metals parts degreasing. The highest 1-hr air concentrations for the spray painting scenario were 27 ppm and 46 ppm for typical and high end exposures, respectively.

Table 1.1 Summary of Xylenes Exposure Scenarios

Exposure Scenarios	Age Group				
	< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
Ambient Exposures					
Outdoor Air					
Urban	✓	✓	✓	✓	✓
Rural	✓	✓	✓	✓	✓
Indoor Air					
In-home	✓	✓	✓	✓	✓
In-School		✓	✓	✓	
Food	✓	✓	✓	✓	✓
Water	✓	✓	✓	✓	✓
Source-Specific Exposures					
Tobacco Smoke					
ETS	✓	✓	✓	✓	✓
Mainstream				✓	✓
Consumer Products					
Users				✓	✓
Non-users	✓	✓	✓		
Gasoline Sources					
In-Vehicle	✓	✓	✓	✓	✓
Refueling				✓ (16 – 18 years old)	✓
Occupational					
Production/Processing					✓
Non-Production					✓

✓ = Included in evaluation.

Risk Assessment

The risk assessment and the underlying hazard assessment and exposure assessment demonstrate the following:

- Very low xylenes exposures are received from everyday background sources of exposure such as ambient air, water, food and in-vehicle exposures. Aggregated background doses result in hazard indices (HIs) that are less than 0.05 at the high end; for all age groups; except the nursing infant of an occupationally exposed mother;

- Total xylenes doses to the nursing infant of an occupationally exposed mother range from a typical dose of 0.0005 mg/kg/day to a high end dose of 0.027 mg/kg/day, which results in HQs ranging from 0.003 to 0.13;

- Chronic, source-specific, inhalation exposures to xylenes from tobacco smoking and vehicle refueling scenarios do not result in exceedances of the health benchmark, even when aggregated with background ambient doses. Tobacco smoke HIs range from 0.0009 for a child exposed only to ETS to 0.034 for an adult exposed to ETS and mainstream smoke. Refueling HIs do not exceed 0.003 for a high end exposure;

- Short term air concentrations of xylenes to which children may be exposed during use of various consumer products are not expected to exceed the interim AEGL-1 value of 130 ppm under typical or high end exposure conditions.

The quantitative risk characterization indicates that reasonably anticipated children's exposures to xylenes from the ambient background environment and specific sources such as gasoline during refueling and consumer product use are unlikely to pose significant health risks.

Data Needs

Given (1) the significant margins between the HIs and estimated exposures, and (2) the extensive data covering the endpoints for the three VCCEP Tiers, this submission concludes no further testing is needed on the VCCEP endpoints.

For chemicals, like xylenes, that are used in consumer products and occur in many environments, additional exposure assessment work is always possible. The VCCEP sponsors believe, however, that the information presented in this document is adequate to demonstrate that reasonably anticipated exposures to xylenes from environmental sources are not likely to present significant health risks to children. In addition, doses from typical and reasonably worst case exposures from use of consumer products that are consistent with product label information are not likely to present significant health risks to children. Accordingly, the VCCEP sponsors believe additional exposure assessment work should be a low priority.

2 Xylenes VCCEP Program Background

In selecting compounds for the VCCEP Pilot Program, EPA relied on biomonitoring and environmental monitoring databases that it considered relevant to assessing the potential for children's exposure. The availability of hazard data was an additional factor that influenced chemical selection decisions. These selection criteria (discussed in Section 2.2) resulted in two xylene isomers - m-xylene and o-xylene – being selected for the VCCEP Pilot program. The Consortium has chosen to include p-xylene and mixed xylenes (a complex product of C8 aromatic hydrocarbons) in this assessment in order to present the full xylenes category that was reviewed under the OECD SIDS program and other assessments (EPA, 2003A, AEGL, etc - see Section 3 for further information about previous reviews/assessments).

2.1 Xylenes Category

The xylenes category for this VCCEP assessment includes:

- m-Xylene (CAS No. 108-38-3),
- o-Xylene (CAS No. 95-47-6),
- p-Xylene (CAS No. 106-42-3),
- Mixed Xylenes (CAS No. 1330-20-7)

The treatment of the individual xylene isomers and mixed xylenes as a single category is common throughout most of the previous xylenes assessments and is well supported by their similar physical and chemical properties, hazard properties, potential health effects, and exposure sources. In this VCCEP assessment, the terms "xylenes" or "xylene" refer to the category as a whole.

Mixed xylenes presents a somewhat unique situation because in addition to containing the three individual xylene isomers, it also frequently contains ethylbenzene. The ethylbenzene content in mixed xylenes varies, though it is generally in the range of 5-20% by weight. In the hazard assessment when mixed xylenes data are presented the ethylbenzene content is noted whenever possible. The xylenes VCCEP exposure assessment presents data on the exposure to the three xylene isomers but does not consider ethylbenzene exposure that might arise from mixed xylenes since ethylbenzene exposure is being evaluated separately under VCCEP.

2.2 VCCEP Pilot Selection Criteria for Xylenes

The Pilot Program selection criteria are discussed in the VCCEP Federal Register Notice (Dec. 26, 2000) at III.Q. Based on these selection criteria, m-xylene and o-xylene were selected for the VCCEP Pilot because they were: (1) evaluated under the Organization for Economic Cooperation and Development (OECD) SIDS Program; (2) found in human blood in the NHANES biomonitoring study; (3) reported in human exhaled air in the TEAM study; (4) detected in drinking water; and (5) detected in indoor air. Table 2.1 provides a summary of the EPA review of the available biomonitoring and environmental monitoring database for these xylenes.

Table 2.1 The results of EPA's VCCEP candidate chemical selection process for o-Xylene and m-Xylene

CAS No.	CHEMICAL NAME	Chemicals found in Human Tissues					Chemicals Found in Human Environment	
		NHANES	NHAT	NHEXAS	TEAMS	Human Milk	NCOD	INDOOR AIR
95-47-5	o-Xylene	Y			Y		Y	Y
108-38-3	m-Xylene	Y			Y		Y	Y

Reference: EPA VCCEP Website (http://www.epa.gov/chemrtk/vccep/vccepmth.htm)

2.2.1 National Health and Nutrition Examination Survey III (NHANES III)

NHANES III was conducted between 1988 through 1994 on 33,994 people and focused primarily on basic health and nutritional parameters such as blood pressure, immunization status, and nutritional blood measures. NHANES III included a special study that looked at the blood levels of 32 volatile organic compounds (VOCs) in a sample of about 800 volunteers from the overall NHANES study. Eleven compounds were found with high frequency and the data on these 11 compounds were sufficient to establish reference levels (e.g., median, 95th percentile) for the nonoccupationally exposed U.S. population. Another five compounds were found in at least 10% of the samples.

Results on xylenes from NHANES III were published in Ashley et al. (1994) and are presented in Table 2.2 (from the EPA VCCEP website). These blood concentrations are consistent with low level xylene exposure and are discussed further in Section 7.3.

Table 2.2 Blood Concentrations for Xylenes from NHANES III Study reported on EPA's VCCEP website

Table 6: Frequency of Detection and Tissue Concentration of Select VCCEP Pilot Chemicals in Human Monitoring Studies				
CAS No.	**CHEMICAL NAME**	**MEDIUM**	**DETECTION FREQUENCY**	**CONCENTRATION**
	m,p-xylene	blood	$\geq$ 75% of 649	med = 0.19 ppb
95-47-6	o-xylene	blood	$\geq$ 75% of 711	med = 0.11 ppb

2.2.2 Total Exposure Assessment Methodology Data

The Total Exposure Assessment Methodology (TEAM) study was designed to develop methods to measure individual total exposure (exposure through air, food, and water) and to apply these methods within a probability-based sampling framework to estimate the exposures of urban populations in several U.S. cities. The TEAM Study data for xylenes are limited to air monitoring data collected from several communities in New Jersey and California in 1982 and 1983. These studies found personal air exposures for m-, p-, and o-xylenes ranged from 13 ug/m^3 to 46 ug/m^3 and indoor air concentrations ranged from 8.5 ug/m^3 to 36 mg/m^3 (Wallace et al., 1987). A detailed exposure assessment on xylenes is presented in Section 7.

2.2.3 National Drinking Water Contaminant Occurrence Database

The National Drinking Water Contaminant Occurrence Database (NCOD) provides data on the occurrence and concentration of unregulated contaminants in drinking water. NCOD was developed to satisfy the statutory requirements set by Congress in the 1996 SDWA amendments. The purpose of the database is to support EPA's decisions related to identifying contaminants for regulation and subsequent regulation development. The NCOD contains occurrence data from both Public Water Systems and other sources (like the U.S. Geological Survey National Water Information System) on physical, chemical, microbial, and radiological contaminants for both detections and non-detects.

NCOD contains occurrence monitoring from sampling locations throughout a Public Water System; therefore, a detection value does not necessarily mean the contaminant would be found at the tap. There are some summary statistics, but no actual analysis of the data is provided. Also, NCOD contains data for only unregulated contaminants required to be monitored by public water systems, even though EPA has not set health-based drinking water maximum contaminant levels for this subset of contaminants. This subset is covered by the Unregulated Contaminant Monitoring Rule, or UCMR. Currently the NCOD does not contain occurrence data for all water systems and all states. The only Public Water System data contained in NCOD is data that has been reported by States to the Safe Drinking Water Information System (SDWIS). Historical data goes back to 1983.

Information on xylenes in drinking water is addressed in Section 7.2.1.2 of the exposure assessment.

2.2.4 Air Monitoring Data

Several of the air monitoring references cited by EPA for the VCCEP program provide data on indoor and/or outdoor air concentrations of xylenes. The air data samples reported in these studies were generally collected between the mid-1980's and 1991. The most recent study was conducted by Shields et al. (1996) in March and April 1991 at telecommunication centers, data centers, and administrative offices. Daisey et al. (1994) collected indoor and outdoor air samples at 12 office buildings in the San Francisco Bay area between June and September 1990, including several buildings with indoor air quality complaints. Brown et al. (1994) compiled the results of several previous indoor air studies on established and new buildings and reported xylenes air concentrations for dwellings, offices, and a hospital. Samfield (1992) and Shah and Singh (1988) also compiled the results of numerous indoor and outdoor air monitoring studies. These studies generally reported average air concentrations in the low part per billion (ppb) range. The results of these and other exposure studies, from the Consortium's exposure assessment, are presented in Section 7.

3 Previous Assessments

This section reviews several previous assessments on xylenes.

3.1 Integrated Risk Information System (EPA, 2003A)

The EPA's Integrated Risk Information System (EPA, 2003A) is an online database of human health effects of various chemicals that may be present in the environment (www.epa.gov/EPA, 2003a/). EPA updated the EPA, 2003A database for xylenes in January 2003 (EPA, 2003a). This update included the derivation of a chronic xylenes oral reference dose (RfD) and a chronic xylenes inhalation reference concentration (RfC).

The oral RfD for xylenes is based on decreased body weights in male rats observed in the National Toxicology Program (NTP 1986) 2-year rat oral gavage study of mixed xylenes (60% m-xylene, 13.6% p-xylene, 9.1% o-xylene, and 17% ethylbenzene). The NOAEL of 250 mg/kg/day was adjusted by 5/7 to account for 5-days per week dosing and divided by a total uncertainty factor of 1,000, resulting in an RfD of 0.2 mg/kg/day. The total uncertainty factor includes a factor of 10X for interspecies differences, a factor of 10X for intraspecies differences for sensitive subpopulations, and a factor of 10X for database uncertainties. The RfD is used for assessing oral exposures in the Risk Assessment (see Section 8).

The inhalation RfC of 0.1 mg/m^3 for xylenes is based on a NOAEL of 50 ppm (217 mg/m3) for rotarod performance in male Wistar rats following 3 months of exposure for 6 hours per day, 5 days per week (Korsak 1994). A LOAEL for decreased performance was observed at 100 ppm m-xylene. The NOAEL as point of departure was adjusted to a continuous exposure concentration of 39 mg/m^3 and divided by a combined uncertainty factor of 300 to derive a reference concentration of 0.1 mg/m^3. The Risk Assessment (Section 8) discusses the derivation of the RfC and alternative chronic inhalation health benchmarks using this same point of departure.

3.2 Acute Exposure Guideline Levels (AEGLs)

The National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL) first met in June 1996 with the purpose of developing and recommending airborne guideline levels for short-term exposures to hazardous substances to the U. S. Environmental Protection Agency (EPA). It was intended that these levels could also be used by other federal, state, and local agencies and the private sector for emergency planning, prevention, and response activities (U.S. EPA http://www.epa.gov/oppt/aegl/history.htm). There are three AEGL levels:

AEGL-1 - is the airborne concentration above which it is predicted that the general population, including susceptible individuals could experience notable discomfort, irritation, or asymptomatic nonsensory effects; however, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 - is the airborne concentration above which it is predicted that the general population, including susceptible individuals could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 - is the airborne concentration above which it is predicted that the general population, including susceptible individuals could experience life-threatening health effects or death.

The AEGL development process consists of four basic stages: (1) draft AEGLs, (2) proposed AEGLs, (3) interim AEGLs, and (4) final AEGLs. Xylenes have gone through the first two stages of the AEGL process. In June 2005, the AEGL committee approved the interim AEGLs presented in Table 3.1 (EPA 2005).

The AEGL-1 value is a based upon slight eye irritation in humans during 30-minute exposure to 400 ppm mixed xylenes (Hastings 1986). An intraspecies factor of 3X was applied because the effect was slight, resulting in an AEGL-1 value of 130 ppm. As this was determined to be a threshold effect, the same AEGL-1 value was applied to all durations. The AEGL-1 value is supported by several other studies, including: no effects at 200 ppm for p-xylene after 3 hours exposure (Ogata 1970); no effects at 200 ppm m-xylene after 3, 4, and 5.5 -hour exposures (Ogata 1970, Savolainen 1981, Laine 1993); eye irritation in a contact lens wearer at 150 ppm p-xylene (Hake 1981); and, mild eye irritation and dizziness in one individual following a 15-minute exposure to 230 ppm mixed xylenes (Ogata 1970). The AEGL-1 value was used in the Risk Assessment (Section 8) as a point of departure for a margin of safety assessment for acute inhalation exposures.

The AEGL-2 values are based on poor coordination in rats following a 4-hour exposure to 1300 ppm mixed xylenes (Carpenter 1975). The AEGL-3 values are based on the same study, though the endpoint of concern was prostration, followed by full recovery, exhibited after 4-hour exposure to 2800 ppm mixed xylenes. PBPK modeling was conducted to develop the AEGL-2 and AEGL-3 values.

Table 3.1: Interim Xylenes AEGLs

(ppm)

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	130	130	130	130	130
AEGL 2	2,500*	1,300*	920*	500	400
AEGL 3	7,200*	3,600*	2,500*	1,300*	1,000*

Lower Explosive Limit (LEL) = 9,000 ppm
* = ≥10% LEL
For values denoted as * safety considerations against the hazard(s) of explosion(s) must be taken into account.
Source: EPA Website (2005): http://www.epa.gov/oppt/aegl/

3.3 IARC

IARC reviewed xylenes in 1999 and classified them as Class 3, "not classifiable as to its carcinogenicity to humans." A summary of the xylenes IARC review can be viewed on the IARC website (http://www-cie.iarc.fr/htdocs/monographs/vol71/052-xylenes.html).

3.4 Other Reviews/Assessments

Previous reviews of the xylenes category have been conducted by the International Programme on Chemical Safety (IPCS), the Organization for Economic Cooperation and Development (OECD), and the Agency for Toxic Substances and Disease Registry (ATSDR) and others. The IPCS evaluated xylenes in the mid-1990's and in 1997 published an Environmental Health Criteria Review on xylenes (EHC 190) evaluating toxicological and environmental effects from xylenes. The OECD evaluated the xylenes category under the Screening Information Data Set (SIDS) program in May 2003 and concluded that while xylenes were potentially hazardous to human health and the environment, the hazards were being managed and as such xylenes are a low priority for further work. The ATSDR released a Toxicology Profile on xylenes in August 1995, which provides a review of hazard, exposure, and pharmacokinetic data.

4 Regulatory Overview

This section provides an overview of the extensive federal environmental, health and safety, and related regulations controlling xylenes exposures.

Xylenes are broadly regulated by many federal agencies, including the Environmental Protection Agency ("EPA"), the Food and Drug Administration ("FDA"), the Consumer Product Safety Commission ("CPSC"), the Occupational Safety & Health Administration ("OSHA"), and the Department of Housing and Urban Development ("HUD"). Given the number and complexity of these regulations, this overview is not an exhaustive survey of all regulations relating to xylenes.

4.1 EPA Regulation

EPA regulates xylenes under numerous statutes, including the Clean Air Act, 42 U.S.C. §§ 7401 *et seq.*; the Clean Water Act, 33 U.S.C. §§ 1251 *et seq*.; the Safe Drinking Water Act, 42 U.S.C. §§ 300f *et seq.* ("SDWA"); the Resource Conservation and Recovery Act, 42 U.S.C. §§ 321 *et seq.* ("RCRA"); the Comprehensive Environmental Response, Compensation, and Liability Act, 42 U.S.C. §§ 9601 *et seq.* ("CERCLA" or "Superfund"); the Superfund Amendments and Reauthorization Act, 42 U.S.C. §§ 9601 *et seq.* ("SARA"); the Emergency Planning & Community Right-To-Know Act ("EPCRA"), 42 U.S.C. §§ 11011 *et seq.*; the Pollution Prevention Act, 42 U.S.C. §§ 13101 *et seq.* ("PPA"); and the Toxic Substances Control Act, 15 U.S.C. §§ 2601 *et seq.* ("TSCA").

4.1.1 Clean Air Act

The Clean Air Act regulates emissions of xylenes from stationary sources (*e.g.*, factories, refineries, and power plants) and mobile sources (*e.g.*, trucks, cars, motorcycles) and as volatile organic compounds in products. Under the Clean Air Act, xylenes are alternately referred to as Hazardous Air Pollutants ("HAPs"), volatile organic compounds ("VOCs"), or Mobile Source Air Toxics ("MSATs").

Hazardous Air Pollutant Regulation

Section 112 of the Clean Air Act establishes a two-step process for protecting the public and the environment from the effects of toxic air pollutant emissions from stationary sources. First, EPA promulgates extensive National Emission Standards for Hazardous Air Pollutants ("NESHAPs"), better known as Maximum Achievable Control Technology ("MACT") standards, as required by section 112(d) of the Act. These technology-based MACT standards are imposed on specific manufacturing sectors on a category-by-category basis. *See generally* 40 C.F.R. Parts 61, 63. Second, within the eight years following the promulgation of each technology-based MACT standard, EPA has to regulate any remaining (or "residual") risk with an "ample margin of safety." CAA § 112(f), 42 U.S.C. § 7412(f). In this second phase, EPA applies a risk-based approach to assess whether the MACT technology-based emission limits sufficiently reduce health and environmental risks.

Thus, emissions of xylenes from stationary sources are subject to both stringent, manufacturing-sector-specific MACT-based standards and any further regulation that EPA determines is

necessary to ensure an ample margin of safety. Virtually all of the MACT standards have been published, and EPA is in the process of considering whether residual risk rules for facilities will be needed.

Volatile Organic Compound Regulations

Numerous regulations affect VOCs in regions where ozone formation is a concern. While these regulations are not necessarily specific to xylenes, they do affect many consumer and commercial products that contain xylenes and many commercial or industrial operations that use xylenes. *See, e.g.*, 40 C.F.R. Part 59 (National VOC emission standards for consumer and commercial products); 40 C.F.R. Part 60 (VOC standards for new stationary sources involving certain activities). In general, the overriding effect of these regulations is a reduction in emissions of xylenes.

Mobile Source Air Toxics, Reformulated Gasoline, and Limits on Gasoline Volatility

"Nationwide, mobile sources represent the largest contributor to air toxics." *See* EPA, Mobile Source Emissions - Past, Present, and Future. The Clean Air Act requires EPA to promulgate regulations to control hazardous air pollutants from motor vehicles and motor vehicle fuels which reflect the greatest degree of emission reduction achievable considering "the availability and costs of the technology, and noise, energy, and safety factors, and lead time." CAA § 202(l)(2), 42 U.S.C. § 7521(l)(2). As a result, numerous regulations reduce emissions of mobile source air toxics like xylenes, including EPA's reformulated gasoline ("RFG") program, limitations on gasoline volatility, and other provisions affecting MSATs.

Upon passage of the 1990 CAA amendments, EPA established the RFG program. This program requires the reformulation of gasoline to reduce emissions of smog-forming and toxic pollutants. *See generally* 40 C.F.R. Part 80.

Other regulations limit gasoline volatility, thereby reducing evaporative emissions. *See, e.g.*, 40 C.F.R. § 80.27. Volatility is a measure of how easily a substance (e.g., gasoline) evaporates. When gasoline evaporates, chemicals such as xylenes that are present in gasoline get into the air. EPA regulates the Reid vapor pressure of gasoline, a common measure of gasoline volatility, from May through September each year for certain "designated volatility nonattainment areas" and "designated volatility attainment areas" as defined in 40 C.F.R. § 80.2(cc) and 40 C.F.R. § 80.2(dd), respectively. *See id.* Moreover, certain classes of motor vehicles are required to have evaporative emission controls, thereby further reducing the amount of gasoline volatiles that get into the air. *See, e.g.*, 40 C.F.R. §§ 86.1811-01(d), 86.1811-04(e), 86.1812-01(d), 86-1813-01(d), 86.1814-01(d), 86.1814-02(d), 86.1815-01(d), 86.1815-02(d), 86.1816-05(d), 86.1816-08(d).

In 2001, EPA promulgated a mobile source air toxics final rule that identified 21 MSATs, including xylenes, and set new gasoline toxic emission performance standards. *See* 66 Fed. Reg. 17230 (March 29, 2001). This rule establishes a framework for EPA's national mobile source air toxics program and requires that refineries maintain the toxics performance of the gasoline they produced during the baseline period 1998-2000. The rule also contains a plan for continuing research and analysis on all MSATs. In addition, EPA has announced plans to propose another mobile source air toxics rule no later then February 28, 2006, and to finalize it by February 9, 2007 (see 70 Federal Register 46168 (August 9, 2005)).

Table 4.1: Timeline of Mobile Source Regulatory Actions Resulting in Reductions of VOCs in Emissions

Year	Description
1970	The Clean Air Act Amendments of 1970 - sets the first standards for emissions from motor vehicles. The standards are phased in over the next 5 years.
1971	New cars must meet evaporative emissions standards for the first time.
1975	New cars are required to use catalytic converters.
1981	New cars meet the amended Clean Air Act standards for the first time.
1983	Second generation catalytic converters required for new cars.
1983	First inspection and maintenance programs established in areas with air pollution problems.
1989	EPA sets first fuel volatility limits aimed at reducing evaporative emissions.
1990	Clean Air Act Amendments of 1990 require further reductions in hydrocarbons, lower tailpipe standards, more stringent emission testing procedures, expanded I/M programs, new vehicle technologies, and clean fuels programs. California adopts a low emission vehicle (LEV) program.
1991	EPA establishes lower tailpipe standards for hydrocarbons.
1992	Winter oxygenated fuel program begins in cities with high carbon monoxide levels. California has a similar "Phase I gasoline" program (oxygenated fuel required to limit carbon monoxide emissions also has a lower hydrocarbon content).
1994	Progressive introduction begins of national Tier 1 emission limits for light duty vehicles. On board diagnostic systems become a requirement for light duty vehicles and trucks.
1995	Phase I RFG is required to be sold in areas of ozone non-attainment (Phase I RFG has lower volatility, contain oxygenated compounds, and lower hydrocarbons). California transitional gasoline introduced as a transition from Phase I to Phase II RFG.
1996	California Phase II RFG is introduced. Phase II RFG has reduced vapor pressure and lower hydrocarbon. National Tier 1 emission limits introduced progressively from 1996 for light duty trucks. Phase-in begins of revised procedures and limits for evaporative emissions for light and heavy-duty vehicles. Dispensing rates for gasoline and methanol pumps are regulated.
1998	Federal Tier 1 tailpipe emissions standards go into effect. California's Low Emission Vehicles (LEV) fleet averaging program begins. National hydrocarbon emission limits introduced for vehicles using clean alternative fuels (provisions under LEV program). Voluntary Agreement for Cleaner Cars: Northeastern states agree to put cleaner cars on the road before they could be mandated under the CAAA. The first Niles under this agreement were released in New England in 1999 and were available nationwide in 2001.
1998	Phase-in begins of on-board refueling controls on passenger vehicles (1998 – 2000).
2000	National Low Emissions Vehicle (NLEV) program starts. California hydrocarbon emission limits introduced for vehicles using clean alternative fuels - provisions under LEV program.
2001	Phase-in begins of onboard refueling controls on light light-duty trucks (2001-2003)
2001	Japanese electric-gasoline hybrid automobiles become available.
2003	Federal Tier 2 tailpipe emissions standard phase-in begins.
2003	Phase-in of California's LEV II program begins.

Year	Description
2003	California requires a maximum level of sulfur in RFG of 600 ppm.
2004	Phase-in begins of onboard on heavy light-duty trucks (2004-2006).
2004	For refiners and importers, EPA requires a maximum level of sulfur in gasoline of 300 ppm, and an average of 120 ppm.
2005	For refiners, EPA requires an average level of sulfur in gasoline of 30 ppm. For importers, the average requirement is 90 ppm, and the maximum is 300 ppm.
2005	California requires a maximum level of sulfur in RFG of 30 ppm.
2006	Phase-in of California's LEV II program complete.
2006	For refiners, EPA requires a maximum level of sulfur in gasoline of 80 ppm. For importers, the average is set at 150 ppm.
2007	Planned finalization of additional EPA rule on mobile source air toxics.
2007	Importers must meet the 30 ppm average and 80 ppm maximum sulfur content in gasoline.
2010	Federal Tier 2 tailpipe emissions standard phase-in complete.

This list also includes regulatory actions that reduce sulfur in gasoline. Lower sulfur content increases catalytic converter efficiency, thus decreasing hydrocarbon emissions. Therefore, the new sulfur regulations have also been included in the table.

4.1.2. Clean Water Act

The Clean Water Act, originally enacted as the Federal Water Pollution Control Act Amendments of 1972, establishes the basic structure for regulating discharges of pollutants into the navigable waters of the United States. It prohibits any person from discharging any pollutant from a point source into navigable waters except as in compliance with the Act's permit requirements, effluent limitations, and other relevant provisions. The Act also grants EPA the authority to set wastewater standards for industry and water quality standards for all contaminants in surface waters.

Xylenes have been designated hazardous substances under the Clean Water Act. *See* 40 C.F.R. § 116.4. Because of this designation, certain discharges and releases are regulated. For example, releases in excess of 100 pounds of xylenes from any facility must be reported. *See* 40 C.F.R. § 117.3. Other EPA regulations permit ocean dumping of wastewater containing xylenes, but only when xylenes are present in concentrations below their solubility in seawater. *See* 40 C.F.R. § 227.7(a).

In addition, EPA has established water quality standards, which vary by body of water, for states not complying with federal guidance for establishing their own standards under the Clean Water Act. *See* 40 C.F.R. §§ 131.31–.40.

4.1.3. Safe Drinking Water Act

The Safe Drinking Water Act creates a comprehensive scheme for regulating drinking water and its sources. Under the authority of the Act, EPA sets standards for approximately 90 contaminants in drinking water and its sources -- rivers, lakes, reservoirs, springs, and ground water wells. For each of these contaminants, EPA sets an enforceable limit, called a Maximum Contaminant Level ("MCL"), and a non-enforceable public health goal, called a Maximum Contaminant Level Goal ("MCLG"), which allows for a margin of safety.

EPA has set both the MCLG and the MCL for xylenes in public drinking water sources at 10.0 mg/L. *See* 40 C.F.R. §§ 141.50, 141.61. This is also the permissible level for xylenes in bottled water products. 21 C.F.R. § 165.110(b)(4)(iii)(B).

In addition to MCLGs, MCLs, and other similar drinking water standards, EPA also promulgates health advisories, or guidance values, based on non-cancer health effects for different durations of exposure (*e.g.*, one-day, ten-day, and lifetime). These health advisories provide technical guidance to EPA, state and local government, and other public health officials regarding health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. EPA has promulgated several health advisory values for xylenes. *See* Office of Water, EPA, 2004 Edition of the Drinking Water Standards and Health Advisories, EPA 822-R-04-005 (Winter 2004).

4.1.4. Resource Conservation and Recovery Act

The Resource Conservation and Recovery Act (RCRA) regulates the transportation, storage, treatment, and disposal of hazardous wastes. Xylenes and certain substances containing xylenes are identified on two of RCRA's three hazardous waste lists – hazardous wastes from nonspecific sources (40 C.F.R. § 261.31) and commercial chemical products (40 C.F.R. § 261.33). Xylenes also are on the ground water monitoring list for owners and operators of hazardous waste facilities. *See* 40 C.F.R. Pt. 264 App. IX. Thus, xylenes are subject to a variety of RCRA controls relating to xylenes' transportation, storage, treatment, and disposal.

4.1.5. Comprehensive Environmental Response, Compensation, and Liability Act

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), as amended by the Superfund Amendments and Reauthorization Act (SARA), provides EPA broad authority to respond directly to releases and threatened releases of hazardous substances, pollutants, and contaminants that may endanger public health or the environment.

Xylenes have been designated as hazardous substances under CERCLA. *See* 40 C.F.R. § 302.4. As a result, xylenes are subject to monitoring and numerous other requirements relating to releases and threatened releases. For example, releases of xylenes in excess of 100 pounds from any facility must be reported. *See* 40 C.F.R. Part 302. In addition, certain amounts of spent solvents containing xylenes are reportable. *See id.* Moreover, xylenes present at listed Superfund sites are subject to varying levels of cleanup.

4.1.6. The Emergency Planning & Community Right-To-Know Act and The Pollution Prevention Act

The Emergency Planning & Community Right-To-Know Act, also known as Title III of SARA, was enacted by Congress to help inform local communities of chemical hazards in their areas. Section 313 of EPCRA requires EPA and state governments to annually collect data on releases and transfers of certain toxic chemicals from industrial facilities. These data are available to the public in the Toxics Release Inventory ("TRI"). In 1990, Congress amended these reporting requirements by passing the Pollution Prevention Act ("PPA"). Section 6607 of

the PPA requires facilities to provide information on pollution prevention and recycling for each toxic chemical subject to reporting under TRI. *See* 42 U.S.C. § 13106.

Xylenes are some of the more than 650 chemicals and chemical categories subject to reporting under TRI. *See* 40 C.F.R. § 372.65; EPA, 2004 Reporting Year List of TRI Chemicals. Thus, users of xylenes in many industries, such as manufacturers, miners, petroleum bulk terminals, and chemical wholesalers, are subject to these reporting requirements.

4.1.7. Toxic Substance Control Act

The Toxic Substances Control Act authorizes EPA to obtain information on all new and existing chemical substances that could cause an unreasonable risk to public health or the environment and to regulate their manufacture, use, distribution, and disposal. Under TSCA, EPA classifies chemical substances as either "existing" chemicals or "new" chemicals. Existing chemicals are those listed on the Toxic Substances Control Act Chemical Substance Inventory, or TSCA Inventory, which EPA must compile, keep current, and publish. All the chemicals in the xylenes category are on the TSCA Inventory. *See* TSCA § 8(b), 15 U.S.C. § 2607(b). TSCA provides authority to EPA to regulate and seek various kinds of safety and health data on existing chemicals, which include mandatory reporting under Section 8, 15 U.S.C. § 2607, and testing under Section 4, 15 U.S.C. § 2603.

4.2 Consumer Product Labeling and Packaging Regulation

The Consumer Product Safety Commission (CPSC) regulates xylenes under the Federal Hazardous Substances Act, 15 U.S.C. §§ 1261 *et seq.* ("FHSA"), and the Poison Prevention Packaging Act (PPPA), 15 U.S.C.§§ 1471 *et seq.* ("PPPA").

The FHSA requires precautionary labeling on the immediate containers of hazardous household products to help consumers safely store and use these products and to provide consumers information about immediate first aid steps in the event of an accident. The FHSA also authorizes CPSC to ban certain products that are so dangerous or where the nature of the hazard is such that the labeling required by the FHSA is not adequate to protect consumers.

Implementing regulations require special labeling of certain products containing xylenes and recommend that hazardous chemicals such as xylenes not be used in children's products. Given that substances containing 10 percent or more by weight of xylenes are "hazardous," products containing xylenes require special labels, including "danger," "Vapor harmful," "poison," and "Harmful or fatal if swallowed." 16 C.F.R. § 1500.14(a), (b).

To reduce the risk of exposure to hazardous chemicals such as xylenes found in liquid-filled children's products, CPSC requests that manufacturers eliminate the use of such chemicals in children's products. *See* 16 C.F.R. § 1500.231. CPSC also recommends that importers, distributors, and retailers that purchase children's products for resale obtain assurances from manufacturers that the products do not contain these hazardous chemicals. *See id.*

The PPPA requires that certain products be packaged in child-resistant packaging to protect children under five from possible poisoning and death in the event that they open containers of hazardous products and eat or drink the contents. CPSC regulations impose special packaging

requirements for numerous substances, including solvents for paint or other similar surface-coating materials that contain 10 percent or more by weight of xylenes, or combinations of xylenes and certain other solvents, and that have a viscosity of less than 100 Saybolt universal seconds at 100 ° F. *See* 16 C.F.R. § 1700.14(a)(15).

4.3 FDA Regulations

Given that FDA regulates a myriad of products ranging from food ingredients and drugs to medical and surgical devices, only a sample of FDA's regulations relating to xylenes are discussed below.

In general, FDA limits the amount, if any, of xylenes that may occur in food and drugs. Xylenes are not approved food additives that may be directly added to food for human consumption. *See* 21 C.F.R. Part 172. Limited amounts of xylenes, however, are permitted as indirect food additives, for example, as a result of processing equipment or packaging.

Although there is no specified limit to the amount of xylenes that is permitted in food adhesives, the regulations do provide guidelines to limit the amount of xylenes. These guidelines state that the adhesive should be separated from the food by a functional barrier, or that in dry foods, the quantity of adhesive that contacts the food shall not exceed the limits of good manufacturing practice, and that in fatty and aqueous foods, the quantity of adhesive that contacts foods shall not exceed the trace amount at seams and at the edge exposure between packaging laminates that may occur within the limits of good manufacturing practice. *See* 21 C.F.R. § 175.105. Similar guidance, with no specified limit, is provided for the use of xylenes in the food-contact surfaces of packaging for processing, transporting, or holding certain foods. *See*, 21 C.F.R. §§ 176.180. Xylenes are not approved for use in food packaging cellophane. *See* 21 C.F.R. § 177.1200.

FDA also limits the permissible amount of xylenes in bottled water. The permissible level of xylenes in bottled water products is 10.0 mg/L. *See* 21 C.F.R. § 165.110(b)(4)(iii)(B).

FDA provides guidance on the amount of residual solvents that are considered safe in pharmaceuticals. According to FDA, use of xylenes should be limited in pharmaceutical products because of their inherent toxicity. If xylenes are used, they should be limited to a permitted daily exposure of 21.7 mg/day or a concentration of 2,170 ppm. FDA, Guidance for Industry, Q3C--Tables and List.

4.4 Workplace Regulations and Standards

The Occupational Safety and Health Administration (OSHA) is the primary federal agency responsible for establishing and enforcing workplace standards, including exposure limits for many substances. The National Institute for Occupational Safety and Health ("NIOSH") and the American Conference of Governmental Industrial Hygienists ("ACGIH") also develop and recommend exposure limits for worker protection, though these limits are not enforceable.

OSHA sets both permissible exposure limits ("PELs") and short-term exposure limits ("STELs"). A PEL is the maximum average concentration to which workers may be exposed in any 8-hour work shift of a 40-hour work week, and a STEL is the maximum 15-minute concentration to which workers may be exposed during any 15-minute period of the workday. For xylenes,

OSHA has set the PEL at 100 ppm (435 mg/m^3) as an 8-hour time-weighted average ("TWA") concentration and 150 ppm (655 mg/m^3) as a 15-minute STEL. *See* 29 C.F.R. § 1910.1000, Table Z-1.

The NIOSH recommended exposure limits ("RELs") for xylenes are 100 ppm (435 mg/m^3) as a TWA for up to a 10-hour workshift and a 40-hour workweek and 150 ppm (655 mg/m^3) for 15 minutes as a short-term limit. *See* NIOSH Pocket Guide to Chemical Hazards.

Workplace Air Standards – Table 4.2 is a summary of the various xylenes occupational exposure limits.

Table 4.2: Summary of Occupational Exposure Limits

Organization	OEL	Description
OSHA	100 ppm	8-hr TWA, PEL (29 CFR 1910.1000)
	150 ppm	15-min STEL (29 CFR 1910.1000)
NIOSH	100 ppm	10-hr TWA, REL
	150 ppm	15-min STEL
	900 ppm	IDLH
ACGIH	100 ppm	8-hr TWA-TLV (2003)
	150 ppm	15-min STEL (2003)

IDLH = Immediately dangerous to life and health
PEL = Permissible exposure limit
REL = Recommended Exposure Limit
STEL = Short Term Exposure Limit
TWA = Time weighted average
TLV = Threshold Limit Value

These exposure limits apply to the individual isomers of xylenes, mixed xylenes, or any combination thereof. OSHA has set workplace air standards for general industry and construction. Only the OSHA PEL is a legally enforceable exposure limit. The permissible exposure limit (PEL) for xylenes is an 8-hour time-weighted average of 100 ppm (435 mg/m^3).

4.5 HUD Regulation

The Department of Housing and Urban Development attempts to minimize exposure to xylenes through regulations relating to the location of HUD-assisted projects. These regulations help calculate the acceptable separation distance between HUD-assisted projects and hazardous operations that store, handle, or process hazardous substances and provide guidance for identifying and assessing these hazardous operations. Xylenes are hazardous substances addressed by these regulations. *See* 24 C.F.R. Part 51, Subpart C, App. I.

4.6 State Regulation

In addition to the Federal regulatory programs briefly described above, xylenes are subject to a wide variety of state regulations. A description of such programs is well beyond the scope of this regulatory overview, but in many instances, these regulatory programs are more stringent

than Federal requirements. Many Federal statutes, such as the Clean Air Act and the Occupational Safety and Health Act, permit or, in some instances, require states to apply additional regulatory measures. For example, California has extensive air toxics and VOC regulations that go well beyond Federal requirements. These include specific air toxics programs, broad regulation of xylenes as VOCs in consumer and commercial products, and stringent mobile source (both fuels and vehicle) controls. Similar regulations have been adopted by other states in recent years particularly those in the northeastern U.S that are part of the Ozone Transport Commission. More recently, several localities have enacted local air toxics programs that provide further controls on releases of xylenes to the environment.

5 CHEMICAL OVERVIEW

This section presents a summary of data on the commercial extraction, production, and uses of xylenes (chain of commerce). The section also presents information on the release to the environment from these processes, and other commercial processes (formation during the process of incomplete combustion) and from sources outside of the chain of commerce (biomass burning). A detailed description of the various chain of commerce sources of xylenes can be found in Chemical Economic Handbook – Xylenes (CEH, 2005). Detailed sector notebooks are also available for several industries that use xylenes (e.g., the organic chemical industry, petroleum refining industry, or printing industry) from the EPA Office of Compliance (EPA, 1995a, 1995b, 2002a).

For the facilities that reported year 2003 Toxic Release Inventory (TRI) data, on-site air emissions accounted for 97% of total facility emissions of *o*-, *m*- and *p*-xylene isomers. Since the vast majority of xylenes released to the environment partition to the air (ATSDR, 1995a), this section focuses primarily on air releases of xylenes to the air. Releases to water and soil are discussed briefly at the end of this section.

5.1 Commercial Xylenes Production and Demand

Mixed xylenes are produced by the petroleum industry and to an appreciably lesser degree, by the steel industry as a byproduct of coke production (Table 5.1). The major chemical processes used in xylene production include catalytic reforming (dehydrogenation of straight-run light naphtha in presence of hydrogen), toluene disproportionation (catalytic conversion of toluene to equal volumes of benzene and xylenes), hydrotreating (subjecting liquid hydrocarbon stream to hydrogen with a catalyst at an elevated temperature and pressure), distillation (chemical separation from crude or light oils based on boiling points), and destructive distillation (separation at high temperature in the absence of oxygen).

Table 5.1: Industrial Sources of Commercial Mixed Xylenes

Industry	Process	Inputs	Percentage of 2003 U.S. Xylenes production (CEH, 2005)
Petrochemical	Catalytic reforming	Hydrotreated light naphthas (e.g., methylcyclohexane)	82%
Petrochemical	Toluene disproportionation	Toluene	17%
Petrochemical	Hydrotreating / distillation	Pyrolysis gasoline (unsaturated aliphatic hydrocarbons produced by steam cracking of gas oil or heavy naphtha)	<1
Steel	Destructive distillation	Coal	<1

Some limited data on historical xylenes production or demand levels are available from trade publications or the EPA. Aggregate production volume data is available under the EPA's inventory update rule (IUR) every four years (http://www.epa.gov/oppt/iur/). However, to protect confidential business information (CBI), the production volumes are reported in broad ranges. The IUR database provides 2002 production volumes for mixed xylenes (> 1 billion pounds), *m*-xylene (>100 million – 500 million) *o*-xylene (> 500 million – 1 billion pounds), and *p*-xylene (> 1 billion pounds).

CEH (2005) reports both consumption and production capacity data for xylenes. The demand for mixed xylenes has increased steadily from 2 million metric tons in 1970 to 6.5 million tons in 2004. During this time period, demand for *o*-xylene has remained fairly constant ranging from 300,000 to 500,000 metric tons per year. Demand for *m*-xylene has steadily increased from approximately 30,000 to 225,000 metric tons and *p*-xylene demand has risen from 865,000 metric tons to more than 5 million metric tons. These demand data include exports, which are significant for the xylene isomers particularly *p*-xylene which in 2003 had total U.S. exports of almost 2 million metric tons.

When consumption rates are compared to facility air releases, it can be seen that even as consumption of all xylenes has increased, the releases show a steady decline. Table 5.2 shows the total TRI air releases for mixed xylene and the three isomers from reporting year 1988 to 2003. During this time period, reported air releases of mixed xylene and individual isomers decreased by more than 70%.

Table 5.2: Annual U.S. Consumption versus Total TRI Air Emissions for Commercial Xylenes

Year	Consumption (thousand metric tons)[b]				Total TRI Air Emissions (million lbs)[c]			
	mixed xylenes	*o*-xylene	*m*-xylene	*p*-xylene	mixed xylenes	*o*-Xylene	*m*-xylene	*p*-xylene
1988	4,048	508	NA	2,248	166	2.5	2.2	6.0
1989	3,894	435	NA	2,116	165	1.5	2.0	5.1
1990	3,763	377	NA	2,041	146	1.6	2.2	4.7
1991	3,897	360	NA	2,190	126	1.5	1.8	5.3
1992	4,144	365	NA	2,245	117	1.5	2.2	4.1
1993	4,170	318	NA	2,236	116	1.9	2.0	4.4
1994	4,308	354	NA	2,424	113	1.2	1.4	3.4
1995	4,433	444	NA	2,487	99	1.2	1.4	2.9
1996	4,311	416	NA	2,514	86	1.3	1.3	2.8
1997	5,272	461	NA	2,866	78	1.2	1.5	2.5
1998	5,204	469	NA	2,881	73	1.2	1.3	1.8
1999	5,838	500	93	2,937	71	0.98	0.90	1.7
2000	5,769	457	107	2,843	61	0.62	0.74	1.3
2001	5,197	415	100	2,683	49	0.54	0.77	1.3
2002	5,741	424	93	2,833	44	0.46	0.74	1.2
2003	6,316	423	91	2,810	40	0.56	0.66	1.3
2004	6,562	432	94	2,909	NA	NA	NA	NA

[a]NA indicates that data was not available.
[b]Data from CEH, 2005.
[c]Original TRI industries (primarily SIC Codes 20-39).

In addition to total industry capacity and production rates, CEH (2005) provides information on xylenes production capacity by petroleum producer parent company (Table 5.3). In general, the production rate is about 60-80% of the total capacity. Most of the xylene production capacity is found in Texas (12 facilities) and Louisiana (2 facilities). In 2004, there were 21 facilities that produced mixed xylenes, 4 facilities that produced *o*-xylene, 2 facilities that produced *m*-xylene, and 9 facilities that produced *p*-xylene.

Table 5.3: U.S. Xylenes Production Capacity (2004)

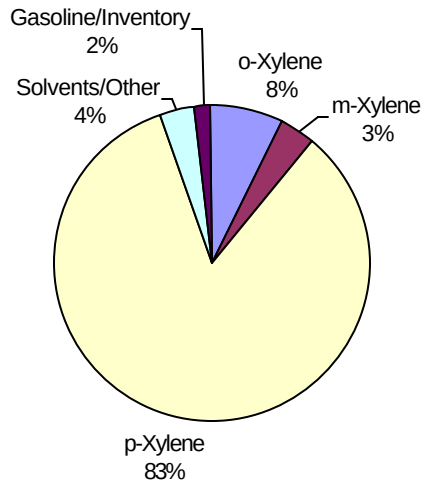
Company and Plant Location[a]	2004 Capacity (thousand metric tons)			
	Mixed xylenes	*o*-xylene	*m*-xylene	*p*-xylene
Total Petrochemicals USA, Inc.				
Port Arthur, TX	388	--	--	--
BP				
Decatur, AL	--	--	--	1,098
Texas City, TX	1,005	--	218	1,222
Whiting, IN	787	--	--	--
Chevron Phillips				
Guayama, PR	--	--	--	330
Pascagoula, MS	410	--	--	454
Citgo Petroleum				
Corpus Christi, TX	246	--	--	--
ConocoPhillips				
Alliance, LA	196	--	--	--
Sweeny, TX	476	--	--	--
ExxonMobil Chemical				
Baytown, TX	776	127	--	597
Beaumont, TX	320	--	--	275
Chalmette, LA	229	68	--	190
Flint Hills Resources				
Corpus Christi, TX	961	185	50	600
Hovensa				
St. Croix, VI	378	--	--	--
Lyondell-Citgo Refining				
Houston, TX	347	123	--	181
Marathon Ashland				
Catlettsburgh, KY	83	--	--	--
Texas City, TX	33	--	--	--
Shell				
Deer Park, TX	161	--	--	--
Sunoco				
Marcus Hook, PA	85	--	--	--
Toledo, OH	171	--	--	--
Westville, NJ	200	--	--	--
Valero Energy				
Corpus Christi, TX	523	--	--	--
Three Rivers, TX	164	--	--	--
Total Capacity (2004)	7,939	503	268	4,947
Total Export (2004)	854	117	139	1,500

[a]Idle plant locations are not included.

