ASSESSMENT REPORT ON

XYLENES

FOR DEVELOPING AMBIENT AIR QUALITY OBJECTIVES

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Prepared by
Cantox Environmental Inc.

IN CONJUNCTION WITH
RWDI West Inc.

for
Alberta Environment

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FOREWORD

Alberta Environment maintains Ambient Air Quality Objectives[1] to support air quality management in Alberta. Alberta Environment currently has ambient objectives for more than thirty substances and five related parameters. These objectives are periodically updated and new objectives are developed as required.

With the assistance of the Clean Air Strategic Alliance, a multi-stakeholder workshop was held in October 2000 to set Alberta's priorities for the next three years. Based on those recommendations and the internally identified priority items by Alberta Environment, a three-year work plan ending March 31, 2004 was developed to review four existing objectives, create three new objectives for three families of substances, and adopt six new objectives from other jurisdictions.

In order to develop a new three-year work plan, a multi-stakeholder workshop was held in October 2004. This study was commissioned in preparation for the workshop to provide background information on alternative, science based, and cost effective methods for setting priorities.

This document is one of a series of documents that presents the scientific assessment for these adopted substances.

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Project Manager
Science and Standards Branch

[1] **NOTE**: The *Environmental Protection and Enhancement Act,* Part 1, Section 14(1) refers to "ambient environmental quality objectives" and uses the term "guidelines" in Section 14(4) to refer to "procedures, practices and methods for monitoring, analysis and predictive assessment." For consistency with the *Act*, the historical term "ambient air quality guidelines" is being replaced by the term "ambient air quality objectives." This document was prepared as the change in usage was taking place. Consequently any occurrences of "air quality guideline" in an Alberta context should be read as "air quality objective."

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ACRONYMS, ABBREVIATIONS AND DEFINITIONS

AAL	Allowable Ambient Level (Massachusetts) or Acceptable Ambient Level (North Carolina)
AAQC	Ambient Air Quality Criteria
AAS	Ambient Air Standard (Louisiana)
ACGIH	American Conference of Governmental Industrial Hygienists
AGC	Annual Guideline Concentration (New York State)
ANR	Vermont Agency of Natural Resources (Vermont)
ASIL	Acceptable Source Impact Level (Washington Department of Ecology)
ATC	Allowable