5.2 Commercial Xylenes Uses

The majority of commercial mixed xylenes are used in the production of the *o*-, *m*-, and *p*-xylene isomers which account for most of the consumption. The U.S. consumption of mixed xylenes is shown graphically in Figure 5.1. The isomers are used as an intermediate feedstock in the production of fibers, plastics, coatings, and inks. Some of the mixed xylenes produced are added to products such as paints and coatings formulations as a solvent. A smaller portion of the mixed xylenes produced annually are added to gasoline to improve octane ratings.

Figure 5.1
2004 U.S. Consumption of Mixed Xylenes



Source: Chemical Economics Handbook, 2005

The chemicals and derived products for which xylene is a building block are summarized in Table 5.4 (ATSDR, 1995a; CMR, 2002; EPA, 1994; Flint Hill Resources, 2003, CEH, 2005).

Table 5.4: Major Uses of Xylenes Isolated from Petroleum Products and Coal

End Use or Chemical Produced from Mixed Xylene	Description of End Use or Typical Use for Derived Chemical
p-xylene	Intermediate for dimethyl terephthalate and terephthalic acid (DMT/TPA), which are used in the production of polyethylene terephthalate (PET). PET is used to manufacture polyester fibers, molded plastic, films and beverage bottles.
o-xylene	Used in manufacture of phthalic anhydride, that is used as plasticizer in PVC pipes or coatings, or in the manufacture of resins.
m-xylene	Intermediate for isophthalic acid, which is used in manufacture of polyesters for coatings, inks or reinforced plastics.
Solvent uses	Used as a solvent in some consumer and commercial products such as adhesives, spray paints, carburetor cleaner or engine cleaner.
Gasoline blending or other uses	Added to gasoline to improve octane ratings.

5.3 Production and Uses of Refined Petroleum Products

Xylenes are frequently constituents in petroleum products, particularly gasoline. Unleaded automobile gasoline generally has a total xylenes content of about 6.6% by weight (ATSDR, 1995b). Xylenes are also found in the aromatic fraction of commercial and military jet fuel and distillate fuel oil (e.g. diesel fuel) (ATSDR, 1995c, 1998). In addition to the xylenes that are naturally present in petroleum streams, a small portion of mixed xylenes may also blended into automobile gasoline to increase the octane rating (See Table 5.4). Aromatic hydrocarbons such as xylenes contribute to the anti-knock properties (prevention of engine pinging or rattling due to secondary detonations) of unleaded automobile gasoline. Table 5.5 summarizes petroleum based fuel production and consumption volumes (DOE, 2000).

Table 5.5: U.S. Petroleum-Based Fuel Production and Consumption

Economic Activity	U.S. Production or Consumption Rate, 1999 (million gallons per day)[a]			
	Motor Gasoline	Jet Fuel	Kerosene	Distillate fuel oil
Consumption (demand)	354	70	3.1	143
Production (supply)	341	66	2.8	150
Net import to U.S. to meet demand	13	5	0.3	7.3

[a]Consumption and production volumes based on assumption of 42 gallons per barrel.

5.4 Releases of Xylenes to Ambient Air

Xylenes are released to the air during a number of processes including xylenes production, xylenes use, combustion of fuel, biomass combustion (mobile and non-mobile sources), and miscellaneous processes such as disposal of municipal solid waste. Each of the various sources of xylenes emissions to air is described in detail by the EPA (1994). Table 5.6 lists various emission sources of xylenes and the section number where more information can be found in this EPA reference. The emissions from most of these identified sources are regulated and limited by the federal government. Environmental regulations governing the xylenes production industry are further discussed in Section 4.

Table 5.6: Summary of Sources of Xylenes to Ambient Air

Type of Activity	Process or Source	Section of EPA (1994)
Releases from mixed xylenes production	Hydrotreating (pyrolysis or straight run gasoline)	Section 4.1.1: Hydrotreating
	Catalytic reforming (straight run gasoline)	Section 4.1.2: Catalytic reforming
	Secondary hydrogenation (pyrolysis gasoline)	Section 4.1.3: Secondary hydrogenation (for pyrolysis gasoline)
	Toluene disproportionation	Section 4.1.4: Xylenes production from toluene disproportionation or transalkylation
	Destructive distillation (coke oven)	Section 4.1.5: Coal-derived mixed xylenes
Releases from xylene isomer production	*para*-xylene	Section 4.2.1: *Para*-xylene production
Releases from xylene isomer production (*continued*)	*ortho*-xylene	Section 4.2.2: *ortho*-xylene production
	meta-xylene	Section 4.2.3: *meta*-xylene production
	ethylbenzene (byproduct of isomer production from mixed xylene)	Section 4.2.4: ethylbenzene production
Releases from xylenes use	Phthalic anhydride (PA) production	Section 5.1: Phthalic anhydride production
	Terephthalic acid (TPA) production	Section 5.2: Terephthalic acid production
	Maleic anhydride (MA) production	Section 5.3: Maleic anhydride production
	Paint and ink manufacturing	Section 5.4: Paint and ink manufacturing
Releases from use of xylene-containing products or materials	Application of surface coatings (e.g. paint, varnish, lacquer or primer)	Section 6.1: Surface coating operations
	Operation of printing presses (e.g. gravure printing)	Section 6.2: Printing and publishing
Releases from mobile sources	On-road and off-road sources	Section 6.3 Gasoline and automotive emissions
Releases from combustion sources	Waste incineration	Section 7.2: Hazardous and solid waste incineration
	Coal combustion	Section 7.1: Coal combustion
Other activities	Storage and distribution of gasoline (marine vessel loading, bulk gasoline plants, terminals and service stations)	Section 6.4: Gasoline marketing
	Wastewater treatment	Section 7.3: Wastewater treatment processes

The EPA Office of Air Quality Planning and Standards (OAQPS) collects emissions inventory data for hazardous air pollutants (HAP) pursuant to the 1990 amendments to the Clean Air Act. The most recent emissions inventory available in final form is the September 21, 2001 revision

to the 1996 National Toxics Inventory (NTI). The NTI emissions estimates are based on the following sources of data:

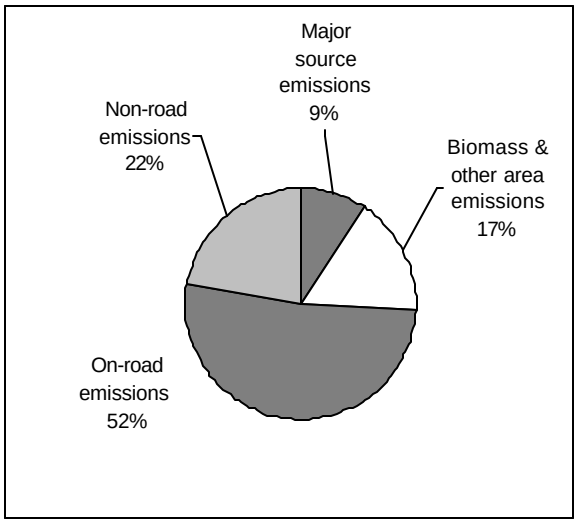
- State and local air pollution control agency HAP inventories;
- OAQPS Maximum Achievable Control Technology (MACT) databases;
- Toxic Release Inventory (TRI) data;
- Mobile source estimates from the EPA's Office of Mobile Sources; and
- Area source emission estimates using emissions factors and activity data.

Emission quantities for four general source categories are provided for the chemicals in the NTI database, including:

- Major sources (stationary facilities with potential to emit 10 tons of any one toxic air pollutant or 25 tons of more than one pollutant);
- Area and other sources (such as biomass burning including wildfires and agricultural burning, as well as small facilities such as dry cleaners with emissions less than that of major sources);
- On-road mobile sources (vehicles that travel on roads and highways such as cars, trucks, and buses); and
- Non-road mobile sources (mobile sources that are not found on roads such as lawn mowers, snowmobiles, and heavy construction vehicles).

Figure 5.2 shows the relative contribution of the various sources to the total xylenes emissions on a nationwide basis based on the NTI 1996 database (EPA, 2000a). It should be noted that the contribution from biomass and other area sources is greater in rural areas, as there is less of a contribution from motor vehicles and more likely to be biomass burning.

Figure 5.2:
Relative Contribution of Various Total *o*-, *m*-, *p*-Xylene Emission Sources to Xylenes Emissions



5.5 Releases of Xylenes to Soil and Water

Xylenes can be released to surface water by discharges of industrial or municipal wastewater that contain xylenes or accidental spills during transfer of petroleum or chemical products (ATSDR, 1995a). Sources of xylenes in groundwater include leaks of gasoline underground storage tanks, accidental spills and leachate from landfills (ATSDR, 1995a). Xylenes are also disposed in on-site industrial underground injection wells as part of the EPA Underground Injection Control (UIC) Program, which is regulated under the Safe Drinking Water Act. Under this program, liquids are pumped into deep, confined, and isolated formations that are located beneath potable water supplies. EPA's Underground Injection Control Program regulates the location, construction, operation, and enclosure of injection wells to insure that underground drinking water supplies are protected. Xylenes can be released to soils as a result of land disposal of xylenes-containing wastes or from gasoline as a result of a leaking underground storage tank (ATSDR, 1995a). The amount of xylenes released to soil is negligible (less than 0.3% of total environmental releases) (ATSDR, 1995a).

The 2001 TRI estimates for xylenes releases are summarized below in Table 5.7. Facilities that are subject to TRI reporting are those with ten or more full-time employees (or the equivalent in man-hours), those that exceed any one threshold for manufacturing (including importing), processing, or otherwise using a toxic chemical listed in 40 CFR Section 372.65, and that fall under the covered SIC codes below:

- Manufacturing (SIC codes 20 through 39);
- Metal mining (SIC code 10, except for SIC codes 1011, 1081, and 1094);
- Coal mining (SIC code 12, except for 1241 and extraction activities);
- Electrical utilities that combust coal and/or oil for the purpose of generating electricity for distribution into commerce (SIC codes 4911, 4931, and 4939);
- Resource Conservation and Recovery Act (RCRA) Subtitle C hazardous waste treatment and disposal facilities (SIC code 4953);
- Chemicals and allied products wholesale distributors (SIC code 5169);
- Petroleum bulk plants and terminals (SIC code 5171);
- Solvent recovery services (SIC code 7389 limited to facilities primarily engaged in solvent recovery services on a contract basis); and
- Federal facilities that meet the thresholds also must report by Executive Order.

Emissions from facilities that are not required to submit reports (i.e., those with few employees or chemical usage/production rates below regulatory threshold) are not expected to have a major impact on the overall evaluation because they would represent minor xylenes sources.

Table 5.7
Xylenes Releases for All Industries Reporting TRI data for 2003

	Release Amount (million pounds/year)				Percent of Total Release			
Type of Release	*o*-,*m*- and *p*- xylene mixture	*o*-xylene only	*m*-xylene only	*p*-xylene only	*o*-,*m*- and *p*- xylene mixture	*o*-xylene only	*m*-xylene only	*p*-xylene only
Total air emissions	37.7	0.66	0.56	1.3	95%	97%	97%	98%
Surface water discharges	0.014	0.000064	0.000036	0.0035	0.04%	0.01%	0.01%	0.3%
Underground injections	0.11	0.012	0.014	0.014	0.3%	1.8%	2.4%	1.1%
Releases to land	1.1	0.000036	0.000008	0.00032	2.8%	0.01%	0.01%	0.2%
Transfer to disposal	0.75	0.0033	0.0043	0.0033	1.9%	0.5%	0.7%	0.3%
Total	39.7	0.68	0.58	1.32	100%	100%	100%	100%

6 Hazard Assessment

6.1 Xylenes Hazard Assessment Summary

This hazard assessment addresses the available xylenes mammalian toxicology data on the VCCEP endpoints and includes a review of the human health studies on xylenes. Studies are presented for mixed xylenes [CAS #1330-20-7] and for the three xylene isomers: meta-(*m*-xylene, CAS #108-38-3), ortho- (*o*-xylene, CAS #95-47-6) and para- (*p*-xylene, CAS #106-42-3). Results used for hazard assessment from animal studies and from human experience are summarized below in Sections 6.1.1 and 6.1.2. Table 6.1 lists key toxicology data by endpoint for the VCCEP tiers. Sections 6.2 through 6.12 address the mammalian toxicology and Section 6.13 reviews the human studies.

6.1.1 Summary of Animal Studies

Acute Toxicity (Tier 1): Mixed xylenes and xylene isomers induce minimal oral (rats and mice), dermal (rabbits), intraperitoneal (rats and mice), or inhalation (rat and mice) acute toxicity. Mixed xylenes, *m*- and *p*-xylene are moderate to marked dermal irritants and induce mild to moderate eye irritation in rabbits.

Repeat Dose Studies (Tier 1 and 2): The predominant effects of repeat exposures to xylenes administered by inhalation or orally were mild hepatic alterations that were considered adaptive responses to hydrocarbon exposure. NOAELs and LOAELs were determined primarily on decreases in body weight and increased liver weight and liver enzyme changes. Inhalation studies performed by different investigators and single dose levels over durations of exposure of 6 weeks to 6 months demonstrated NOAELs in the range of 800-1000 ppm. Oral administration of mixed xylenes for 13 weeks (5 days/week) to rats or mice resulted in LOAELs of 1000 mg/kg/day for rats and 2000 for mice (NTP, 1986). Treatment of rats for 90 consecutive days with mixed xylenes (Condie et al., 1988), *m*- or *p*-xylene (Wolfe, 1988) demonstrated decreased body weights at doses of 750-800 mg/kg/day.

Meta-, para- or ortho-isomers produced similar activity for general toxicity in rats at comparable doses (Condie et al., 1988), required similar alveolar concentrations to induce anesthesia (Fang et al., 1996), and demonstrated similar minimal dose to induce narcosis (Molnár et al., 1986), although lower doses showed somewhat different effects on motor activity between isomers. Moser et al. (1985) showed operant response and motor performance in mice was similar for all three isomers while Korsak et al. (1990) reported that *o*-xylene altered motor performance by rats on the rotarod more severely than *m*- or *p*-xylene.

Genetic Toxicity (Tier 1 and 2): Xylenes do not induce gene mutation or DNA damage in bacteria, or gene mutation or cytogenetic damage to mammalian cells in culture. No chromosome aberrations or increased incidence of sister chromatid exchanges were seen in animal or human subjects. Xylenes are not genotoxic.

Reproductive and Developmental Toxicity (Tiers 1 and 2): Reproduction parameters in rats were not adversely affected by exposure to mixed xylenes in a 1-generation study at concentrations up to 500 ppm (API, 1983) nor in two dominant lethal studies in which male rats and mice were treated by injection and mated with untreated females, weekly throughout the spermatogenic cycle (API 1973). Nylén et al. (1989) did not observe effects on testes,

accessory sex glands, or circulating male hormones of rats exposed to 1000 ppm mixed xylenes for 61 days. Extremely high anesthetizing doses of xylene, administered daily for 7 days did affect testes weight, testosterone levels, and spermatozoa counts in Wistar rats (Yamada, 1993).

A number of studies have examined standard developmental toxicity endpoints in offspring of animals exposed to xylenes. Developmental effects in offspring of pregnant animals exposed to xylenes have been observed although generally at dose levels high enough to induce maternal stress and toxicity. Saillenfait et al. (2003) conducted the most comprehensive developmental studies of xylenes in rats, evaluating o-, *m*-, *p*-xylene, and mixed xylenes under the same laboratory conditions at concentrations of 0, 100, 500, 1000, or 2000 ppm, 6 hr/day during GD 6-20, in accordance with OECD protocol 414 (2001) and EPA OPPTS 870.3700 (1998) testing guideline. All materials caused maternal toxicity (reduction in maternal body weight gain) at 1000 and 2000 ppm. Decreased corrected weight gain (without gravid uterus) and food consumption were observed at 1000 and 2000 ppm *o*-, *m*-, and *p*-xylene and at 2000 ppm of mixed xylenes. No fetal malformations were induced by any test material. Decreased fetal body weight occurred at the maternally toxic doses of 1000 and 2000 ppm for all materials, and also at 500 ppm and greater for *o*-xylene and mixed xylenes. Significant increase in mean percent fetuses with skeletal variations of all types/litter was seen at 2000 ppm concentrations of *o*- and *p*-xylene. No single skeletal variation occurred at an incidence significantly higher than that in controls.

Immunotoxicity (Tier 2): Xylenes do not appear to affect the immune system in animals and limited human data does not demonstrate diminished immunological reactivity. Mice exposed by inhalation to para-xylene at concentrations up to 1200 ppm did not exhibit adverse effects on natural killer (NK) cells (Selgrade et al., 1993). Repeated oral exposure to meta-, para-, or ortho-isomers for 10 days at oral doses up to 2000 mg/kg/day increased liver weight but slight decreases in thymus or spleen weight were only seen with *p*-xylene exposure (Condie et al., 1988). Mixed xylenes did not induce any organ weight changes.

Metabolism (Tier 2): Xylenes are rapidly absorbed by the respiratory tract with uptake increased by physical exercise. Absorption is also positively correlated with the amount of body fat. Liquid *m*-xylene is well absorbed through the skin, but *m*-xylene vapor (up to 600 ppm) does not appear to be appreciably dermally absorbed. Xylenes are highly soluble in blood and are taken up primarily in lipid-rich tissues (e.g., fat, brain) and in organs highly perfused with blood (e.g., liver, kidney). Small amounts of *p*-xylene and *o*-xylene have been reported to cross the placenta and distribute in amnionic fluid and fetal tissue (Ghantous and Danielsson, 1986; Ungváry et al., 1980b). Xylenes undergo extensive metabolism, primarily side-chain oxidation and conjugation with glycine and glucuronic acid for *m*- and *p*-xylenes (Sugihara and Ogata, 1978; Ogata et al., 1980; Elovaara et al., 1984) and by glucuronide formation with a small amount of sulfate conjugates for *o*-xylene (Ogata et al., 1980).

Metabolites are primarily excreted in urine with small amounts of xylenes released unchanged in expired air. About 90% of the absorbed dose is excreted in the urine as methylhippuric acid, the glycine conjugate of methylbenzoic acid, following inhalation or dermal (liquid) exposure.

Adult Neurotoxicity and Auditory Effects (Tier 3): Exposure to mixed xylenes and its isomers by the oral or inhalation routes can result in nervous system effects such as tremors, incoordination, muscle spasms, respiratory distress, hearing loss or elevated auditory

thresholds, lethargy, hyperactivity, and changes in brain enzyme activity and levels of brain protein.

Korsak et al. (1994) demonstrated that exposure to *m*-xylene for 3 months decreased rotarod performance at 100 ppm in trained male rats beginning after 1 month of exposure and continuing at the same level throughout the exposure period without altering body weight, organ weight or clinical chemistry parameters; no effect was observed at 50 ppm m-xylene. Korsak et al. (1992) previously reported the same decreased rotarod performance at 100 ppm in trained male rats following 6 months of exposure.

Auditory impairment in rats induced by xylenes exposure at high inhalation concentrations (800-1800 ppm) over durations of 5 days to 6 weeks have been reported (Pryor et al., 1987; Nylén and Hagman, 1994; Crofton et al., 1994). Pryor et al. (1987) also noted that some hearing loss measured by the conditioned avoidance test occurred in rats exposed to 1450 ppm xylenes for 8 hours but exposure of 1700 ppm for 4 hours did not induce ototoxic effects, indicating that the duration of exposure as well as xylenes concentration is important in assessing auditory impairment.

Neurobehavioral effects are considered critical endpoints to assess xylenes toxicity and assays for these effects are used by regulatory agencies to set acceptable levels for human exposure. The work of Korsak et al. (1994) with *m*-xylene was used to establish the EPA, 2003A RfC and to derive the chronic inhalation health benchmark of 0.66 mg/m^3 in the VCCEP Risk Assessment (see Section 8.1).

Developmental Neurotoxicity (Tier 3): There are several studies that have assessed developmental neurotoxicity in xylenes. The available studies have some limitations, including the absence of dose response data, lack of definitive NOAEL levels, and variability of the results of the various test batteries. However, the study by Hass et. al. (1995, 1997), while only a single dose level of 500 ppm, was a well-conducted sophisticated evaluation of the postnatal development and behavior of rats exposed prenatally to mixed xylenes. There were some slight effects of on learning and memory performance based on Morris water maze in female offspring that were not seen significantly in males or in females with various toys in their cages. In a study on p-xylene in rats, there were no neurobehavioral effects in the offspring of dams exposed to 800 and 1600 ppm prenatally (Rosen 1986). EPA concluded in the xylenes IRIS database that the LOAEL for developmental neurobehavioral effects is 500 ppm, based primarily on the Hass 1995 study, and that the developing organism is not more sensitive than the adult to xylenes exposure (EPA 2003a).

Chronic Toxicity and Carcinogenesis (Tier 3): Chronic oral toxicity/carcinogenicity studies have been performed in rats and mice. Studies of 103 weeks duration completed by National Toxicology Program (NTP 1986) did not result in significant toxicological changes beyond increased levels of hyperactivity after dosing in high dose rats and mice and slightly lower body weight in high dose male rats exposed to 500 mg/kg mixed xylenes (top dose). Increased mortality in rats at the 500 mg/kg dose was attributed to dosing errors but still was used as the basis for the establishing a tentative LOAEL of 500 mg/kg and a NOAEL of 250 mg/kg. In mice, the LOAEL was set at the maximum dose of 1000 mg/kg and the NOAEL was 500 mg/kg.

6.1.2 Human Experience Summary

Effects of xylenes in humans have been noted in a variety of studies, including controlled experiments with volunteers for acute or limited duration exposures, very high accidental or abusive exposures, and from occupational studies in which exposures frequently have been to mixtures of compounds rather than to just xylenes. Occupational studies have confounders in addition to co-exposure with other materials, such as smoking, alcohol use, and other lifestyle factors.

Acute poisoning and mortality in humans have occurred after very high exposure to xylenes. Loss of consciousness occurs at approximately 10,000 ppm (Morely et al., 1970). Individuals recovering from severe overexposure exhibit EEG alterations, confusion, coma, nystagmus, gastrointestinal effects, and impaired renal and hepatic function (Ghislandi and Fabiani, 1957; Recchia et al., 1985). Respiratory irritation and eye and throat irritation are induced by exposure to concentrations of 400-600 ppm xylene for 15-30 minutes (Hastings 1986). Controlled human studies demonstrate that 4-hour exposure to xylenes at approximately 200 ppm can cause impairment of sensory motor and information processing in the CNS (Savolainen 1979, 1981, 1982, 1985 and Seppäläinen 1991), though these effects were reversible upon termination of exposure. Some evidence of effects on reaction times in humans was also observed above 100 ppm, though the results were varied. A study at 103.5 ppm for 4 hours showed prolonged reaction time (Dudek, 1990) while similar studies at higher levels – 138 ppm for 4 hours – showed no effect on reaction time (Savolainen 1980, 1981). No effects were observed were below 100 ppm.

High-level exposure to xylenes or solvents containing xylenes can induce a variety of neurological symptoms in humans ranging from dizziness, headache, nausea, difficulty in concentrating, to slurred speech, ataxia, tremors at higher acute exposures, and in isolated instances, unconsciousness, amnesia, and epileptic seizures (ATSDR, 1995).

Xylenes do not appear to induce genetic toxicity in humans exposed occupationally or under controlled laboratory conditions. No differences in frequency of sister chromatid exchange (SCE), micronuclei, or chromosome aberrations were reported in worker monitoring studies (Haglund et al., 1980; Zhong et al., 1980; Pap and Varga, 1987), or in a study of service station attendants exposed to mixed solvents (Pitarque et al., 1997a, b). Richer et al. (1993) performed a controlled study with male volunteers exposed to xylenes daily for 3 days, repeated 3 times at 2 week intervals and did not identify any significant effects on sister chromatid exchange (SCE), cell cycle delay, or cell mortality.

No occupational or environmental studies are available to address developmental or teratogenic effects of xylenes, in the absence of other chemical agents, and limited data are available to address fecundity and reproductive effects. Effects on pregnancy outcome vary from no increase in miscarriage rate (Axelsson et al., 1984) to increased spontaneous abortions among laboratory workers also exposed to formalin and other solvents (Taskinen et al., 1994). Two case reports suggest that congenital defects observed in the CNS of children were associated with maternal occupational exposures to mixed xylene vapors (Holmberg and Nurminen, 1980; Kucera, 1968). These studies had many limitations and no conclusions can be drawn about causation.

Limited human data are available to evaluate the immunological effects of xylenes in humans. Decreased lymphocyte counts have been reported in workers exposed to xylenes in the

presence of other solvents without systemic changes or diminished immunological reactivity (Moszczynsky and Lisiewicz, 1983, 1984).

Metabolic profiles for xylenes are similar for humans and animals. Absorption and metabolism have been studied in human volunteers by both inhalation and dermal routes of exposure. Inhalation absorption occurs in 2 phases, a short phase (0-15 minutes) and a longer phase of approximately one hour that represents a steady state between blood and inhaled xylene. Retention does not appear to differ with gender. Dermal absorption was found to be directly proportional to vapor concentration. After systemic absorption, xylene is largely distributed to adipose tissue. Metabolism in humans, like animals, proceeds primarily via side-chain oxidation to methyl benzoic acid, which is conjugated mainly with glycine to form methylhippuric acid and excreted in the urine with small amounts released as unchanged xylene in expired air. Half-lives for excretion of xylenes metabolites in humans are in the range a few hours to 10-20 hours.

Conclusion

From the animal and human toxicology data, xylenes can be characterized as neurotoxic chemicals at moderate to high doses inducing symptoms in humans of dizziness, headache, nausea, and neuromuscular effects, speech impairment, and amnesia at high doses. Ototoxicity has been reported in animals but not in humans. Other effects of inhaled xylenes in rodents were mild hepatic alterations consistent with adaptive response to hydrocarbon exposure. Effects of mixed xylenes compared with effects of individual isomers indicate similarities in type and severity of response. Absorbed xylenes are rapidly metabolized and excreted in humans and animals with only a small percentage retained in adipose tissue.

Xylenes have not demonstrated genotoxic activity in animals or humans and do not appear to be immunotoxic. No adverse effects on reproductive performance were seen in laboratory studies and developmental toxicity (fetal weight decrements) occurred at doses that were typically also produced maternal toxic. Several developmental neurotoxicity studies have shown learning deficits in offspring of treated animals which resolved as offspring matured. No conclusive reproductive or developmental effects have been reported in human exposure studies. Current data indicate that xylenes are not likely to be carcinogenic to humans.

Neurobehavioral effects are considered the critical endpoint to assess xylene toxicity and assays for these effects are used by regulatory agencies to set acceptable levels for human exposure. The work of Korsak et al. (1994) with *m*-xylene was used to establish the EPA, 2003A RfC and to derive the chronic inhalation health benchmark in the Risk Assessment (see Section 8.1).

Table 6.1. Xylenes Hazard Assessment: Key Studies for VCCEP Endpoints

Endpoint	Study	Result	Reference
TIER 1			
Acute Toxicity Inhalation	Rat-4hr (mixed xylenes)	LC50 = 6350 ppm	Hine and Zuidema, 1970
	Rat-4hr (mixed xylenes)	LC50 = 6700 ppm	Carpenter et al., 1975
	Mice- female- 6hr m-xylene o-xylene p-xylene	 5267 ppm 4595 ppm 3907 ppm	Bonnet et al., 1979
	Rat- male- 6hr m-xylene o-xylene p-xylene	 5984 ppm 4330 ppm 4591 ppm	Bonnet et al., 1979
Oral	Rat (mixed xylenes)	LD50 = 8640 mg/kg	Hine and Zuidema, 1970
	Rat (m- xylenes)	LD50 = 6661 mg/kg	Smyth et al., 1962
	Rat m-xylene o-xylene p-xylene mixed xylenes	 5010 mg/kg 3580 mg/kg 4020 mg/kg 5830 mg/kg	Ungváry et al., 1979
Dermal	Rabbit (mixed xylenes)	>4.3g/kg	Hine and Zuidema, 1970
	Rabbit (m-xylene)	12.1g/kg	Smyth et al., 1962
Repeat Dose Screening Studies: Superceded by definitive subchronic, reproductive and developmental studies			
Genetic Toxicity Bacterial Reverse Mutation	Ames Assay m-xylene o-xylene p-xylene	 Negative +/- S9	Bos et al., 1981
In Vitro cytogenetics	Human lymphocytes	Negative	Richer et al., 1993
TIER 2			
Subchronic Toxicity	Rat/ Oral: 13 weeks m-xylene	 NOAEL[M] = 100 mg/kg NOAEL[F] = 200 mg/kg	Wolfe, 1988
	p-xylene	NOAEL [M&F] = 200 mg/kg	
	Rat/Mouse – Oral 13 wks; mixed xylenes	NOAEL rats = 500 mg/kg NOAEL mice = 1000 mg/kg	NTP, 1986

Endpoint	Study	Result	Reference
TIER 2 (CONT.)			
Developmental toxicity	Rat/ Inhalation m-xylene o-xylene p-xylene Mixed xylenes	 NOAEL = 500 ppm NOAEL = 500 ppm NOAEL = 100 ppm NOAEL = 100 ppm	Saillenfait et al., 2003
Reproductive and Fertility	Rat: 1generation, Inhalation	NOAEL F1 = 500 ppm	API, 1983
Immunotoxicity	Rat/Oral m-xylene o-xylene p-xylene Mixed xylenes	 NOAEL = 1000 mg/kg NOAEL = 1000 mg/kg NOAEL = 1000 mg/kg NOAEL = 1500 mg/kg	Condie et al., 1988
In vivo Cytogenetics	Micronucleus –Mice Intraparitoneal m-xylene o-xylene p-xylene SCE - humans Mixed xylenes [3day inhalation, 3 times over 2 wk intervals]	 Negative NOAEL = 650 mg/kg NOAEL = 440 mg/kg NOAEL = 650 mg/kg Negative NOAEL =40 ppm	Mohtashamipur et al., 1985 Richer et al., 1993
Metabolism/ Pharmacokinetics	Multiple studies Toxicokinetics		EPA 2003a, Tardiff 1995 Ogata et al., 1980 Engström et al., 1984 Riihimäki et al., 1979a, b
TIER 3			
Neurotoxicity	Rat-male: Inhalation m-xylene	NOAEL = 50 ppm LOAEL = 100 ppm	Korsak et al., 1994
Chronic/Carcinogenesis	Rat/mouse 2 year Oral (mixed xylenes)	NOAEL tumors Rats = 500 mg/kg NOAEL tumors mice = 1000 mg/kg	NTP, 1986
Developmental Neurotoxicity	Rat Inhalation (mixed xylenes)	LOAEL = 500 ppm (single dose tested)	Hass et al. (1995, 1997)

6.2 Acute Toxicity (see Table 6.2)

Inhalation: Inhalation toxicity in rodents ranged from approximately 3900 ppm (*p*-xylene in mice, 6-hour exposure) to 6700 ppm (mixed xylene in rats, 4-hour exposure). In an early acute study by Cameron et al. (1938) with 24-hour exposure, Wistar rats and mice (strain unknown) were exposed to 1531, 3062 and 6125 ppm. Although an LC50 was not calculated, results indicated no deaths at 1531 ppm, 1/10 rat and 4/10 mice died at 3062 ppm, and 8/10 rats and 9/10 mice died at 6125 ppm. In the same study, 2010 ppm *m*-xylene caused deaths in 6/10 mice after 24-hour exposure. In more recent studies the inhalation LC50 for mixed xylenes in rats ranged from 5267-6700 ppm with 6-hour exposure (Bonnet et al., 1979) or 4-hour exposure (Carpenter et al., 1975; Hine and Zuidema, 1970). Meta-xylene LC50 in rats was 5984 ppm, and in mice 5267 ppm with 6-hour exposure; *o*-xylene LC50 in rats was 4330 ppm, and in mice 4595 ppm with 6-hour exposure; and *p*-xylene LC50 with 6-hour exposure in rats was 4591 ppm, in mice, 3907 ppm (Bonnet et al., 1982 [rats], 1979 [mice] respectively), or with 4-hour exposure in rats, LC50=4740 ppm (Harper et al., 1975).

Oral: A single gavage dose of undiluted mixed xylenes to rats at graded dose up to 25 ml/kg [21.4g/kg] resulted in an LD50 of 8640 mg/kg (Hine and Zuidema, 1970). In the 1986 NTP series of studies on toxicity and carcinogenicity, the LD50 for mixed xylenes in oil for rats was 3523 mg/kg and for mice, LD50 for males was 5627 mg/kg; LD50 for females was 5251 mg/kg. Meta-xylene (undiluted) administered orally by gavage induced LD50 of 6661 mg/kg in male rats (Smyth et al., 1962). Similar results had been reported by Gerarde (1959) when treatment of rats with 4400 mg/kg *o*-xylene in oil caused death in 7 of 10 rats and treatment with *p*-xylene in oil at 4305 mg/kg caused death in 6 of 10 rats. Oral administration of neat mixed xylenes or each isomer to rats ranked acute LD50 toxicity as *o*-xylene (3580 mg/kg) > *p*-xylene [4029 mg/kg] > *m*-xylene (5010 mg/kg) > mixed xylenes (5830 mg/kg) (Ungváry et al., 1979). Intraperitoneal administration of *p*-xylene to rats produced an LD50 range of 2880-3680 mg/kg in female Sprague Dawley rats (Drew and Fouls, 1974).

Dermal: Dermal toxicity in rabbits from treatment with *m*-xylene produced an LC50 of 12.1 g/kg (Smyth et al., 1962). Hines and Zuidema (1970) also reported high dermal toxicity concentrations for *m*-xylene with a dermal LC50 greater than 4.3 g/kg, the highest dose tested, at which only 1/3 rabbits died.

Irritation: Mixed xylenes and the *m*- and *p*- isomers are demonstrated to be moderate to marked dermal irritants in rabbits (Hine and Zuidema, 1970; Smyth et al., 1962; Jacobs, 1992). Hine and Zuidema (1970) reported mixed xylenes as a moderate conjunctival irritant. Para-xylene was a slight to mild eye irritant (Kennah et al., 1989) and *m*-xylene was a slight irritant in rabbit eyes (Smyth et al., 1962). No skin or eye irritation tests on *o*-xylene were found.

Table 6.2: Representative Hazard Studies for Xylenes Toxicity: Acute (Tier 1)

Study Type	Test Article	Species	LD50/LC50	Comments	Reference
Acute: Inhalation	Mixed xylenes	Rat-male (Harlan-Wistar)	6700 ppm	4 hr exposure	Carpenter et al., 1975
		Rat-male (Long Evans)	6350 ppm	4 hr exposure	Hine and Zuidema, 1970
		Mouse	5267 ppm	6 hr exposure, observed 14d	Bonnet et al., 1979
	Meta-xylene	Rat	5984 ppm	6 hr exposure, observed 14d	Bonnet et al., 1982
		Mouse-female (SPF-Of1)	5267 ppm	6 hr exposure, observed 14d	Bonnet et al, 1979
	Ortho-xylene	Rat	4330 ppm	6 hr exposure, observed 14d	Bonnet et al, 1982
		Mouse	4595 ppm	6 hr exposure, observed 14d	Bonnet et al, 1979
	Para-xylene	Rat	4591 ppm	6 hr exposure, observed 14d	Bonnet et al., 1982
		Mouse	3907 ppm	6 hr exposure, observed 14d	Bonnet et al., 1979
		Rat	4740 ppm	4 hr exposure	Harper et al., 1975
Acute: Oral	Mixed xylenes	Rat-male (Long Evans)	8640 mg/kg	Graded single undiluted doses/group to 25ml/kg	Hine and Zuidema, 1970
		Rat-male (F344/N)	3523 mg/kg	Single gavage dose in oil	NTP, 1986
		Mouse Male	5627 mg/kg	Single gavage dose in oil	NTP, 1986
		(B6C3F1) Female	5251 mg/kg		
	Meta-xylene	Rat-male	6661 mg/kg	Single gavage dose	Smyth et al., 1962
	Ortho-xylene Para-xylene Meta-xylene Mixed xylenes	Rat	3580 mg/kg 4029 mg/kg 5010 mg/kg 5830 mg/kg	Single dose	Ungváry et al, 1979
Acute: Intraperitoneal	Para-xylene	Rat- female	2880-3680 mg/kg	Single doses	Drew and Fouls, 1974
	Meta-xylene Ortho-xylene Para-xylene	Mouse (NMRI)	2.003ml/kg (1.73g/kg) 1.550ml/kg (1.36g/kg) 2.450ml/kg (2.11g/kg)	Single dose	Mohtashamipur et al, 1985 (micronucleus paper)

Table 6.2: Representative Hazard Studies for Xylenes Toxicity: Acute (Tier 1) continued

Study Type	Test Article	Species	LD50/LC50	Comments	Reference
Acute: Dermal	Meta-xylene	Rabbit-Male (NZW)	12.1g/kg (14ml/kg)	-	Smyth et al., 1962
		Rabbit-Male	>4.3g/kg (>5ml/kg)	-	Hine and Zuidema, 1970
Irritation: Inhalation	Mixed xylenes	Human	LOAEL = 460 ppm (eye) LOAEL =690 ppm (throat)	15 min exposure	Carpenter et al., 1975
		Human	NOAEL = 396 ppm (eye and respiratory)	30 min exposure	Hastings et al., 1984
Skin Irritation	Mixed xylenes	Rabbit-male (NZW)	Moderate irritant	PII = 2.21; intact and abraded skin; Draize scoring	Hine and Zuidema, 1970
	Meta-xylene	Rabbit-male (NZW)	Irritant	-	Smyth et al., 1962
	Para-xylene	Rabbit – male (NZW)	Mild Irritant	OECD 404 (1981)	Jacobs, 1992
Eye Irritation	Mixed Xylenes	Rabbit-male (NZW)	Moderate Irritant conjunctiva effect	Avg. score = 5.33 at 24hr; 6.33 at 48 hr; 6.67 at 72hr	Hine and Zuidema, 1970
	Meta-xylene	Rabbit-male (NZW)	Slight Irritant	-	Smyth et al, 1962
	Para-xylene	Rabbit (NZW)	Mild Irritant	0.1ml instilled in one eye; other eye control	Kennah et al., 1989

6.3 Repeated Dose Toxicity - Subchronic Toxicity (See Table 6.3)

Inhalation:
Several inhalation studies have investigated the subchronic systemic effects of xylenes and no specific target organ effects have been consistently observed. The most predominant effects were body weight and weight gain changes and mild hepatic alterations, which may be indicative of adaptive response to hydrocarbon exposure rather than toxic effects. The studies are summarized below.

Jenkins et al. (1970) exposed rats (12-14/group), guinea pigs (15/group), beagle dogs (2/group), and squirrel monkeys (2-3/group) to 0 or 780 ppm *o*-xylene (3358 mg/m3), 8 hours/day, 5 days/week for 6 weeks or 78 ppm (337 mg/m^3) 24 hours/day, 7 days/week for 90 days. Guinea pigs showed a marked decrease in body weight but no other clinical, neurological, or pathological effects. One of 2 dogs experienced tremors throughout the exposure period, and one monkey died on day 7 of exposure. No other signs of toxicity were reported. Carpenter et al. (1975) exposed groups of 25 male rats and four male beagle dogs to concentrations of 180, 460, and 810 ppm of mixed xylenes for 6 hours/day, 5 days/week for 65-66 days. No treatment related effects were observed in either species. Ungváry et al. (1980) evaluated biochemical effects in rats exposed to 4500 ppm *o*-xylene, 8 hours/day for 6 weeks. At the end of the first week of exposure, relative liver weight was increased, hexobarbitol sleeping time was shortened, the concentration of cytochrome P450 increased, and the activities of analine dehydroxylase (AH) and aminopyrine N-demethylase (ApN-D) were decreased. By six weeks exposure, similar effects in liver, sleep time, and P450 were seen but AH and ApN-D activities had increased. These changes in liver weight and the mixed function oxidase (MPO) system activity were considered adaptive responses to exposure to a xenobiotic agent. In a study by Tátrai and Ungváry (1980), groups of 30 male, CFY rats were exposed to 0 or 3500 ppm *o*-xylene, 8hr/day for 6 weeks. Body weight gain was reduced by xylenes exposure. Exposed rats had hepatic changes including: increased absolute and relative liver weights, hepatocellular hypertrophy, increased proportion of smooth endoplasmic and rough endoplasmic reticulum, decreased glycogen, and increased peroxisomes. It was concluded that the liver effects were adaptive and probably reflected induction of enzymes. In a follow-up study to evaluate the potential for xylenes to cause hepatotoxicity, Tátrai et al. (1981) exposed male CFY rats to concentrations of 0 and 1090 ppm *o*-xylene for 8hr/day, 7days/week, for 6 or 12 months. Ortho-xylene caused reduced body weight gain, increased absolute and relative liver weight, and induction of mixed function oxidase (MFO) enzymes. However, microscopic evaluation of the liver did not reveal any abnormalities, but there was proliferation of endoplasmic reticulum. In 1990, Ungváry exposed male CFY rats to mixed xylenes (10% *o*-; 50% *m*-; 20% *p*-xylene, and 20% ethylbenzene) at levels of 0, 140, 350, and 920 ppm for 8 hr/day, 7 days/week for 6 weeks, then 5 days/week for 6 months. Exposure related hepatic effects included increased relative liver weight, hypertrophy of the centrilobular zone, increased hepatocyte volume, proliferation of smooth endoplasmic reticulum; increased concentration of CYP-450 and b5; and increased activities of NADPH:cytochrome c-reductase, alanine *p*-hydroxylase, succinate dehydrogenase and aminopyrine N-demethylase; decreased barbiturate sleeping time, and transient increase in glycogen. Additional exposure studies in mice, rats, and rabbits produced similar liver changes. The authors considered these effects adaptive rather than adverse.

Rydzynski et al. (1992) exposed Wistar rats to 1000 ppm *m*-xylene for 6 hr/day, 5 days/week for 3 months and to 100 ppm for 6 months. Slight ultrastructural changes, including proliferation of smooth endoplasmic reticulum, were found in hepatocytes. Bowers et al. (1982) examined ultrastructural changes in livers of young rats exposed to *o*-xylene at dose of 73 mg/kg/day for 3 days intraperitoneal [IP] injection, or in livers of aging rats exposed to 200 mg/kg diet daily for 6 months. IP treatment of *o*-xylene to young rats did not cause ultrastructurally observable

abnormalities in hepatocytes but chronic oral ingestion did cause formation of vacuolar structures in hepatocytes of older rats.

Several studies have specifically investigated the effects of xylenes on induction of enzymes of xenobiotic metabolism in liver (Toftgard and Nilsen, 1982; Toftgard et al., 1981; 1983a,b; Elovaara et al., 1982). The basic conclusion of these studies was that xylenes, and especially *m*-xylene, are phenobarbitol-like inducers of xenobiotic metabolism in liver. The findings indicate that the hepatic effects of xylene exposure are adaptive pharmacologic responses related to xylene elimination and should not be considered toxic effects in determining adverse effects levels.

Oral: Subchronic oral studies do not consistently show effects on a single organ system. Effects in different studies have included increased mortality (possibly related to test article inspiration), reduced body weight gain, salivation, nephrotoxicity, and hepatic changes observed by electron microscopy.

In an NTP oral study (1986), 10 male and 10 female rats received doses of 0, 62.5, 125, 250, 500, and 1000 mg/kg/day mixed xylenes (60% *m*-, 13.6% *p*-, 9.1% *o*-xylene, 17% ethylbenzene), 5 days/week for 13 weeks. At termination necropsy was performed on all rats and comprehensive histological examinations were performed on rats from control and high dose groups. High dose males and females gained 15% and 8% less body weight than controls after 13 weeks of exposure. No sign of toxicity or gross and microscopic pathologies were noted. In the same study, groups of 10 male and 10 female mice received 0, 125, 250, 500, 1000, and 2000 mg/kg/day of mixed xylenes in corn oil 5 days/week, for 13 weeks. As with rats, necropsy was performed on all mice and comprehensive histologic examinations were performed on mice in the high dose and control groups. High dose mice exhibited transient CNS effects 5-10 minutes after dosing that lasted 15-60 minutes.

A subchronic oral gavage study of mixed xylenes was conducted by Condie et al. (1988). Groups of 10 male and 10 female rats received 0, 150, 750, or 1500 mg/kg/day xylene in corn oil for 90 consecutive days. Effects included decreased body weight in high-dose males, dose-related increased liver weight and relative liver weight in mid- and high-dose males and females. Increased kidney weight and relative kidney weight were seen in mid- and high-dose males and high-dose females. It was suggested that the liver findings were adaptive rather than toxic. Microscopic examination revealed a dose-related increase of kidney hyaline droplet formation in males and the appearance of minimal chronic nephropathy in females.

In studies conducted by Wolfe (1988 a, b) *m*- and *p*-xylene were separately evaluated in the rat. Groups of 20 male and 20 female rats received gavage doses of 0, 100, 200, and 800 mg/kg/day, in corn oil for 90 consecutive days. With *m*-xylene, high levels of salivation were observed in high-dose males and females. Body weight gains were reduced in males at the 200 and 800 mg/kg doses (75-89% of controls) and in females at 800 mg/kg (85% of controls); this was associated with decreased food consumption. There were no other treatment related toxic effects and no abnormal gross or microscopic pathological findings. With *p*-xylene, treatment related clinical effects were limited to increased salivation in high dose males and females. Body weight gain was slightly reduced in both sexes at the high dose. No other treatment related toxic effects were observed and there were no gross or microscopic pathologic findings.

The LOAELs and NOAELs for all subchronic studies are shown in Table 6.3

Comparison of Toxicity of Individual Xylene Isomers

Several studies have compared *o*-, *m*-, and *p*-isomers for their toxicological effects and differences have been reported for some endpoints. Condie et al. (1988) found no significant differences

between the three isomers in a 10-day subacute oral gavage study in the rat. In a 4-hour inhalation study in the rat, Molnár et al. (1986) found that the minimal narcotic dose was similar for the three isomers (*o*- xylene, 2180 ppm; *m*-xylene, 2100 ppm; *p*-xylene, 1940 ppm). However, at lower doses, *o*-xylene (150-1800 ppm) caused a slight depression in motor activity, *m*-xylene (130-1500 ppm) caused a slight increase in activity, and *p*-xylene (130-1500 ppm) caused a marked increase in activity. Fang et al. (1996) showed that the alveolar concentrations of the three isomers needed to produce anesthesia in the rat were similar. Moser et al. (1985) showed that operant response and motor performance in mice were similar for the three isomers. However, Korsak et al. (1990) found that *o*-xylene was the more potent than *m*- or *p*-isomers in altering motor performance in the rat as indicated by the number of failures in the rotarod test. Potency was decreased in the following order: *o*-xylene > *m*-xylene > *p*-xylene (see Section 6.8 Adult Neurotoxicity).

Table 6.3: Representative Hazard Studies for Xylenes Toxicity: Repeat Dose (Tier 1 and 2)

Study Type	Test Article	Species	NOAEL	LOAEL	Duration of Exposure	Reference
Repeat Dose Toxicity Inhalation	Ortho-xylene	Rat-male	None-one dose level only	3500 ppm – decr. body weight, inc. liver weight	6 weeks – 8hr/d, 7 d/wk	Tatrái and Ungváry, 1980
		Rat-male	None – one dose level only	1090 ppm – decr. body weight, inc. liver weight, induced MFO enzymes	6-12 months, 8hr/d, 7 d/wk	Tatrái et al, 1981
	Meta-xylene	Rat – male & female	1000 ppm	None	6 months, 6hr/d, 5d/wk	Rydzynski et al., 1992
	Mixed xylenes	Rat – male	920 ppm	None; changes in liver weight and enzymes not considered adverse.	6 wks, 8hr/day, 7d/wk, then 5d/wk for 6 mon 0, 140-920 ppm	Ungváry et al., 1990
	Mixed xylenes	Rat-male; Dog-male	810 ppm	Not determined	65-66 days 6hr/d, 5d/wk; 0, 180-810 ppm,	Carpenter et al., 1975
Oral gavage	Mixed xylenes	Rat – male & female	500 mg/kg	1000 mg/kg: decr. body weight in both sexes	90 days, 5d/wk by gavage in corn oil 0, 62.5-1000 mg/kg	NTP, 1986
		Mouse – male & female	1000 mg/kg	2000 mg/kg- decr. body wt., neurotoxicity (lethargy, tremors 5-60 min after dosing)	0, 125-2000 mg/kg	
		Rat – male & female	150 mg/kg	750 mg/kg – inc. liver & kidney weight in mid & high dose males and high dose females	90 consecutive days; 0, 150 to 1500 mg/kg in corn oil	Condie et al., 1988
	Meta-xylene	Rat – male & female	100 mg/kg [M] 200 mg/kg [F]	800 mg/kg –body weight decrease	90 consecutive days; once a day	Wolfe, 1988a
	Para-xylene	Rat – male & female	200 mg/kg [M&F]	800 mg/kg – slight body weight decrease	in corn oil 0, 100, 200, 800 mg/kg/day	

6.4 Genetic Toxicity - (See Table 6.4)

Mixed xylenes and the xylene isomers have been tested in both *in vitro* and *in vivo* assays and are substantially non-genotoxic. *In vitro* studies of mixed xylenes and xylene isomers in bacterial cells, including *Salmonella typhimurium, Escherichia coli,* and *Bacillus subtilis*, for mutation or DNA damage with and without metabolic activation were negative, as was a mitotic gene conversion study in yeast, *Saccharomyces cerevisiae*, D4. Although most *Salmonella* studies were performed using plate incorporation, the API Litton Bionetics study (1978a) employed a suspension assay as well in order to optimize interaction between bacteria and mixed xylenes; no increase in gene mutation was observed by either method.

When mouse lymphoma cells were exposed to mixed xylenes at doses of 0, 5.6-87.0 µg/ml with or without metabolic activation, no mutational events were induced (API, 1978a). Cytogenetic damage, expressed as sister chromatid exchange (SCE) or chromosome aberrations were not observed in Chinese hamster ovary cells with or without activation (Anderson et al., 1990), or in cultured human lymphocytes that retain endogenous metabolic activity (Gerner-Schmidt and Friedrich, 1978; Richer et al., 1993).

Exposure to mixed xylenes (18.3% ethylbenzene) caused recessive lethal mutations in *Drosophila melanogaster*, but exposure to *m*-xylene or *o*-xylene alone did not cause this effect (Donner et al., 1980). The same report stated that exposure of rats to 300 ppm mixed xylenes, 6 hours/day, 5 days/week for 9, 14, or 18 weeks did not induce chromosome aberrations in bone marrow cells. Results of other studies in laboratory animals were also negative for xylenes-induced cytogenetic effects. The American Petroleum Institute (1978a) sponsored chromosome aberration studies in rats using mixed xylenes (11.4% *o*-xylene, 0.3% *p*-xylene, 36.1% ethylbenzene, and 52% *m*-xylene). Sprague Dawley rats were treated intraperitoneally with 0, 0.044, 0.147, and 0.441 ml/kg (approximately 0, 38, 127, and 381 mg/kg) xylenes in a single dose or daily for 5 days. Chromosome aberrations were not induced in femoral bone marrow of treated rats under either regime. Mohtashamipur et al. (1995) administered each xylene isomer to male NMRI rats intraperitoneally in 2 similar doses, 24 hours apart over a range of concentrations from 0, 0.12-0.75ml/kg (105-650 mg/kg) and evaluated femoral bone marrow 30 hours after the first injection. No increase in micronucleated polychromatic erythrocytes was observed for any xylene isomer (or for ethylbenzene which was also tested) at any dose level.

Two dominant lethal assays in rat and mouse have been performed (API, 1973). Male animals were treated with a single 1 ml/kg (865 mg/kg) of mixed xylenes and mated with untreated females at intervals throughout the spermatogenic cycle. Rats were treated intraperitoneally and mice were treated subcutaneously. Females were euthanized during the later part of gestation and uteri were examined for living and dead implantations and total number of implantation sites. Xylenes did not increase pre- or post-implantation loss from matings at any stage of the spermatogenic cycle and was not considered mutagenic to sperm in this assay. Ortho-xylene was examined for its potential to induce abnormal sperm by injecting Sprague Dawley rats with 0.5 or 1.5 ml/kg (440 or 1320 mg/kg) *o*-xylene in corn oil (Washington et al., 1983). Animals were euthanized 5 weeks after treatment and the sperm examined for abnormalities. Rats housed at room temperature of 20-24^{0}C showed no significant increase in abnormal sperm, while those housed at a higher temperature of 24-30^{0}C showed a significant increase in abnormal sperm at the low dose only. The authors suggested a synergistic effect between *o*-xylene and temperature, but since no increase in abnormal sperm or other adverse effects were observed at the high dose, the significance of this result is questionable.

There is sufficient evidence of overall negative results in a variety of *in vitro* and *in vivo* tests, including occupational exposure in humans, to conclude that mixed xylenes, *m*-xylene, *o*-xylene, and *p*-xylene are not genotoxic (ATSDR, 1995; EPA 2003a).

Table 6.4: Representative Hazard Studies for Xylenes Toxicity: Genetic Toxicity (Tier 1 and 2)

Study Type	Test Article	Species	Result	Reference
Genetic Toxicology: Bacterial- reverse mutation +/-S9	Mixed xylenes	*Sal. Typhimurium* TA98, 97, 100, 1535: plate incorp.	Negative +/-S9	NTP, 1986; Zeiger et al., 1987
	Meta-xylene Para-xylene Ortho-xylene	*Sal. typhimurium* TA98, 100, 1535, 1537: plate incorp.	Negative +/-S9	Haworth et al., 1983
	Meta-xylene Para-xylene Ortho-xylene	*Sal. typhimurium* TA98, 100, UTH8414, UTH8413: plate incorp.	Negative +/-S9	Conner et al., 1985
	Meta-xylene Para-xylene Ortho-xylene	*Sal. typhimurium* TA98, 100, 1535, 1537, 1538: plate incorp.	Negative+/-S9	Bos et al., 1981
	Meta-xylene Para-xylene	*Sal. typhimurium* TA98, 100, 1535, 1537: plate incorp. and spot test	Negative+/-S9	Florin et al., 1980
	Mixed xylenes	*Sal. typhimurium* TA98, 100, 1535, 1537, 1538: *Saccharomyces cerevisiae:* plate incorp. and suspension	Negative +/-S9	API 1978a
	Para-xylene	*Sal. typhimurium* TA98, 100, 1535, 1537, 1538: *Escherichia coli* WP2uvrA plate incorporation.	Negative+/- S9 Negative +/- S9	Shimizu et al., 1985
E.coli prophage induction assay ± S9	Mixed xylenes	*E. coli* WP2 (?)(Ionii, sulA1, trpE65, uvrAa55, IamB+),	Negative +/- S9	DeMarini et al., 1991
E coli DNA repair suspension assay +/-S9	Technical grade xylene	*E. coli* WP2, WP2uvrA, WP67, CM611, WP100, WP3110polA+, p3478pol a- [DNA damage]	Negative +/- S9	McCarroll et al., 1981a
Bacillis subtilis Modified rec assay	Technical grade xylene	*B. subtilis* H17, M45 [DNA damage]	Negative +/-S9	McCarroll et al., 1981a

Table 6.4: Representative Hazard Studies for Xylenes Toxicity: Genetic Toxicity (Tier 1 and 2) continued

Study Type	Test Article	Species	Result	Reference
Genetic Toxicology: Mammalian cells in culture	Mixed xylenes	Mouse lymphoma cells (L5178Y, TK+/-) forward mutation.	Negative +/-S9	API, [Litton Bionetics], 1978
	Xylene undefined	Cultured human lymphocytes endogenous metabolism: SCE & Chromosome aberrations	Negative for SCE and chromosome aberrations	Gerner-Schmidt and Friedrich, 1978
	Mixed xylenes	Cultured human lymphocytes endogenous metabolism: SCE	Negative for SCE	Richer et al., 1993
	Mixed xylenes	Chinese hamster ovary cells (CHO) +/-S9; SCE and chromosome aberrations	Negative+/-S9 for SCE and chromosome aberrations	Anderson et al., 1990
Genetic Toxicology *In vivo* Animals Cytogenetics	Meta-, para-, ortho-xylene	Mouse-male/ Intraperitoneal injection. Micronucleus assay (0,105-650 mg/kg, 2 doses 24hr apart)	NOAEL=650 mg/kg [max.dose], for meta-& para-xylenes NOAEL=440 mg/kg for ortho No increased micronuclei/PCE	Mohtashamipur et al., 1995
	Mixed xylene	Rat/intraperitoneal injection. Chromosome aberrations assay (0, 38, 127, 381 mg/kg in a single dose or daily for 5 days)	NOAEL= 381 mg/kg No chrom aberration in bone marrow cells under either regime.	API, 1978a
Cytogenetics Human	Mixed xylene	Male/Inhalation: 40 ppm only dose (3 days exposure, repeated 3 times at 2 wk intervals)	NOAEL=40 ppm No increase in SCE, cell cycle delay or cell death	Richer et al., 1993
	Mixed xylene	23 workers; Sister chromatid exchange assay (SCE) exposed to 11 and 13 ppm (duration of exposure between 4 mon –23 yrs)	NOAEL=11 ppm (47.3 mg/m3) and 13 ppm (55.9 mg/m3) No increase in SCE	Pap and Varga, 1987
Dominant Lethal assay	Commercial xylene	Mouse-male; singe subcutaneous injection of 865 mg/kg; Rat-male single intraperitoneal injection of 865 mg/kg [1ml/kg] mated with untreated females through spermatogenic cycle	NOAEL=865 mg/kg No affect on mating, reproductive No increase in pre- or post-implantation loss from any week of mating; not mutagenic to sperm.	API, 1973

6.5 Reproductive Toxicity (see Table 6.5)

Reproductive data on xylenes include a single one-generation inhalation study in rats and two dominant lethal studies (rat, mouse), as well as evaluation of male and female reproductive organs in repeated dose studies, all of which indicate that xylenes do not affect reproductive performance.

In the one generation reproduction study, no adverse reproductive effects were found following inhalation exposure of male and female CD rats to mixed xylenes concentrations as high as 500 ppm during premating, mating, pregnancy, and lactation (API 1983). Groups of male and female CD rats were exposed to 0, 60, 250, or 500 ppm mixed xylenes (20.3% *p*-xylene, 44.2% *m*-xylene, and 20.4% *o*-xylene, 12.8% ethylbenzene and 2.4% toluene) by inhalation, 6 hours/day, 5 days/week for 131 days prior to mating, and during 20 days of mating. Mated females were exposed during gestatation days (GD) 1-20 and days 5-20 of lactation; pups were exposed only through the milk. Additional animals exposed to 500 ppm were mated to unexposed partners to identify any sex-specific effects. One half of all parental (F0) males were euthanized after mating for post-mortem examination; the remaining males were sacrificed and examined 21 days later. One half of 500 ppm and control females were euthanized on GD21 for developmental toxicity evaluation and the remaining parental females delivered litters and were maintained through lactation to weaning. Litters were culled, if possible, to 8 pups (4M, 4F) on lactation day (LD) 4. Pups were weighed, sexed, and given gross external examinations on LD1, 4, and 21. Randomly selected pups from each group (1/sex/litter) and all F0 dams with litters were euthanized on LD21. Remaining pups were maintained for a post-weaning interval of 28-49 days and weighed and sacrificed on day 49. No adverse effects were observed in parental rats. No differences were seen in testes weight or histological examination of reproductive tissue in xylene-exposed males. Male mating index and fertility index were comparable among exposed and control rats. Although the female mating index was significantly below the 100% in controls, 85% in the 250 ppm (both sexes treated), and 85% in the 500 ppm (females only treated) groups; a significant decrease in mating did not occur at the 500 ppm (both sexes treated) and 500 ppm (males only treated) groups. The authors did not consider these decreases to be xylenes-induced because the effect was not seen in the highest dose when both sexes were treated and the controls had an unusually high mating performance. There were no treatment-related effects in mean duration of pregnancy, mean litter size, or pup survival. Mean pup weight in the 500 ppm (both sexes treated) group was slightly but significantly lower than controls on lactation day 14 and 21, and at sacrifice on day 49. Despite these marginal decreases in pup weight in the 500 ppm (both sexes treated) group, no decrease in pup body weight was observed in the 500 ppm (females only treated) group. Thus, these decreases were not considered adverse effects of treatment. Female pups sacrificed at weaning in the 250 and 500 ppm groups had statistically significant decreases in absolute and relative ovary weight at 21 days of age, but the decreases were not concentration-related and were not observed at 49 days of age. Among the females evaluated for teratogenesis, there were no significant effects on litter size, implantations, or malformations. Mean fetal weight in the 500 ppm group was lower than controls but the difference was significant only in female fetuses. Parental systemic and developmental NOAEL was 500 ppm.

The dominant lethal studies (API 1973) involved a single injection of 1 ml/kg (864 mg/kg) mixed xylenes to male rats intraperitoneally and to male mice, subcutaneously, followed by sequential mating to untreated females throughout the spermatogenic cycle. No xylenes-induced effects were seen on the incidence of pre- or post-implantation loss in either species.

The absence of xylenes-induced toxicity in male reproductive organs and performance correlates with the negative results from a study by Nylén et al. (1989) in which male SD rats were exposed to 1000 ppm mixed xylenes, 18 hours/day, 7 days/week for 61 days. No alterations in testes,

accessory glands, or circulating male hormone levels were observed. When Yamada (1993) exposed Wistar rats for 7 days to xylenes (not characterized), twice a day until disappearance of righting reflex, anesthesia was produced within 10 min (actual doses not reported). Animals were sacrificed on day 8. Decreases in body weight, testes weight, and weight of accessory reproductive organs, reduced acid phosphate activity in prostate, and reduced plasma testosterone levels, and decrease in spermatozoa count in the epididymides were observed in rats exposed to extremely high, anesthetic doses of mixed xylenes.

There were no reported oral animal reproductive studies available for mixed xylenes or individual isomers. However, histological examination of rodents administered mixed xylenes at doses as high as 1000 mg/kg/day in rats and 2000 mg/kg/day in mice for 13 weeks, and up to 500 mg/kg/day in rats and 1000 mg/kg/day in mice for 103 weeks, revealed no adverse effects on prostate/testes, ovary/uterus, or mammary glands (NTP, 1986). Similarly, no adverse histopathological changes were observed in reproductive organs of rats given *m*- or *p*-xylene at doses as high as 800 mg/kg/day for 13 weeks (Wolfe, 1988a,b).

All studies indicate that xylenes do not substantially affect reproductive performance or induce histologically observable structural damage to reproductive organs of laboratory animals at non-anesthetic doses. The comprehensive one-generation animal inhalation reproductive study (API, Biodynamics, 1983) demonstrated that xylenes are not a reproductive toxicant. Although this study may not meet current test guidelines that generally call for a two-generation study, the lack of reproductive effects at exposure up to 500 ppm suggests that xylenes do not present a reproductive hazard. It is unlikely that xylenes exposure would induce adverse effects in a second generation in the absence of damage to parental or the F1 generation. This is further supported by evaluating data for similar chemicals with multigeneration studies. The NOAELs from the second generation of the studies are similar to the NOAEL for the first generation. For toluene, the NOAEL and LOAEL for parents and offspring of both generations are 500 ppm and 2000 ppm, respectively (Roberts et al. 2003). For C_9 aromatic naphtha, the NOAEL and LOAEL are 500 ppm and 1500 ppm, respectively, for both parent and offspring from the first and second generation (McKee et al., 1990). The International Life Sciences Institute's (ILSI) Health and Environmental Sciences Institute (HESI) also recently concluded that the second generation of a multigeneration study has little impact on the chronic RfD based on an evaluation of 200 pesticides representing very different classes of chemistry. ILSI-HESI concluded that a multigeneration study need not be conducted unless triggered by results in the first generation such as (1) an adverse effect on fertility or fecundity of the parental generation, (2) indications of abnormal sexual development of the F1 pups, or (3) deaths or evidence of toxicity to the F1 pups pre-weaning (http://www.ilsi.org/file/LifeStagesDraftPaperJan05.pdf). Xylenes did not cause effects that would trigger a multigeneration study.

Of even greater importance is the availability of developmental neurotoxicity studies that provide focused and sophisticated neurobehavioral evaluation on pups following developmental exposures to mixed xylenes and p-xylene. Neurobehavioral endpoints are the critical effects of concern based on both the human and animal literature on xylenes and related solvents. They are likely to be more sensitive than the standard endpoints required on a multigeneration study. Gestational exposure of animals to xylenes resulted in slight neurodevelopmental effects (Hass et al, 1995; 1997) at 500 ppm. Though this study is limited because it was conducted at only one dose level, it evaluated multiple neurobehavioral endpoints including developmental landmarks, auditory startle, air righting, rotarod, 3-minute open field activity, brain weight, and Morris water maze. In a separate study, other neurological endpoints such as acoustic startle response and figure-8 maze activity were not affected in male or female offspring of rats exposed to up to 1600 ppm p-xylene 6 hours per day on GDs 6-15 (Rosen et al., 1986). It would be unlikely for a multigeneration study to be more sensitive to xylenes exposure compared to these developmental neurobehavioral studies.

6.6 Developmental Toxicity (see Table 6.5)

Developmental studies in pregnant animals indicate that xylenes are fetotoxic at dose levels that are high enough to induce maternal stress and often maternal toxicity, making it difficult to determine whether effects are from direct action of xylene or secondary to maternal toxicity. ATSDR (1995) observed that large variations in concentrations of xylenes producing developmental effects, and of those producing no developmental effects, were influenced by strain and species of animal, purity of xylene, method of exposure, exposure pattern, and duration.

Oral exposure-Mice: Marks et al. (1982) administered mixed xylenes (60.2% *m*-, 9.1% *o*-, 13.6% *p*-xylene, 17% ethylbenzene) by gavage in cottonseed oil to pregnant CD-1 mice, 3 times/day at doses of 0, 520, 1030, 2060, 2580, 3100, or 4130 mg/kg/day (0.6, 1.2, 2.4, 3.0, 3.6, and 4.8ml/kg/day) from GD6-15; sacrifice was on GD 18. Maternal lethality of 100% and 32% occurred at 4130 and 3100 mg/kg, respectively, with a 40% decrease in body weight gain in remaining 3100 mg/kg maternal mice over GD1-18 compared to controls. Fetal resorptions increased at the maternally toxic dose of 3100 mg/kg, and significantly reduced fetal body weights and increased incidence of cleft palate were observed at 2060 mg/kg and above. Maternal toxicity LOAEL was 3100 mg/kg/day and the NOAEL was 2580 mg/kg/day. Fetal toxicity LOAEL was 2060 mg/kg/day and the NOAEL was 1030 mg/kg/day. It should be recognized that mice under stress are predisposed to produce offspring with cleft palate and that maternal stress induced at high levels of xylenes could impact both fetal weight and malformations (Brown et al., 1972; 1974; Khera 1984). These investigators found that cleft palate in mice is associated with maternal stress and may be due to elevated levels of corticosterol.

Nawrot and Staples (1980) gave pregnant CD-1 mice *m*-, *p*- or *o*-xylene by gavage at approximate total daily doses of 0, 780, 1960, or 2610 mg/kg (0, 0.30, 0.75, 05, and 1.0ml/kg/dose, 3 times a day) on GD 6-15, or 2610 mg/kg/day on GD12-15. Overt maternal toxicity and significantly increased incidences of resorptions and cleft palate occurred at 1960, 2610 mg/kg doses of *o*- or *p*-xylene and maternal toxicity and resorptions only at 2610 mg/kg *m*-xylene, given from GD6-15. Targeted exposures to 2610 mg/kg/day on GD12-15 resulted in significant increases in maternal lethality and increased incidence in fetal malformations particularly cleft palate in *p*- and *m*-xylene groups. Subsequent exposure to *m*-xylene at 1960 and 2610 mg/kg/day on GD12-15 induced maternal toxicity and cleft palate at 2610 mg/kg, and a small but statistically significant increase in cleft palate at 1960 mg/kg/day in the absence of maternal toxicity (4.4% vs 0% in controls). Authors considered the increase to be low and characterized *m*-xylene as a weak teratogen. However, in a separate screening teratology study in mice, 2000 mg/kg/day *m*-xylene administered from GD8-12 did not induce fetal toxicity or malformations (Seidenberg et al., 1986).

Inhalation: A number of developmental inhalation studies from xylenes are available. The quality and interpretability of these studies vary considerably and a complete assessment of the results was sometimes hampered due to the absence of key data and reporting, particularly in early studies. The Saillenfait et al. (2003) was selected as the key study for this endpoint because it is the most modern and comprehensive study, concurrently evaluating mixed xylenes, the individual xylene isomers and ethylbenzene, and providing key data and statistics.

Saillenfait (2003) exposed Sprague Dawley rats to *o*-, *m*-, and *p*-xylene, mixed xylenes, and ethylbenzene at concentrations of 0, 100, 500, 1000, or 2000 ppm, 6 hours/day during gestation days (GD) 6-20, in accordance with OECD protocol 414 (2001) and EPA OPPTS 870.3700 (1998) testing guideline. All materials caused maternal toxicity (reduction in maternal body weight gain) at 1000 and 2000 ppm. Decreased corrected weight gain (without gravid uterus) and food consumption were observed at 1000 and 2000 ppm *o*-, *m*-, and *p*-xylene, and ethylbenzene, and at 2000 ppm mixed xylenes. No fetal malformations were induced by any test material. Decreased

fetal body weight occurred at the maternally toxic doses of 1000 and 2000 ppm for all materials, and also at 500 ppm and greater for *o*-xylene and mixed xylenes. Significant increase in mean percent fetuses with skeletal variations of all types/litter was seen at 2000 ppm concentrations of *o*- and *p*-xylene, and ethylbenzene. No single skeletal variation occurred at an incidence significantly higher than that in controls.

In a 1978 teratology study from American Petroleum Institute (API 1978), no maternal or developmental effects were observed following exposure of pregnant CD rats to 0, 100, or 400 ppm mixed xylenes (52% *m*-, 11% *o*-, 0.31% *p*-xylene, and 36% ethylbenzene), 6 hours/day, during GD6-15. The NOAEL for maternal and developmental effects was 400 ppm. In the teratogenic portion of the 1-generation reproduction study (API 1983) one-half of the control and 500 ppm high dose pregnant females were euthanized on GD21 for developmental toxicity evaluation. Animals had been exposed to mixed xylenes for 151 days prior to and during mating, and GD1-20. No effects were observed on maternal body weight, food consumption or utilization, or postmortem examination. No statistically significant differences were reported for mean number of corpora lutea, implantations, live fetuses, live fetus/implantation, or fetal sex ratios. A slight increase in mean number of resorption sites (1.6 vs. 1.2 in controls) was not statistically significant. Fetuses from exposed dams had slightly higher incidence of unossified sternebrae and incompletely ossified cervical vertebral processes, reported by fetal incidence. Mean body weight of female fetuses on GD21 was marginally but statistically decreased (93% of control values), but male fetuses were comparable to controls. This marginal decrease occurring in only one sex was difficult to assess due to small sample size (12 litters compared to 20 litters in controls). Maternal toxicity NOAEL was 500 ppm and the developmental LOAEL was 500 ppm (decreased female fetal weight) with a NOAEL of 250 ppm. In the animals allowed to deliver litters, mean pup weights were statistically significantly decreased in treated litters on lactation day (LD) 4 probably as a consequence of elevated mean pup weights in the control group where the mean litter size was smaller that all treated litters in any group (9.6 live pups/litter in controls vs. 10.8-12.5 pups/litter in treated groups). Marginally decreased mean pup weight in 500 ppm (both sexes treated) litters was observed on LD21 and at 49 days of age (92% males, 93% females of control values), but no decrease in pup weights was observed in offspring of litters in which only the dam or the male parent was exposed to 500 ppm, suggesting these marginal weight decreases were not an effect of xylenes exposure. Offspring NOAEL was 500 ppm.

Ungváry et al. regularly employed 24-hour exposure periods when treating rats with solvents compared to the 6-8 hour exposures used by other investigators. Hudák and Ungváry (1978) treated pregnant CFY rats with 0, or 230 ppm (1000 mg/m3) mixed xylenes ([10% *o*-, 50% *m*-, 20% *p*-xylene, 20% ethylbenzene), 24 hours/day, GD9-14; study was terminated on GD 21. No effects were observed for any parameter (maternal body weight, fetal deaths, fetal or placental weights, or malformations) other than an increased frequency of fused sternebrae and extra ribs. However, frequency was based on number of fetuses, rather than affected litters. Subsequently, Ungváry and Tátrai (1985) exposed pregnant CFY rats (19-23/group) to a wider range of doses - 0, 60, 440, and 780 ppm (0, 250, 1900, and 3400 mg/m^3) xylenes again for 24hours/day, GD 7-15; animals were euthanized on GD 21. Pregnant CFLP mice (17-18/group) and pregnant New Zealand white rabbits (10) were exposed to 0, 115, or 230 ppm (0, 500 or 1000 mg/m3) mixed xylene 3 times for 4 hours/day intermittently or to 115 ppm *o*-, *p*-, or *m*-xylene on GD6-15 or 7-20, respectively; animals were sacrificed on GD 18 or 30, respectively. Although an increase in percentage of skeletal retardation (no specifics given) was reported in mouse and rat fetuses, the increases were not concentration-related, the occurrence/litter was not reported, and incidences were not statistically significant compared to controls. Rats exposed to 780 ppm had an increased percentage of dead or resorbed fetuses (13% vs. 5% in controls). Maternal toxicities in rats were reported as moderate and concentration-related. Rats exposed at all doses had approximately 30% incidence of fetal skeletal abnormalities and an average 13% weight reduction at 780 ppm.

Mice had a slight increase in skeletal abnormalities and fetal weight reduction at 115 ppm for each isomer and for mixed xylenes at 230 ppm but not at 115 ppm. In rabbits, exposure to 230 ppm resulted in 3 maternal deaths, increased relative liver weight in dams, and an increased number of abortions. Exposure of pregnant rabbits to 115 ppm o-, m-, p-xylene or mixed xylenes, produced only slight decrements in fetal weight of female offspring. The authors considered xylenes to be, at most, only slightly developmentally toxic. ATSDR (1995) concluded that effect levels could not be determined from this study.

Ungváry et al. (1980) also explored differences in maternal and developmental effects induced by the 3 isomers in CFY pregnant rats exposed to 0, 35, 350, or 700 ppm *o*-, *m*- or *p*-xylene continuously from GD7-14; study termination was on GD 21. Signs of maternal toxicity at 700 ppm included decreased maternal weight gain, decreased food consumption, and increased liver to body weight ratio. Exposure to *m*-xylene was the only isomer that resulted in lasting maternal growth inhibition or maternal mortality (4 dams died). Meta-xylene at 700 ppm caused decreased number of mean implantations/dam; and 700 ppm *p*-xylene had increased postimplantation loss with corresponding decreased litter size. Fetal body weight was statistically decreased in the 350 and 700 ppm *o*-xylene groups, and at 700 ppm in *p*- and *m*-xylene groups with corresponding increases in weight-retarded fetuses. Histochemical analysis of 700 ppm fetuses in the *o*- and *p*-xylene groups showed decreased staining of alkaline phosphatase, succinic hydrogenase, acid phosphatase, and glucose-6-phosphatase in the kidney; succinic dehydrogenase and glucose-6-phosphatase also showed decreased activity in the liver and thymus cells of 700 ppm groups of all 3 isomers. No structural effects were observed histopathologically. Enzyme changes, especially in the liver, are likely adaptive responses to exposure and are not considered adverse (see repeated dose section - subchronic toxicity). The authors reported statistically significant increases in extra ribs in fetuses of 700 ppm *o*-xylene, and all *p*-xylenes groups on a per fetus basis; litter incidence data was not reported.

To study effects of xylenes on sex steroids during pregnancy, Ungváry et al. (1981) exposed CFY rats to 0 or 681 ppm *p*-xylene for 24 hours on GD 10 and continuously on GD9-10; sacrifice was on GD11. No data on maternal toxicity were provided. The sex hormones, progesterone and 17ß-oestradiol, in uterine and femoral veins were decreased in the exposed group. The authors suggested that this reduction in hormones may play a role in embryotoxicity. Balogh et al. (1982) observed an increase in placental weight in CFY rats exposed continuously to mixed xylenes at concentrations of 438 and 775 ppm on GD7-14. These data suggested that relatively high concentrations of xylenes could limit oxygen delivery to the placenta that, in turn, can lead to increased placental weights, increased postimplantation loss and delayed ossification that occurred at 775 ppm.

Kükner et al. (1997,1998) examined the effects of inhaled xylenes on the liver of non-pregnant and pregnant Wistar rats and pups of exposed litters, at concentrations of 0 or 2600 ppm mixed xylenes (composition not specified), 8 hours/day, GD6-21 or equivalent days for non-pregnant rats. Controls were pregnant unexposed rats. Xylenes induced minimal increases in asparate aminotransferase (18%), alanine aminotransferase (19%), alkaline phosphatase (17%), and arginase (63%) in pregnant rats. Electron microscopic evaluation of liver tissue from pregnant and non-pregnant rats showed mitochondria that concentrated near the periphery of hepatocytes and nuclei, increased number of lysosomes, and expanded smooth endoplasmic reticulum (ER). In fetal livers, expanded smooth ER and granular ER and structurally deformed mitochondria were observed. No structural defects were seen in kidney or pancreas of any exposed animal.

A study by Mirkova et al. (1983) in which pregnant Wistar rats were exposed to 0, 3, 12, or 110 ppm mixed xylenes, 6 hours/day on GD 1-21 resulted in effects not reported by other investigators at higher doses or longer exposures. Effects included low pregnancy rate, increased

postimplantation losses, reduced fetal weights, and statistically significant increases in visceral abnormalities (e.g. hydrocephalus, micropthalmia, hematomas) and ossification defects in sternum and skull at concentrations of 12 ppm and above. Maternal toxicity was not addressed. Incidence rates for anomalies were not presented. A statistically significant decrease in pup weight on postnatal days 7 and 21 was reported in the 12 and 100 ppm groups, but no data were supplied. A significant increase in percentage of hemorrhages in fetuses was also reported. ATSDR (1995) speculated that these results may have been influenced by poor animal health as indicated by low pregnancy rates (81, 61, 67, and 73% in control, 3, 12, and 110 ppm, respectively) and the high incidence of fetal hemorrhage in control and treated rats. Further, incomplete reporting of methods and results, and inadequate litter sizes for proper evaluation prohibit establishment of a maternal or developmental effect level. Hass and Jakobsen (1993) attempted to replicate some of these results by exposing 36 pregnant Wistar rats to clean air or 200 ppm mixed xylenes, 6 hours/day on GD4 –20. No maternal toxicity, no decrease in fetal weight, or increases in soft tissue or skeletal malformation were seen. However, a large increase in the incidence of delayed ossification in the os maxillare of the skull was observed (53% of exposed fetuses vs. 2% in control). Rotarod performance was impaired in 2-day old pups and later in female pups on post-natal days 22 and 23, and in male pups on postnatal day 23. However, the authors of this paper questioned the rotarod results from this study because experimental bias could have been introduced because evaluators were aware of animals' exposure status. In a subsequent study, this effect could not be repeated at the higher dose of 500 ppm (Hass 1995). See Section 6.10 Developmental Neurotoxicity for more discussion on these studies.

Rosen et al (1986) conducted an inhalation study in rats to assess the postnatal effects of prenatal exposure to p-xylene. The study design was a Chernoff/Kavlock "teratology screen" and did not include all of the procedures and assessments normally incorporated into a conventional developmental toxicity study, though postnatal neurobehavioral tests were included in this study (see Section 6.10 Developmental Neurotoxicity). Maternal toxicity (significantly decreased body weight gain) was reported at the highest exposure level. No adverse effects were observed in the offspring. Based on these findings, the developmental NOAEL is 1600 ppm.

In vitro exposures of 9.5-day old Sprague Dawley postimplantation embryos to 0.1, 0.5, or 1.0 ml/l medium of mixed xylenes (60% p-xylene, 22% o-xylene, 0% m-xylene, 18% ethylbenzene) did not induce teratogenic effects after 48hr growth (Brown-Woodman et al., 1991). Dose-dependent growth retardation and development was observed. In a similar study, Brown-Woodman et al. (1994) incubated rat embryos *in vitro* with up to 2.7 µmol xylene/ml for 40 hours. Concentrations = 1.89 µmol/ml retarded embryo growth and development; no gross morphological malformations were observed.

These studies indicate that xylenes can produce fetotoxic effects, although most effects occur in the presence of maternal toxicity, making it difficult to determine whether xylenes are selectively toxic to the fetus or the observed developmental toxicity was secondary to maternal toxicity and stress (ATSDR, 1995). In addition maternal effects were not always addressed in all studies. EPA concluded that adverse developmental effects occur only at doses higher than doses producing the critical neurobehavioral effects observed in adult rats, suggesting that the developing fetus is not at special risk from low-level xylenes exposure (EPA 2003a).

Table 6.5: Representative Hazard Studies for Xylenes Toxicity: Reproductive and Developmental Toxicity (Tier 2)

Study Type	Test Article	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Reproductive Toxicity	Mixed xylenes	Rats- male & females/ inhalation	500 ppm – max. dose parents & F1 offspring	None	151d, 5d/wk 35d, 7d/wk, 6hr/d gest. (1-20); lact. (5-20)	API (1983) 1-generation
	Mixed xylenes	Rats – males/ inhalation	1000 ppm – only dose: no effect on testes or accessory organs	None	61 days; 18h/day, 7d/wk	Nylén et al, (1989)
Developmental Toxicity	Meta-xylene Para-xylene Ortho-xylene Technical xylene	Rats – female/ inhalation	m-, p- =500 ppm (dams/fetal) o-, mixed xylenes = 500 ppm (dam) 100 ppm (fetal)	1000 ppm- decr. dam & fetal wt (m-, p-xylene). 1000 ppm dam; 500 ppm fetal 2000 ppm ortho- & para-xylene - inc % fetuses with skeletal variations/litter	GD 6-20, 6hr/day, 7d/wk 100-2000 ppm	Saillenfait et al., 2003
	Mixed xylenes	Rats-female/ inhalation	400 ppm (dam/fetal)	None	GD 6-15, 6 hr/d 0, 100, 400 ppm	API, 1978
	Meta-xylene Ortho-xylene Para-xylene	Rats – female/ inhalation	350 ppm 35 ppm not determined	700 ppm – maternal and fetal wt decr. reduced implants 350 ppm –9% decr. in fetal wt 35 ppm – inc in fetal ribs	GD7-14, 24hr/d for 8 days	Ungváry et al. (1980)
	Mixed xylenes	Mice-female/Oral	1030 mg/kg (fetal) 2580 mg/kg (dam)	2060 mg/kg- (fetal) decr. body wt, cleft palate 3100 mg/kg (dam)- decreased body wt, inc resorptions	GD6-15, sacrificed on GD18	Marks et al., 1982
	Meta-xylene Para-xylene Ortho-xylene	Mice-female/Oral	780 mg/kg for para-, ortho-xylenes 1960 mg/kg for ortho-	1960 mg/kg: maternal toxicity, inc. resorptions, cleft palate 2610 mg/kg: maternal toxicity, increased resorptions	GD6-15, 0, 780, 1960, 2610 mg/kg	Newrot and Staples, 1980
	Meta-xylene	Mice-female/Oral	2000 mg/kg (only dose)	None	GD8-12	Seidenberg et al., 1986

6.7 Immunotoxicity (see Table 6.6)

Mice exposed to *p*-xylene at concentrations of 0, 600, or 1200 ppm, 6 hours/day for 4 days, did not exhibit adverse effects on splenic natural killer (NK) cell activity by exposure to concentrations as high as 1200 ppm (Selgrade et al., 1993). Significant synergistic effects between cytomegalovirus administered concurrently and 1200 ppm *p*-xylene were seen at four but not at seven days post-infection, including serum SGPT, SGOT, and LDH activities indicative of liver damage. Significant increases in SGTP and LDH due to virus alone and in cholinesterase due to *p*-xylene were still apparent seven days post-infection. No synergistic effect was seen in serum enzymes following exposure to 600 ppm *p*-xylene. Para-xylene significantly enhanced and virus significantly suppressed P-450 levels measured four days post-infection. Increased mortality appeared to be due to synergistic effects of virus and *p*-xylene in the liver, and not to immunosuppression.

Repeated oral exposure of male and female rats to *m*-, *o*-, or *p*-xylene at dose levels of 0, 250, 1000, or 2000 mg/kg/day for 10 consecutive days resulted in increased liver weight in both sexes for all 3 isomers at 2000 mg/kg/day. Decreases in thymus and spleen weight were seen less frequently, primarily for *p*-xylene (2000 mg/kg/day), and no corroborative histopathological changes were seen in spleen or thymus (Condie et al., 1988). Weight decrements in spleen and thymus may be indicative of slight immunological impairment or may be in response to systemic stress induced by ingestion of high doses of xylenes over several days. Exposure of rats to 0, 150, 750, or 1500 mg/kg/day mixed xylenes for 90 days did not cause decreases in thymus or spleen weights (Condie et al., 1988). Intermittent exposure of rats and dogs to mixed xylenes for 10 to 13 weeks showed no effect on spleen weight (Carpenter et al., 1975).

6.8 Adult Neurotoxicity (see Table 6.7)

Exposure to xylenes by the oral or inhalation routes can result in nervous system effects such as tremors, incoordination, muscle spasms, respiratory distress, hearing loss or elevated auditory thresholds, lethargy, hyperactivity, and changes in brain enzyme activity and levels of brain protein.

Oral: CNS effects were reported in the NTP (1986) oral studies. In an acute oral study, rats and mice (5/sex/group) were given a single dose of 0, 500, 1000, 2000, 4000, or 6000 mg/kg mixed xylenes in corn oil (NTP 1986). Significant mortality was observed at 4000 (30% rats died) and 6000 mg/kg (100% rats, 70% mice). Clinical signs at 4000 and 6000 mg/kg included tremors, prostration, and/or slowed breathing in mice; and lack of coordination, loss of hind limb movement, prostration, and hunched posture in rats within 48 hours. Surviving animals did not exhibit any clinical signs by the end of the first week of observation.

B6C3F1 mice were administered mixed xylenes in corn oil at concentrations ranging from 125-2000 mg/kg/day, 5 days/week for 13 weeks (NTP, 1986). Death of 2 female mice occurred at the 2000 mg/kg dose. Clinical signs included lethargy, short and shallow breathing, unsteadiness, tremors, and paresis which began 5-10 min post-dosing and lasted 15-60 min in both sexes. Decreased body weight gain was observed in males (7% below control) and females (17% below control). No treatment related gross or microscopic changes were observed. For neurological effects LOAEL was 2000 mg/kg/day; NOAEL was 1000 mg/kg/day.

Table 6.6: Representative Hazard Studies for Xylene Toxicity: Immunotoxicity (Tier 2)

Study Type	Test Article	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Immunotoxicity	Para-xylene	Mouse/Inhalation	1200 ppm, no effect on natural killer cells	None	4 days, 6hr/d 0, 600, 1200 ppm	Selgrade et al., 1993
	Para xylene	Mouse/Inhalation	600 ppm	1200 ppm: liver damage at 4 d post-infection with cytomegalovirus	Mortality due to liver damage, not to immunotox.	
	Meta-xylene Para-xylene Ortho-xylene	Rat/Oral	1000 mg/kg	2000 mg/kg: inc. liver with for all isomers; decr. relative thymus wt for para-xylene	10 days, o, 250, 1000, 2000 mg/kg/d	Condie et al., 1988
	Mixed xylenes	Rat/Oral	1500 mg/kg	None: no effect on thymus or spleen wt	90 days, 0, 150, 750, 1500 mg/kg/d	

Inhalation: Neurological effects of acute exposures to xylenes in rats and mice vary in the dose range of 114 ppm mixed xylenes effects on operant conditioning or self-stimulation behavior (Ghosh et al., 1987; Wimolwattanapun et al, 1987) to 1000 ppm, o-xylene induction of immobility in a behavioral despair swimming test (DeCeaurriz et al., 1983), cited in ATSDR, 1995. Bushnell (1989) reported hyperactivity in rats at 1600 ppm p-xylene and Carpenter et al. (1975) observed incoordination in rats given 1300 ppm mixed xylenes which did not persist after exposure ended; no overt toxicity was observed at 580 ppm. At 2000 ppm, all three xylene isomers can induce narcosis in rats after 1-4 hours of exposure (Molnar et al., 1986).

In the Korsak et al. (1992) study, 12 male Wistar rats were exposed to toluene, m-xylene, or a 1:1 mixture, 6hr/day, 5 days/week at a concentration of 100 ppm for 6 months or 1000 ppm for 3 months. Rats were trained on the rotarod (2 min evaluation period) prior to exposure. Meta-Xylene alone induced significantly decreased rotarod performance and decreased spontaneous activity 24 hrs after termination of exposure. Failure rate was 60% after 1000 ppm for 3 months and 35% after 100 ppm for 6 months (values taken from graph). No exposure related changes in body weight, absolute or relative organ weight, clinical chemistry or hematology were reported. The LOAEL was 100 ppm; NOAEL was not determined. In a subsequent study at exposure concentrations of 50 or 100 ppm, m-xylene for 3 months, decreased rotorod performance was observed at both concentrations beginning at 1 month of exposure and remaining at the same level until the end of 3 months (Korsak 1994). This study does not specify the timing of the neurologic examinations, but an assumption is made by EPA that it was the same as the earlier study by the same investigators; namely, 24 hours after termination of exposure (EPA 2003a). Failure rate was 8% at 50 ppm (not statistically significant) and 33% ($p<0.05$) at 100 ppm. Thus, the effect on rotarod did not change following 1, 2, 3 or 6 months of exposure. LOAEL was 100 ppm and the NOAEL was 50 ppm. A limitation of these studies is that the methods section did not provide sufficient detail to determine whether experimental bias was controlled for (e.g. observer blind to treatment level; time of testing balanced across dose groups; animals tested alone or adjacent to other animals). This can make an important difference in the study as discussed by Hass et al. (1995) who questioned the significance of their own rotarod effects following developmental exposure to xylenes because of lack of control of experimental bias. In addition Hass et al. (1995) reported that pilot studies showed that the noise when the first animal fell off the rotarod often made the other animals fall off. The lack of methodological detail in the Korsak et al. studies raises some uncertainty about the reliability of these results. Nevertheless, this effect on rotarod was repeated in two separate studies (Korsak 1992, 1994) with a clearly defined NOAEL of 50 ppm.

Gralewicz et al. (1995) investigated whether xylenes exposure resulted in accelerated aging of the CNS by exposing 8 month old male LOD-Wistar rats (total of 20 male rats divided into 3 groups of unspecified numbers of animals) to 0, 100 or 1000 ppm m-xylene, 6 hours/day, 5 days/week for 3 months. Brain aging was evaluated by EEG, and spatial learning abilities in an 8-arm radial maze. Exposed rats demonstrated some differences in radial maze performance and EEG spike and wave discharge activities compared to controls 70-83 days after exposure, but effects were inconsistent with the authors' hypothesis that xylenes causes accelerated brain aging. There were no significant group or group by consecutive recordings interaction in any of the EEG measurements. After multiple *a posteriori* analysis were conducted, a single difference on day 84 after exposure between controls and treated, but there was no difference between 100 and 1000 ppm group. No effects were noted on days 14, 28 and 56 days after exposure. The overall pattern is not consistent with a treatment-related effect, and the effect that was noted is of uncertain biological significance. There was a statistically significant group difference in trial duration on the radial arm maze. The trial duration in the control group was significantly shorter than in both the exposed groups, but there were no dose-related differences between the 100 and 1000 ppm group. There were no statistically significant effects in total number of entries, omission errors or

perseveration errors with respect to group effect, group by days interaction or effect of days. The 1000 ppm group had fewer omission errors initially, but both the 100 and 1000 ppm group had higher omission errors compared to controls by the last (5^{th}) trial. The sample sizes of 7 or 6 make it difficult to interpret the significance of these findings on radial arm maze without repeating the study and evaluating the laboratory's historical control data. This effect on radial arm maze was not reproduced in a later study (Gralewicz and Wiaderna., 2001), although differences in duration of exposure and time of testing after exposure between the two experiments could have been a factor.

This same group of investigators found no treatment-related effects of m-xylene (100 ppm; 4 weeks of exposure) on open field activity and active avoidance, but did find significantly shorter step-down time (trial 6 only; no difference in trials 1-5) in the passive avoidance test and significantly greater paw-lick latency in the hot plate - shock behavior test (Gralewicz and Wiaderna, 2001). The results of the passive avoidance test are difficult to interpret because there was no shock applied for trials 4, 5, and 6. This means there was no negative consequence of stepping down more quickly. The hot plate test involved shocking the animal every 2 seconds for 2 minutes after the 1^{st} of 3 hot plate trials but not after trials 2 (several seconds after shocking) or 3 (24 hours after trial 2). Meta-xylene exposed animals had a longer paw-lick latency for the 3^{rd} trial but not the 1^{st} or 2^{nd} trial. This indicates that m-xylene had no effects on hot plate paw-lick latency per se, but did have an effect following repeated shocking of the animals immediately after the first hot plate trial. The biological significance of this finding to humans is uncertain. This result was not repeated by these investigators. In summary the same group of investigators (Gralewicz and Wiaderna, 2001; Gralewicz et al., 1995) evaluated several behavioral endpoints and performed multiple statistical comparisons that resulted in selected effects depending on statistical analysis conducted as well as many negative results. The statistically significant effects are difficult to interpret because these investigators usually did not repeat these findings using the same behavioral endpoints under the same exposure conditions. In addition, the methods sections did not indicate whether the behavioral experiments were conducted with appropriate control of experimental bias (e.g. observers should be unaware of treatment level; time of testing should be balanced across dose groups). Based on these results, the LOAEL was 100 ppm and the NOAEL was not determined.

In studies measuring xylenes induced changes in brain enzymes and activity, Savolainen et al. (1979) observed transient, decreased preening frequency and an increase in microsomal superoxide dismutase activity in the brain of 20 male Wistar rats exposed to 300 ppm mixed xylenes (85% *m*-, 15% *o*- and *p*- xylenes) 6hr/day, 5 days/week for 5-18weeks with or without concomitant exposure to ethanol in drinking water. Anderson et al. (1981) reported decreased acetylcholine and norepinephrine in the hypothalamus of Sprague Dawley rats exposed to 2000 ppm of one of the three isomers, 6 hours/day for 3 days. These results were suggestive of effects on motor control, sleep, and memory maintenance. Rosengren et al. (1986) measured increased regional brain concentrations of glial fibrillary acetic protein (GFAP), S-100 protein, and DNA in brains of Mongolian gerbils (4 male and 4 female/group) exposed to xylenes (uncharacterized) at concentrations of 0, 160, or 320 ppm for 3 months, followed by a 4-month post-exposure period. These increases in GFAP, S-100 protein, and DNA were considered compatible with the presence of astrogliosis. Padilla and Lyerly (1989) observed decreased axonal transport after acute exposure to 800 ppm *p*-xylene, but the decrease was not apparent 3 days post-exposure. At 1600 ppm, decreased axonal transport persisted for 13 days after exposure ceased.

In summary, the weight of evidence indicates that slight effects on rotarod are noted at the LOAEL of 100 ppm that do not change in severity with increasing duration of exposure. The NOAEL for this endpoint is 50 ppm, based on the same study (Korsak 1994), and this is used as the critical effect and point of departure in the Risk Assessment (see Section 8.1).

6.9 Auditory Toxicity (see Table 6.7)

Pryor et al. (1987) demonstrated ototoxicity in male weaning F344 rats exposed to 0, 800, 1000, or 1200 ppm mixed xylenes (10% *p*-, 80% *m*-, 10% *o*-xylene) 14 hours/day for 6 weeks. All exposed rats had concentration dependent increases in behavioral auditory thresholds and measured brainstem auditory evoked response (BAER) relative to controls at some frequency (4, 8, 12, or 20 kHz). LOAEL was 800 ppm; a NOAEL not determined. Pryor et al. (1987) also reported that hearing loss occurred in rats exposed to 1450 ppm mixed xylenes for 8 hours, but exposure to 1700 ppm for 4 hours did not affect hearing, indicating that duration of exposure is important for the observation of ototoxic effects in the conditioned avoidance test. Male Sprague Dawley rats exposed to air containing 1000 ppm mixed xylenes (1.5% *o*-, 65% *m*-, 32% *p*-xylene, 2.5% ethylbenzene) 18 hours/day. 7 days/week for 61 days demonstrated statistically significant decreased body weight and slight loss of auditory sensitivity by BAER compared to controls 2 days after exposure ended (Nylén and Hagman, 1994). No adverse effects were observed on flash evoked potentials or nerve and muscle action potentials measured in the tail. Adult male Long-Evans rats were exposed by inhalation to 1800 ppm mixed xylenes, 8 hours/day for 5 days. Testing of auditory function was conducted five to eight weeks after exposure using reflex modification audiometry (RMA). RMA thresholds were determined for frequencies from 0.5 to 40 kHz. The RMA thresholds were increased for the mid-frequency tones (e.g., 8 to 16 kHz), and at 24 kHz for the xylene-exposed animals (Crofton et al., 1994). Gagnaire et al. (2001) exposed male rats to *o*-, *m*- or *p*-xylene by inhalation at concentrations of 450, 900, or 1800 ppm, 6hours/day, 6 days/week for 13 weeks and sacrificed the rats 8 weeks after end of exposure. Brainstem auditory evoked responses were used to determine auditory thresholds at different frequencies. Only *p*-xylene produced moderate to severe ototoxicity in 900 and 1800 ppm exposed rats and thresholds did not reverse after 8 weeks recovery. Moderate to severe losses of outer hair cells in the organ of Corti were seen in the *p*-xylene exposed rats. The NOAEL for *p*-xylene was 450 ppm and the NOAEL for *m*- and *o*-xylene was 1800 ppm.

Table 6.7: Representative Hazard Studies for Xylene Toxicity: Adult Neurotoxicity and Auditory Toxicity (Tier 3)

Study Type	Test Article	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Adult Neurotoxicity	Meta-xylene	Rat-male/ Inhalation	50 ppm	100 ppm – decr. motor activity; decr. rotorod activity beginning at 1 mon exposure to end of study at same level	3 months, 6hr/d, 5 d/wk	Korsak et al., 1994
	Mixed xylenes	Mouse/Oral Rat/Oral	2000 mg/kg	4000 mg/kg: CNS effects within 48hr of exposure	Single dose, 0, 500, 1000, 2000, 4000, 6000 mg/kg: mortality at 4000 & 6000 mg/kg	NTP, 1986
	Mixed xylenes	Rat/Oral	500 mg/kg [per ATSDR, 1995]	None	103 weeks, 5 d/wk- 0, 250, 500 mg/kg/d [see Sect. 6.10 Chronic)	NTP, 1986
Astrogliosis [GFAP]	Xylene uncharacterized	Gerbils/ Inhalation	None	160 ppm: incr. GFAP conc., S-100protein and DNA in brains	3 months, 0, 160, 320 ppm; sacrificed 4 months post-exposure.	Rosengren et al., 1986
Auditory Toxicity	Mixed xylenes	Rat-weanling male/ Inhalation	None	800 ppm; incr. auditory threshold, inc. BAER Hearing loss also at 1450 ppm for 8 hr. No effect at 1700 ppm for 4 hr.]	6 wks, 14hr/d 0, 800, 1000, 1200 ppm	Pryor et al., 1987
	Mixed xylenes	Rat-male/ Inhalation	None	1000 ppm (only dose): decr. body wt, inc. BAER at 2 days post-exposure	61 days, 14hr/d, 7d/wk	Nylén and Hageman, 1994
	Meta-xylene Para-xylene Ortho-xylene	Rat-male/ Inhalation	1800 ppm 450 ppm 1800 ppm	None 900 ppm None	13 wks, 6hr/d, 6d/wk 0, 450, 900, 1800 ppm	Gagnaire et al., 2001

6.10 Developmental Neurotoxicity (see Table 6.8)

Several investigators have evaluated effects of prenatal exposure to xylenes on neurobehavioral development. The currently available developmental neurotoxicity studies are limited by the absence of dose response data and a definitive NOAEL level. However, they provide very comprehensive evaluation of the critical endpoint of concern during a period of *in utero* development when the brain is rapidly developing. Hass et al. (Hass and Jakobsen, 1993, Hass 1995, Hass 1997) has done the majority of this research, conducting two separate developmental neurotoxicity of mixed xylenes in rats. The first study conducted at 200 ppm (Haas and Jakobsen, 1993) was not considered by the authors to be as reliable as the second study (Haas et al., 1995) which was conducted at 500 ppm. Some animals from the second study were maintained for up to a year for additional follow –up examination (Haas et al., 1997).

The Hass and Jakobsen (1993) study is discussed in Section 6.6. The only developmental neurotoxicity evaluation from this study was a decrease in rotarod performance in rats exposed in utero to 200 ppm mixed xylenes. In a later publication, these researchers noted methodology concerns with the rotarod evaluation of the 1993 study. These effects were not considered treatment related because there were no effects at 500 ppm mixed xylenes when experimental conditions to reduce bias were better controlled (Hass 1995).

Hass et al (1995) exposed pregnant Wistar rats to 0 or 500 ppm mixed xylenes (19% o-, 45% m- , 20% p-xylene, 15% ethylbenzene) 6 hours/day on GD7-20. From each litter, 2 of each sex were selected for behavioral testing: one/sex/litter were kept in standard housing [2 same sex, same dose rats/cage], left undisturbed except for feeding and weighing until 3 months of age when they were tested in the Morris water maze; one/sex//litter were kept in an enriched environment (4-5 same sex, same dose rats/cage; cages contained toys) and tested for rotarod, open field and Morris water maze performance at 3 months. Mixed xylenes exposure did not adversely affect maternal clinical signs, body weight gain or food consumption. Both control and exposed groups had similar gestation periods, number of pups/litter and sex distribution/litter. Litters from exposed dams had a slight decrease in mean birth weight (5%) and a trend toward lower body weight during the postnatal period (not statistically significant). At necropsy on postnatal day 28, absolute brain weights were statistically significantly decreased for males and females combined but not when sexes were analyzed separately for absolute weight or for relative brain/body weight ratios separately or sexes combined.

There were no statistically significant effects on rotarod performance at 500 ppm indicating that the investigators were unable to repeat effects on rotarod performance at 200 ppm in their earlier study (Haas and Jacobson, 1993). The mean time on the rotarod was shorter and a higher percentage of animals in the exposed group failed to stay on the rod for 30 seconds compared to controls with females more affected than males. The air-righting reflex was delayed by one day in exposed litters due to the ability of only 4 pups from 4 litters to right themselves. All animals were able to right themselves on postnatal day 17. No differences were observed in open field activity. Offspring from xylene-exposed rats raised in cages with various toys showed no difference in the Morris water maze compared to controls. Offspring raised in standard housing showed impaired performance at 12 weeks when a non-significant trend for increased latency in finding the platform in the beginning of the learning test was evident. The effect was attributed to a slight increase in latency during the first 2 trials of a 5-trial learning phase with no difference in learning during the last 3 trials. At 16 weeks, females also used significantly more time to find a hidden platform in the center of the pool and showed an increase in swimming length, while speed was not affected. Although these effects are statistically significant, the latency for treated females was less than 6-13 seconds which is comparable to male control values and also similar to the latency during the 5^{th} day of the initial learning phase for all control offspring. Male offspring of exposed dams

performed comparably to controls. The overall effects on developmental neurotoxicity from this study, especially noting the lack of effects in a separate group of treated females that had various toys in their cages, appear to be relatively slight effects.

In a follow-up study to assess persistence of the decreased water maze performance, these same female offspring raised in standard housing were maintained and evaluated at 28 and 52 weeks. (Hass et al, 1997). At 28 and 55 weeks, an increased latency in finding the platform in the center was not repeated. There was an effect in finding the platform when placed in a new position not earlier used on the rim (original starting point) and animals were placed in a new starting point. Increased latency again corresponded to increased swimming length was measured on the first trial but resolved itself by the second and third of 3 trials. No other significant differences were observed for other testing situations in the water maze and no statistically significant differences of any kind were observed at 55 weeks. Xylene exposure during development may cause subtle deficits in some learning and memory tasks of offspring, which eventually resolve in the absence of additional exposure as the animal matures. These data were limited because no dose-response can be determined and no clear effect in other neurological tests was observed (EPA, 2003a). The learning and memory test involved 10 component phases each with four to five trials. While this extended evaluation may increase the possibility of detecting very subtle effects, there is also increased opportunity for statistically significant effects that may not be treatment related.

An additional developmental neurotoxicity study was conducted, by a separate laboratory, on p-xylene in rats (Rosen et al., 1986). In this study, the Chernoff/ Kavlock screen was used on exposed pregnant Sprague Dawley rats (25/group) to 0, 800 or 1600 ppm para-xylene (99% pure) on GD7-16. No adverse effects were observed on litter size or pup weight at birth or on postnatal day 3. No effects were seen on central nervous system (CNS) development measured by acoustic startle response on postnatal day 13, 17, 21 and 63, or the figure 8 maze activity on days 22 and 65; or on pup growth rate. The only effect of exposure was a significant decrease in maternal body weight in 1600 ppm dams (74% of control values). The maternal LOAEL was 1600 ppm; the developmental neurotoxicity NOAEL was 1600 ppm.

Previous shorter term studies did not indicate a consistent difference in effects of p-xylene or m-xylene on neurobehavioral endpoints (Moser et al., 1985; Gagnaire et al., 2001; Korsak et al., 1990).

In summary, developmental neurotoxicity data have been developed on mixed xylenes, by Hass et al. (1993, 1995, 1997), in which exposure of pregnant rats at 500 ppm during most of gestation resulted in some learning and memory effects in offspring tested from 2 days to 16 weeks postnatally. These investigators questioned the significance of their own results at 200 ppm conducted in the earlier study (Hass 1993) because of lack of control of experimental bias and because these decreases in rotarod performance could not be replicated at the higher exposure levels of 500 ppm with improved methods (Hass 1995). A different group of investigators from EPA Health Effects Research Laboratory demonstrated that p-xylene did not affect neurobehavior in offspring of dams exposed to 800 and 1600 ppm prenatally (Rosen 1986). Taken together, these studies provide comprehensive sophisticated evaluation of many neurobehavioral endpoints at multiple time points following exposure during the vulnerable period of rapid brain development. Although each study is limited in the number of dose levels, they collectively provide sufficient evaluation to conclude that there are slight effects in offspring at exposure levels of 500 ppm. These slight effects were measured primarily in female offspring and were not measured in males or in females with various toys in their cages. These studies support a LOAEL of 500 ppm for developmental neurobehavioral effects and support EPA's conclusion that the developing organism is not more sensitive than the adult to xylene exposure (EPA 2003a).

Table 6.8: Representative Hazard Studies for Xylene Toxicity: Developmental Neurotoxicity (Tier 3)

Study Type	Test Article	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Developmental Neurotoxicity	Mixed-xylene	Rat-female/ Inhalation	None	200 ppm – (only dose) decr. rotorod activity by pups at postnatal days 22, 23; delayed skull ossification; no other reproductive effects.	GD 6-20, 6hr/d, 7d/wk	Hass and Jakobsen, 1993
	Mixed xylenes	Rat-female/ Inhalation	None	500 ppm – (only dose) slight decreased pup wt; air righting reflex delayed 1 day; decr. water maze performance in female pups (std. housing) at 12, 16 wks, resolved by 55 wks	GD7-20, 6hr/d, 7d/wk	Hass et al., 1995, 1997
	Para- xylene	Rat-female/ Inhalation	1600 ppm	None: no effect on offspring developmental parameters, acoustical startle response or figure 8 maze performance Maternal LOAEL=1600 ppm	GD 7-16, 0, 800, 1600 ppm [Chernoff-Kavlock screen]	Rosen et al., 1986

6.11 Chronic Toxicity and Carcinogenicity (see Table 6.9)

Chronic Toxicity:

The NTP (1986) conducted studies in rat and mouse with mixed xylenes (60% *m*-, 13.6% *p*-, 9.1% *o*-xylene, 17% ethylbenzene) dissolved in corn oil and administered by gavage, 5 days/week for 103 weeks. Clinical signs and effects on tissues and organs were evaluated. Gross necropsies were performed on all animals, and comprehensive histologic examinations were conducted. Groups of 50 male and 50 female rats received doses of 0, 250, or 500 mg/kg/day. Effects of exposure were limited to high dose males, which weighed 4% less than controls at termination and showed increased mortality that was likely related to gavage errors; however, definitive evidence that gavaging errors were responsible for increased mortality was not obtained. Groups of 50 male and 50 female mice received doses of 0, 250, 500, or 1000 mg/kg/day. Hyperactivity was observed 5-30 minutes after dosing in all high dose mice from week 4 until termination. No other effects were noted.

In the mouse, NOAEL and LOAEL were 500 mg/kg/day and 1000 mg/kg/day, respectively, based on hyperactivity. In the rat, based on increased mortality, a tentative NOAEL of 250 mg/kg/day and a LOAEL of 500 mg/kg/day were assigned. However, these values should be taken in the context of possible gavaging errors.

Carcinogenicity**:**

Cancer studies have been performed by the oral route. These studies include the NTP (1986) chronic study in rat and mouse described above and a rat study conducted by Maltoni et al. (1983, 1985) with mixed xylenes. In the NTP (1986) studies there were no treatment related tumors in mice or rats ascribed to treatment with mixed xylenes and indicate no potential for caricongenic activity up to the highest doses tested in rats (500 mg/kg/day) and mice (1000 mg/kg/day). In the Maltoni study, groups of 40 male and 40 female rats were dosed by gavage with a mixture of *o*-, *m*-, and *p*-xylenes (in unknown proportions), dissolved in olive oil, at doses of 0 or 500 mg, 4-5 days/week for 104 weeks, after which dosing was discontinued and the rats were observed until natural death. An increase in total number of tumors was induced by xylene treatment. However, tumor types were not specified, the aged rats died at different times, and the work was incompletely reported. Thus, there is no acceptable basis for assessing the validity of the results.

Table 6.9: Representative Hazard Studies for Xylene Toxicity: Chronic Toxicity and Carcinogenesis (Tier 3)

Study Type	Test Article	Species/Route of Exposure	NOAEL	LOAEL	Duration of Exposure	Reference
Chronic Toxicity	Mixed-xylene	Rats/oral: male female	250 mg/kg 500 mg/kg	500 mg/kg – mortality > 500 mg/kg	103 wk, 5d/wk	NTP (1986)
Carcinogenesis	Mixed xylenes	Rats/oral (M&F) Mice/oral (M&F)	500 mg/kg 1000 mg/kg	>500 mg/kg >1000 mg/kg	103 wk, 5d/wk	NTP (1986)

6.12 Toxicokinetics and Metabolism

The absorption, distribution, metabolism, and elimination of xylenes have been extensively studied and are well characterized. Xylenes are rapidly absorbed by the respiratory tract with uptake increased by physical exercise. Absorption is also positively correlated with the amount of body fat. Liquid *m*-xylene is well absorbed through the skin, but dermal absorption of *m*-xylene vapor (up to 600 ppm) does not appear to be appreciably absorbed. Xylenes are highly soluble in blood and fat, and are distributed widely in the body. Xylenes undergo extensive metabolism and are primarily excreted as metabolites in the urine with small amounts released unchanged in expired air. About 90% of the absorbed dose is excreted in the urine as methylhippuric acid, the glycine conjugate of methylbenzoic acid, following inhalation or dermal (liquid) exposure.

Absorption

Animals: Whole body exposure of mice to ^{14}C-*m*-xylene vapor for 10 minutes showed that absorption was mainly via respiration (Bergman, 1979, 1983). In pregnant mice, approximately 30% of inhaled *p*-xylene (600 ppm) was absorbed after 10 minutes of exposure (Ghantous and Danielsson, 1986).

Almost complete absorption of 1.8 g *m*-xylene, or 1.7 g *p*- or *o*-xylene was observed in orally dosed rodents (Bray et al., 1949). Absorption after oral administration was rapid and peak levels of *m*-xylene were seen 20 minutes after a dose of 0.27 mg/kg (Turkall et al., 1992). After oral administration, absorption rate was faster in females.

Dermal absorption has been studied by *in vivo* exposure of rat skin to liquid or vapor (Skowronski et al., 1990; McDougal et al., 1990). Permeability constants were determined and were higher than those for humans. In excised rat skin preparations, duration of exposure correlated with level of skin penetration (Tsuruta, 1982); rate was 0.967 nmole/ cm^2/min. Skin:air partition coefficient for *m*-xylene was 50.4±1.7 (Mattie et al., 1994) and this correlated with the permeability constant (McDougal et al., 1990).

Distribution

Animals: In rats and mice (Ghantous and Danielsson, 1986; Carlsson, 1981), *m*- and *p*-xylene are distributed primarily to lipid-rich tissues, such as fat, blood, and brain and also in organs highly perfused with blood such as kidney and liver. Small amounts of *p*-xylene and *o*-xylene cross the placenta and distribute to amnionic fluid and fetal tissue (Ghantous and Danielsson, 1986; Ungváry et al., 1980b).

Oral administration of *m*-xylene to rats led to distribution of ^{14}C-*m*-xylene in adipose tissue, approximately 0.3% of dose in female and 0.1% in males (Turkall et al., 1992). There were no available studies in which systemic distribution of xylene was determined after dermal administration.

Metabolism

Animals: The principal pathway in the rat for *m*- and *p*-xylene is the same as that in humans, side-chain oxidation and conjugation with glycine and glucuronic acid (Sugihara and Ogata, 1978; Ogata et al., 1980; Elovaara et al., 1984). For *o*-xylene, the glucuronide formation predominates (Ogata et al., 1980) and a small amount of sulfate conjugate also is produced. Hydroxylation of the aromatic ring of xylenes is also a minor pathway in the rat (Bakke and Scheline, 1970; Elovaara et al., 1984).

Generally in animals, the metabolism of xylenes is similar to that of humans but there are some qualitative differences (Figure 1). The major difference is in the metabolism of methylbenzoic acid as noted above for *o*-xylene. Metabolism of xylenes may be influenced by prior exposure (Elovaara et al., 1987). Rats pretreated with *m*-xylene showed an approximately 10% increase in the percentages of methylhippuric acid and thio ethers in urine. Gastric intubation of rats with 1.1-1.4 ml/kg of *m*-xylene for 3 consecutive days was found to induce CYP2B and CYP2E1 in liver microsomes (Raunio et al., 1990). In the Wistar rat, 4 days of inhalation of xylene at 4 g/m^3, 20 hours/day, induced CYP2B1 but reduced CYP2E1 (Gut et al., 1993).

Elimination

Animals: After an oral dose of radiolabeled *m*-xylene, rats excreted most of the radioactivity [50-59%] in urine within 12 hours of dosing, with expired air secondary [8-22%] (Turkall et al., 1992). *m*-Methylhippuric acid conjugates were 67-75% of the label with xylenol , 2-18%, and unchanged *m*-xylene approx. 1%. Excretion in expired air was less in males (8%) than in females (22%), suggesting a higher metabolic capacity in males.

After dermal administration, the primary route of excretion of *m*-xylene was in expired air (62% of dose) with 43% in urine (Skowronski et al., 1990). Most of the air excretion was in the first 24 hours. Less than 0.5% was excreted in feces. The urinary metabolites of xylenes are similar when dosing is by different routes but the quantities of the different metabolites vary more with degree of absorption than with dose or duration of exposure (ATSDR, 1995).

The neurotoxic effects of xylenes are commonly attributed to the distribution and accumulation of the xylenes in neuronal membranes. However, metabolites have also been mentioned as possible sources of toxicity. Savolainen and Pfäffli (1980) suggested that brain cell microsomal enzymes might oxidize xylenes to toxic intermediates such as methylbenzaldehyde and arene oxides. Inhibition of pulmonary enzymes has also been attributed to the formation of reactive intermediates (Patel et al., 1978; Smith et al., 1982) that bind to microsomal protein and inactivate the enzymes.

6.13 Human Experience

This section summarizes the available human data, but does not analyze the studies in depth as human studies are not used in the quantitative development of the RfD and RfC. In general, these human studies are not well reported and have few numbers of observations, with no systematic review of confounding exposures from smoking or other occupational and environmental sources. They frequently include exposures to a variety of solvents and chemicals in addition to than xylenes. Moreover, many of the studies report subjective symptoms common in the general population, such as headache and dizziness.

6.13.1 Acute Toxicity

Acute poisoning and mortality have occurred after very high exposures, such as that resulting from oral ingestion. Loss of consciousness occurs at approximately 10,000 ppm (Morely et al., 1970). Individuals recovering from severe overexposure exhibit EEG alterations, confusion, coma, nystagmus, gastrointestinal effects, and impaired renal and hepatic function (Ghislandi and Fabiani, 1957; Recchia et al., 1985). Recchia et al. (1985) reported that recovery was generally complete.

TABLE 6.10. **Single inhalation exposure to xylene in humans**

Exposure Concentration (mg/m^3)	Time	Effect	Reference
3,000 (690 ppm)	1 hr	Dizziness, irritation	Klaucke et al. (1982)
3,000 (690 ppm)	15 min	Dizziness	Carpenter et al. (1975)
1300 during exercise (299 ppm)	2 hr	Performance decrement	Gamberale, et al. (1978)
900: peak values of 1800 mg/m^3	4 hr	Prolonged reaction times	Laine et al. (1993)
900 (207 ppm)	4 hr	Impairment of vestibular and visual function and prolonged reaction time	Savolainen et al. (1979, 1981, 1982, 1985)
900 (207 ppm)	4 hr	Minor effect on EEG	Seppäläinen et al. (1991)
600 (138 ppm)	4 hr	No effect on reaction time	Savolainen et al. (1980, 1981)
450 (103.5 ppm)	4 hr	Prolonged reaction time	Dudek et al. (1990)
300 (69 ppm)	4 hr	No effects in psychophysiological test	Anselm-Olsen et al. (1985)

From IPCS, 1997

Information on controlled acute toxicity studies in humans is summarized in Table 6.10 (IPCS, 1997). These studies demonstrate that 4-hour exposure to xylenes at approximately 200 ppm can cause impairment of sensory motor and information processing in the CNS, though these effects were reversible upon termination of exposure. Some evidence of effects on reaction times in humans was also observed above 100 ppm, though the results were varied. A study at 103.5 ppm for 4 hours showed prolonged reaction time (Dudek, 1990) while similar studies at higher levels – 138 ppm for 4 hours – showed no effect on reaction time (Savolainen 1980, 1981). No effects were observed were below 100 ppm.

Carpenter et al. (1975) reported that 15-minute inhalation exposure to mixed xylenes induced eye irritation at a LOAEL of 460 ppm and throat irritation at a LOAEL of 690 ppm. Hastings et al. (1986) showed similar results with 30-minute inhalation exposure, reporting NOAEL of 400 ppm for respiratory and eye irritation. The Hastings et al. (1986) study was the basis for the AEGL-1 values (see Section 3.2).

6.13.2 Repeat Dose Toxicity

Case reports and occupational studies are often difficult to evaluate because exposure conditions are either not well characterized or subjects may have been exposed to other chemicals in addition to xylenes. High-level exposure to xylenes or solvents containing xylenes can induce a variety of neurological symptoms in humans ranging from dizziness, headache, nausea, difficulty in concentrating, to slurred speech, ataxia, tremors at higher acute exposures, and in isolated instances, unconsciousness, amnesia, and epileptic seizures (ATSDR, 1995).

Seizures following exposure to products that contain xylenes and other chemicals have been reported in case reports by several investigators. Goldie (1960) reported that 8 painters exposed to paint containing 80% xylenes and 20% methylglycolate complained of headache, vertigo, gastric discomfort, and slight drunkenness after 30 minutes. After 2 months exposure, an 18-year old worker exhibited symptoms of convulsive seizure including weakness, dizziness, inability to speak, and unconsciousness but recovered 20 minutes later. Arthur and Curnock (1982) reported major and minor seizures in an adolescent worker using a glue containing xylenes and other chemicals for building model airplanes. Exposure concentrations were not reported in either case report.

Exposure to up to 700 ppm xylenes in the workplace for at least 1 hour resulted in vomiting, vertigo, nausea, headache, eye and nasal irritation, and dizziness in a group of 15 employees (Klaucke et al., 1982). Hipolito (1980) reported severe symptoms (e.g., leukopenia, chest pain, ECG abnormalities, dyspnea, impaired lung function, mental confusion, and complete disability) in 5 female workers after 1.5-1.8 years exposure to xylene**.**

Long term exposure (10-44 years) of 83 spray painters to mixed solvents at levels predominantly below historical TLVs was associated with an increase ($p<0.05$) 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., 1992 a,b). Chinese factory workers reported a variety of subjective symptoms after being exposed for an average of 7 years to xylenes levels of 21 ppm TWA arithmetic mean (14 ppm TWA geometric mean), measured with a diffusion sampler (Uchida et al., 1993). Peak exposures were not reported or considered. Xylenes were reported to comprise the

majority of the total workplace solvent exposure that also included 1 ppm toluene and 3 ppm ethylbenzene. No information on other chemicals in the workplace was reported. The symptoms included increased prevalence of anxiety, forgetfulness, inability to concentrate, and dizziness.

6.13.3 Genetic Toxicity

Limited human data are available regarding genotoxic effects of mixed xylenes following inhalation or oral exposure and no studies have been reported on genotoxic effects from *m*- *o*- or *p*-isomers individually. Haglund et al. (1980) examined workers in the Swedish paint industry exposed to mixtures of organic solvents, mainly toluene and xylene. The threshold limit value was 436 mg/m^3. No differences in the frequency of sister chromatid exchanges or chromosome aberrations were found in peripheral blood lymphocytes from 16 exposed workers and a matched unexposed reference group (0.192 or 0.193 SCE/chromosome, respectively). No correlation was found between xylene or toluene exposure and SCE frequency. The frequency of chromosome aberrations was also investigated in the 5 most exposed workers and a matched reference group and no differences were found. Sister chromatid exchange in peripheral lymphocytes were also studied in two groups of 23 workers each with exposures of 11 and 13 ppm (47.3 and 55.9 mg/m^3) mixed xylenes (containing ethylbenzene) for between 4 months and 23 years (Pap and Varga, 1987). No differences in SCE frequency were seen. A worker study by Zhong et al. (1980) gave similar negative results. Studies of filling station attendants exposed to xylene among other petroleum derivatives (chemical exposure levels were not provided) did not demonstrate increases in sister chromatid exchanges (SCE) or micronucleus frequencies (Pitarque et al., 1997a,b). Although Funes-Cravioto et al. (1977) described increased incidences of chromosome aberrations or effects on SCE in laboratory and rotogravure printing workers, results are difficult to assess because exposure levels of xylene were not defined or xylene was accompanied by exposure to other solvents including benzene. Richer et al. (1993) performed a controlled study with 5 adult, white male volunteers to examine cytogenetic effects of xylene (40 ppm) or toluene (50 ppm) alone or in combination, administered 7 hours/day over 3 consecutive days. Exposures were repeated 3 times at 2-week intervals with blood samples taken before and after each exposure cycle. No significant effects on SCE, cell cycle delay, or cell mortality were induced by xylene or toluene, or the mixture. *In vitro* exposure of human blood lymphocytes to xylene (0-2 mM) for 72 hours did not cause significant cytogenetic effects at lower concentrations and only increased cell death at high concentration. These studies indicate that mixed xylenes do not induce genetic toxicity in humans exposed occupationally or under controlled conditions (ATSDR, 1995).

6.13.4 Reproductive and Developmental Toxicity

No studies have been located which address fecundity and reproductive effects in humans following oral exposure to mixed xylenes or individual isomers and very limited data is available by the inhalation route. Effects on pregnancy outcome were studied among university laboratory workers exposed to xylenes primarily by inhalation (exposure levels not identified) during the first trimester of pregnancy. There were no differences in miscarriage rate compared to controls not exposed to solvents (Axelsson et al., 1984). A similar case control study by Taskinen et al. (1994) reported an increase in spontaneous abortion among 37 workers exposed to xylene and formalin as well as other solvents used

in histology and pathology laboratories, three or more days per week during the first trimester of pregnancy. Exposures also appeared to be associated with an increase in birth weight. Occupational exposure of men to solvents in the same study were reported to increase the potential of their wives to experience spontaneous abortion. Because of exposure to multiple solvents, the exact role of xylenes could not be determined.

There are no occupational or environmental studies available that address the developmental or teratogenic effects of xylenes in the absence of other chemical agents in humans. There are limited studies that involve concurrent exposure to chemical agents in addition to xylenes, but they cannot be used to assess the relationship between xylenes exposure and developmental effects. Two case reports suggest that congenital defects observed in the CNS of children were associated with maternal occupational exposures to mixed xylene vapors (Holmberg and Nurminen, 1980; Kucera, 1968). These studies had many limitations and no conclusions can be drawn about causation.

6.13.5 Immunotoxicity

Little human data are available to evaluate the immunological or lymphoreticular effects of xylenes. Decreased serum complement (Smolik et al., 1973) and decreased lymphocyte counts (Moszczynski and Lisiewicz, 1983, 1984) were reported in workers exposed to 0.13 ppm xylenes and other chemicals, including benzene and toluene for 0.25-18 years. Moszczynski and Lisiewicz (1984) reported that workers, after service of 4-10 years, showed decreased T-lymphocyte count without alteration in function. No clinical signs of diminished immunological reactivity were noted in the subjects. Palmer and Rycroft (1993) reported immunological contact uticaria in one worker exposed to xylenes vapor.

6.13.6 Adult Neurotoxicity

Neurological effects in humans following oral or dermal exposure to xylene have not been studied, but there are some experimental studies, case reports, and occupational studies by the inhalation route. Results of experimental studies with human volunteers indicate that acute inhalation exposure to mixed xylenes or *m*-xylene caused impairment of short-term memory, reaction time, performance decrements in numerical ability, and alteration in equilibrium and body balance. These effects are reversible upon termination or removal from exposure. Effects appear to occur in the range of 100 to 200 ppm with a NOAEL of 70 ppm (Olson 1985).

In controlled experimental studies, Carpenter et al. (1975a) stated that dizziness was reported by four of six subjects exposed to 690 ppm *p*-xylene for 15 minutes but only 1 in 6 subjects exposed to 460 ppm. No impairment in performance test results were observed in 10 male sedentary subjects exposed to 400 ppm xylenes for 30 minutes (Hastings et al., 1986). No impairment was observed in 15 male subjects exposed to 300 ppm mixed xylenes (40% ethylbenzene) for 70 minutes, but exposure to 300 ppm for 70 minutes with exercise resulted in impaired short-term memory and reaction time (Gamberale et al., 1978). The increased CNS response may have resulted from increased xylenes respiratory uptake during exercise. Dudek et al. (1990) determined that exposure to 100 ppm mixed xylenes for 4 hours induced prolonged reaction time. Exposure to 70 ppm *p*-xylene for 4 hours did not adversely affect heart rate, subjective symptoms, simple reaction time, choice reaction time, or short-term memory (Olson 1985). When

Seppäläinen et al. (1991) exposed 9 male volunteers to 200 ppm (TWA) *m*-xylene for 4 hr with short-term peak exposures up to 400 ppm, effects on electroencephalography (EEG) were minor and no deleterious effects were observed. Under comparable exposure conditions, Laine et al. (1993) saw no clear effects on visual reaction time or auditive choice reaction time in 9 male volunteers exposed to levels of *m*-xylene fluctuating between 135-400 ppm (TWA 200 ppm), although Seppäläinen et al. (1989) had reported a slight decrease in the latency of visual evoked potentials. Exposure of subjects to *p*-xylene for 4 hours, or up to 7 hours/day for 5 days at concentrations ranging from 69-150 ppm did not affect objective measures of neurological function, including EEG, motor activity or cognitive performance (Hake et al., 1981; Olsen et al., 1985). Hake et al. (1981) did observe some sex differences in subjective reports of CNS effects. Women exposed to 100 ppm *p*-xylene for 1 to 7.5 hours/day for 5 days reported headache and dizziness as a result of exposure although no effects were seen on EEG, evoked potentials, or cognitive performance. Men exposed at concentrations up to 150 ppm under a similar regimen reported no increase in headaches or dizziness. Overall, experimental human studies suggest that exposure to 100 to 200 ppm (435-870 mg/m^3) xylenes over 4 hours may have caused a slight impairment in reaction time performance and vestibular function. Adaptation at 200 ppm *m*-xylene to the impairment occurred over 5 successive days.

6.13.7 Metabolism

Absorption: Absorption of xylenes has been studied via inhalation and dermal routes of administration. After 5 to 10 minutes of inhalation exposure to 100 ppm (430 mg/m^3), pulmonary retention of *m*-xylene was relatively constant at approximately 60% (Riihimäki et al., 1979a). Pulmonary retention of *o*-, *m*-, and *p*-xylene at 45-90 ppm (196–391 mg/m^3) was reported by Sedivec and Flek (1976) to be 62-64% for exposure up to 7 hours. During rest and intermittent exercise, *m*-xylene retention was 59% at exposures of 70-220 ppm (304-957 mg/m^3). Exercise induced increased rates of breathing associated with increased retention (Riihimäki et al., 1979b; Åstrand et al., 1978). Similar rates of pulmonary absorption of ethylbenzene and xylenes were observed by Engström and Bjurström (1978). Retention does not appear to differ with gender (Senczuk and Orlowski, 1978). Absorption occurred in two phases, a short phase (0-15 minutes exposure) and a longer phase of approximately 1 hour that represented a steady state between blood and inhaled xylenes.

Dermal absorption of *m*-xylene vapor has been studied in volunteers exposed at 300 ppm (1305 mg/m^3) and 600 ppm (2610 mg/m^3) for 3.5 hours (free of respiratory exposure). Dermal absorption was found to be directly proportional to the vapor concentration. At 1305 mg/m^3, absorption was approximately 0.01 µg/cm^2 skin/min (Riihimäki and Pfäffli, 1978). Dermal absorption of liquid xylenes has been studied via determination of uptake after a 15-20 minute hand immersion in neat *m*-xylene. Uptake was estimated by measuring the level of *m*-methylhippuric acid (*m*-xylene metabolite) in urine of 8 volunteers. Mean absorption was approx. 2 µg/cm^2 skin/min (Engström et al., 1977) with total amount of absorption through two hands approx. 35 mg. This amount of absorption was about the same as that of 15-20 minutes of inhalation exposure to 100 ppm (435 mg/m^3). Lauwerys et al. (1978) obtained similar values for dermal absorption.

Permeability coefficient data for xylenes (i.e., the rate at which a chemical penetrates the outer layer of epidermis normalized by concentration) is shown in Table 6.11. The permeability constants vary by orders of magnitude depending on the xylenes solution or vehicle tested.

Table 6.11: Xylenes Permeability Coefficients

Chemical	Vehicle	Study Type	Skin	Permeability Constant (cm/h)	Reference
Mixed Xylenes	Neat Liquid	*in vivo*	Human forearm skin	3.41E-04	Kezic et al., 2001
Mixed Xylenes	Water	Predictive Equation	--	9.50E-02	EPA, 1992
Mixed Xylenes	Xylene Vapor	*in vivo*	Human forearm skin	1.20E-01	Kezic et al., 2000

Absorption factors for volatile chemicals are available from EPA Region III for dermal contact with soil. These values are also appropriate estimates for products such as lacquer adhering to the skin because their magnitude is based on the chemical's volatility and the permeability of human skin to volatile organic chemicals. Recommended absorption factors are also available from EPA Region IV. However, Region IV's absorption factors do not take into account the volatility of the chemical. Absorption factors proposed by the EPA are summarized below in Table 6.12.

Table 6.12: EPA Absorption Factors

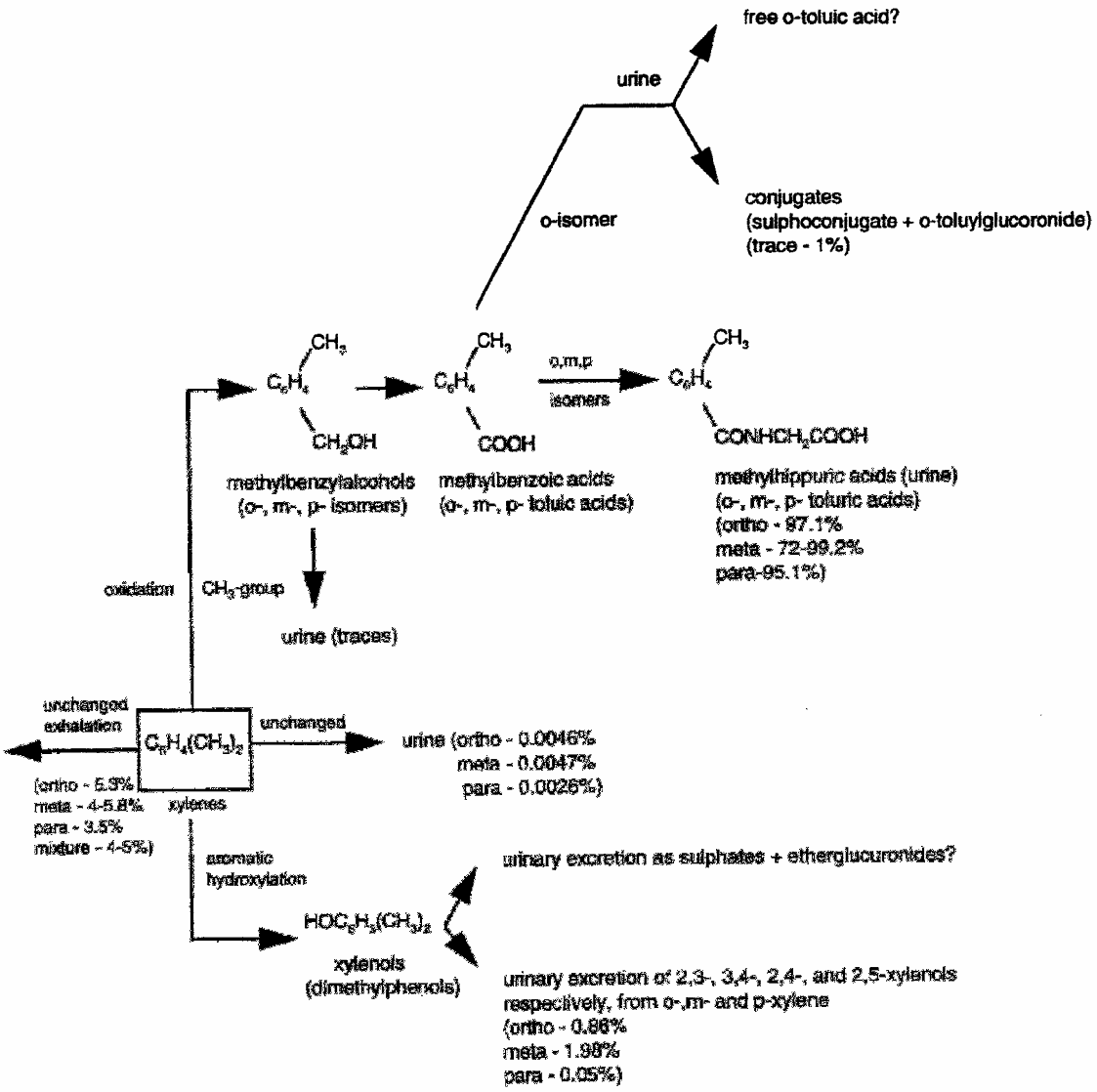
Chemical Type	(EPA 1995a) Region III	(EPA 1995b) Region IV
Semivolatile Chemicals	10%	1%
Volatile Chemicals (moderate vapor pressure chemicals including toluene and *o*-, *m*- and *p*-xylene isomers)	3%	1%
Volatile Chemicals (high vapor pressure chemicals including benzene)	0.05%	1%

Distribution: About 90% of xylene in blood is bound to serum proteins and approximately 10-15% is in protein-free serum. After systemic absorption, xylene is largely distributed to adipose tissue. After inhalation exposure, adipose tissue accumulates 5-10% of the absorbed dose (Åstrand, 1978; Engström and Bjurström, 1978) and this is increased by exercise (Riihimäki et al., 1979a,b).

Metabolism: The metabolism of xylenes in humans proceeds primarily via side-chain oxidation to methyl benzoic acid (Fig. 1), which is conjugated mainly with glycine to form methylhippuric acid, which is excreted in urine. Small amounts of methyl benzoic acid are excreted as the glucuronide. In addition, trace amounts of methylbenzyl alcohol are also found in urine as well as small amounts of dimethylphenol isomers, formed by hydroxylation of the aromatic ring, and their conjugates (Sedivec and Flak, 1976; Riihimäki et al., 1979a,b; Ogata et al., 1980; Engström et al., 1984).

Elimination: Xylenes are primarily excreted as metabolites in urine with small amounts released unchanged in expired air. Excretion in feces is unimportant. Clearance of *p*-xylene from blood was calculated to be 2.6L/kg/hr at exposure of 20 ppm [87 mg/m^3] and 1.6L/kg/hr at 70 ppm (304 mg/m^3) (Wallén et al., 1985). In human volunteers exposed to *o*-, *m*-, or *p*-xylene, 95-97% was excreted as *m*-methyl benzoic acid conjugates (primarily hippuric acid) and 0.1-2% of the metabolites were 2,4-dimethylphenol conjugates (Riihimäki et al., 1979a,b; Sedivec and Flek, 1976). A linear relationship has been observed between intensity of exposure to xylenes and the concentration of methylhippuric acid in urine (Kawai et al., 1991a; Huang et al., 1994). Urinary methylhippuric acid excretion of xylene-exposed workers occurred in two phases: 3.6 hours for the first 10 hours and 30.1 hours for the following 24 hours (Engström et al., 1978). After *m*-xylene exposure, excretion of *m*-methylbenzoic acid conjugates was triphasic with half times of 1-2, 10 and 20 hours (Riihimäki et al., 1979a).

Fig 1. Metabolic Scheme for Xylenes – Humans



From ATSDR, 1995

* 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

7.0 Exposure Assessment

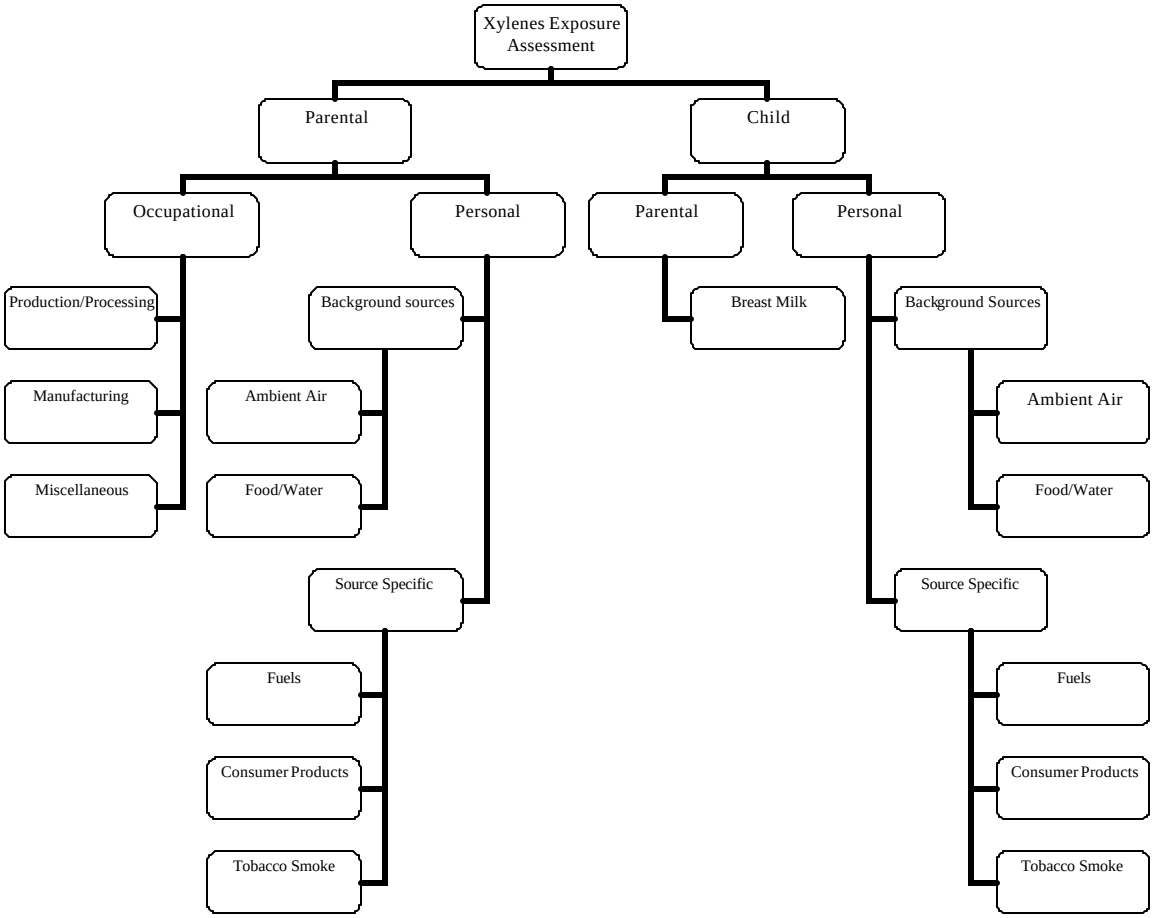
This section summarizes the methodology, results, and conclusions of the exposure assessment for the xylenes category under VCCEP. As part of this pilot program, EPA has requested that exposure information be submitted to determine the extent of children's and prospective parents' exposure to xylenes. The types of exposure information needed for the assessment includes the identification and characterization of the population groups exposed, sources of the exposure, as well as frequencies, levels, and routes of exposure. The methodology employed in this assessment provides a comprehensive analysis of potential childhood exposures to xylenes and uses the available data to focus on those sources of exposure that are likely to have the most significant impact on children's total xylenes exposures. As discussed in previous section, mixed xylenes may contain ethylbenzene. Ethylbenzene exposure from mixed xylenes was not considered in this assessment as ethylbenzene is being assessed separately in VCCEP.

7.1 Methodology/Scope of Assessment

As suggested by EPA, exposure assessments for both children and prospective parents were conducted. Sources of exposure to xylenes in the ambient environment can come from both chain-of-commerce and non-chain-of-commerce sources, and in many environments, it is impossible to quantify the exposure contribution from each type of source. In accordance with the notice of the program published in the Federal Register (2000), exposures for xylenes chain-of-commerce sources were assessed and quantified. In addition, exposure to xylenes from petroleum chain-of-commerce sources (e.g., gasoline) were also assessed and quantified. Contribution to xylenes exposure from non-chain of commerce sources such as automobile exhaust, cigarettes, and other sources of combustion are frequently captured in the exposure data presented (e.g., indoor air monitoring data, in-vehicle monitoring data). Additionally, the exposure assessment does not include exposures from accidents or intentional misuse of products containing xylenes.

A child-centered approach was used to define realistic exposure scenarios for children's interaction with sources of xylenes including environmental (ambient) sources, and use of consumer products. Figure 7.1 shows the relevant sources of xylenes exposure for children and prospective parents. For most people, exposure to xylenes is a daily occurrence. Xylenes exposures to children and prospective parents have been quantified by evaluating the ambient or background xylenes levels in a child's/parent's air (indoor and outdoor), diet, and water, as well as specific sources and microenvironments to which subpopulations of children may be exposed. Available data indicate that all children are exposed to background levels of xylenes in the ambient air, water, and food supply as a result of releases from natural sources, mobile sources, and the chain of commerce sources described in Section 5. In addition to these ubiquitous sources, certain subpopulations of children may be exposed to xylenes in microenvironments depending on specific activities such as transportation via gasoline powered vehicles, use of xylenes-containing consumer products, or living in a home where tobacco smoking occurs (either used by parents or teenage children).

Figure 7.1


Xylenes Exposure Assessment
Parental
Child
Occupational
Personal
Parental
Personal
Production/Processing
Manufacturing
Miscellaneous
Background sources
Ambient Air
Food/Water
Source Specific
Fuels
Consumer Products
Tobacco Smoke
Breast Milk
Background Sources
Ambient Air
Food/Water
Source Specific
Fuels
Consumer Products
Tobacco Smoke

In evaluating prospective parents, only prospective mothers have been included in the exposure assessment because xylenes are not associated with male reproductive health effects. Thus, a prospective father's exposure to xylenes does not impact his children. Consideration of prospective mothers' exposures provides a picture of potential fetal exposures as well as consideration of the human milk pathway. As discussed in Section 6, xylenes are not mutagenic or teratogenic, and are only toxic to the fetus at levels associated with maternal toxicity. Therefore, fetal exposures have not been quantified separately. Table 7.1 is a summary of the age groups considered in the exposure assessment.

Table 7.1: Age Groups for the Xylenes Exposure Assessment

Age Group	Category	Subcategory
< 1 year old	Children	Infant
1-5 year old		Toddler
6-13 year old		Child
14-18 year old		Teenager
Female 19-35 * year old	Adult	Prospective Mother

*It is acknowledged that some women conceive children later in life, however, the largest percentage of pregnancies occur in women between the ages of 19 and 35.

Exposures from each source of xylenes are characterized using exposure scenarios. The exposure scenarios define the population, source of exposure, the routes of exposure, and the values for the exposure factors that determine the dose and dose rate received from the source. A summary of ambient and the source-specific exposure scenarios for specific age groups is provided in Table 7.2.

Table 7.2: Summary of Xylenes Exposure Scenarios

Exposure Scenarios		Age Group				
		< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
Ambient Exposures						
Outdoor Air						
	Urban	✓	✓	✓	✓	✓
	Rural	✓	✓	✓	✓	✓
Indoor Air						
	In-home	✓	✓	✓	✓	✓
	In-School		✓	✓	✓	
Food		✓	✓	✓	✓	✓
Water		✓	✓	✓	✓	✓
Source-Specific Exposures						
Tobacco Smoke						
	ETS	✓	✓	✓	✓	✓
	Mainstream				✓	✓
Consumer Products						
	Users				✓	✓
	Non-users	✓	✓	✓		
Gasoline Sources						
	In-Vehicle	✓	✓	✓	✓	✓
	Refueling				✓ (16 – 18 years old)	✓
Occupational						
	Production/Processing					✓
	Non-Production					✓

✓ = Included in evaluation.

A child's exposure to xylenes depends upon a number of variables, or exposure factors. These exposure factors include the activities of the child that bring the child into contact with the source of exposure and which determine the dose resulting from the interaction and the physiology of the child. The relevant exposure parameters associated with each exposure scenario are presented in Appendix A-1.

For the various types of exposure, efforts were made to characterize both typical exposures and high-end exposures. In general, typical exposures were calculated using central tendency descriptors such as the average or median exposure concentrations in a given dataset and the average or median exposure parameters (e.g., exposure frequency, body weight, inhalation rate, etc.). High-end exposures for sources of xylenes other than consumer products were calculated using exposure concentrations representative of a 90 - 95th percentile of the range of values in a dataset (where data were sufficient to allow the determination of a range). In defining high-end exposure scenarios for the consumer

product scenarios, 90th percentile product usage amounts were used to estimate airborne concentrations. It should be noted that the high-end scenario is meant to represent a reasonable, higher than average exposure, but not the absolute "worst case" estimate for exposure.

Defining the high-end scenarios raises a number of challenges in the assessment of xylenes exposure from consumer products. In this assessment the following decisions were made on the characterization of consumer exposure. First, the assessment does not consider exposures that occur from the intentional misuse of the products (solvent abuse). Second, the product uses that are considered in this assessment are those that are consistent with label directions. Thus, xylenes containing products with label directions instructing the user to avoid skin contact and use with adequate ventilation will not be assessed in a manner that contradicts these instructions (extensive dermal contact or use in small unventilated spaces). Third, exposures from use of consumer products occur in a wide range of situations where various amounts are used, under varying conditions (frequencies of use, room sizes, and ventilation rates), and in the presence or exclusion of children. Scenarios based on conservative (exposure enhancing) values for all possible exposure factors will result in situations that contradict label directions (i.e., use with adequate ventilation). Therefore, the high-end consumer product exposure scenarios considered in this assessment are based on above average but not the theoretical maximum values of all exposure-related factors.

7.2 Sources of Xylenes Exposure

This section provides a summary of the sources of potential exposure to xylenes for children and prospective parents. Xylenes exposure has been quantified based on information provided in the scientific peer-reviewed literature or through exposure modeling using various EPA exposure models. The sources of xylenes are defined in terms of two general source categories: ambient sources of exposures and exposures resulting from the use of consumer products.

7.2.1 Ambient Environmental Exposures

Ambient childhood exposures to xylenes could occur from four general sources: 1) ambient air, 2) food, 3) drinking water, and 4) human milk. Potential exposures to each source are described further below.

7.2.1.1 Ambient Air

During the 1980s and early 1990s the EPA funded and provided oversight for human exposure research with the objective of directly measuring exposure using personal air samplers. The conclusion of this extensive research project, known as the EPA Total Exposure Assessment Methodology (TEAM) Studies, was that the most important sources of exposure are small and originate close to the person (Wallace, 2001). The presence of major point sources, such as refineries, was not correlated with increased personal exposure to organic chemicals. For many chemicals, including xylenes, distant sources of air release, such as refineries and chemical facilities play a smaller part in the determination of total dose than localized sources such as consumer products, use of petroleum products, time spent in vehicles, and use of tobacco products.

The Clean Air Act Amendments of 1990 provided for creation of the National Urban Air Toxics Research Center (NUATRC). The goal of this organization is to promote, develop and support research related to human health risks from air toxics. As part of the NUATRC mission, several studies have been conducted where VOC exposures to children have been evaluated. The Health Effects Institute (HEI) and the Mickey Leland National Urban Air Toxics Research Center (NUATRC) are jointly funding a project called the Relationship between Indoor, Outdoor and Personal Air (RIOPA); a large urban air toxics project that is comprised of three studies. The RIOPA project tests the hypothesis that personal exposure to air toxics is influenced by outdoor sources of these air toxics. It involves 3 cities with different air pollution source profiles: Los Angeles, California is dominated by mobile sources; Houston, Texas is dominated by industrial point sources; and Elizabeth, New Jersey includes a mixture of mobile and point sources. In each city, 100 homes were monitored for 48 hours in each of the 2 seasons. The homes were monitored indoors and outdoors for $PM_{2.5}$ VOCs, and aldehydes. In addition, personal exposure to $PM_{2.5}$, VOCs, and aldehydes, and in-vehicle exposure to aldehydes were measured for residents of these homes. At the time of this assessment, the data for the VOCs had not been formally published, although summary data was made available for preliminary review by HEI. In general it was found that indoor air xylene concentrations were higher than outdoor air, but lower than the personal xylene concentrations.

A community based study conducted by Buckley et al.,(2005) in Baltimore evaluated the impact of industry on community air quality and individual resident exposure to 15 VOCs. The study was designed to examine the potential industry effect by comparing indoor, outdoor, and personal air concentrations in South Baltimore to those in Hampden, an urban Baltimore community with a less intense industrial presence. Buckely et al. concluded that except for ethylbenzene and m,p-xylene, the VOC concentrations at all three levels of monitoring (outdoor, indoor, and personal) were comparable in the two communities, suggesting no industrial impact or an impact smaller than that detectable with the sample size of the study. For the m/p-xylene, where there appeared to be a possible impact, the indoor and outdoor differences did not translate into significant differences in personal exposure levels between the two communities.

Inhalation of xylenes in outdoor and indoor air was evaluated for each childhood age grouping and the prospective mother. For ambient outdoor air, both urban and rural settings were considered, as xylenes concentrations are highly dependent on mobile source emissions. For indoor air, exposures from both in-home and in-school environments were considered.

Ambient Outdoor Air

Urban and rural ambient air concentrations of xylenes were obtained from EPA's AirData database (http://www.epa.gov/aqspubl1/annual_summary.html; accessed 8/20/03). This database contains annual summaries from air monitoring stations, pulling data from three EPA databases: 1) Air Quality System, 2) National Emissions Trends, and 3) National Toxics Inventory. Collectively, these databases represent measured data from air monitoring stations, as well as estimated air data from point, area and mobile source emission measurements.

The most recent year for which data was available was 2004. The 2004 data for two geographical setting categories, rural and urban were evaluated. The AirData database presents xylenes data for *m*/*p*-xylenes and *o*-xylenes. Therefore, these two isomer

concentrations were summed together to calculate the concentration of total *o*-, *m*-, and *p*-xylene isomers. A summary of the geographical diversity of the AirData for xylenes is provided in Table 7.3 below.

Table 7.3: Summary Description of the AirData Database for Xylenes

Setting	States	Number of Counties	Number of Monitoring Stations
Rural	AZ, CA, CT, DE, FL, GA, LA, ME, MI, MN, MO, MS, NH, NJ, NY, NC, ND, OH, PA, SC, TX, VT, VA, WI	42	49
Urban	AZ, CA, CO, CT, DE, D.C., FL, IL, IN, IA, LA, MD, MA, MI, MN,MS, MO, NH, NY, NC, OH, PA, RI, SD, TN, TX, VT, VA, WI	73	123

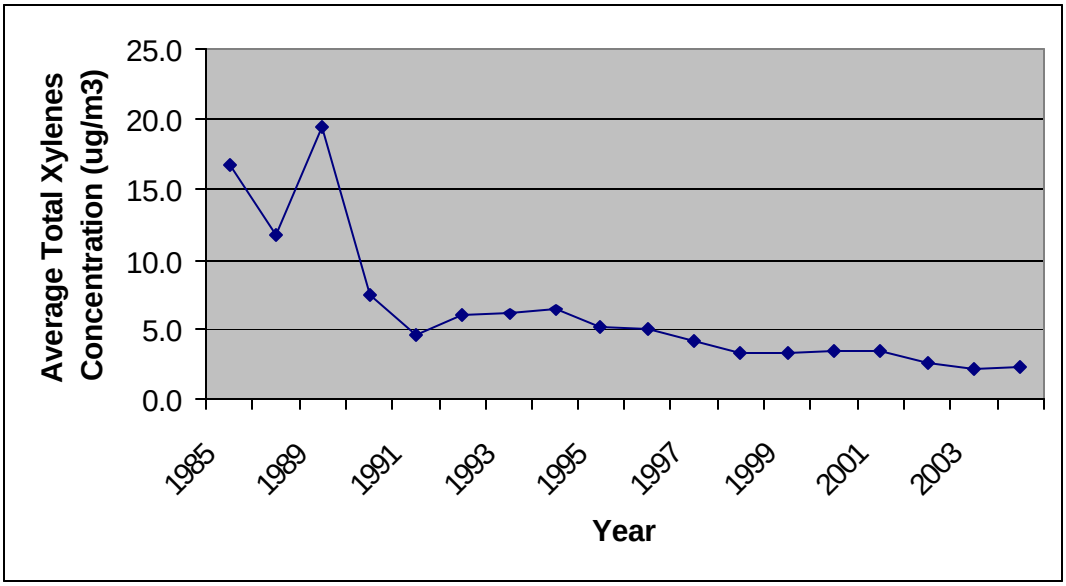
The 2004 AirData data for total xylenes are presented in Table 7.4. It should be noted that this data was collected from photochemical assessment monitoring stations (PAMS). PAMS stations are located in areas of ozone non-attainment, and are used to measure ozone precursors such as xylenes. Therefore, they are likely to be located in areas where xylenes concentrations are higher than in other areas. However the HAPs data from AirData only provided m-xylene and p-xylene from California. Therefore it was determined that the PAMS data had broader geographic coverage and therefore, more representative of total xylenes concentrations.

Table 7.4: 2004 Ambient Air Xylenes Concentrations from EPA's AirData Database

Setting	Mean Total Xylenes Air Concentration ($\mu g/m^3$)	95^{th} Percentile Total Xylenes Air Concentration ($\mu g/m^3$)
Rural	1	2.4
Urban	2.5	5.9

Ambient outdoor air concentrations have been steadily declining over time. The average total xylenes ambient air concentrations across the US, as measured at the PAMS stations since 1985 are shown on Figure 7.2.

Figure 7.2 Trend in Total Xylenes Ambient Air Concentrations in the U.S. (1985 – 2005)



* Note the data in Figure 7.2 were converted from the units of ppbC in the AirData database

As shown on this graph, significant decreases in total xylenes concentrations have occurred since the mid 1980s. Therefore, use of the most recent air monitoring data (as shown on Table 7.4) to characterize typical and high-end exposure concentrations is appropriate. As such, the mean rural concentration of 1.0 µg/m^3 and the mean urban concentration of 2.5 µg/m^3 have been selected as representative of typical exposure concentrations for the child and prospective mothers in the rural and urban settings, respectively. The 95th percentile concentrations of 2.4 µg/m^3 and 5.9 µg/m^3 have been selected as representative of high-end exposure concentrations for rural and urban settings, respectively.

Average daily doses were calculated for residents living in urban and rural settings. Exposure was quantified according to the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD	=	average daily dose (mg/kg/day)
C	=	concentration of xylene in ambient air (µg/m^3)
ED	=	exposure duration (years)
EF	=	exposure frequency (days/year)
ET	=	exposure time (hours/day)
IR	=	inhalation rate (m^3/hour)
ABSi	=	xylene inhalation absorption factor; 0.6 (unitless)
CF	=	conversion factor (0.001 mg/µg)
BW	=	body weight (kg)
AT	=	averaging time (days)

Age-specific doses are presented below in Tables 7.5 and 7.6. In this exposure assessment, ambient doses were calculated so as to appropriately represent the exposure frequencies and exposure times for school days and non-school days. For children, ambient outdoor exposures for school and non-school days were summed to derive average daily doses representing a full year of exposure. For the infant and prospective mother, it was assumed that all days are non-school days. Table 7.7 presents the total doses from outside ambient air exposures.

Table 7.5: ADDs for School Day Exposure to *o*-, *m*-, and *p*-Xylene Isomers in Ambient Air

Exposure Parameter	Units	1-5 year old	6-13 year old	14-18 year old	1-5 year old	6-13 year old	14-18 year old
		Rural - Typical			Rural – High-End		
C	µg/m^3	1.0	1.0	1.0	2.4	2.4	2.4
ET	hours/day	2.1	2.0	1.9	2.1	2.0	1.9
EF	days/year	180	180	180	180	180	180
ED	Years	5	8	5	5	8	5
IR	m^3/h	0.31	0.51	0.60	0.31	0.51	0.60
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001
AT	Days	1825	2920	1825	1825	2920	1825
BW	Kg	15.4	35	61	15.4	35	61
ABSi	Unitless	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***1.3E-05***	***8.6E-06***	***5.5E-06***	***3.0E-05***	***2.1E-05***	***1.3E-05***
		Urban - Typical			Urban – High-End		
C	µg/m^3	2.5	2.5	2.5	5.9	5.9	5.9
ET	hours/day	2.1	2.0	1.9	2.1	2.0	1.9
EF	days/year	180	180	180	180	180	180
ED	Years	5	8	5	5	8	5
IR	m^3/h	0.31	0.51	0.60	0.31	0.51	0.60
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001
AT	Days	1825	2920	1825	1825	2920	1825
BW	Kg	15.4	35	61	15.4	35	61
ABSi	Unitless	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***3.1E-05***	***2.2E-05***	***1.4E-05***	***7.4E-05***	***5.1E-05***	***3.3E-05***

Table 7.6: ADDs for Non-School Day Exposure to *o*-, *m*-, and *p*-Xylene Isomers in Ambient Air

Exposure Parameter	Units	< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old	< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
		Rural - Typical					Rural- High-End				
C	µg/m^3	1.0	1.0	1.0	1.0	1.0	2.4	2.4	2.4	2.4	2.4
ET	h/d	1.4	3.1	2.2	2.3	1.5	1.4	3.1	2.2	2.3	1.5
EF	d/y	365	185	185	185	365	365	185	185	185	365
ED	years	1	5	8	5	17	1	5	8	5	17
IR	m^3/h	0.19	0.31	0.51	0.60	0.47	0.19	0.31	0.51	0.60	0.47
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	365	1825	2920	1825	6205	365	1825	2920	1825	6205
BW	kg	7.2	15.4	35	61	62.4	7.2	15.4	35	61	62.4
ABSi	unitless	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***2.2E-05***	***1.9E-05***	***9.7E-06***	***6.9E-06***	***6.8E-06***	***5.3E-05***	***4.6E-05***	***2.3E-05***	***1.7E-05***	***1.6E-05***
		Urban - Typical					Urban – High-End				
C	µg/m^3	2.5	2.5	2.5	2.5	2.5	5.9	5.9	5.9	5.9	5.9
ET	h/d	1.4	3.1	2.2	2.3	1.5	1.4	3.1	2.2	2.3	1.5
EF	d/yr	365	185	185	185	365	365	185	185	185	365
ED	Years	1	5	8	5	17	1	5	8	5	17
IR	m^3/h	0.19	0.31	0.51	0.60	0.47	0.19	0.31	0.51	0.60	0.47
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	Days	365	1825	2920	1825	6205	365	1825	2920	1825	6205
BW	Kg	7.2	15.4	35	61	62.4	7.2	15.4	35	61	62.4
ABSi	Unitless	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***5.5E-05***	***4.7E-05***	***2.4E-05***	***1.7E-05***	***1.7E-05***	***1.3E-04***	***1.1E-04***	***5.8E-05***	***4.1E-05***	***4.0E-05***

Table 7.7: Total ADDs for Exposure to *o*-, *m*-, and *p*-Xylene Isomers in Ambient Air (mg/kg/d)

Setting	<1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
Rural Typical	2.2E-05	3.1E-05	1.8E-05	1.2E-05	6.8E-06
Rural High-End	5.3E-05	7.6E-05	4.4E-05	3.0E-05	1.6E-05
Urban Typical	5.5E-05	7.9E-05	4.6E-05	3.1E-05	1.7E-05
Urban High-End	1.3E-04	1.9E-04	1.1E-04	7.3E-05	4.0E-05

Analysis of Ambient Xylenes Concentrations in Industrial Source Areas

A common misconception regarding individuals' exposures to xylenes and other volatile compounds is that those living near industrial air emitters (stationary sources) have higher exposures than those who live elsewhere. For many chemicals this has been shown not to be true (Buckley et al., 2005; Ott and Roberts, 1998; Wallace, 1996; Wallace, 1989). In this assessment, an analysis of exposure from stationary sources was conducted to determine the contribution from this source.

The approach used was to develop a reasonable high-end estimate of the long-term average concentration for an individual living near a facility. This value is then compared to the levels that typically occur in urban and rural environments. At the time of this assessment, the most recent TRI release data was that for reporting year 2003. In 2003, 2,875 facilities reported total *o*-,*m*- and *p*-xylene isomer emissions. The top 5 urban and rural facilities based on total pounds released to the air are listed on Table 7.8.

Table 7.8: Top Five Sources of Xylenes Isomers in Rural and Urban Settings

Urban	Total Air Releases (pounds)	Rural	Total Air Releases (pounds)
1. GM Pontiac Assembly Center, *Oakland County, MI*	975,000	1. Honda of America Mfg., *Union County, OH*	492,450
2. McChord Air Force Base, *Pierce County, WA*	586,171	2. Sanderson Plumbing Products, *Lowndes County, MS*	472,122
3. Ford Motor Company, *Clay County, MO*	552,900	3. American Woodmark Corp., *Hardy County, WV*	168,642
4. Nissan Smyrna Manufacturing Plant, *Rutherford County, TN*	515,646	4. Roll-Offs of America, *Bryan County, OK*	145,764
5. BP Chemical Texas City Plant B, *Galveston Co., TX*	496,000	5. Wood-Mode Inc., *Snyder County, PA*	141,388

Of the 2,875 facilities, no facilities reported emissions exceeding 1 million pounds, with the top emitting facility located in an urban county of Michigan. Only 4 facilities, or approximately 0.1%, reported emissions exceeding 500,000 pounds.

To determine a reasonable high-end for exposure, the air concentrations surrounding the top TRI facility, the GM Pontiac Assembly Center located in Pontiac, MI, were estimated using EPA's SCREEN3 air dispersion model. Details of the modeling are presented in Appendix A-2. Results of this model run predicted long-term xylenes concentration at the hypothetical fenceline would be 64 $\mu g/m^3$.

The SCREEN3 model prediction for the top TRI emitting facility is about 8 times greater than the high-end air concentration of 7.7 $\mu g/m^3$ selected for urban settings. However, it is believed that the vast majority of individuals living near facilities would not experience air concentrations that differ from the range of background concentrations in the rural or urban environments (Table 7.4). The reason for this is that the total xylenes concentration

of 64 µg/m^3 is predicted to only occur for a home located 500 meters (576 yds) from the highest TRI emitter. Given that >99% of the TRI reporting facilities emit far less xylenes than the GM Pontiac, MI facility did in 2003, the high-end for the majority of the U.S population is believed to be reasonably characterized by the measured xylenes data presented on Table 7.4. Despite the conservative nature of this modeling, the predicted air concentration is less than the IRIS RfC of 0.1 mg/m^3.

Ambient Indoor Air

The indoor environment in which children and prospective mothers spend most of their time is the home. Indoor air concentrations of *o*-, *m*-, and *p*-xylene isomers were obtained from the summary of the residential indoor air data presented in the ATSDR Toxicological Profiles for xylenes (ATSDR, 1995a), various residential indoor air studies, and indoor air quality studies of schools. The available data indicate that indoor air generally has higher concentrations of xylenes than the outdoor ambient air.

Xylenes in the indoor air environment occur as a result of a variety of indoor sources, including the use of common household products, smoking tobacco products, wood stoves, cooking, and infiltration from attached garages. Xylene levels in the home may also be influenced by outdoor air levels and the whole house air exchange rates, which vary with the season and are lower in cold weather (Murray and Burmaster, 1995). Within the home, the two most common sources of xylenes are household products and cigarette smoke (ATSDR, 1995a). Source specific exposures to xylenes from use of consumer products and exposure to tobacco smoke and are addressed separately in Sections 7.6 and 7.9, respectively.

The ATSDR review of xylenes presents measurement data from two indoor air studies published in the 1980s, which measured levels of *m*- and *p*-xylenes (combined) that ranged from 10 - 47 µg/m^3, and weighted median indoor *o*-xylene and combined *m*- and *p*-xylenes of 4.9 µg/m^3 and 14 µg/m^3, respectively (ATSDR, 1995a). A review of the recent peer-reviewed literature of indoor air studies was conducted and focused on residential studies. Several studies from the mid-1990s to the present were identified, although those conducted in the US are limited (Adgate et al., 2004a,b; Buckley, et al., 2005; Bozzelli et al., 1995; Hodgson et al., 2000; Kinney et al., 2002; Phillips et al., 2004; and Van Winkle and Scheff, 2001). Table 7.9 summarizes the data from these studies.

Table 7.9
Summary of Current Published Indoor Air Studies of Xylenes

Study	Location	Indoor concentration: Total Xylenes ($\mu g/m^3$)	Notes
Adgate et al., 2004a	Minneapolis, MN, St. Paul, MN, Rice County MN, and Goodhue County MN	10.8 (mean) 5.2 (25^{th} percentile) 6.7 (50^{th} percentile) 28.4 (95^{th} percentile)	Evaluated 101 private residences in 1997 for indoor air, outdoor air and personal air concentrations of VOCs. Examined both urban and nonurban households and included smoking and non-smoking households and those with and without attached garages.
Adgate et al., 2004b	Minneapolis, MN	4.7 (avg of winter and spring medians) 2.5 (avg of winter and spring 10^{th} percentiles) 15.5 (avg of winter and spring 90^{th} percentiles)	Evaluated 113 different households measuring indoor home air, outdoor air concentrations of VOCs in an urban area. Both single family homes 43%) and apartments (55%) were surveyed, and included both smoking and non-smoking households.
Bozzelli, et al, 1995	Elizabeth, NJ	12.5 – 13.6	Evaluated indoor air impacts during use of kerosene heaters. Data on this table is without the heaters in use.
Buckley et al., 2005	South Baltimore and Hampden MD	9.7 (mean) 3.3 (10^{th} percentile) 21 (90^{th} percentile)	Evaluated 36 non-smoking homes in South Baltimore and 21 non-smoking homes in Hampden, MD for outdoor, indoor and personal air VOC exposures. Children were included in the personal monitoring program. Questionnaires were provided to each household to document indoor activities and home characteristics.
Hodgson et al., 2000	East and Southeast US	2.2 – 50 4.34 – 16.9 (range of geometric means)	Measured values in newly constructed homes prior to occupancy. Both manufactured and site-built homes included.
Kinney et al, 2002	New York City, NY	11 (mean, range not reported)	Study of 8 homes to characterize personal exposures to urban air toxics in inner city neighborhoods.
Phillips et al., 2004	Oklahoma City, OK; Tulsa, OK; Ponca City, OK; Stillwater, OK	2.6 (median day) 3.9 (median night) 70 (95^{th} percentile day by rank) 49 (95^{th} percentile night by rank)	Study conducted of 37 U.S. homes in 2000 – 2001 in urban and rural Oklahoma to characterize indoor, outdoor and personal air concentrations of various VOCs. Presence of refinery was a primary factor investigated.
Van Winkle and Scheff, 2001	Chicago, IL	6.85 – 604 17 (median)	Study of 10 homes in 1994 -1995

None of the recent studies are necessarily representative of the current overall U.S. demographic because of differences in home construction, presence of an attached garage, and outdoor ambient air concentrations. Phillips et al. (2004) found that for xylenes, there was no significant correlation between the indoor and outdoor air concentrations. Also, recent studies in Germany have shown that for xylenes, outdoor air is not the predominant source of xylenes in the indoor air, with perhaps the exception in high traffic density areas (Ilgen et al., 2001a,b). Therefore, it was determined that the difference (i.e., I-O delta) between the indoor and outdoor values could be used to estimate indoor air concentrations, as it represents the incremental total xylenes concentration attributable to indoor sources.

Of the studies listed on Table 7.9, only Adgate et al. (2004b) had paired indoor and outdoor data for individual homes. Therefore, this study was used to derive typical and high-end I-O deltas. These are presented on Table 7.10. It should be noted that this data was not published. However, the Minnesota Department of Health provided the raw air sampling data (personal communication with J. Panko, 2004).

Table 7.10
I-O Deltas from Adgate et al. (2004b)

Study	Typical I-O Delta (µg/m^3)	High-End I-O Delta (µg/m^3)
Adgate et al., 2004b	6.6	30

As such, because of the limited data from recent representative studies of xylenes in the indoor air, typical and high-end indoor air concentrations have been estimated by applying the I-O delta as follows:

$$C_{indoor} = C_{outdoor} + C_{\Delta indoor\,source}$$

The results are summarized on Tables 7.11 and 7.12 below.

Table 7.11: Typical Representative Ambient Air *o*-, *m*-, and *p*-Xylene Concentrations in Rural and Urban Areas

Setting	Typical Outside Exposure Concentration (µg/m^3)	Typical Indoor Exposure Concentration (µg/m^3)
Rural	1.0	7.6
Urban	2.5	9.1

Table 7.12: High-End Representative Ambient Air *o*-, *m*-, and *p*-Xylene Concentrations in Rural and Urban Areas

Setting	High-End Outside Exposure Concentration (µg/m^3)	High-End Indoor Exposure Concentration (µg/m^3)
Rural	2.4	32.4
Urban	5.9	35.7

The estimated typical and high-end indoor air exposure concentrations are consistent with the mean or median and high-end values presented in the recent literature.

In-Home Dose Calculations

Age-specific average daily doses were calculated for in-home exposures with the representative indoor concentrations provided in Tables 7.11 and 7.12 for typical and high-end exposures, respectively. Urban and rural exposure was quantified according to the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg/day)
C = concentration total xylenes in home air (µg/m^3)
ED = exposure duration (years)
EF = exposure frequency (days/year)
ET = exposure time (hours/day)
IR = inhalation rate (m^3/hour)
ABSi = xylenes inhalation absorption factor; 0.6 (unitless)
CF = conversion factor (0.001 mg/µg)
BW = body weight (kg)
AT = averaging time (days)

The age-specific doses from in-home xylenes exposures are presented in Tables 7.13-7.15.

Table 7.13: ADDS for School Day In-Home *o*-, *m*-, and *p*- Xylene Isomers Exposures

Exposure Parameter	Units	1-5 year old	6-13 year old	14-18 year old	1-5 year old	6-13 year old	14-18 year old
		Rural - Typical			**Rural – High-End**		
C	µg/m^3	7.6	7.6	7.6	32.4	32.4	32.4
ET	hours/day	17.8	15.0	14.2	17.8	15.0	14.2
EF	days/year	180	180	180	180	180	180
ED	years	5	8	5	5	8	5
IR	m^3/h	0.31	0.51	0.60	0.31	0.51	0.60
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001
AT	days	1825	2920	1825	1825	2920	1825
BW	Kg	15.4	35	61	15.4	35	61
ABSi	unitless	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***8.1E-04***	***4.9E-04***	***3.1E-04***	***3.4E-03***	***2.1E-03***	***1.3E-03***
		Urban - Typical			**Urban – High-End**		
C	µg/m^3	9.1	9.1	9.1	35.7	35.7	35.7
ET	Hours/day	17.8	15.0	14.2	17.8	15.0	14.2
EF	days/year	180	180	180	180	180	180
ED	Years	5	8	5	5	8	5
IR	m^3/h	0.31	0.51	0.60	0.31	0.51	0.60
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001
AT	Days	1825	2920	1825	1825	2920	1825
BW	Kg	15.4	35	61	15.4	35	61
ABSi	unitless	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***9.6E-04***	***5.9E-04***	***3.8E-04***	***3.8E-03***	***2.3E-03***	***1.5E-03***

Table 7.14 ADDS for Non-School Day In-Home *o*-, *m*-, and *p*- Xylene Isomers Exposures

Exposure Parameter	Units	< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old	< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
		Rural – Typical					Rural- High-End				
C	µg/m^3	7.6	7.6	7.6	7.6	7.6	32.4	32.4	32.4	32.4	32.4
ET	h/d	21.4	19.7	20.8	20.3	21.2	21.4	19.7	20.8	20.3	21.2
EF	d/y	365	185	185	185	365	365	185	185	185	365
ED	Years	1	5	8	5	17	1	5	8	5	17
IR	m^3/h	0.19	0.31	0.51	0.60	0.47	0.19	0.31	0.51	0.60	0.47
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	Days	365	1825	2920	1825	6205	365	1825	2920	1825	6205
BW	Kg	7.2	15.4	35	61	62.4	7.2	15.4	35	61	62.4
ABSi	unitless	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***2.6E-03***	***9.2E-04***	***7.0E-04***	***4.6E-04***	***7.3E-04***	***1.1E-02***	***3.9E-03***	***3.0E-03***	***2.0E-03***	***3.1E-03***
		Urban – Typical					Urban – High-End				
C	µg/m^3	9.1	9.1	9.1	9.1	9.1	35.7	35.7	35.7	35.7	35.7
ET	h/d	21.4	19.7	20.8	20.3	21.2	21.4	19.7	20.8	20.3	21.2
EF	d/yr	365	185	185	185	365	365	185	185	185	365
ED	Years	1	5	8	5	17	1	5	8	5	17
IR	m^3/h	0.19	0.31	0.51	0.60	0.47	0.19	0.31	0.51	0.60	0.47
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
AT	Days	365	1825	2920	1825	6205	365	1825	2920	1825	6205
BW	Kg	7.2	15.4	35	61	62.4	7.2	15.4	35	61	62.4
ABSi	unitless	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***3.1E-03***	***1.1E-03***	***8.4E-04***	***5.5E-04***	***8.7E-04***	***1.2E-02***	***4.3E-03***	***3.3E-03***	***2.2E-03***	***3.4E-03***

Table 7.15: Total ADDS for Exposure to *o*-, *m*-, and *p*- Xylene Isomers in In-Home Air (mg/kg/d)

Setting	<1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
Rural Typical	**2.6E-03**	**1.7E-03**	**1.2E-03**	**7.8E-04**	**7.3E-04**
Rural High-End	**1.1E-02**	**7.3E-03**	**5.1E-03**	**3.3E-03**	**3.1E-03**
Urban Typical	**3.1E-03**	**2.1E-03**	**1.4E-03**	**9.3E-04**	**8.7E-04**
Urban High-End	**1.2E-02**	**8.1E-03**	**5.6E-03**	**3.6E-03**	**3.4E-03**

In-School Air

There is no systematic program in the United States requiring the collection of indoor air samples for VOC analyses in schools. In cases where data are collected, the data are usually collected by a private consultant in response to an indoor air quality complaint. Results from these studies are not usually published; rather, they are typically presented as a private report to the school administration. Thus, database searches of the scientific published literature did not identify a large number of studies of schools and indoor concentrations of xylenes that would be representative of schools nationwide.

EPA conducted 10 indoor air studies (n =39) of schools from 1995-1998 (EH&E, 2000). The purpose of these studies was to determine whether intervention actions could improve indoor air quality and other endpoints. For *o*-xylene, the in-school detection frequency was 85%, and the mean and high-end (95th percentile) concentrations were 2.3 µg/m^3 and 4.9 µg/m^3, respectively. For *m*- and *p*-xylenes, the in-school detection frequency was 97%, and the mean and high-end concentrations were 7.9 µg/m^3 and 19 µg/m^3, respectively. The summed *o*-, *m*-, and *p*-xylene mean and high-end concentrations were 9.6 µg/m^3 and 23.9 µg/m^3, respectively. These values are consistent with those estimated for in-home air concentrations described in Section 7.2.

This study did not include information regarding the setting of the schools (e.g., urban, suburban, or rural). The representativeness of the data is questionable for schools nationwide, because the schools that were studied were those for which complaints about the air quality had been made and the air samples were collected prior to implementation of any interventions in any given building. Additionally, no data regarding the outdoor xylenes concentrations were presented.

Two other studies of indoor air at public schools indicate that the in-school levels of xylenes are likely more comparable to concentrations found in the outside ambient air than concentrations typically found in homes. This was most evident in a nine-school study conducted in the Saugus Union School District in Santa Clarita, California (Spielman, 2000). In-school summed *o*-, *m*-, and *p*-xylene concentrations ranged from 2.7 to 8.1 µg/m^3 and had an average of 4.5 µg/m^3, and outdoor concentrations ranged from 2.7 to 8.22 µg/m^3 and had an average of 4.8 µg/m^3. The study was initiated under the EPA's Tools for Schools Program, which was developed to evaluate and ensure healthy indoor air quality for students and staff at U.S. schools. Indoor levels of total VOCs were measured concurrently with outdoor levels in each of the schools, and the researchers found that the indoor school concentrations were similar to the outdoor ambient concentrations. An additional study for a portable school building in the Saugus District (Spielman, 1999) indicated similar results, with in-school concentrations ranging from 1.4 to 5.1 µg/m^3 with an average of 2.39 µg/m^3, and outdoor concentrations ranging from 0.96 to 1.5 µg/m^3 with an average of 1.2 µg/m^3.

In addition to the Spielman studies, an investigation by Brown et al. (1994) provides summary indoor air concentration data from numerous U.S. and overseas sources. The total VOC concentrations measured in this study indicated that the concentrations in-school were on average 6 times lower than those measured in homes.

Because none of the published studies are necessarily representative of in-school air quality nationwide, exposures have been estimated using both the findings of the Spielman and the EPA studies. The typical exposure is represented by the urban outdoor

ambient concentration and the high-end exposure is represented by the high-end concentration from EPA's 10-school study (EH&E, 2000). These values are presented in Table 7.16.

Table 7.16: Typical and High-End In-School Xylenes Exposures

Exposure	*o*-, *m*- and *p*- Xylene Concentration (µg/m^3)
Typical	2.6
High-end	23.9

In-School Dose Calculation

Both typical and high-end total xylenes doses from in-school exposures were calculated using the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg/day)
C = concentration of total xylenes in school air (µg/m^3)
ED = exposure duration (years)
EF = exposure frequency (days/year)
ET = exposure time (hours/day)
IR = inhalation rate (m^3/hour)
ABSi = xylenes inhalation absorption factor; 0.6 (unitless)
CF = conversion factor (0.001 mg/µg)
BW = body weight (kg)
AT = averaging time (days)

The in-school total xylenes doses were calculated and are presented on Table 7.17.

Table 7.17: Summary of Age-Specific Doses from In-School Xylenes Exposure

Exposure Parameter	Units	1-5 year old	6-13 year old	14-18 year old	1-5 year old	6-13 year old	14-18 year old
		Typical			High-End		
C	$\mu g/m^3$	2.6	2.6	2.6	23.9	23.9	23.9
ET	h/d	2.9	6.0	6.5	2.9	6.0	6.5
EF	d/y	180	180	180	180	180	180
ED	years	5	8	5	5	8	5
IR	m^3/h	0.31	0.51	0.60	0.31	0.51	0.60
CF	mg/µg	0.001	0.001	0.001	0.001	0.001	0.001
AT	d	1825	2920	1825	1825	2920	1825
BW	kg	15.4	35	61	15.4	35	61
ABSi	unitless	0.6	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***4.5E-05***	***6.7E-05***	***4.9E-05***	***4.1E-04***	***6.2E-04***	***4.5E-04***

7.2.1.2 Food and Tap Water

The *o*-, *m*-, and *p*-xylene isomers occur in both food and water; therefore, exposure to xylenes can occur as a result of diet and tap water consumption. Xylenes in tap water also cause exposure by inhalation and dermal routes during showering. Xylenes exposures from these sources and routes are evaluated using LifeLine™ Version 2.0, a publicly available software program for the simulation of aggregate exposures to chemicals (The Lifeline Group, 2002). This software allows the determination of the total concurrent dose from the oral exposures, ingestion of food and tap water, from dermal exposure to xylenes in shower water, and inhalation exposures to xylenes that are released from shower water. Infant exposures to xylenes in human milk were determined separately as described in Section 7.2.1.3.

Exposure concentrations for food were derived from FDA's Total Diet Survey (FDA, 2003). In the Total Diet Survey, FDA personnel purchased foods from supermarkets or grocery stores four times per year from each of the four U.S. geographic regions. Each collection, referred to as a Market Basket, is a composite of similar foods purchased in three cities in each of the four regions (12 cities). Foods are prepared for consumption (i.e., as they will be eaten) and analyzed.

One Market Basket per quarter from the third quarter of 1995 through the fourth quarter of 2001 was available for analysis (totaling 24 applicable Market Baskets). The analytical results for *o*-xylene and *m/p*-xylene in the various foods range from non-detect up to 76 ppb and 291 ppb, respectively. The FDA only presents in summary form the number of times *o*- or *m/p*-xylene was detected in a food item (N) and the mean concentration for that food item for those times it was detected (detect mean) and the maximum and minimum measured values. Appendix A-3 provides details of the Market Basket analysis.

The sources of the xylenes residues are unclear, but are not likely to be a function of the commercial use of the chemical. Xylenes are not used in food processing and are not approved as a direct or indirect food additive (See Section 4.2). One source of exposure could be the concentration of xylenes in fatty foods by absorption from air. This may explain the levels reported in fatty materials such as cheese or butter. Second, detectable levels of xylenes have been found in the polystyrene packaging for products such as eggs (ATSDR, 1995). Finally, xylenes were consistently found in a variety of cooked meats. Because of its volatility and solubility and the ability of mammals to metabolize xylenes, the compound is not anticipated to bioaccumulate in animals. This suggests that the xylenes would not be present in uncontaminated raw meat but may have been formed during the cooking processes.

The total xylenes food concentrations were entered into the Lifeline program and doses were calculated for the various age ranges. A detailed description of the food consumption modeling process is provided in Appendix A-4.

Exposure concentrations for the determination of xylenes exposure from drinking water were obtained from EPA's National Drinking Water Contaminant Occurrence Database (NCOD) for water from public water supplies and the U.S. Geological Survey (USGS) National Water Quality Assessment (NAWQA) program for a representation of private well

users. The typical and high-end concentrations were characterized by mean and 95th percentile values as shown on Table 7.18 and 7.19 below.

Table 7.18: Public Water Supply Summary Statistics (January 1993 through November 2000)[a]

Statistic	Public Water Supply Concentration (N= 25,302) (µg/L)
Maximum Detect	172[b]
Mean	0.55
Median	0.25
95th Percentile (by rank)	0.25

[a]The mean, median, and 95th percentile values were calculated using half the detection limit for non-detects.
[b]A sample value of <10,000 µg/L was also identified.

Table 7.19: Summary Statistics for Total *o*-, *m*-, and *p*- Xylene Isomer Analyses from Ambient Groundwater and Surface Water (May 1993 through March 1996)[a]

Statistic	Groundwater (N = 1,620) (µg/L)	Surface Water (N = 20) (µg/L)	All (N = 1,640) (µg/L)
Maximum Detect	36	5.2	36
Mean	0.13	0.37	0.13
Median	0.10	0.10	0.10
95th Percentile (by rank)	0.10	0.45	0.10

[a]The mean, median, and 95th percentile values were calculated using half the detection limit for non-detects.

Details of the determination of exposure concentrations for drinking water and the input into the Lifeline model are contained in Appendix A-5. The results of the food and drinking water exposure analysis are presented on Tables 7.20 through 7.24 below and are based on model results for specific ages ('actual age') rather then the general age ranges. These actual ages are the median age of each of the age ranges. Both the typical dose and high-end doses are presented. The typical dose is estimated based on the median dose of a simulated population of 1,000 individuals. The high-end is based on the 95th percentile of the 1,000 simulated individuals. For food, the percentile results for *o*-xylene and *m/p*-xylene were summed to obtain the total xylene isomer dose.

For oral ingestion, the highest high-end total annual average dose that occurs to total *o*-, *m*-, and *p*- xylene isomers is 0.00037 mg/kg/day for children ages 1 to 5. The majority of this dose is from oral exposure from diet (0.00033 mg/kg/day). For inhalation exposures during showering, the highest high-end annual average dose is 0.00026 mg/kg/day for infants. The highest dermal dose from showering is 0.0000066 mg/kg/day for children ages 1 to 5.

The total xylenes doses from food presented in this exposure assessment can be compared with other estimates made recently. For instance, the UK Ministry of Agriculture, Fisheries and Food (MAFF; now known as the Department for Environment, Food and Rural Affairs) determined in a Total Diet Study that the average UK intake of xylenes varied from 0.9 to 4.6 µg/day for *o*-xylene and 1.2 to 4.9 µg/day for *m/p*-xylene (MAFF, 1995). The lower bound estimate of the average was determined by assigning a concentration of zero to food group samples where the result was below the detection limit. The high-end estimate of the average was determined by using a concentration of ½ the detection limit when the result was below the detection limit. The survey consisted of twenty food groups collected at 10 UK locations and included retail food products in amounts representative of UK consumption patterns. The method detection limit of 2 ppb was higher than the FDA's TDS detection limit of 1 ppb.

The median dietary intakes (excluding tap water) derived from the Lifeline dose estimates are presented in Table 7.25. For *m/p*-xylene, the average median intake among the age groups of 2.0 µg/day is within the range of the UK estimates of 1.2 to 4.9 µg/day. The average median intake from Lifeline for *o*-xylene of 0.24 µg/day is below the UK range for average intake of 0.9 to 4.6 µg/day. One reason for the difference may be the higher detection limit in the UK study.

Table 7.20: Oral Exposures to Total *o*-, *m*-, and *p*- Xylene Isomers from Tap Water

Age Range	Actual Age	Annual Average Daily Dose (mg/kg/day)	
		Median	95th
<1	1	2.94E-05	3.84E-05
1 to 5	3	2.59E-05	3.40E-05
6 to 13	9	1.15E-05	1.72E-05
14 to 18	16	7.01E-06	1.32E-05
Female 19 to 35	27	8.12E-06	1.46E-05

Table 7.21: Oral Exposures to Xylenes from Diet

Age Range	Actual Age	Annual Average Daily Dose (mg/kg/day)					
		o-xylene		m,p-xylene		o,m,p-xylene (sum)	
		Median	95th	Median	95th	Median	95th
<1	1	1.03E-05	1.81E-05	1.35E-04	2.82E-04	1.45E-04	3.00E-04
1 to 5	3	1.46E-05	2.26E-05	1.64E-04	3.03E-04	1.78E-04	3.25E-04
6 to 13	9	8.58E-06	1.46E-05	6.95E-05	1.20E-04	7.81E-05	1.34E-04
14 to 18	16	5.10E-06	1.05E-05	3.57E-05	7.18E-05	4.08E-05	8.22E-05
Female 19 to 35	27	5.04E-06	9.40E-06	3.25E-05	6.47E-05	3.76E-05	7.41E-05

Table 7.22: Total Oral Exposures to Total *o*-, *m*-, and *p*-Xylene Isomers from Tap Water and Diet

Age Range	Actual Age	Annual Average Daily Dose (mg/kg/day)	
		Median	95th
<1	1	1.8E-04	3.6E-04
1 to 5	3	2.1E-04	3.7E-04
6 to 13	9	9.0E-05	1.6E-04
14 to 18	16	4.8E-05	9.5E-05
Female 19 to 35	27	4.6E-05	8.8E-05

Table 7.23: Inhalation Exposure to Total Xylenes in Tap Water While Showering

Age Range	Actual Age	Annual Average Daily Dose (mg/kg/day)	
		Median	95th
<1	1	5.1E-05	2.6E-04
1 to 5	3	2.3E-05	9.1E-05
6 to 13	9	3.3E-06	1.3E-05
14 to 18	16	2.3E-06	1.0E-05
Female 19 to 35	27	1.7E-06	9.7E-06

Table 7.24: Dermal Exposure to Total Xylenes in Tap Water While Showering

Age Range	Actual Age	Annual Average Daily Dose (mg/kg/day)	
		Median	95th
<1	1	2.8E-06	6.1E-06
1 to 5	3	3.4E-06	6.6E-06
6 to 13	9	2.3E-06	4.6E-06
14 to 18	16	1.8E-06	3.6E-06
Female 19 to 35	27	1.8E-06	4.3E-06

Table 7.25: Oral Intake Based on Lifeline Dietary Doses

Age Range	Actual Age	Body Weight (kg)	Annual Average Intake (mg/day)					
			o-xylene		*m,p*-xylene		*o-,m-,p*-xylene (sum)	
			Median	95th	Median	95th	Median	95th
<1	1	7.2	0.07	0.13	1.0	2.0	1.0	2.2
1 to 5	3	15.4	0.22	0.35	2.5	4.7	2.7	5.0
6 to 13	9	35	0.30	0.51	2.4	4.2	2.7	4.7
14 to 18	16	61	0.31	0.64	2.2	4.4	2.5	5.0
Female 19 to 35	27	62.4	0.31	0.59	2.0	4.0	2.3	4.6
		Average	0.24	0.44	2.0	3.9	2.3	4.3

7.2.1.3 Human Milk

Xylenes have been detected in the milk of nursing mothers, although it has not been quantified. Therefore, transfer of xylenes to nursing infants from human breast milk is possible. Lactational transfer of xylenes to nursing infants whose mothers return to the workplace following birth was assessed by Fisher et al. (1997). Fisher et al. developed a physiologically based pharmacokinetic (PBPK) model for lactating women to estimate the amount of volatile organic chemical that a nursing infant ingests for a given nursing schedule and maternal occupational exposure. The results of this modeling predict that a nursing infant would ingest approximately 6.5 mg of xylenes per day if its mother were exposed at the ACGIH TLV of 100 ppm.

Because it is believed that the majority of occupational exposures are well below the TLV (See Section 7.2.3), and non-occupationally exposed mothers have much lower ambient air exposures, the estimation of xylenes concentrations in breast milk and lactational transfer of xylenes were recalculated. In doing so, the maternal exposure levels estimated in this assessment were used in conjunction with the conservative schedule described by Fisher et al. (1997). Accordingly, during the workday, the mother was assumed to be exposed at the respective workplace TWA concentrations for 8 hours and background concentrations of xylene for the remainder of the day. Eight nursing events were assumed to occur each day, lasting 12 minutes each, with 115 mL of milk ingested per nursing event, yielding a daily milk consumption of 0.92 L. Three individual nursing events were assumed to occur during working hours and the remainder five nursing events were assumed to occur after working hours. The nursing events that occurred during working hours all occurred after the xylene blood concentrations had reached steady-state with the workplace exposures and occurred at 2.1, 4.1 and 7.1 hours into the workday. The remaining five nursing events occurred at 2, 5, 10, 13 and 15 hours post-work-shift. If the working day were assumed to begin at 8:00 a.m., this would amount to nursing events occurring at 2:00 a.m., 5:00 a.m., 7:00 a.m., 10:00 a.m., 12:00 p.m., 3:00 p.m., 6:00 p.m., and 9:00 p.m.

All parameters for the PBPK model of xylenes were obtained from Fisher et al. (1997), except the metabolic rate constants for xylenes which were obtained from Tardif et al. (1995). The Fisher et al. (1997) model was reproduced successfully before using it to simulate the lactational transfer of xylenes according to the defined exposure scenarios. The human milk concentrations for both the non-occupationally exposed mother (urban, typical and high-end) and the occupationally exposed mother were calculated.

The parameters of the model and the simulations of lactational transfer are included in Appendix C. The results of the model are summarized in Table 7.26 below.

Table 7.26
Summary of Mass of Total Xylenes Ingested

Scenario	Mass Ingested (mg/day)
Urban, typical	0.00013
Urban, high-end	0.000513
Occupational, typical	0.0027
Occupational, high-end	0.1896

Average daily doses of total xylenes in terms of mass per body weight for an infant were calculated and are presented on Table 7.27 below.

Table 7.27
Average Daily Doses of Total Xylenes to Nursing Infant of Occupationally Exposed Mothers

Scenario	Average Daily Dose (mg/kg/day)
Urban, typical	1.8E-05
Urban, high-end	7.1E-05
Occupational, typical	3.8E-04
Occupational, high-end	2.6E-02

7.2.1.4 Summary of Ambient Background Xylenes Exposures

Of the ambient background sources described in Section 7.2.1, inhalation of indoor air is the predominant pathway of exposure for children and prospective parents (See Figure 7.2). It should be noted that for nursing infants of occupationally exposed mothers, the contribution of xylenes exposure from human milk ingestion, results in a higher percentage of the background dose (i.e.15%) (See Figure 7.3). Section 7.5 provides further discussion of estimated total xylenes doses from exposure to various sources.

Figure 7.2 Predominant Pathways of Xylene Exposure for Children and Prospective Parents from Ambient Sources

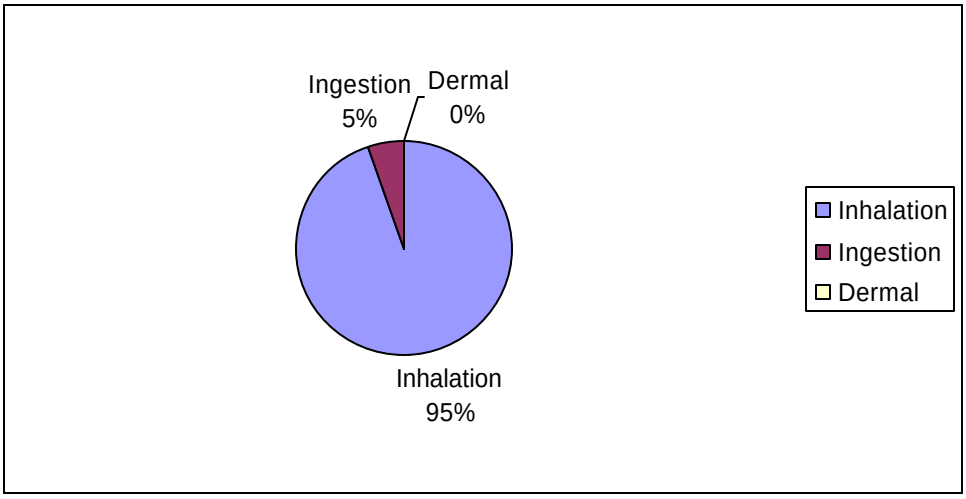
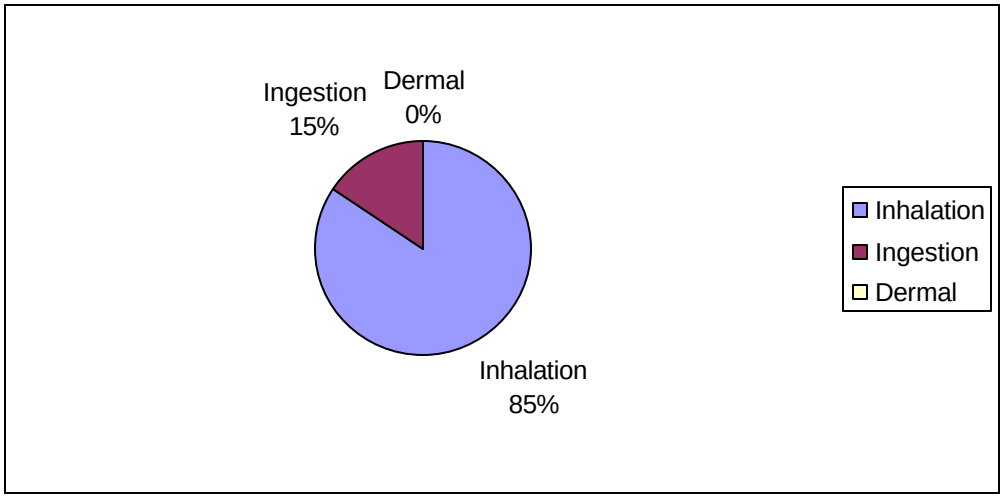


Figure 7.3 Predominant Pathways of Xylene Exposure for Nursing Infants of Occupationally Exposed Mothers*



* Typical occupational exposure levels (See Section 7.2.3)

7.2.2 Source Specific Exposures

In addition to the ambient sources of xylenes exposure, certain subpopulations of children and prospective mothers may be exposed to xylenes in specific microenvironments related to automotive transportation, use of xylene-containing consumer products, or living in a home with tobacco smokers. Exposures to each of these specific sources have been quantified and are discussed below.

7.2.2.1 Gasoline Sources of Exposure

Xylenes are common constituents in gasoline. Exact levels in gasoline will vary, but previous assessments indicate that the typical range is 5-10% by weight (See Section 3). While xylenes in gasoline contribute to the overall concentration of xylenes in the ambient air, exposures to gasoline may also occur while riding in a vehicle and during refueling of a vehicle. As such, xylenes exposures from these specific activities have been assessed. It is recognized that there are other sources of gasoline exposure beyond those associated with in-vehicle travel and refueling (e.g., use of small engine equipment such as lawn mowers, chain saws, leaf blowers, edge trimmers, snow blowers, ATVs, and snowmobiles). However, monitoring data for xylenes are not available for characterizing these exposures. Additionally, while data for small engine emissions are available, adequate models are not available for predicting personal exposures from these sources. As such, xylenes exposures from small engine equipment have not been quantified.

In-Vehicle Xylenes Exposure

Vehicle emissions of xylenes contribute to xylenes concentrations measured inside vehicles during driving. In-vehicle exposure to VOCs and xylenes are due to the penetration of xylenes in roadway air (e.g., tailpipe emissions) and from engine running loss into the vehicle cabin while driving (Fedoruk and Kerger, 2003; Batterman et al., 2002; Weisel et al., 1992). In-vehicle VOC exposure levels can be affected by various conditions including mode of transportation, driving route, time of day (rush vs. non-rush), type of fuel distributions system, season of the year, meteorological conditions, and vehicle ventilation conditions (Chan et al., 1991a,b; Dor et al., 1995; Lawryk and Weisel, 1996; Batterman et al., 2002; Fedoruk and Kerger, 2003). In many cases, the findings of the various studies can be conflicting, and in-vehicle VOC concentrations can vary considerably with sampling day and time (Lawryk et al.,1995; Batterman et al., 2002).

Of all modes of transportation involving potential non-occupational exposure to gasoline constituents (e.g., automobile, bus, subway, walking, biking), in-vehicle exposures while driving in an automobile are the highest (Chan et al., 1991a). Although many children commute in school buses, studies show that, because of variables including vehicle height, location of engine, ventilation conditions, and fuel type, exposure in a car is greater (Chan et al., 1991a; Jo and Choi, 1996; Jo and Park, 1999a,b; Jo and Yu, 2000) or similar (Batterman et al., 2002) as that of a bus. The transportation route and traffic density (e.g., urban or rural, following closely or far behind a lead car, rush or non-rush) have been determined to be the most important in-vehicle exposure variables (Batterman et al., 2002). It is expected that in-vehicle exposures in suburban areas, rural areas, and in general, areas with lower automobile densities will have lower in-vehicle concentrations.

Numerous studies have been conducted in the U.S., which have evaluated in-vehicle xylenes exposures (Batterman et al., 2002; CARB, 1998; Chan et al., 1991a,b; Chang et al., 2000; Fedoruk and Kerger, 2003; Lawryk et al., 1995; SCAQMD et al., 1989; Weisel et al., 1992). Due to the emission reduction initiatives discussed in Section 5, only the most recent U.S. data were included in this analysis. Although the CARB (1998) study is relatively recent, it was excluded because the study design required evaluation of highly unusual and unrealistic conditions (i.e., travel behind a high emitting vehicle for 2 hours). It is unlikely that a driver would closely tail a high-polluting vehicle for the entirety of his or her driving time. It is more likely that the driver would move from behind such a vehicle, either intentionally or as the result of the general movement of vehicles in traffic, and therefore would be behind a variety of vehicles while driving during any given time period. The studies used to derive representative exposure concentrations are summarized in Table 7.28 below. Each of the automobile studies evaluated specifically excluded smokers and/or the influence of smoking on VOC in-vehicle concentrations.

Table 7.28: Summary of Key In-Vehicle Studies

Study	Type of Vehicle Used	Comments
Chang et al., 2000	Minivan, occasionally a bus	Baltimore, MD, Summer 1998 - Winter 1999. This study was designed to simulate activities performed by older adults. Samples were obtained in 1-hour increments. The data used in this study was not published with the paper, but obtained separately. Reformulated gasoline (RFG) was in regular use in Baltimore at the time of the study.
Batterman et al., 2002	Car	Detroit, MI, Fall 1999. This study was conducted during 2- 3 hour urban rush hour commutes. Information on the car used was not provided. Use of RFG was not required in Detroit.
Fedoruk and Kerger, 2003	Car	Los Angeles, CA, 1997. This study was conducted during urban commutes. 90 minute TWAs were obtained. A 1993 Toyota, in good condition, was used. The time of day that measurements were obtained was not reported. RFG was in regular use in Baltimore at the time of the study.

In-vehicle exposure scenario concentrations were derived from means presented in the three studies above and are representative of a person of any age. Table 7.29 presents the means from the various studies and an average of the means for all of the studies.

Table 7.29: Average of Mean In-Vehicle Concentrations

		Mean In-Vehicle Concentration (µg/m^3)		
Study	Description	*m*,*p*-xylene	*o*-xylene	total *o*-, *m*- and *p*-xylene
Chang et al. (2000)	Urban	18.9[a]	7.4[b]	26.3
Batterman et al. (2002)	Urban	6.8	2.2	9.0
Fedoruk and Kerger (2003)	LA Freeway	2.4	11.8	14.2
Average of study means:		***4.5***	***5.9***	***13.5***

[a]Mean of *m*-/*p*-xylene summer and winter averages of 4.0 and 4.7 µg/m^3, respectively.
[b]Mean of *o*-xylene summer and winter averages of 5.6 and 1.8 µg/m^3,respectively.

Due to various driving conditions under which a person may be exposed to in-vehicle concentrations of xylenes, mean concentrations best portray long-term exposure concentrations. An average total *o*-, *m*-, and *p*-xylene isomer concentration was derived using the means of each of the three key studies above. This average is used as the

typical representative in-vehicle exposure concentration and is considered to be an average of a high-end scenario, as it is representative of urban exposures where traffic densities are highest.

As noted in Section 5, VOC emissions from motor vehicles, including xylenes, are on the decline as a result of the 1990 Clean Air Act Amendments, which called for lower tailpipe standards, more stringent emissions testing, expanded inspection and maintenance programs, new vehicle technologies and clean fuels programs. Therefore, as these programs are matured, the exposure estimates described above are likely to overestimate in-vehicle exposures in the future.

In-Vehicle Dose Calculations

Age-specific in-vehicle xylenes exposures were quantified according to the following equation:

$$ADD = \frac{C \times ED \times EF \times ET \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD	=	average daily dose (mg/kg/day)
C	=	concentration of total xylenes in vehicle air (µg/m^3)
ED	=	exposure duration (years)
EF	=	exposure frequency (days/year)
ET	=	exposure time (hours/day)
IR	=	inhalation rate (m^3/hour)
ABSi	=	xylenes inhalation absorption factor; 0.6 (unitless)
CF	=	conversion factor (0.001 mg/µg)
BW	=	body weight (kg)
AT	=	averaging time (days)

The average of the mean study concentrations presented in Table 7.29 was utilized with exposure factors presented in Section 6 to quantify ambient exposures. The in-vehicle ADDs are presented below in Table 7.30.

Table 7.30: Summary of ADDs From In-Vehicle Total Xylenes Exposure

Exposure Parameter	Units	< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
		Typical				
C	µg/m^3	13.5	13.5	13.5	13.5	13.5
ET	h/d	1.2	1.2	1.0	1.4	1.3
EF	d/y	365	365	365	365	365
ED	years	1	5	8	5	17
IR	m^3/h	0.19	0.31	0.51	0.6	0.47
CF	mg/µg	0.001	0.001	0.001	0.001	0.001
AT	d	365	1825	2920	1825	6205
BW	kg	7.2	15.4	35	61	62.4
ABSi	unitless	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***2.6E-04***	***2.0E-04***	***1.2E-04***	***1.1E-04***	***7.9E-05***

Refueling Exposures

A variety of researchers have reported that self-serve automobile refueling generates the greatest and most common source of gasoline exposure to the general population (Backer et al., 1997; Pope and Rall, 1995; Wixtrom & Brown, 1992). As such, xylenes exposures while refueling an automobile have been assessed. Exposure occurs primarily via inhalation of vapors during refueling. There are many potential sources of exposure to gasoline vapors at service stations, including breathing and working losses from underground storage tanks, displacement air losses from filler pipes during refueling, fill spillage during refueling, and evaporative and exhaust emissions from motor vehicles in the station. The displacement of fuel vapors from the gas tank while refueling, however, generates the majority of exposure to gasoline vapors (Backer et al., 1997; Guldberg, 1992).

The Northeast States for Coordinated Air Use Management (NESCAUM) reviewed nine pre-1989 refueling studies and determined mean and high-end exposure concentrations for xylenes and other VOCs (NESCAUM, 1989). Data were reviewed and weighted, yielding mean and high-end total *o*-, *m*-, and *p*-xylene exposure estimates of 0.87 and 4.8 mg/m^3. Two more recent studies, API (1993) and Backer et al. (1997), however, were selected as having the best representative data for this exposure assessment. This is because data collected before 1990 are not reflective of exposures associated with current gasoline formulations, which have reduced VOC emissions and the implementation of vapor recovery systems at the pump and on the cars.

The API study was conducted in 3 cities across the U.S and the Backer et al. study was conducted in Fairbanks, AK. These key studies focus on the exposure of a self-service customer while refueling; occupational exposure concentrations were excluded. The xylenes content of gasoline in each study is similar (3.9 to 9%), and the presence or absence of VRS controls at the pump was also documented in the studies. The selected data are representative of potential refueling exposures in different U.S. regions, using

different blends, grades, and types of gasoline, and using a variety of controls at the pump. A summary of the key studies is provided in Table 7.31.

Table 7.31: Summary of Key Refueling Studies

Study	Date/location data collected	Controls at the Pump	Type of Gasoline
API, 1993	October - November Cincinnati, OH Phoenix, AZ Los Angeles, CA	Only LA had Stage II VRSs and extensively used pump safety latches	Three grades of gasoline were evaluated: regular unleaded, mid-grade
Backer, et al., 1997	January - March, 1995 Fairbanks, AK	No Stage II VRS	Regular gasoline and E10 gasoline

An individual will refuel under a variety of conditions, which are collectively represented by the two key studies. For example, they will spend varied amounts of time, under varied meteorological conditions, at different gasoline stations, filling their tanks.

Personal breathing zone exposure measurements have been used as representative exposure point concentrations. Thus, although displacement of vapors from the gas tank is the dominant exposure source, the measurements in the studies will capture the contributions from any other sources of xylenes that are present at the gas stations. Exposure data from the key studies are presented in Table 7.32.

Table 7.32: Total *o*-, *m*-, and *p*-Xylene Air Concentrations During Refueling (mg/m^3)

Study	Mean	Maximum
API, 1993	0.55	1.5
	0.75	2.2
	0.54	1.2
Backer, et. al., 1997	0.81	1.8
	0.53	2.9
Average	**0.64**	**1.9**

Averaging the mean exposure concentrations in each of the key studies resulted in a mean exposure concentration of 0.64 mg/m^3; this value is used to describe a typical exposure. Obtaining an average of the maximum concentrations from each study resulted in a maximum exposure concentration of 1.9 mg/m^3; this value is used to describe a high-end exposure.

A comparison of the NESCAUM mean of 0.87 mg/m^3 and high-end estimate of 4.8 mg/m^3 to the exposure concentrations shown on Table 7.32 demonstrates that the refueling exposure concentrations of xylenes have decreased by approximately 30 to 60% over the years. This decrease can be attributed to the changes in gasoline formulations, pump controls, and on-board emission controls of newer vehicles. Thus, xylenes exposure concentrations during refueling are likely lower than those represented in the key studies

due to RFG phase-in across the country and fleet vehicle changeovers since the mid-1990s. For these reasons, it is expected that exposures during refueling will continue to decline in the future.

Refueling Dose Calculations

Age-specific dose calculations were made for a typical and high-end exposed individual while refueling. Doses were estimated for a woman of child-bearing age and a teenager 16 to 18 years old. It was assumed for the purposes of this assessment that children younger than 16 would not pump gasoline on a regular basis. The exposure estimates are limited to refueling only (i.e., the time spent pumping gasoline into the vehicle); the total amount of time spent at the service station is not evaluated. It is also assumed that the refueler remains at the pump the entire time that he or she is refueling.

Exposure was quantified according to the following equation:

$$ADD = \frac{C \times ED \times EF \times IR \times ABSi \times CF}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg/day)
C = concentration of total xylenes in refueling air (mg/m^3)
ED = exposure duration (years)
EF = exposure frequency (days/year)
CF = conversion factor (0.001 mg/µg)
ABSi = xylenes inhalation absorption factor; 0.6 (unitless)
IR = inhalation rate (m^3/day)
BW = body weight (kg)
AT = averaging time (days)

Age-specific refueling ADDs are presented in Table 7.33 below.

Table 7.33: Summary of ADDs from Refueling *o*-, *m*-, and *p*-Xylene Exposure

Exposure Parameter	Units	16-18 year old	Female 19-35 year old	16-18 year old	Female 19-35 year old
		Typical		High-end	
C	mg/m^3	0.64	0.64	1.9	1.9
ET	h/d	0.027	0.027	0.062	0.062
EF	d/y	70	70	104	104
ED	years	3	17	3	17
IR	M^3/h	0.5	0.5	0.5	0.5
AT	D	1095	6205	1095	6205
BW	Kg	62.9	62.4	62.9	62.4
ABSi	unitless	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***1.6E-05***	***1.6E-05***	***1.6E-04***	***1.6E-04***

It should be noted that in-vehicle-while-refueling xylenes concentrations appear to be lower than ambient concentrations at gasoline service stations and in-vehicle concentrations while commuting (Vayghani and Weisel, 1999; API, 1993). Thus, a child who remains in the car while it is being refueled was not evaluated, as it was determined that the xylenes exposure concentrations were much lower (i.e., about 1 order of magnitude) than measured refueling exposures.

7.2.2.2 Consumer Products

A number of specialty consumer products contain at least a trace amount of xylene isomers. As part of an EPA study, 1,159 consumer products from 65 product categories were analyzed for VOC content by GC/MS with a detection limit of 0.1% by weight (Sack et al., 1992). The Sack et al. study was reviewed to determine which product categories had products that contained greater than 0.1% by weight *o*-, *m*-, and/or *p*-xylene isomers. Appendix A-6 contains tables which summarize the products that contain xylenes. Based on this review, 13 product categories were identified for which at least one product contained one or more of the xylene isomers.

Because the Sack et al. (1992) study is somewhat dated (i.e., from 1987), steps were taken to verify the xylenes composition information by obtaining current material safety data sheets (MSDS) for the various products. From each of the Sack et al. product categories, five products were randomly selected and the total xylene isomer content verified using the product MSDSs. This analysis is presented in Appendix A-7. The sources of consumer product MSDS information included the product manufacturer when possible, as well as:

- Vermont Safety Information Resources, Inc. – 180,000 MSDS archived at http://www.hazard.com
- Cornell University Planning Design and Construction – 250,000 MSDS archived at http://msds.pdc.cornell.edu/msdssrch.asp; and
- Seton Compliance Resource Center – 350,000 MSDS archived at http://www.setonresourcecenter.com/MSDS/index.htm.

The EPA's Source Ranking Database (SRD) (EPA, 2000) was also reviewed to determine products that contain xylene isomers. The SRD is a compilation of product composition information from a variety of sources. While the SRD has the same limitation that Sack et al. does in that the information is dated, it contains information from a variety of sources and is not limited to just those products that may have contained chlorinated VOCs. The SRD was developed to rank consumer products for screening a large number of indoor air pollution sources and prioritizing them for future evaluation. Because the Sack et al. study is one of the major sources of data in the SRD, much of the same information from Sack et al. is included in the SRD. When comparing the two consumer product data sources, it was found that the same product categories that contained xylene isomers were identified in Sack et al. and SRD and that the percent xylenes composition was similar with the exception of commercial mixed xylenes. Mixed xylenes as a neat solvent were identified in the SRD as miscellaneous use aromatics. Mixed xylenes (70-95% *o*-, *m*-, and *p*- xylene isomers and 5-25% ethylbenzene) is sold in gallon-sized or smaller containers at various hardware/home improvement stores for use as a paint thinner or degreaser, and therefore it was also included in the exposure assessment.

As presented in Appendix A-7, it can be seen that a variety of consumer products contain xylene isomers; however, the majority of those products contain the isomers at less than 1% by weight and therefore are unlikely to be important sources of exposure. Thus, this assessment has focused on those consumer products that have the greatest potential for resulting in significant exposures to children. Those consumer products, which contain xylene isomers greater than 1% by weight are listed on Table 7.34. Each of these products was then considered in the context of how they would be used and the likelihood of children being exposed during their use.

Table 7.34: Typical and High-End Xylenes Content of Consumer Products

Usage Scenario	Product Category[a]	Typical Content (%)[b]	High-End Content (%)[c]
Surface preparation / Metal parts degreasing	Commercial mixed xylene	81	95
Spray Painting	Spray primer	11	20
	Spray paint	9.5	16
Automobile maintenance	Carburetor and choke cleaner	29	60
	Ignition wire dryer	6.1	50

[a]Based on MSDS records for product categories identified by Sack et al and Source Ranking Database

[b]Average of four lowest weight contents listed on five representative MSDS records.
Where the MSDS provided a range, the highest weight content was used.

[c]Maximim weight content listed on five representative MSDS records.

It is believed that all of the products listed on Table 7.34 could be used in the home. However, the number of homes where some of these products (e.g., automotive products such as carburetor and choke cleaner and ignition wire dryer) are used is small and the uses would be restricted to areas of the home (garages) and times when children are less likely to be present.

Evidence of this can be seen in an EPA sponsored consumer product survey (WESTAT, 1987). This survey found that the fraction of the surveyed individuals ever using

carburetor cleaners or ignition wire dryers were 4.8 and 22%, respectively. Of those that have used these products, the majority (86 to 88%) reported that the products were used outdoors. Less than 1.5% of the product users used these products in the home, with the remainder reporting that they were used in a garage.

For these reasons, the paint-related products and commercial mixed xylenes were selected for a quantitative exposure assessment. Based on the likelihood of use by or in the presence of children in the home, the paint products and commercial mixed xylenes were evaluated for exposure in two scenarios. These scenarios include:

- residential metal parts degreasing scenario (mixed xylene solvent); and
- residential spray painting scenario (spray primer and spray paint).

Generic Scenario Assumptions

In the consumer scenarios the residence was assumed to be divided into two microenvironments: 1) room of use and 2) other rooms in house. Current consumer product exposure models are not sufficiently sophisticated to accurately characterize the difference between product users and non-users in the same room (i.e., near field exposures are difficult to accurately predict). Thus, in this situation both the user and non-user would be assumed to have the same exposures. In order to best approximate exposure to the product user, a small room size (20 m^3) was selected in accordance with default values for the various E-Fast scenarios. Typical and high-end exposure estimates were made based on the amount of product used. In addition, typical and high-end short-term one-hour average exposure estimates were calculated for both scenarios.

One-hour, eight-hour, and 24-hour time-weighted average exposure concentrations were calculated using the EPA Multi-Chamber Concentration and Exposure Model Version 1.2 (MCCEM) and the conceptual framework (i.e., base exposure scenario including activity pattern, emissions models, and interzonal airflow equation) of the EPA Exposure, Fate Assessment Screening Tool Version 1.1 (EFAST) Consumer Exposure Module (CEM). Exposure concentrations were calculated using MCCEM rather than EFAST to take advantage of the more detailed output of MCCEM (e.g., concentration versus time) and the ability to save input files for future review. MCCEM and EFAST use the same computational engine for indoor air quality modeling.

For products formulated with xylenes, manufacturers recommend that if using the product indoors, it should be done in a well-ventilated area. Excerpts from a typical xylenes-containing consumer product are provided in Table 7.35.

Table 7.35: Excerpts from Typical Consumer Product Label Instructions and Warnings

Label Section	Text	Example Source
Directions	"Use in a well ventilated area."	All Pro Cover Shield Stain Killer Instructions dated March 2002. (http://www.allprocorp.com/techbuls/SeymourTB/7000TB11069CoverShield.cfm accessed 8/12/2003.)
Caution	"**Use only with adequate ventilation**. Do not breathe dust, vapors or spray mist. Open windows and doors or use other means to ensure fresh air entry during application and drying. If you experience eye watering, headaches or dizziness, increase fresh air or wear respiratory equipment protection (NIOSH/MSHA approved) or leave the area. Close container after each use."	

Recently, the EPA conducted a residential ventilation study of carbon monoxide in which whole house air exchange rates were determined under various ventilation conditions of windows and doors open (Johnson et al., 1998, 1999). This study indicated that median air exchange rate for a house with at least one window open was 1.34 air changes per hour (ACH) and a high-end air exchange rate was 3.0. Higher air exchange rates are achievable by using a window fan or whole house fan. The Air King™ brand window box fan has a reported airflow ranging from 2100 cfm at low speed to 4300 cfm at high speed. Assuming the fan is 50% efficient (to account for losses due to presence of a screen or an incomplete seal at the window), whole house air exchange rates of 5 to 10 air changes per hour are achievable in a 369 m^3 home. The importance of using exhaust fans to achieve air exchange rates in the range of 10 to 15 air changes per hour during large solvent-based projects is discussed as part of a recent exposure modeling study of home paint-stripper users (Riley et al., 2000).

When products containing xylenes are used in the home in accordance with consumer product labeling, it is expected that the user will open windows or doors for small to moderate sized projects. For large projects, it can be assumed that user will conduct the activity outside or will introduce additional fresh air into the home by using a window fan or whole house fan. For a typical usage amount, the windows are assumed to be open for a 24-hour period to induce cross-ventilation as specified on product labels found on products containing xylenes. Therefore, an air exchange rate of 1.3 ACH was used during the modeling of the typical scenario. For the high-end usage amount, the user is assumed to operate a window fan at the highest speed for the duration of the product use and for one-half hour after use. It is also assumed that the user leaves the windows open for the remainder of the 24-hour period after use began. Therefore, an air exchange rate of 5 ACH was applied during the modeling of the high-end scenario.

It should be noted that the modeled air concentration is relatively linear with the whole house air exchange rates used in this assessment. If one were to assume that no additional ventilation measures were taken when using the product, the default air exchange rate would be 0.45 ACH. This value is approximately 3 times less than the air exchange rate used for the typical scenario, and approximately 11 times less than the air exchange rate used for the high-end scenarios. Thus, the under a "no additional ventilation" scenario, the predicted air concentrations would be 3 and 11 times higher for the typical and high-end scenarios modeled in this assessment, respectively. It should be

noted that the “no additional ventilation” scenario was not considered in this assessment as it is contrary to the manufacturer instructions for product use (See Table 7.35).

Modeled indoor air concentrations available in one-minute increments were averaged to calculate short-term one-hour average concentrations. The short-term one-hour average concentration is the maximum one-hour average that occurs during the scenario or individual product use.

Residential Metal Parts Degreasing Scenario

There are no published data on xylene isomer exposures from the use of solvents for metal parts degreasing in the home. Paint thinners or pure solvents are commonly used as metal parts degreasers in hobbies such as firearms restoration or classic automobile restoration. While it is expected that common solvents such as mineral spirits or acetone are most frequently used in metal parts degreasing, from time to time a hobbyist may choose to use mixed xylenes (consisting of 81-95% *o*-, *m*-, and *p*-xylene isomers) which is commercially available in hardware stores in quart or half-gallon sized containers. In this scenario, the typical and high-end uses are distinguished by the xylene isomer weight content in mixed xylenes, usage time, and usage amount.

EPA sponsored survey data (Westat, 1987) indicate that among the U.S. population ages 18 years and older, approximately 28% of the population have used a solvent type cleaning fluid or degreaser in their lifetime. Of those that have used a degreaser, 59% used the product in the home. Survey data also indicate that users generally read the directions (68%) and open a door or window during indoor use (57%). With respect to a conservative estimate of children's exposures, the population of interest is those limited number of households where mixed xylenes is used indoors.

Because degreasers are usually applied to a surface using a cloth, the EFAST product applied to surface scenario was selected as the baseline scenario. The parameter values used in the models were taken from the Exposure Factors Handbook (EPA, 1997a), the Toxicological Profile for Xylenes (ATSDR, 1995), and professional judgment. These values are presented on Tables A-8-1 and A-8-2 in Appendix A-8. Likewise, the activity patterns for users and observers in the room of use and non-users in the other room, which are based on the default EFAST activity pattern, are presented in Table A-8-3 in Appendix A-8.

The Westat (1987) survey of solvent product usage provides a distribution of the volume of solvent used per degreasing event for the United States population (Table D-18). Detailed information regarding specific uses of mixed xylenes were not found in the peer-reviewed or gray literature. However, websites for do-it-yourself/hobbyists indicate that mixed xylenes may be used as a degreaser for automobile repair, firearm restoration, metal surface preparation, etc. However, the usage data reported by Westat is likely much greater than that which would be used for because it is representative of a wide variety of products including Easy-Off™ oven cleaner, Fuller Brush™ cleaners, Woolite™ and Dawn™, none of which contain xylenes. In addition, despite the likelihood that larger projects involving volatile solvents would be performed outdoors, the Westat usage survey also does not provide separate usage amount distributions for indoor and outdoor uses. As such professional judgment was used in combination with a ‘bench scale’ simulation

using water to estimate the amount of degreaser that might be used for a typical indoor project (i.e., small object with a surface area of 1 ft^2) and a high-end usage amount for a larger project (i.e., object with a surface area 10 ft^2). The estimated usage amounts are provided in Table 7.36.

Table 7.36: Degreaser Usage Amount

Usage	ounces/use	cups/use	grams /use
Typical	0.4	0.05	10
High-End	4	0.5	102

For this scenario, a typical use is characterized by typical usage amounts and usage times along with the typical weight content provided in Table 7.34. The high-end use is characterized by high-end usage amount and time, along with the high-end weight content given in Table 7.34.

The model was run to estimate exposure concentrations for users and non-users of a degreaser according to the usage distributions provided above. Only inhalation exposures have been assessed in this scenario. While there could be dermal contact during use, there is likely to be significant volatilization from the skin surface, as it is not expected to be submersed in the product. The predicted total *o*-, *m*-, and *p*-xylene isomer air concentrations are shown on Table 7.37. The typical use corresponds to the use of a moderate amount of a product containing a typical level of *o*-, *m*-, and *p*-xylene isomers as a metal parts degreaser under well-ventilated conditions (e.g., open windows). The high-end use represents an above average usage amount of degreaser containing a high-end weight content of xylenes under well-ventilated conditions (e.g., with an exhaust fan at low speed).

Table 7.37: Predicted Total *o*-, *m*-, and *p*-Xylene Isomer Concentrations for Residential Metal Parts Degreasing Scenario

Usage	TWA (1-Hour) Exposure Concentration (ppm)		TWA (8-Hour) Exposure Concentration (ppm)		TWA (24 Hour) Exposure Concentration (ppm)	
	Child Non-User	Child and Adult User	Child Non-User	Child and Adult User	Child Non-User	Child and Adult User
Typical usage amount with open windows (ACH =1.34)[a]	2.3	9.5	0.42	1.4	0.14	0.45
High-end usage amount with exhaust fan (ACH = 5)[b]	8.9	30	1.5	4.3	0.49	1.4

[a]ACH = air changes per hour.
[b]Exhaust fan is assumed to be turned off one-half hour after end of product use and the windows are assumed to be left open, resulting in a post-usage air exchange rate of 1.34 hr^{-1}.

Residential Spray Painting Scenario

There are no published data on xylenes exposures from the use of aerosol painting products or paint removers in the home. Spray paints are commonly used to coat metal surfaces, such as lawn furniture or automobile parts. A typical project where metal surfaces are being repainted consists of two steps:

- surface priming with an aerosol spray can product; and
- surface painting with an aerosol spray can product.

The Westat (1987) survey data indicate that among the U.S. population ages 18 years and older, approximately 35.4% of the population have used spray paint in their lifetime. Of those that have used spray paint, only 17.8% painted indoors the last time they used spray paint. Survey data also indicate that spray paint users generally read the directions (73.2%) and open a door or window during indoor spray paint use (62.9%). With respect to a conservative estimate of children's exposures, the population of interest is those limited number of households where spray painting is performed indoors.

The EFAST product sprayed on a surface baseline scenario was used for spray primer and spray paint. The parameter values used in the models were taken from the Exposure Factors Handbook (EPA, 1997a), the Toxicological Profile for Xylenes (ATSDR, 1995a), and professional judgment. These values are presented on Tables A-9-1 and A-9-2 of Appendix A-9. Likewise, the activity patterns for users and observers in the room of use and non-users in the other room, which are based on the default EFAST activity patterns, are presented in Table A-9-3 of Appendix A-9. The Westat (1987) survey of solvent product usage provides a distribution of the volume of spray paint used per painting event for the United States population (Table Q-18).

The usage amount of both products used in this scenario (spray primer and spray paint) is correlated because each of these three products is used on the same surface area. It was assumed that equal amounts of spray primer and spray paint were used based on an assumption of one coat of primer and paint, and similar wet film thickness for each product.

Despite the likelihood that larger projects involving spray paints would be performed outdoors, the Westat usage survey does not provide separate usage amount distributions for indoor and outdoor uses. Therefore, it was assumed the 90th percentile of the Westat distribution (slightly less than 2 cans of spray paint) represents the high-end usage quantity for spray paint. Table 7.40 summarizes the usage amounts used in the assessment.

Table 7.40: Spray Paint Scenario Usage Amount

Product	Usage	Percentile	ounces/ use [a]	ml/ use	cans/ use [b]	grams product/use [c]
Spray Primer	Typical	50th	8	237	0.6	204
	High-End	90th	26	769	1.9	661
Spray Paint	Typical	50th	8	237	0.6	187
	High-End	90th	26	769	1.8	607

[a]The volume of spray paint and spray primer is based on the distribution for spray paint from Westat (1987) Table Q-18.
[b]Cans of spray paint or spray primer calculated using standard can size in Table 14.14
[c]grams/use= (ounces/use) * (29.57 ml/ounce) * (density g/ml)

The model was run to estimate exposure concentrations for users and non-users of the paint products according to the usage distributions provided above. Only inhalation exposures have been assessed in this scenario. While there could be dermal contact with these products during use, there is likely to be significant volatilization from the skin surface as it is not expected to be submersed in the product. The predicted total *o*-, *m*-, and *p*- xylene isomer air concentrations are shown on Table 7.41. The typical use corresponds to the use of moderate amounts of spray primer and spray paint containing typical amounts of xylenes under well-ventilated conditions (e.g., open windows). The high-end use represents an above average usage amount and weight content of xylenes under well-ventilated conditions (e.g., with an exhaust fan at low speed).

Table 7.41: Predicted Total *o*-, *m*-, and *p*-Xylene Isomer Concentrations for Residential Spray Paint Scenario

Usage	TWA (1-Hour) Exposure Concentration (ppm)		TWA (8-Hour) Exposure Concentration (ppm)		TWA (24-Hour) Exposure Concentration (ppm)	
	Child Non-User	Child and Adult User	Child Non-User	Child and Adult User	Child Non-User	Child and Adult User
Spray Primer (1-hour usage time)						
Typical usage amount with open windows (ACH =1.34)[a]	6.2	26	1.2	3.8	0.39	1.3
High-end usage amount with exhaust fan (ACH = 5)[b]	12	43	1.8	6.1	0.61	2.1
Spray Paint (1-hour usage time)						
Typical usage amount with open windows (ACH =1.34)[a]	4.9	21	0.91	3.0	0.31	0.99
High-end usage amount with exhaust fan (ACH = 5)[b]	8.9	30	1.5	4.2	0.49	1.4
Cumulative Scenario (2-hour total usage time)						
Typical usage amount with open windows (ACH =1.34)[a]	7.2	27	2.1	6.7	0.69	2.2
High-end usage amount with exhaust fan (ACH = 5)[b]	13	46	3.3	10	1.1	3.5

[a]ACH = air changes per hour.
[b]Exhaust fan is assumed to be turned off one-half hour after end of last product use and the windows are assumed to be left open, resulting in a post-usage air exchange rate of 1.34 hr^{-1}.

7.2.2.3 Tobacco Smoke

While not a chain-of-commerce source, xylenes are present in both the mainstream tobacco smoke inhaled by the smoker directly from the cigarette and sidestream smoke released to the environment from the smoldering end of a cigarette. Because cigarette smoke is a significant source of exposure for smokers, and a contributor to indoor xylenes concentrations, cigarettes as a source of exposure have been evaluated (ATSDR, 1995a; Wallace, 1987).

Environmental tobacco smoke (ETS) is comprised of both sidestream smoke and exhaled mainstream smoke (Daisey et al., 1994; NAP, 1986). Children may be exposed to xylenes from tobacco smoke directly as smokers (mainstream smoke) or indirectly as non-smokers (ETS). Numerous studies have been conducted to identify and quantify the individual chemical constituents from tobacco smoke. Researchers have identified over 4,800

individual constituents, including xylenes, in both mainstream smoke and ETS. Due to physical and chemical differences in burning conditions, xylenes have a higher rate of release per cigarette into sidestream smoke than into mainstream smoke (Wallace and O'Neill, 1987; Daisey et al., 1994; Fowles et al., 2000; NAP, 1986; Darrall et al., 1998).

Smoking occurs almost anywhere there are people; however, on a daily basis, children spend most of their time inside at home and therefore their greatest potential for xylenes exposure from ETS would be if they lived with a smoker. Also, although significant decreases in teenage smoking have been demonstrated in recent years, many teenagers are cigarette smokers. Thus, exposures to xylenes via tobacco smoke were quantified for children from mainstream smoke and ETS. Since smoking is not permitted on school properties and is now banned in most indoor public places, xylenes exposure from ETS has been assumed to occur primarily in the home.

In order to calculate exposure to xylenes from tobacco smoke exposure, the xylenes cigarette mainstream and sidestream emission rates were determined. Numerous studies have been conducted to evaluate the chemical emission rates. These are summarized in Table A-10-1 in Appendix A-10. In order to evaluate the exposure to xylenes from tobacco smoke, the general school year weekday microenvironment activity patterns for children as presented in Table A-10-2 of Appendix A-10 were considered. Exposure to ETS was assumed to occur in the home, as ETS exposure in outdoor environments was assumed to be negligible. Because most studies evaluate the *m*- and *p*-xylene isomers together, the emission rates and exposure concentrations were calculated for total xylenes (e.g., sum of *o-, m-,* and *p*-xylene isomers).

Environmental Tobacco Smoke (ETS) Exposures

The total time spent with smokers was obtained for children and adults from the Exposure Factors Handbook (EFH), and is presented in Table A-10-3 in Appendix A-10. In accordance with the information provided in Table A-10-2, it was assumed that a smoker was actively smoking inside the home for up to 6 hours per day in the presence of a child or female adult.

It was assumed that an adult female smokes one pack of cigarettes per day (20 cigarettes) and that half of the pack is smoked indoors at home, which is equivalent to 10 cigarettes smoked at home indoors per day. This assumption is consistent with EPA estimates (EPA, 1997b). The total mass of xylenes released in cigarette smoke was calculated based on the sum of the *m*/*p*- and *o*-xylene emission factors presented in Daisey et al., (1994). The total mass was divided by the 6 hours that the adult is awake and at home to account for smoking "off and on" during this time. Table 7.44 lists the emission factor and resulting emission rate.

Table 7.44: Emission Factor and the Calculated Emission Rate

Isomer(s)	Emission factor (µg/cig)	Usage (cig)	Time (hours)	Emission rate (mg/hr)
m/*p*-xylene	299	10	6	0.50
o-xylene	67	10	6	0.11
total *o*-, *m*- and *p*- xylene	366	10	6	0.61

Air concentrations were modeled using the Multi-Chamber Concentration and Exposure Model (MCCEM). This model accounts for the emission of xylenes over discrete time periods and exposure of the individual based on their activity patterns (see Appendix A-10). A hypothetical house was created where all the living space was on one floor such that all exposures were modeled to occur in one zone. This scenario was developed because it was assumed that the smoker would move throughout the house and that all areas of the house would have similar xylenes air concentrations as it is known that the various rooms of the house come into equilibrium in a short period of time (Johnson et al., 1999). Default values of 0.45 ACH for the air exchange (which assumes no open doors or windows) and 369 m^3 for the volume of the residence were used (EPA, 1997). The following equation was used to calculate the average daily dose of xylene from ETS exposure:

$$ADD = \frac{C \times ET \times EF \times ED \times IR \times ABSi}{BW \times AT}$$

where:

ADD = average daily dose (mg/kg/day)
C = exposure concentration of total xylenes (mg/m^3)
ET = exposure time (hr/day)
EF = exposure frequency (days/yr)
ED = exposure duration (years)
IR = inhalation rate (m^3/hr)
ABSi = xylenes inhalation absorption factor (0.6)
BW = body weight (kg)
AT = averaging time (days)

Age-specific xylenes concentrations and doses resulting from ETS exposure in the home were calculated and are presented on Tables 7.45 and 7.46.

Table 7.45: Summary of Average Daily [Xylenes] Concentrations (ADCs) from ETS Exposure (µg/m^3)

Isomer(s)	< 1 year old	1-5 years old	6-13 years old	14-18 years old	Female 19-35 years old
m/*p*-xylene	0.66	0.65	0.57	0.50	0.66
o-xylene	0.15	0.14	0.13	0.11	0.15
total *o*-, *m*- and *p*- xylene	0.81	0.79	0.69	0.61	0.81

Table 7.46: Summary of ADDs from ETS Xylenes Exposure (mg/kg/day) (total isomers)

Exposure Parameter	Units	< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
		Typical				
C	µg/m^3	0.81	0.79	0.69	0.61	0.81
ET	h/d	24	24	24	24	24
EF	d/y	365	365	365	365	365
ED	years	1	5	8	5	17
IR	m^3/h	0.19	0.31	0.51	0.6	0.47
CF	mg/µg	0.001	0.001	0.001	0.001	0.001
AT	d	365	1825	2920	1825	6205
BW	kg	7.2	15.4	35	61	62.4
ABSi	unitless	0.6	0.6	0.6	0.6	0.6
Dose	***mg/kg/d***	***3.1E-04***	***2.3E-04***	***1.5E-04***	***8.7E-05***	***8.8E-05***

As Table 7.45 indicates, the personal exposure concentration increases by 0.61 to 0.81 µg/m^3 as a result of having one smoker in the home. The personal exposure concentration for a particular age range is a function of the time spent in the home and the number of hours in the home while active smoking is occurring. Additional exposure would be expected if there were more than one smoker residing at the house. Due to the activity patterns, the personal exposure concentrations in Table 7.46 are less than the average concentration of xylenes in the home (attributable to ETS) of 0.89 µg/m^3.

Mainstream Tobacco Smoke Exposures

Exposure to xylenes from mainstream smoke was evaluated for adults (19-35 years) and teenagers (14-18 years). Breathing patterns for the inhalation of mainstream smoke (MS) and ETS differ considerably; active smokers inhale intensely and intermittently and usually hold their breath for some time at the end of inspiration. This increases the amount of

smoke components that are deposited and absorbed (EPA, 1992). Thus, an absorption factor was not used.

$$ADD = \frac{C \times SF \times CF}{BW}$$

where:

ADD = average daily dose (mg/kg/day)
C = concentration of xylenes in mainstream smoke (µg/cigarette)
SF = smoking frequency (cigarettes/day)
CF = conversion factor (0.001 mg/µg)
BW = body weight (kg)

The dose was calculated using the sum of the *m*/*p*-xylene mainstream smoke emission rate (9.2 µg/cig) and *o*-xylene emission rate (2.0 µg/cig) average emission factors from Darrall et al. (1998), or 11 µg/cig. A teenager smokes an average of about 7 cigarettes per day, whereas, an adult female smokes an average of 14 cigarettes per day (EFH Table 15-146), which results in a daily intake of xylenes from mainstream smoke of 0.08 mg/day for the teenage smoker and 0.2 mg/day for the adult smoker. The annual average daily doses were calculated and are presented in Table 7.47.

Table 7.47: Summary of ADDs from Exposure to Xylenes in Mainstream Smoke (mg/kg/day) (total isomers)

Exposure Parameter	Units	14 – 18 years old	Female 19 – 35 years old
C	µg/cigarette	11	11
SF	cigarette/day	7	14
CF	mg/µg	0.001	0.001
BW	kg	61	62.4
Dose	***mg/kg/day***	**1.3E-03**	**2.5E-03**

Wallace (1989) assumed a smoking frequency of 32 cigarettes/day. However, of the smoking data reported in EFH, only 14% of smokers indicated that they smoke more than 24 cigarettes in a day and of those who reported smoking at home, only 6% reported smoking more than 24 cigarettes. Thus, the uncertainty surrounding chemical dose from mainstream cigarette smoke is primarily associated with the smoking frequency. Therefore, the smoking frequency used by Wallace is a high-end estimate.

7.2.3 Occupational Exposure

Occupational exposure to *o*-, *m*-, and *p*- xylene isomers occurs primarily in one of three types of occupations: (1) production/processing of xylene, (2) use of xylenes as feedstock for the manufacturing of other chemicals, and (3) use of chemical products containing xylene isomers in a commercial or skilled trade occupation (e.g., solvents, paints, or lacquers). Exposure data relevant to these general occupational settings were obtained from industry trade organizations, the recent peer-reviewed literature, and the "Occupational Exposure Database – Solvents End-Use" prepared by the American Chemistry Council and European Chemical Industry Council (Caldwell et al., 2000).

Inhalation Exposures

Production/Processing and Manufacturing Exposure Concentrations

In order to assess recent xylenes exposure to workers in the chemical manufacturing and distribution industries, industrial hygiene monitoring records from January 1995 through December 2001 were collected from members of the BTX VCCEP Consortium. As this survey was originally conducted to develop information on actual exposure, only data from employees who were not wearing respirators have been summarized. The analysis of these industrial hygiene data is summarized in Table 7.48. The exposure concentrations were converted to the units of mg/m^3 for use in subsequent dose calculations by multiplying the units in ppm by 4.34.

Table 7.48: ACC BTX VCCEP Consortium Members' Occupational Xylene Exposure Survey

Operation	Number of Samples	Total *o*-, *m*-, and *p*-Xylene Isomer Exposure Concentrations for Normal Full-Shift Operations			
		Mean		95th Percentile	
		(ppm)	(mg/m^3)	(ppm)	(mg/m^3)
Manufacturing	1,450	0.11	0.48	0.27	1.2
Distribution	42	0.11	0.48	0.16	0.69

Solvent End Use Exposure Concentrations

To improve the state of knowledge of occupational exposure concentrations to VOCs found in common solvents, a database was prepared for the American Chemistry Council and European Chemical Industry Council (Caldwell et al., 2000). Summary statistics and the database structure were published in the American Industrial Hygiene Association Journal. The database consists of air concentration exposure data from about 100 journal articles from 1961-1988, which were selected from an initial list of 22,000 papers. For the VCCEP occupational exposure assessment, this database was accessed and queried for records that met the following criteria:

- The exposure occurred in the United States;
- At least one discrete sample or an average concentration and sample number was available for xylenes;
- The sample was collected in the breathing zone; and
- For TWA exposures, the exposure time was greater than 15 minutes.

The xylenes query of the database resulted in identification of numerous publications of occupational exposure studies. Based on the above criteria, occupational exposures data for xylenes are available to characterize exposures in the following industries:

- Automobile (adhesive, painting);
- Electronics (general use);
- Rubber (curing, mixing, extruding);
- Furniture (painting); and
- Plastics (polyurethane molding).

From the database, a typical (average of all samples) and high-end (95th percentile of all job task averages) TWA exposure concentration have been estimated and are presented in Table 7.49 below.

Table 7.49: Xylenes Solvent End-Use Occupational Exposure Concentrations

Parameter	Exposure Concentration (ppm)	Exposure Concentration (mg/m^3)
TWA – Mean (N = 892)	3.5	15
TWA – 95^{th} Percentile (N = 892)	7.8	34

A search of recent occupational literature published since 1997 was also conducted to supplement the Caldwell et al. database. The primary database searched was the National Library of Medicine's PubMed/Medline citation database, which indexes major occupational hygiene journals and medical journals. In addition to this database, the NIOSH Health Hazard Evaluations and OSHA publications printed since 1997 were reviewed. An emphasis was placed on exposures occurring in the United States. This search resulted in identification of xylene exposure data for the following occupational categories:

- Exposure to solvents used in graffiti removal;
- Exposure to jet fuel during military aircraft maintenance;
- Exposure to lacquers, stains, or construction adhesive during residential construction activities; and
- Exposure to smoke during structural firefighting activities, especially during overhaul (i.e., the post-suppression inspection for hidden fires).

The recently published (1997-2001) literature is summarized on Table 7.50.

Table 7.50: Recently Published Data on Occupational Exposure to Xylene Isomers

Occupation	Average 8-hour TWA Concentration (ppm)	Reference
Graffiti Removal	0.07	Anundi, 2000
Aircraft Maintenance Personnel – Military	0.006 - 0.3	Lemasters, 1999; Smith, 1997
Municipal Firefighter	1.7	Austin 2001a,b;
Painter Applying Stains and Laquers Used in New Home Construction	8.3	Methner, 2000

Upon review of Tables 7.48-7.50, it is apparent that the occupational exposures to xylenes in the production/processing and manufacturing industry and the end-use industries are significantly lower than the OSHA PEL and the ACGIH TLV of 100 ppm as an 8-hr TWA. The recently published data are consistent with that of the production/processing industry, with the exception of the painter applying lacquer or stain during new home construction, where the TWA exposure concentrations are consistent with the high-end exposure concentrations obtained using the extensive database of Caldwell et al. (2000). As such, the typical occupational exposure concentration is represented by the mean concentration on Table 7.48 and the high-end concentration is represented by the 95th percentile concentration on Table 7.49.

Dermal Exposures

Occupational chemical exposure studies typically do not report dermal dose due to the difficulty of properly estimating the contribution of the dermal route, and very few *in vivo* human studies of dermal exposure to solvents have been published (Kezic et al., 2001). It is important to note that because inhalation and dermal exposure could co-occur in an occupational environment, interpretation of occupational *in vivo* studies can be difficult. Controlled *in vivo* studies are relatively rare (Kezic et al., 2000).

Of the limited number of studies investigating dermal exposure to xylenes, one study that investigated exposure to xylenes in the autobody painting (Daniell et al. 1992) industry found a correlation between a biological exposure index (i.e., methylhippuric acid in urine) and dermal exposure to xylenes. However, the researchers concluded that the amount of xylenes absorbed was of little clinical importance because the level of methylhippuric acid in the urine was well below the ACGIH biological exposure index (BEI) for xylenes. The post-shift level of methylhippuric acid in the urine of painters was 4.9% of the BEI.

In an occupational setting such as the petroleum processing or chemical manufacturing industries, xylenes or products containing xylenes are generally handled in closed systems in order to minimize volatile emissions, avoid product loss, and to minimize the risk of fire. As such, dermal exposure to the product is not common except under “upset” conditions,

where personal protective clothing including gloves and suits would be worn. However, it is recognized that occasional dermal occupational exposure to xylenes could occur during the use of products containing xylenes.

There are few screening level exposure models available for occupational dermal exposure to chemicals. As of this time, the best screening level model is EASE (United Kingdom Health and Safety Executive, 1997), which is a knowledge-based system that can be used when exposure data are limited or not available. This model provides estimates of product adherence to the skin during the work shift based on use pattern and contact level. Estimates are provided in units of mg of product per area of skin per day.

In using EASE to evaluate occupational dermal exposures, assumptions have been made regarding the quantity of the chemical product that is in contact with the skin and the percent weight content of the xylenes in the product. As such, it has been assumed that the adult female of average body weight and skin surface area occasionally exposes her hands to xylenes during application of a stain or varnish. During the work shift, the coating covers about ½ of each hand during application. Exposures are assumed to occur under non-occluded skin conditions. The coating contains about 10% xylenes. Typical exposures are characterized by the intermittent, non-dispersive use of the xylenes-containing product in contact with the skin and high-end dermal exposures are characterized by extensive wide dispersive use of the xylenes-containing product (United Kingdom Health and Safety Executive, 1997) and a xylene weight content of 20%.

Typical and high-end doses of total *o*-, *m*-, and *p*-xylene isomers from occupational dermal exposures have been quantified using the following equation:

$$AD_{dermal} = \frac{Q_{dermal} \times F_{xylene} \times ABS_{xylene} \times A_{skin} \times EF}{BW \times 365 \frac{\text{day}}{\text{year}}}$$

where,

AD_{dermal}	Absorbed dose (mg/kg/day)
Q_{dermal}	Quantity of commercial product (paint, solvent, etc.) adhering to skin (mg/cm^2-day) from EASE model
F_{xylene}	Fraction of applied product that contains xylenes by weight (unitless)
ABS_{xylene}	Absorption factor for xylenes, equal to 0.03
A_{skin}	Area of skin exposed to commercial product (cm^2)
EF	Exposure frequency (days/year)
BW	Body weight (kg)

The dermal dose results are presented in Table 7.51.

Table 7.51: Dose of *o*-, *m*-, and *p*-Xylene Isomers from Typical and High-End Occupational Dermal Exposures

Exposure Parameter	Units	Typical	High-End
		Female 19-35 year old	Female 19-35 year old
Q_{dermal}	mg/cm^2-day	0.55	10
A_{skin}	cm^2	373	373
EF	day/year	12	12
F_{xylene}	% weight	0.1	0.2
ABS_{xylene}	Unitless	0.03	0.03
BW	kg	62.4	62.4
Dose	***mg/kg/day***	***3.24E-04***	***1.18E-02***

7.3 Discussion of Biomonitoring Data

In addition to the NHANES III blood concentration data for xylenes (See Section 2.1), a focused study on children's blood levels of xylenes is reported by Sexton et al. (2005). In this study, blood concentrations of 11 VOCs were measured up to four times over two years in a probability sample of more than 150 children from Minneapolis, MN. The blood concentrations for xylenes reported by Sexton et al. are presented on Table 7.52.

Table 7.52: Blood Concentrations of Xylenes in Children from Sexton et al. (2005)

Chemical Name	Date	Number of Samples	Detection Frequency (%)	Percentile (ug/L)			
				10th	50th	75th	95th
m-/p-Xylene	Feb. 2000	113	98	0.10	0.13	0.17	0.22
	May 2000	115	98	0.09	0.11	0.13	0.17
	Feb. 2001	63	66	0.15	0.19	0.23	0.31
	May 2001	88	99	0.23	0.37	0.47	0.60
o-Xylene	Feb. 2000	113	73	0.02	0.03	0.05	0.08
	May 2000	114	44	0.02	0.02	0.03	0.05
	Feb. 2001	63	32	0.03	0.03	0.04	0.06
	May 2001	88	66	0.03	0.07	0.11	0.14
Sum of m-/p-Xylene and o-Xylene	Feb. 2000	--	--	0.12	0.16	0.22	0.30
	May 2000	--	--	0.11	0.13	0.16	0.22
	Feb. 2001	--	--	0.18	0.22	0.27	0.37
	May 2001	--	--	0.26	0.44	0.58	0.74

The median levels of *m-/p*-xylenes are comparable to those measured in the NHANES III, whereas the median levels of *o*-xylene are nearly 3 times lower than the NHANES III concentrations.

Sexton et al. (2005) also collected matched personal air samples for each child and analyzed them for xylenes. The mean total xylenes concentration was 10.8 ug/m^3. Although the authors found that the personal air samples were primarily influenced by time spent in the home, they also found only moderate statistical correlation (i.e., R^2 ~0.2) between matched personal air concentrations of xylenes and blood concentrations of xylenes.

Human physiologically-based pharmacokinetic (PBPK) models can be used to estimate internal doses of a chemical from external exposures. A human PBPK model for xylene was used to estimate blood concentrations that would be predicted in children of various ages given the inhalation exposure concentrations for background exposures used in this assessment (see Appendix C for additional information). The results are provided on Table 7.53.

Table 7.53: Predicted Average Blood Concentrations in Children Based on VCCEP Exposure Estimates

Age	Mixed xylenes 24-hour TWA (ug/m^3)		Mixed xylenes blood concentration (ug/L)	
	Typical	High-End	Typical	High-End
9 months	8.9	35	0.047	0.19
3 years	8.4	33	0.040	0.16
10 years	8.6	34	0.037	0.15
16 years	8.6	34	0.032	0.12
Adult females	8.8	35	0.032	0.13

The blood levels were predicted using the inhalation exposure information based on the typical 24-hr time weighted average air concentrations to which children may be exposed. Consequently, the predicted blood values do not account for the small amounts of xylene that may be ingested via food or water or dermally absorbed. As shown on Table 7.55, the predicted mixed xylenes blood concentration ranges from 0.032, for typical exposures to both 16-year olds and adult females, to 0.19 for high-end exposures of infants. Across age groups, the predicted mixed xylenes blood concentration is reasonably consistent. The typical predicted blood values (range, 0.032-0.047 ug/L) are about five to ten times lower than the median concentrations reported by Sexton et al. (2005) (range, 0.16-0.44 ug/L). Similarly, the predicted high-end blood concentrations (range, 0.12-0.19 ug/L) are about two to four times lower than the Sexton et al. (2005) 95th percentile mixed xylenes blood concentrations (range, 0.22-0.74 ug/L). Because the PBPK model of Tardiff et al. (1995) (see Appendix C for additional information on the PBPK model) was calibrated for occupational exposures to xylene (i.e., 80 ppm), it would not necessarily be expected to accurately predict mixed xylenes blood concentrations from background exposures.

7.4 Uncertainties in the Exposure Assessment

Uncertainties are associated with any exposure assessment, and for this Tier I assessment, they are primarily associated with the use of published monitoring data to represent exposures for the U.S. population, and in the absence of monitoring data, the use of mathematical models to estimate human exposures. Each of these is described further below.

7.4.1 Monitoring Data

Published monitoring data were used to characterize children's and prospective mothers' exposures to xylenes from ambient air, in-vehicle exposures, vehicle refueling activities, occupational environments, and drinking water. Each of these is discussed further below.

Outdoor Ambient Air

The outdoor ambient air monitoring data for xylenes were obtained from EPA databases, which included data from 18 rural counties and 32 urban counties nationwide. This monitoring data may not be representative of the entire U.S. outdoor ambient air because the monitoring stations are sparsely distributed geographically. However, ambient air concentrations vary by geographical area and the monitoring data that are available include that for both rural and urban settings. The urban settings include those city locations which have the greatest population densities (e.g., Los Angeles, Chicago, New York, and Philadelphia), and thus the highest potential for xylenes loading to the ambient air from mobile and non-mobile sources. While there may be significant variation around the typical exposures estimated from use of the monitoring data, the high-end exposure concentrations used in this assessment were the 95th percentile values of the datasets and thus are reasonable high-end estimates.

Indoor Ambient Air

There are few monitoring data that are representative of current indoor xylenes concentrations throughout the U.S. Although earlier data are available, use of monitoring data from the 1980s would have introduced uncertainty into the exposure assessment because of the dramatic decrease in outdoor air concentrations, and improved emissions controls on automobiles and gasoline reformulations which can impact in-home xylenes concentrations from attached garages and infiltration from ambient air. Additionally, in most of the studies reviewed, insufficient information is provided to understand the potential indoor sources of xylenes, which results in a wide range of reported concentrations. Therefore, efforts were made to determine more realistic exposures that might capture some of the differences between current indoor air levels of xylenes and those from the 1980s. To do so, a delta value representing the incremental increase in xylenes concentrations due to indoor sources was applied to the outdoor ambient air values. The typical delta used was 6.3 µg/m^3 and the high-end delta was 47 µg/m^3, both of which were derived from studies done in New York City in 1999, Chicago in 1994-1995, a series of studies done in the eastern and southeastern U.S. in 1997 and 1998, a series

of studies done in Minnesota, and a series of studies conducted in Oklahoma in 2000 and 2001. These deltas, therefore, may be higher or lower than in individual homes across the country. Insufficient data are currently available to determine the range of indoor to outdoor deltas, which would account for all variations in housing characteristics, whole house air exchange rates, and personal characteristics of the residents of individual houses. However, it is unlikely that the indoor to outdoor deltas would vary by more than an order of magnitude on a long term basis, and therefore the uncertainty associated with the use of the delta is likely to be inconsequential in terms of estimating chronic background exposure from the indoor air. It is recognized that over short durations, the I/O delta may be more than an order of magnitude higher than that used in this exposure assessment; however, that condition would likely result from introduction of a source of xylenes into the home. This has been demonstrated by Bozzelli et al. (1995) in their study of kerosene heater use, and by Ilgen et al. (2001b) during redecoration activities using of certain paint products. Since these types of source specific exposure concentrations have been estimated in Section 7.2.2.2 aggregate exposures from background indoor air and temporary excursions of xylenes concentrations due to consumer product use can be determined.

In-Vehicle Exposures

In-vehicle xylenes exposure levels can be affected by various conditions including mode of transportation, driving route, time of day (rush vs. non-rush), type of fuel distribution system, season of the year, meteorological conditions, and vehicle ventilation conditions. The data used in this exposure assessment to characterize in-vehicle xylenes exposures come from three studies, all of which were conducted in urban areas. Because in-vehicle exposures are influenced by the ambient air immediately outside of the vehicle, xylenes data collected in vehicles during an urban commute are likely to be higher than those which would occur in-vehicle during a typical rural commute. Thus, the data used in this exposure assessment likely overestimate in-vehicle exposures in rural areas.

In addition to ambient environmental conditions surrounding the vehicle, on-board emission controls also affect the in-vehicle xylenes levels. Only one of the three in-vehicle studies provided information on the model year of the vehicle in which the xylenes measurements were made (i.e., Fedourek and Kerger, 2003). Because the study dates for the other investigations were 1998 and 1999, it is likely that the vehicles were of the early 1990s fleet. Given that present day vehicles have better on-board emission controls that will continue to improve with future models, it is likely that use of data from older model years overestimate current and future in-vehicle xylenes exposures.

It is recognized that a high-end in-vehicle exposure estimate has not been quantified. This is because the studies used in this assessment only provided mean xylenes concentrations, and the data do not support use of professional judgment to estimate a high-end exposure concentration. A high-end exposure, however, could be defined by increasing the exposure time (i.e., time spent in the vehicle each day). In doing so, the in-vehicle exposure time would be increased which would result in a decreased exposure time at the indoor air concentration estimate. However, because the indoor air concentrations are similar to the mean in-vehicle concentrations, the net result would be no significant change in the overall aggregate xylenes exposure.

Vehicle Refueling

The data used to represent xylenes exposures during refueling were collected in 3 cities across the continental U.S. and in Fairbanks, AK. Additionally, a variety of refueling scenarios were evaluated and use of various grades of gasoline was considered. Thus, it is believed that while the data are generally representative of typical and high-end refueling exposures, some uncertainty exists and is related to on-board emission controls, use of vapor recover systems (VRS) at the pump, and continued reduction in aromatic content in gasoline blends. The three studies used to quantify refueling exposures were conducted in 1993 through 1997. As such, the vehicle fleet represented would have included vehicles without significant on-board vapor controls. Additionally, only one of the cities where xylenes measurements were made had Stage II VRS at the pump. Thus, based on the technology available for later fleet years and the requirement for use of Stage II VRS in some ozone non-attainment areas, the data used in this assessment may overestimate current and future xylenes exposures during refueling.

Occupational Exposure Estimates

The monitoring data used to derive typical and high-end occupational exposure estimates come from recent data collected from xylenes production/processing and chemical manufacturing industry and an extensive database of end-use occupational solvent exposures including 100 studies where xylenes were specifically evaluated (Caldwell et al., 2000). The exposure data for end-use occupational exposures derived from the more current (1997 – present) peer-reviewed literature is consistent with the relatively low exposures observed in the production/processing and manufacturing industries. Thus, there is high confidence that the typical occupational xylenes exposures have been well characterized by use of the mean exposure levels observed in the production/processing and chemical manufacturing industries. The high-end exposures were characterized using the data from Caldwell et al. (2000). While not a worst-case estimate, the high-end estimate is believed to be reasonable, based on a limited comparison of high exposure scenarios available in the current peer-reviewed literature.

Tap Water

The monitoring data used to characterize exposures to xylenes from tap water were obtained from 25,302 recent measurements of public water systems from 32 states throughout the U.S. and 1,640 measurements from non-public water systems including groundwater and surface water sources. As such, a robust dataset was available for evaluation. Because xylenes in drinking water are regulated, public water supplies are unlikely to serve a source of elevated xylenes levels on a chronic basis and therefore it is believed that the children's and prospective mother's exposure estimates made in this assessment adequately characterize the typical and high-end exposures from tap water. Contamination of groundwater in source specific areas is, however, uncertain. While contamination of groundwater from various sources has occurred, potential childhood exposures for these conditions have not been quantified in this VCCEP exposure assessment, as regulatory programs are in place whereby site-specific risk assessments are performed for clean-up purposes.

7.4.2 Exposure Modeling

The uncertainties associated with any modeling exercise are typically those associated with the various model parameters. In this exposure assessment most of the uncertainty errs on the conservative side (i.e., exposure enhancing). To address the uncertainties with the consumer product exposure modeling, a sensitivity analysis was conducted to determine which of the parameters had the greatest effect on predicted air concentrations. The parameters most sensitive were: 1) amount of product used, 2) whole house air exchange rate, and 3) total home volume. A complete discussion of the sensitivity analysis is presented in Appendix A-11.

In addition to modeling parameter uncertainties, there are also scenario specific uncertainties. Each is briefly described below.

Residential Metal Parts Degreasing Scenario: The primary uncertainty with this scenario is the intended use of mixed xylenes sold in quart size containers. Searches of the peer reviewed and other literature alluded to its use as a degreaser, but provided no information regarding the amount of product to be used or whether it would be used indoors. The Westat survey data regarding product usage amounts for solvent-based cleaners is likely much greater than for a paint thinner containing xylenes or for mixed xylenes because it is representative of a wide variety of products including Easy Off oven cleaner, Fuller Brush cleaners, Woolite and Dawn, none of which contain xylenes. As such, a 'bench scale' degreasing simulation was done using water to estimate the amount of degreaser that might be used indoor for small (i.e., 1 ft^2) and larger (i.e., 10 ft^2) projects.

An additional uncertainty is that regarding human behavior when using the solvent; specifically whether the product is used under adequate ventilation conditions. Because the Westat survey indicated that most people read the product directions and some opened windows or doors, the xylenes exposures were modeled assuming adequate ventilation. Although, it is recognized that some people will not follow the directions or heed the warnings, reasonable exposure bounds have been evaluated in this assessment given the conservative nature of the other assumptions including: 1) indoor use of the solvent and 2) small room of use (i.e., 20 m^3). If it were assumed that adequate ventilation is not provided, the whole house air exchange rate would be assumed to be 0.45 ACH, which is approximately one-third of the ventilation rate under open windows/door conditions. Thus, because the air exchange rate and the predicted air concentrations are linearly related over this range, the predicted xylenes concentrations would increase 3-fold.

Residential Spray Painting Scenario: The uncertainties associated with this scenario are the amount of products used, the correlation of amount of product used to location of use (inside versus outside), the steps taken to ventilate space (opening windows or exhaust fans) and the compounding effect in the high-end scenario regarding the use of two paint products, both with high-end xylenes weight content. The Westat survey provides some useful information on these points. Some of the relevant details of the survey results are discussed below.

Over 80% of the survey respondents indicated that the last time they used spray paint, it was used outside or in a garage. In the residential spray paint scenario presented in Section 7.2.2.2, the assumption was made that the activity would take place within a room integral to the house. However, according to the Westat survey, this is not a common practice for most spray paint users. Thus, the assumption of indoor use may overestimate the xylenes exposure during spray painting, particularly for high-end usage amounts (i.e., 2 cans of spray paint), which are unlikely to be used indoors.

For those survey respondents that used products inside, 63% opened a window, 10% used an exhaust fan, and 61% left the inside door of the room open. In the sensitivity analysis, the whole house air exchange rate was determined to be a sensitive parameter, thus using a default value for the air exchange rate would not be representative of typical use conditions. Of the survey respondents, 73% indicated that they read the directions on the label. Most spray paint labels contain a warning to use the product outdoors or in a well-ventilated space. Thus, it is reasonable to assume that a majority of the product users will heed the warnings and that the additional ventilation will minimize typical exposures during spray painting. As indicated in the degreaser uncertainty discussion, failure to use adequate ventilation would result in estimates of exposure approximately 3-fold higher.

The use of two paint products both containing high-end weight content of xylenes on the same day within a 2 hour window of time is uncertain. Although, consumer product data regarding the correlation between the uses of related paint products was not identified, this scenario was evaluated in an effort to capture a reasonable high-end for a single day use.

Although it is often preferable to use actual air monitoring data to characterize exposures, no studies of residential use of spray paint were identified. It is believed however, because of the wide variation in consumers' use of various products, the modeled exposure assessment likely provides a broader picture of potential exposures. For instance, in using the consumer product models, various scenario conditions can be evaluated (e.g., usage amounts, various ventilation conditions, rates of application, etc.). These types of variables are not likely to be documented or accounted for in a monitoring study, thus limiting the usefulness of the monitoring data. To assess reasonableness of the xylenes exposure estimates for the spray paint scenario, comparisons can be made to the limited occupational spray paint studies that have been conducted. For instance, in the Methner (2000) occupational study of residential construction activities, a total xylenes concentration of 8 ppm was measured during an application of spray lacquer indoors over a 1.7-hour period. The commercial use of spray lacquer in a residential construction project is representative of a high-end indoor use of a product containing xylenes. Thus, comparing the high-end 1-hr time weighted average of 30 ppm from the modeled residential spray paint scenario, it can be seen that the high-end exposure estimate used in this assessment is adequate to capture the potential high-end exposures.

7.5 Summary of Exposures

Childhood exposures to xylenes have been quantified in terms of background exposures (e.g., ambient air, food, and water) and specific source exposures, some of which are associated with xylene chain of commerce (e.g., consumer products) and some that are non-chain of commerce sources (e.g., gasoline, and tobacco smoke). Table 7.54 is a

summary of annual average daily doses calculated for each exposure due to background sources. From Table 7.54, it can be seen that the inhalation pathway is the primary pathway of exposure with doses at least one order of magnitude higher than those received from ingestion or dermal contact. The exception to this is that of the nursing infant with a high-end occupationally exposed mother, where the dietary ingestion pathway dominates as a source of exposure. Of the inhalation sources of exposures, indoor air contributes the most to overall inhalation doses. These findings are graphically presented on Figures 7.4 and 7.5, which show doses from background exposures to xylenes from typical and high-end urban exposures.

Age-specific doses for chronic exposures to xylenes from specific sources are presented on Table 7.55. From this table, it can be seen that for children (<1 to 13 yrs old) exposure to ETS is the only chronic source specific exposure that was identified, and exposures are approximately 10-fold lower than that from typical urban background. For the teenagers and adults, ETS adds insignificantly to background doses, as does exposure to xylenes from refueling. Exposure to total xylenes from mainstream smoke are nearly equal to that of typical total background exposures, but approximately three to five times lower than high-end total background exposures. These findings are graphically presented on Figures 7.6 and 7.7, which show the comparison of the total high-end urban background dose for children to that received from other chronic-type exposures to tobacco smoke, and fuel-related sources.

Table 7.54: Summary of Age-Specific Background Total Xylenes Doses (mg/kg/day)

Scenario	Age Group < 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
BACKGROUND DOSES - OUTDOOR AIR					
Ambient Outdoor Air - School Day					
Rural - Typical	--	1.3E-05	8.6E-06	5.5E-06	--
Rural - High-end	--	3.0E-05	2.1E-05	1.3E-05	--
Urban - Typical	--	3.1E-05	2.2E-05	1.4E-05	--
Urban - High-end	--	7.4E-05	5.1E-05	3.3E-05	--
Ambient Outdoor Air - Non-School Day					
Rural - Typical	2.2E-05	1.9E-05	9.7E-06	6.9E-06	6.8E-06
Rural - High-end	5.3E-05	4.6E-05	2.3E-05	1.7E-05	1.6E-05
Urban - Typical	5.5E-05	4.7E-05	2.4E-05	1.7E-05	1.7E-05
Urban - High-end	1.3E-04	1.1E-04	5.8E-05	4.1E-05	4.0E-05
Ambient Outdoor Air - Total					
Rural - Typical	2.2E-05	3.1E-05	1.8E-05	1.2E-05	6.8E-06
Rural - High-end	5.3E-05	7.6E-05	4.4E-05	3.0E-05	1.6E-05
Urban - Typical	5.5E-05	7.9E-05	4.6E-05	3.1E-05	1.7E-05
Urban - High-end	1.3E-04	1.9E-04	1.1E-04	7.3E-05	4.0E-05
BACKGROUND DOSES - INDOOR AIR					
In Home - School Day					
Rural - Typical	--	8.1E-04	4.9E-04	3.1E-04	--
Rural - High-end	--	3.4E-03	2.1E-03	1.3E-03	--
Urban - Typical	--	9.6E-04	5.9E-04	3.8E-04	--
Urban - High-end	--	3.8E-03	2.3E-03	1.5E-03	--
In Home - Non-School Day					
Rural - Typical	2.6E-03	9.2E-04	7.0E-04	4.6E-04	7.3E-04
Rural - High-end	1.1E-02	3.9E-03	3.0E-03	2.0E-03	3.1E-03
Urban - Typical	3.1E-03	1.1E-03	8.4E-04	5.5E-04	8.7E-04
Urban - High-end	1.2E-02	4.3E-03	3.3E-03	2.2E-03	3.4E-03
In Home - Total					
Rural - Typical	2.6E-03	1.7E-03	1.2E-03	7.8E-04	7.3E-04
Rural - High-end	1.1E-02	7.3E-03	5.1E-03	3.3E-03	3.1E-03
Urban - Typical	3.1E-03	2.1E-03	1.4E-03	9.3E-04	8.7E-04
Urban - High-end	1.2E-02	8.1E-03	5.6E-03	3.6E-03	3.4E-03
In School					
Typical	--	4.50E-05	6.70E-05	4.90E-05	--
High-end	--	4.10E-04	6.20E-04	4.50E-04	--
In-Vehicle					
Typical	2.60E-04	2.00E-04	1.20E-04	1.10E-04	7.90E-05
BACKGROUND DOSES - FOOD & WATER					
Food & Tap Water Ingestion					
Typical	1.80E-04	2.10E-04	9.00E-05	4.80E-05	4.60E-05
High-end	3.60E-04	3.70E-04	1.60E-04	9.50E-05	8.80E-05
Human Milk					
Urban, typical	1.81E-05	--	--	--	--
Urban, high-end	7.13E-05	--	--	--	--
Occupational, typical	3.75E-04	--	--	--	--
Occupational, high-end	2.63E-02	--	--	--	--
Showering - Dermal					
Typical	2.80E-06	3.40E-06	2.30E-06	1.80E-06	1.80E-06
High-end	6.10E-06	6.60E-06	4.60E-06	3.60E-06	4.30E-06
Showering - Inhalation					
Typical	5.10E-05	2.30E-05	3.30E-06	2.30E-06	1.70E-06
High-end	2.60E-04	9.10E-05	1.30E-05	1.00E-05	9.70E-06

Table 7.54: Summary of Age-Specific Background Total Xylenes Doses (mg/kg/day) (continued)

BACKGROUND DOSES - SUM OF AMBIENT AIR, INDOOR AIR, FOOD & WATER

	Age Group				
Scenario	< 1 year old	1-5 year old	6-13 year old	14-18 year old	Female 19-35 year old
Inhalation Pathway					
Rural - Typical	2.91E-03	2.02E-03	1.40E-03	9.49E-04	8.16E-04
Rural - High-end	1.16E-02	8.12E-03	5.88E-03	3.91E-03	3.21E-03
Urban - Typical	3.45E-03	2.41E-03	1.66E-03	1.12E-03	9.69E-04
Urban - High-end	1.27E-02	8.98E-03	6.46E-03	4.29E-03	3.55E-03
Ingestion Pathway					
Typical	1.98E-04	2.10E-04	9.00E-05	4.80E-05	4.60E-05
High-end	4.31E-04	3.70E-04	1.60E-04	9.50E-05	8.80E-05
Dermal Pathway					
Typical	2.80E-06	3.40E-06	2.30E-06	1.80E-06	1.80E-06
High-end	6.10E-06	6.60E-06	4.60E-06	3.60E-06	4.30E-06

Figure 7.4: Contribution of Various Ambient Sources to Typical Total Chronic Background Dose

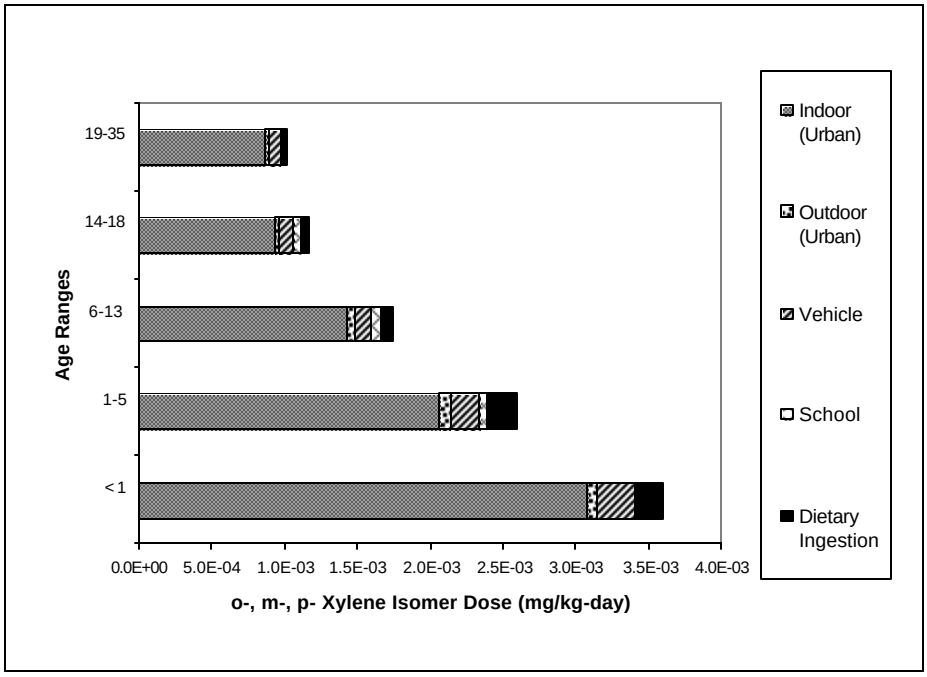
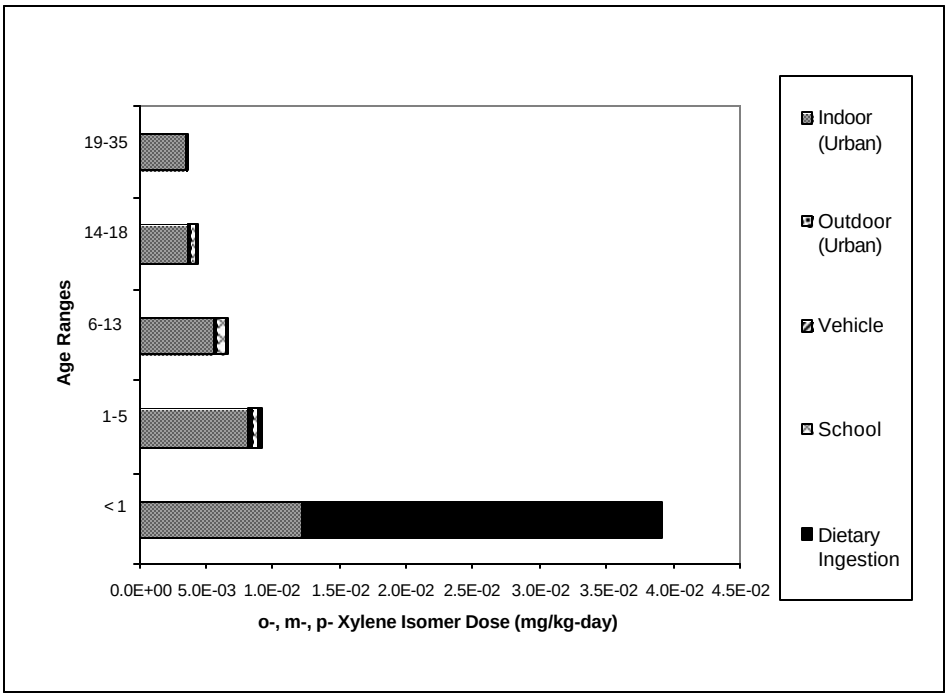


Figure 7.5: Contribution of Various Ambient Sources to High-end Total Chronic Background Dose



*The dose for the <1yr old includes exposure from human milk of a high-end occupationally exposed mother.

Table 7.55: Summary of Source-Specific Total Xylenes Doses (mg/kg/day)

Scenario	Age Group					
	< 1 year old	1-5 year old	6-13 year old	14-18 year old	16-18 year old	Female 19-35 year old
SOURCE SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	3.1E-04	2.3E-04	1.5E-04	8.7E-05	--	8.8E-05
Mainstream (smoker's dose)	--	--	--	1.3E-03	--	2.5E-03
Refueling						
Typical	--	--	--	--	1.6E-05	1.6E-05
High-end	--	--	--	--	1.6E-04	1.6E-04

Figure 7.6: Summary of Various Source Specific Doses at Typical Exposures

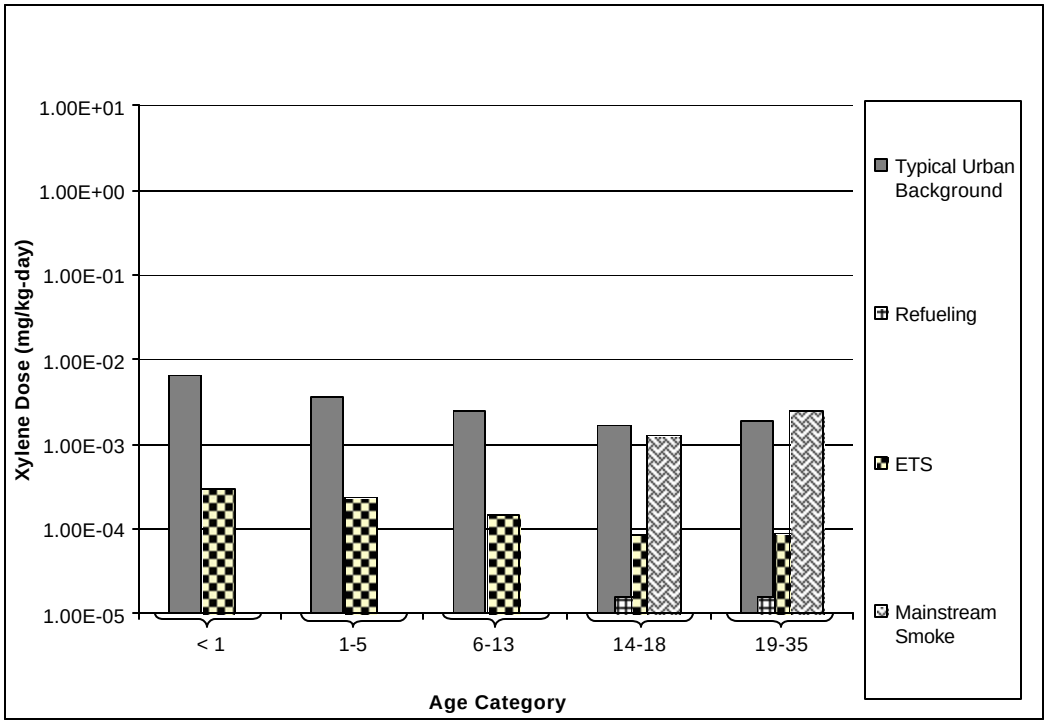
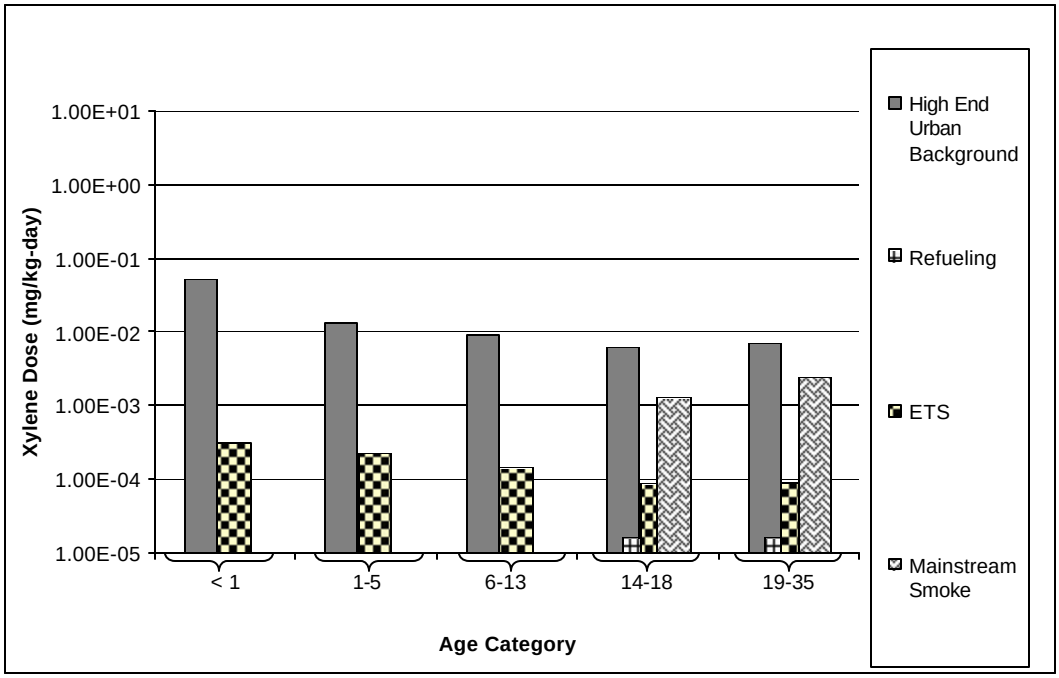


Figure 7.7: Summary of Various Source Specific Doses at High-end Exposures



8.0 Risk Assessment

Risk assessment is the integration of the findings of the Hazard Assessment and the Exposure Assessment to provide numerical characterizations of risk. As discussed in the Hazard Assessment (Section 6), xylenes may cause both short-term acute and chronic health effects. The primary health effects are irritation, impairment of neurobehavioral function, and CNS depression. This risk assessment presents an evaluation of the potential for the occurrence of these effects in the exposed populations following acute and chronic exposures.

The general EPA guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure (EPA, 1998b). Therefore, the short-term episodic exposures such as those associated with the consumer products, were evaluated in terms of the potential risks from the acute effects of xylenes using the peak 1-hour and 8- hour exposure concentrations. This approach is appropriate for acute exposures for volatile solvents because concentration plays a stronger role in determining the strength of the effects than does time (Bushnell, 1997; Boyes 2005). Acute effects appear to be more closely related to momentary and maximum exposures rather than cumulative exposure. Therefore, acute exposures were compared against the AEGL-1 value to protect against threshold effects resulting from acute exposures. Chronic exposures were compared against a chronic health benchmark that is based on the same point of departure used by EPA to derive the IRIS inhalation RfC (EPA 2003a). In this assessment, the potential for the occurrence of chronic adverse health effects is evaluated based on the background xylenes exposure concentrations and annual average doses developed in Section 7.

This section consists of the following sections: (1) a brief overview of the hazard assessment information and regulatory health benchmarks; (2) derivation of a health benchmark for chronic inhalation exposure (3) the evaluation of the risk of the chronic hazards of xylenes; and (4) an evaluation of the risk of the acute hazards from the use of selected consumer products. Uncertainties are also discussed. Finally, overall conclusions are presented concerning the potential for xylenes exposure to pose health risks to children.

8.1 Benchmarks Used to Characterize Chronic and Acute Adverse Health Effects of Xylenes

8.1.1 Benchmarks Used to Evaluate the Chronic Effects of Xylenes

As discussed in Section 7, chronic exposures to xylenes can occur via inhalation, ingestion and dermal contact. Therefore, in evaluating the potential health risks associated from these exposures, route-specific health benchmarks were required. Oral and dermal exposures were evaluated using EPA's oral reference dose (RfD) of 0.2 mg/kg/day. Inhalation exposures were evaluated using an inhalation reference concentration of 0.66 mg/m^3 as discussed in greater detail below. The values for these health benchmarks are presented in Table 8.1.

Table 8.1: Xylenes Chronic Health Benchmarks for the VCCEP Risk Assessment

Route	Health Benchmark
Oral	0.2 mg/kg/d
Inhalation	0.66 mg/m^3

The chronic inhalation health benchmark of 0.66 mg/m^3 (VCCEP chronic inhalation health benchmark) is based on many of the same assumptions and adjustments that were made by EPA in deriving the RfC, including selection of the point of departure. The derivation of this health benchmark and an alternative health benchmark based on PBPK modeling are presented in Table 8.2 and discussed in the next section.

8.1.1.1 Derivation of the IRIS RfC and Alternative Chronic Inhalation Health Benchmarks

This section discusses the basis for EPA's derivation of the inhalation RfC, the derivation of the chronic inhalation health benchmark used in this risk assessment (VCCEP Chronic Inhalation Health Benchmark) and another alternative chronic inhalation health benchmark using PBPK models.

Table 8.2: Analysis of the Adjustment and Uncertainty Factors for the Xylenes EPA IRIS RfC, the Xylenes VCCEP Chronic Inhalation Health Benchmark and an Alternative PBPK Inhalation Health Benchmark

Adjustment Factors	IRIS	VCCEP	PBPK	Comment
Point of Departure (mg/m^3)	217	217	217	Based on rotarod effects from study with limited description of methods. PBPK value of 217 mg/m^3 is EPA model estimate for continuous human exposure level needed to achieve same internal peak blood concentration as that estimated for rat at NOAEL for rotarod effects.
Duration adjustment (5 days/week, 6 hours/day to 7 days/week, 24 hours/day.	Divide by 5.56	Divide by 5.56	Divide by 5.56	This factor may have been accounted for in PBPK model estimate of human equivalent continuous exposure level.
Adjustment for human equivalent concentration	Multiply by 1	Multiply by 1.7	Multiply by 1	Rats have higher blood:gas partition coefficient. Data should be used instead of default policy assumption. PBPK model already accounts for rat-human differences.

Adjustment Factors	IRIS	VCCEP	PBPK	Comment
Interspecies pK uncertainty factor	1	1	1	Adjustment for pK factor is already accounted for when adjusting for human equivalent concentration
Interspecies pharmacodynamic uncertainty factor	$10^{1/2}$	$10^{1/2}$	$10^{1/2}$	
Intraspecies pharmacokinetic and pharmacodynamic uncertainty factor	10	10	$10^{1/2}$	PBPK modeling by Pelekis et al. (2001) suggests no adult-children pharmacokinetic differences. In assessing children's risk, the intraspecies uncertainty factor could then be lowered to $10^{1/2}$ accounting for human for pharmacodynamic uncertainty only.
Subchronic to chronic duration uncertainty factor	$10^{1/2}$	$10^{1/2}$	$10^{1/2}$	Rotarod performance did not increase with time following 1, 3 and 6 months of exposure.
Database uncertainty factor for lack of multigeneration study.	3	1	1	It is unlikely for multi-gen repro study to result in NOAEL lower than the point of departure of 50 ppm based on 1-gen NOAEL of 500 ppm; DNT LOAEL of 500 ppm.
(TOTAL UF) x (other dose adjustment factors)	300 x 5.56	100 x 3.27	27 x 5.56	The NOAEL of 217 mg/m^3 (50 ppm) should be DIVIDED by these total factors
RfC (mg/m^3)	0.1	0.66	1.44	

Each of the adjustment and uncertainty factors in deriving these chronic inhalation health benchmarks are discussed below. The adjustment and uncertainty factors for the EPA IRIS RfC are further discussed in Section 5.2.3 of the IRIS Toxicology Review (EPA 2003a):

1. The point of departure is based on a NOAEL of 50 ppm (217 mg/m^3) for neurobehavioral effects in rats following 3 months of exposure.

2. A standard adjustment was made by multiplying the point of departure by 5 days/ 7 days and by 6 hrs/day/24 hours /day. Thus, the NOAEL of 217 mg/m^3 was divided by 5.6 to derive a duration adjusted NOAEL for continuous exposure of 39 mg/m^3. EPA refers to this adjustment as a duration adjustment.

3. The EPA's duration adjusted NOAEL of 39 mg/m^3 was expressed as a human equivalent concentration by using the default assumption of 1. This value does not take into consideration the ratio of 1.7 for blood:gas partition coefficient for the laboratory animal species to the human value. The VCCEP health benchmark considers this factor in adjust the HEC to 66.3 mg/m^3 – 39 mg/m^3 x 1.7 = 66.3 mg/m3.

4. A UF of 3.16 ($10^{½}$) was applied to account for toxicodynamic interspecies differences between laboratory animals and humans. The toxicokinetic portion of the UF is 1 because human equivalent concentration dosimetric adjustments were already accounted for. This is supported by the data and should be applied after using data derived adjustments based on pharmacokinetic data.

5. A UF of 10 was applied to the RfC for intraspecies uncertainty to account for human variability and sensitive populations. Briefly, this intraspecies uncertainty factor is based on a combination of uncertainty factors for pharmacokinetic ($10^{½}$) and pharmacodynamic ($10^{½}$) differences - $10^{½}$ x $10^{½}$ = 10. There is pharmacokinetic data to suggest that the pharmacokinetic portion of the intraspecies uncertainty factor can be reduced to 1. Specifically, Pelekis et al. (2001) compared adult-to-child pharmacokinetic intraspecies difference using conventional physiological-based pharmacokinetic models and physiological parameters from the literature for an average 10-kg child, 1 year of age, and a range of physiological parameters for adults. The results of this comparison of pharmacokinetic differences between children and adults ranged between 0.033-0.88 for xylenes suggesting no adult-children differences in the internal concentrations of xylenes that are likely to be observed during inhalation exposures. In fact, values less than "1" indicate that children may have lower internal concentration than adults for same inhalation exposure levels. As discussed below, the UF for intraspecies uncertainty factor was not adjusted for the VCCEP health benchmark (i.e. total intraspecies UF remained 10). However, the intraspecies factor was reduced to $10^{½}$ for the alternative PBPK chronic inhalation health benchmark which makes use of the available pK data. This analysis does not address potential pharmacodynamic differences and that factor ($10^{½}$) is retained for all of the health benchmarks. However, there are data to indicate that offspring exposed during gestation are not more vulnerable to effects on neurobehavioral endpoints which is the critical effect of xylenes.

6. A UF of 3.16 ($10^{½}$) was applied for extrapolation from subchronic to chronic duration. EPA used this UF because the changes in rotarod performance did not increase with time from 1 to 3 months, and they were similar to those described in a separate study of 6 months duration. The same uncertainty factor was used in the derivation of the alternative inhalation health benchmarks.

7. A UF of 3 was applied for database uncertainty primarily due to the lack of a two-generation reproduction study. This UF was reduced to 1 for both of the alternative health benchmarks because a one-generation reproductive study, two dominant lethal studies, and comprehensive developmental neurotoxicology studies have been conducted. Neurobehavioral endpoints are the most sensitive endpoint for xylenes and other solvents in animals and humans. Therefore, these developmental neurotoxicity studies provide much more comprehensive evaluation of the sensitive endpoint of concern in offspring than would be obtained from a guideline multi-generation reproduction study. Database uncertainty factors should not be applied if there is good reason to conclude that the missing study is unlikely to impact the RfC.

Xylenes VCCEP Chronic Inhalation Health Benchmark:

The above comparison of chronic inhalation health benchmarks indicates a possible range of 0.1 to 1.44 mg/m^3. The Consortium has selected the VCCEP chronic inhalation health benchmark of 0.66 mg/m^3 because it is in the middle of this range and because the Consortium believes that the adjustments for blood:gas partition coefficient and database uncertainty factor are well supported.

Blood:Gas partition coefficient:

Typically the duration adjusted NOAEL is multiplied by the ratio of the blood:gas partition coefficient for the laboratory animal species to the human value. However, since this ratio is 1.7, EPA used the value of 1 for policy reasons. Recently, EPA has suggested that this practice should be reconsidered for category 3 gases (i.e., a gas that is relatively water-insoluble and unreactive in the respiratory tract and for which the site of toxicity is generally remote to the site of absorption in the pulmonary region). EPA encouraged the use of data-derived values even when the ratio is much greater than 1 (EPA, 1998; page 4-33). Therefore, the human equivalent concentration should be 39 * 1.7 = 66.3 mg/m3.

Data-base uncertainty factor:

The data-base uncertainty factor of 3 should be removed because there are comprehensive developmental neurotoxicity studies, a one generation reproductive toxicity study, and two dominant lethal studies. Exposure in the one-generation reproductive toxicity study was via inhalation. In addition to the required groups of male and female CD rats exposed to 0, 60, 250 and 500 ppm mixed xylenes, there were two additional 500-ppm groups similarly exposed, except that only the F0 males were exposed in one group and only the F0 females were exposed in the other group. There were no effects on F0 or F1 generation at 500 ppm. Two dominant lethal studies in male rats and mice were treated by injection and mated with untreated females, weekly throughout the spermatogenic cycle. Xylenes did not cause treatment-related effects on reproduction or toxicity to offspring in any of these studies. In addition, several developmental neurotoxicity studies have been conducted. This is of relevance because neurobehavioral endpoints are the most sensitive endpoints of concern based on both the human and animal literature on xylenes and related solvents. A LOAEL of 500 ppm is estimated for developmental neurotoxicity based on exposure during one of the most critical periods of rapid brain development. Thus, it is unlikely that xylene exposure would induce adverse effects in the second generation of a guideline 2-generation study that would be more sensitive than the reproductive data from the 1-generation study, dominant lethal studies, and the extensive neurobehavioral endpoints measured on F1 generation. It is even more unlikely for effects in the 2nd generation of a guideline 2-generation study would occur at doses below the NOAEL of 50 ppm for adult toxicity.

This conclusion is further supported by evaluating data for similar solvents with multigeneration studies. For toluene, the NOAEL and LOAEL for parents and offspring of both generations are 500 ppm and 2000 ppm, respectively (Roberts et al. 2003). For C_9 aromatic naphtha, the NOAEL and LOAEL are 500 ppm and 1500 ppm, respectively, for both parent and offspring from the first and second generation (McKee et al., 1990. In addition, The International Life Sciences Institute's (ILSI) Health and Environmental Sciences Institute (HESI) recently concluded that the second generation of a multigeneration study has little impact on the chronic RfD based on an evaluation of 200

pesticides representing very different classes of chemistry (ILSI, 2005 publication is in peer review).

In conclusion, the overall weight of evidence indicates that the comprehensive evaluation of neurotoxic effects in adults and offspring provide the most sensitive data for risk assessment. These studies indicate a LOAEL of 500 ppm. This together with the lack of effects in the 1-generation study at 60, 250 and 500 ppm indicate that it is unlikely that conducting a multi-generation study would yield results that are not already protected by the NOAEL of 50 ppm based on motor coordination in adult rats which is currently used as the point of departure for the chronic RfC.

8.1.1.2 Discussion of use of PBPK data from Xylenes IRIS in Deriving Chronic Inhalation Health Benchmarks

Rat and human PBPK models for xylenes have been developed (Tardiff et al., 1993, 1995; see also Appendix C) and were used in the xylene IRIS assessment to support the derivation of the RfC (EPA 2003a). Rat PBPK models for xylene inhalation can be applied to the rat NOAEL of 50 ppm (217 mg/m3) and the actual exposure protocol used in the Korsak et al. (1994 rat study (6 hours per day, 5 days per week, for 3 months) to predict arterial blood concentration in rats as a function of time up to 13 weeks. The results show a daily rise and fall of xylene concentrations consistent with rapid elimination from the blood

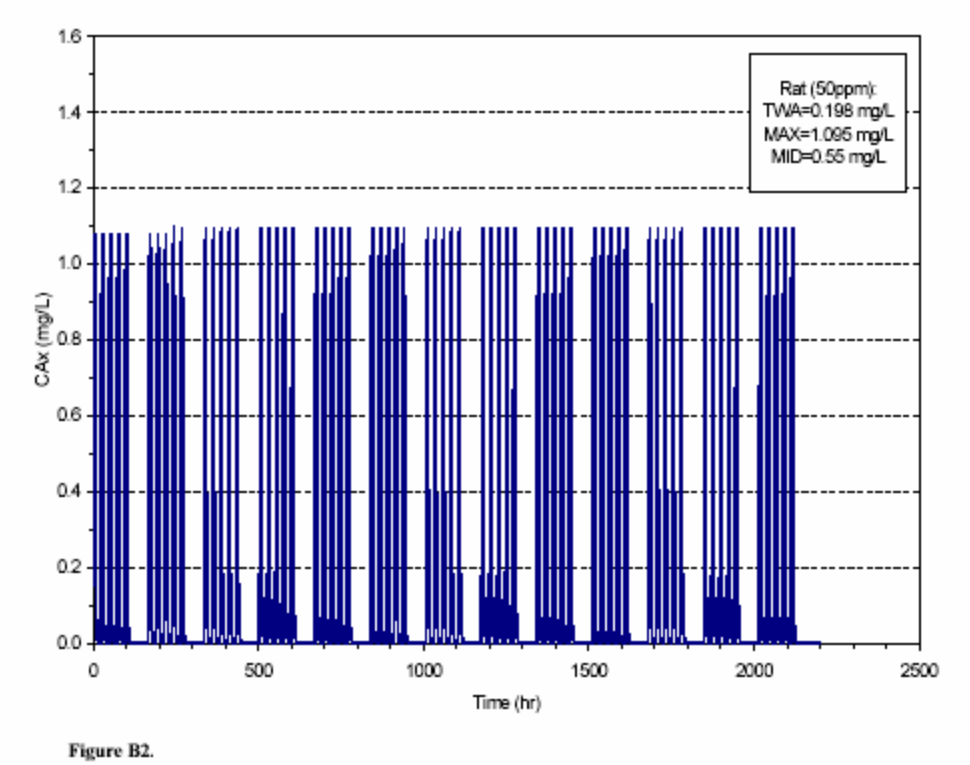


Figure B2.

Figure 8.1: PBPK predicted arterial blood levels in rats exposed to 50 ppm xylene 6 hours/day, 5 days/week for 13 weeks from Xylene IRIS Appendix B

Blood levels rapidly approach maximum levels during exposure, and then rapidly approach 0 mg/L immediately after exposure as is illustrated in the figure below (Tardiff et al., 1993).

Figure 8.2 PBPK Model Prediction Comparisons from Xylenes IRIS

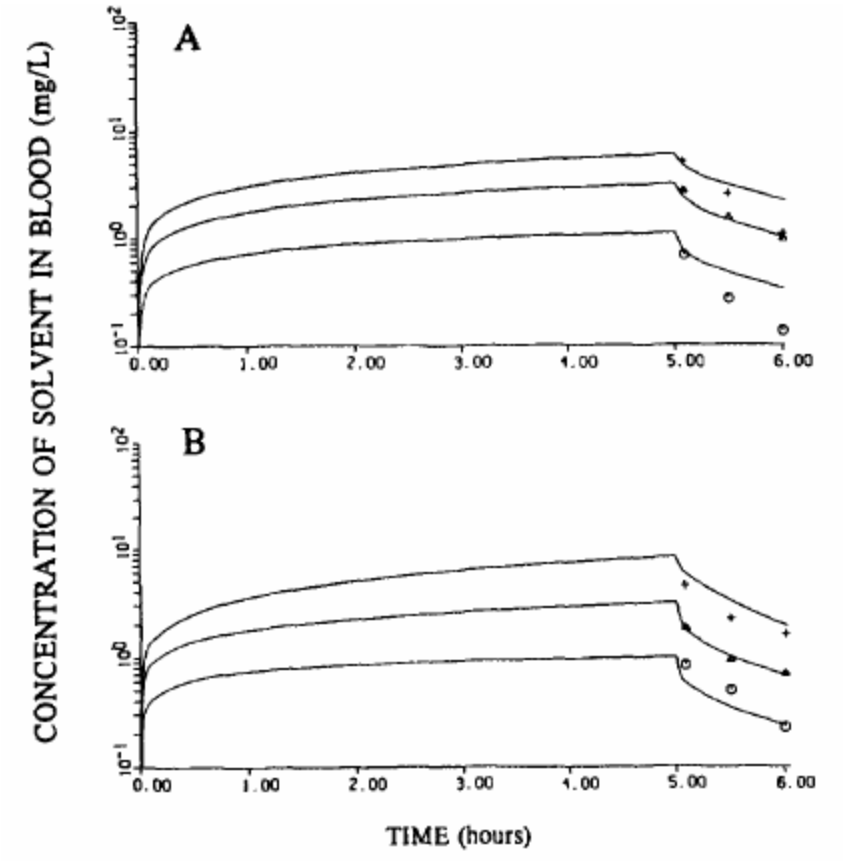


FIG. 2. Comparison of model predictions and experimental observations of the venous blood concentration of toluene (A) and *m*-xylene (B) observed after a 5-hr exposure of rats to 75, 150, or 225 ppm of each solvent. Experimental data are from Tardif *et al.* (1992) and each data point represents the average for five rats.

EPA calculated three following dose surrogates for internal animal dose (EPA 2003a):

- An overall TWA blood concentration (0.198 mg/L, averaged over 1-hour intervals across 13 weeks),
- The maximum (MAX) blood concentration attained on any given day during exposure (1.09 mg/L, essentially a constant over 13 weeks), and
- The mid-point (MID) concentration between the maximum (1.09 mg/L) and the minimum (0 mg/L) concentration on any given day during exposure (0.55 mg/L)

The TWA blood concentration ignores the contribution of the maximum peak effects that are considered to play an important role in both acute and repeated exposure to solvents (Lammers 2005). There is no scientific rationale to use the mid-point (MID) concentration between maximum and minimum concentration because the model predicts exposures

rapidly approach mid-concentration within the first hour of exposure. It is more reasonable to assume that the rotarod effects in the animal study are related to repeated exposure to the maximum blood levels during the 6 hours of exposure rather than a time weighted average blood concentration that is averaged over 1-hour intervals across all 24 hours and 13 weeks including the long periods when blood levels are at 0 mg/L. This analysis is further supported by the lack of decrease in rotarod performance after 1, 2, 3 or 6 months of exposure (Korsak 1994, 1992). These data suggest that the effect is unlikely to be due to cumulative exposures and most likely due to peak exposures.

The use of peak levels is biologically plausible even if it is assumed that rotarod testing occurred 24 hours after exposure when blood and fat concentrations are estimated to approach zero following repeated daily exposures. Preliminary *in vitro* data indicate that solvents can block NMDA receptors, alter function of voltage sensitive calcium channels and augment function of GABA and glycine receptors (see review by Bushnell et al. 2005). With repeated exposures there are opportunities for receptor up or down regulation and other compensation which have not been well described as yet for the solvents, but which may account for effects seen after repeated exposures and clearance of tissue levels of the compound. For example, the acute effects following exposure to toluene by van Lammers et al. (2005) were not easily explained by brain tissue concentration, but the intermittent exposure paradigm left room for receptor modifications or other physiological changes. Thus, the maximum rat blood concentration of 1.09 mg/L should be used as the point of departure for derivation of an RfC based on PBPK modeling.

Alternative PBPK Inhalation Health Benchmark

Based on human PBPK modeling, EPA estimates that the external air concentrations predicted to attain steady state blood concentrations of 1.09 mg/L in humans with continuous exposure is 50 ppm (217 mg/m^3). In other words, the continuous human exposure level (24 hours/day, 7 days/week) that will result in the maximum daily rat blood levels that were rapidly attained each exposure day for 13 weeks (3 months) is 217 mg/m^3. The duration exposure adjustment factors (5.56 and 3) were applied. However, it is debatable if the duration adjustment of 5.56 to account for continuous exposure (24 hours/day, 7 days/week) is needed because the human PBPK modeling adjusts for continuous exposure. Based on PBPK modeling by Pelekis et al (2001), the intraspecies uncertainty factor was reduced from the default 10 to $10^{1/2}$. Overall, PBPK modeling of adult and child pharmacokinetic intraspecies uncertainty factors for xylene and other volatile organic compounds suggests that there are no adult-children differences in the parent chemical concentrations that are likely to be observed during inhalation exposures. In addition, the database (reproduction, developmental, developmental neurotoxicity studies) indicates that the developing fetus and offspring are not more sensitive than adults to the effects of xylene. Taken together, these data support a reduction of the intraspecies uncertainty factor to 3.

The PBPK chronic inhalation health benchmark is derived by using the human equivalent exposure level of 217 mg/m^3 and dividing by 5.56 (duration adjustment for continuous exposure), 3 (interspecies factor), 3 (intraspecies) and 3 (subchronic to chronic extrapolation) resulting in a health benchmark of 1.44 mg/m^3. This PBPK health benchmark was not used in the risk assessment calculations as a decision was made to use the VCCEP health benchmark of 0.66 mg/m^3 which is approximately the mid-point of the range between the RfC of 0.1 mg/m^3 and this health benchmark of 1.44 mg/m^3. The

decision not to use this chronic inhalation health benchmark was based on practical considerations to simplify the presentation of the quantitative results and is not a reflection on its appropriateness. As Section 8.6 (Uncertainty) discusses, the choice of chronic inhalation health benchmarks would have little impact on the overall results of the risk assessment as all chronic inhalation exposures are below all three health benchmarks.

8.1.2 Benchmark Used to Evaluate the Acute Effects of Xylenes

The acute effects are associated with short-term high-level exposures. In the case of xylenes, the short-term acute exposures are dominated by inhalation exposures. For this reason, an inhalation-based criterion was used to evaluate acute effects. The EPA has begun a process for deriving acute RfCs, however, one is not currently available for xylenes (Strickland and Fourman, 2002; EPA, 1998, 2004). Therefore, the criteria that were used to evaluate potential acute health risks are the 1-hr and 8-hr Interim Acute Exposure Guideline Levels (AEGL-1) of 130 ppm (EPA, 2005). AEGLs represent threshold exposure limits that the EPA believes are applicable to the general population (including children and susceptible subpopulations) for emergency periods ranging from 10 minutes to 8-hours. Three AEGL levels are developed for the various time periods and are differentiated by varying degrees of severity of toxic effects. The AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population could experience notable discomfort, irritation or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

The AEGL-1 for xylenes was derived from a human exposure study where volunteers were exposed to mixed xylenes at a concentration of 400 ppm for 30 minutes (Hastings et al., 1986). The sensitive endpoint for this study was eye irritation. An interspecies uncertainty factor was not applied because the key study used human data. However, an intraspecies uncertainty factor of 3 was applied because eye slight irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals.

8.2 Risk Assessment Methodology

The risk characterization methodology used for xylenes employs a Hazard Quotient (HQ) approach where, calculated chronic doses and compared to the chronic RfC or RfD. Hazard quotients represent the potential occurrence of adverse effects from single exposure scenarios, or single route exposures. HQs were determined for both chronic and acute exposures to xylenes. For chronic effects, the HQ was determined based on the following equation:

$$HQ = \frac{Exposure}{Health\ Benchmark}$$

where:

HQ	= Hazard quotient (unitless)
Exposure	= Annual average daily dose (mg/kg/d) or exposure concentration
Health Benchmark	= Reference Dose (RfD) or Reference Concentration (RfC)

When a person receives concurrent exposure (i.e., has exposures from more than one scenario or exposure pathway), the HQs associated with each dose are summed to give a Hazard Index (HI).

$HI = HQ_1 + HQ_2 + \ldots HQ_i$

where:

HI	=	Cumulative hazard index (unitless)
HQ	=	Hazard quotient (unitless) for the i^{th} exposure route and source

A complete description of this approach is given in Risk Assessment Guidance for Superfund Sites (EPA, 1989). Under this approach, HQs are determined for each exposure scenario (both ambient and source specific) in the assessment. Findings of values less than 1 indicate that adverse effects are unlikely to occur in even sensitive members of the exposed population. Where exposures to multiple sources occur to the same individual at the same time, the values of the relevant HQs are added to produce the HI values. If the total HI is less than 1, risks from all routes of exposure are considered negligible. It is important to note that an HI >1 is not a bright line dividing actual health hazard from non-hazard. Given that the xylenes RfC is based on a NOAEL and incorporates a total uncertainty factor of 300, an HI of 10 for example, still leaves a factor of 30 between the estimated exposure and the NOAEL. This line of reasoning is the basis for the recommended risk-based prioritization scheme within the1990 Amendments to the Clean Air Act for determining and managing residual risk after MACT implementation (Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). In this guidance, it has been recommended that if after a screening level risk assessment of an air toxic, the HI is less than 10, further action is not deemed necessary in terms of a more detailed assessment or risk control options.

8.3 Evaluation of the Risk of Chronic Effects

8.3.1 Evaluation of the Risk of Chronic Effects from Background Sources of Exposure

The HQs associated with the oral, dermal and inhalation exposure to background sources (ambient air, food and tap water, and in-vehicle exposures) were summed to generate a total background hazard index (HI). For the background evaluation, ambient air incorporates outdoor and indoor air, as well as in-vehicle exposures. In-vehicle exposures have been considered as part of a person's background exposure because, while they may be thought of as source-specific, in the general population they occur on a daily basis. The age-specific HIs for typical and high-end exposures are well below 1 and are presented in Table 8.2.

Table 8.2
Chronic Risk Evaluation for Children's Background Exposures to Xylenes

	Typical Exposure Hazard Quotients					High End Exposure Hazard Quotients				
Source	<1 year old *	1-5 year old	6-13 year old	14-18 year old	19-35 year old	<1 year old *	1-5 year old	6-13 year old	14-18 year old	19-35 year old
Air										
Rural	0.01	0.01	0.01	0.01	0.01	0.05	0.04	0.04	0.04	0.04
Urban	0.01	0.01	0.01	0.01	0.01	0.05	0.05	0.05	0.05	0.05
Food & Tapwater Ingestion	0.001	0.001	0.0005	0.0002	0.0002	0.002	0.002	0.0008	0.0005	0.0004
Breast Milk-Occupational	0.003	--	--	--	--	0.133	--	--	--	--
Showering - dermal	0.0001	0.0002	0.0001	0.00009	0.00009	0.0003	0.0003	0.0002	0.0002	0.0002
Showering – inhalation	0.0002	0.0001	0.00002	0.00002	0.00002	0.001	0.0005	0.0001	0.0001	0.0001
Ambient HIs										
Rural	0.02	0.01	0.01	0.01	0.01	0.2	0.04	0.04	0.04	0.05
Urban	0.02	0.01	0.01	0.01	0.01	0.2	0.05	0.05	0.05	0.05

*The total HI for the <1 yr old includes ingestion of breast milk from an occupationally exposed mother. The hazard index for the nursing infant of a non-occupationally exposed mother would be less.

The background sources of exposure either individually or in aggregate result in HIs ranging from 0.01-0.1. Thus, the health risks from background exposures to xylenes are negligible.
The largest HI is calculated for the infant where the high-end exposure to food and tapwater results in an HI of 0.1. For all age groups except the infant, the inhalation hazard quotients contribute the most to the total hazard index.

8.3.2 Evaluation of the Risk of Chronic Effects from Source-Specific Exposures

Source specific exposures may occur on a frequent or infrequent basis. The source-specific exposures that are frequent or continuous in nature, such as from refueling and smoking are more important in a chronic evaluation than those where exposures are more sporadic (e.g., spray paint, degreasing, etc.). Tables 8.3 and 8.4 present the HIs for source-specific xylenes exposures and the aggregate result when high-end background is considered as well.

Frequent Source-Specific Exposures

The HI resulting from refueling exposures range from 0.00022 to 0.0025, and the total HIs, including background xylenes exposures, range from 0.01 to 0.1. Thus, as shown on Table 8.3, the addition of xylenes exposures from refueling, do not appreciably change the potential health risk beyond that of typical and high-end background exposures.

Table 8.3

Chronic Hazard Evaluation of Children's Exposure to Xylenes from Refueling

Scenario	Typical Exposure Hazard Quotients		High-end Exposure Hazard Quotients	
	16-18 year old	19-35 year old	16-18 year old	19-35 year old
Refueling	0.00025	0.00022	0.0025	0.0022
Background HI (urban)	0.01	0.01	0.05	0.1
	Typical Refueling Hazard Indices		**High-end Refueling Hazard Indices**	
Total HI	0.01	0.01	0.05	0.1

The HIs from tobacco smoke exposures range from 0.0009 for ETS to 0.03 for mainstream smoke. The total HIs incorporating background exposures and tobacco smoke therefore range from 0.01 to 0.05. As shown on Table 8.4, the contribution of xylenes from ETS to background health risks is not significant. However, for mainstream smoking, the total HI increases by a factor of 3, although the total HI is still less than 1 when aggregated with background exposures.

Table 8.4
Chronic Hazard Evaluation of Children's Exposure to Xylenes from Tobacco Smoke

Scenario	Tobacco Smoke Exposure Hazard Quotients				
	<1 year old	1-5 year old	6-13 year old	14-18 year old	19-35 year old
ETS	0.0012	0.0012	0.0010	0.00092	0.0012
Mainstream Smoke	--	--	--	0.014	0.034
Background HI (urban)	0.04	0.01	0.01	0.01	0.01
	Typical Tobacco Smoke Hazard Indices				
Total HI	0.04	0.01	0.01	0.03	0.05

8.4 Evaluation of the Risk of Acute Effects from Short-Term Infrequent Sources of Exposure

The risks from the acute effects of xylenes were evaluated using the short-term exposure concentrations that result during consumer product use. The estimates of concentration used in this analysis were the time weighted air concentrations for 1-hour and 8-hour exposure durations previously presented in Section 7.2.2.2 of the Exposure Assessment.

The HI values for the degreasing and spray painting scenarios are presented on Tables 8.5 and 8.6.

Table 8.5
Hazard Evaluation for Children's Short Term Exposure to Xylenes from Residential Metal Parts Degreasing

Exposure Scenario		Typical Exposure HI	High End Exposure HI
1-hr TWA	User	0.073	0.23
	Non-User	0.018	0.068
8-hr TWA	User	0.011	0.033
	Non-User	0.0032	0.012

Table 8.6
Hazard Evaluation for Children's Short Term Exposure to Xylenes from Residential Spray Painting

Exposure Scenario		Typical Exposure HI	High End Exposure HI
1-hr TWA	User	0.21	0.35
	Non-User	0.055	0.10
8-hr TWA	User	0.052	0.077
	Non-User	0.016	0.025

The HIs for both the consumer product users and non-users range from 0.01 to 0.3. Thus, the short-term exposure concentrations associated with the indoor use of xylenes as a degreaser or a component of spray paint in accordance with manufacturer instructions are unlikely to produce noticeable discomfort or irritation to the general public and susceptible individuals.

8.5 Occupational Exposures

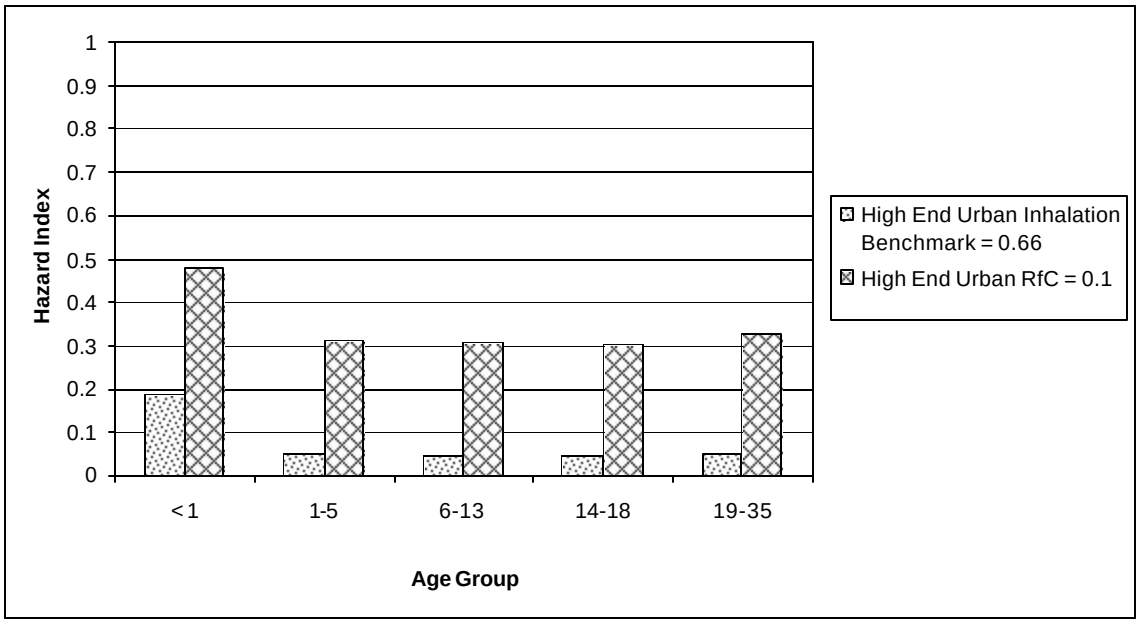
A HI for the maternal dose received from occupational exposure has not been calculated because occupational risk is not evaluated using the hazard index – reference dose approach. Occupational exposure levels are established primarily on human data and the 100 ppm TLV for xylenes was established using human studies of workers exposed via inhalation (ACGIH, 2005). Exposures below the TLV are considered safe for nearly all workers exposed daily. Current data from the xylenes production industry and from the general literature indicate that typical occupational exposures (0.11 ppm) and high-end

exposures (8 ppm) are well below the TLV of 100 ppm. As explained in Section 6.0 (Hazard Assessment), xylene data do not suggest a developmental or reproductive hazard. Therefore, information on maternal occupational exposures has been used only to estimate an infant's exposure to xylenes through human milk when the mother is occupationally exposed.

8.6 Discussion of Uncertainties

Uncertainties in the exposure estimates are described in the Exposure Assessment (Section 7). The strengths and weakness of the underlying hazard data used in the development of the health benchmarks are discussed in the Hazard Assessment (Section 6). A comparison of the uncertainty and adjustment factors that went into the chronic inhalation health benchmark are discussed in Section 8.1. Neither hazard assessment nor exposure assessment is an exact science, but conservative (i.e., health protective) assumptions have been employed in each area, such that margins of safety are more likely to be overprotective than underprotective.

Figure 8.3: Comparison of Hazard Indices from IRIS RfC and VCCEP Chronic Inhalation Health Benchmark



To understand any potential uncertainty in the characterization of risk from the use of an alternative chronic inhalation health benchmark, a comparison of the hazard indices calculated for the chronic background exposures using both the value used in the Risk Assessment and the EPA RfC value was made. Figure 8.3 presents a comparison of the urban chronic background high-end scenario HIs calculated using both inhalation benchmarks.

As shown on Figure 8.3, the HIs calculated using the EPA RfC of 0.1 ug/m^3 are still below 1. Therefore, use of the more conservative inhalation benchmark does not change in any significant fashion the characterization of risk to children from chronic xylenes exposure.

8.7 Conclusions

The information in this risk assessment and the underlying hazard assessment and exposure assessment demonstrates the following:

- Very low xylenes exposures are received from everyday background sources of exposure such as ambient air, water, food and in-vehicle exposures. Aggregated background doses result in HIs that are less than 0.05 at the high-end for all age groups, except the nursing infant of an occupationally exposed mother;

- Total xylenes doses to the nursing infant of an occupationally exposed mother range from a typical dose of 0.004 mg/kg-day to a high end dose of 0.03 mg/kg-day, which results in HQs ranging from 0.02 to 0.2.

- Chronic, source-specific, inhalation exposures to xylenes from tobacco smoking and vehicle refueling scenarios do not result in exceedances of the health benchmark, even when aggregated with background ambient doses. Tobacco smoke HIs range from 0.0009 for a child exposed only to ETS to 0.034 for an adult exposed to ETS and mainstream smoke. Refueling HIs do not exceed 0.003 for a high-end exposure; and

- Short term air concentrations of xylenes to which children may be exposed during use of various consumer products are not expected to exceed the interim AEGL-1 value of 130 ppm under typical or high-end exposure conditions. HIs for the product users ranged from 0.01 to 0.3.

The quantitative risk characterization indicates that reasonably anticipated children's exposures to xylenes from the ambient background environment and specific sources such as gasoline during refueling and consumer product use are unlikely to pose significant health risks.

9.0 VCCEP Data Needs Assessment

9.1 Hazard

Toxicity data on xylenes are available for all the Tier 1 VCCEP endpoints and most of the higher tiered endpoints, including subchronic and chronic repeated-dose, reproductive/developmental toxicity, neurotoxicity, developmental neurotoxicity, immunotoxicity, and metabolism. These data are reviewed in Section 6 (Hazard Assessment). While the available data for some endpoints are not the exact study indicated in the VCCEP Federal Register notice, the available toxicity data adequately address the endpoints of interest. On the reproductive and developmental toxicity endpoints, a one-generation reproductive study, two dominant lethal studies, and several comprehensive developmental and developmental neurotoxicology studies are available. As neurobehavioral effects appear to be the most sensitive endpoint for xylenes and there are no indications of reproductive performance effects in the available data, there appears to be little to gain from conducting a two-generation reproductive toxicity study (see Section 6.5 for addition discussion). The existing developmental neurotoxicity studies provide much more comprehensive evaluation of the sensitive endpoint of concern in offspring than would be obtained from a guideline multi-generation reproduction study. A LOAEL of 500 ppm can be identified based on subtle behavioral effects in rats following *in utero* exposure to xylene. The NOAEL for the 1-generation study is also 500 ppm. Based on these results and that of related chemicals, it would be unlikely that a new multigeneration study will result in a NOAEL that is lower than the NOAEL of 50 ppm that is used as the point of departure. Furthermore, the large significant margins between the HIs and estimated exposures make it unlikely for a new multigeneration study to have significant impact on the risk assessment.

9.2 Exposure

For compounds, like xylenes, that are used in consumer products and occur in many environments, additional exposure assessment work is always possible. The VCCEP sponsors believe, however, that the information presented in this document is fully adequate to demonstrate that reasonably anticipated exposures to the compound from environmental sources are not likely to present significant health risks to children. The hazard indices from the Risk Assessment are very small, indicating low potential for chronic risk, and there are considerable margins of safety for short-term acute exposures. Equally important, xylenes exposures have been declining for the last few decades due to regulatory and other factors. As described in Section 4, extensive regulatory controls are already in place and additional anticipated controls will further reduce exposures in the years to come.

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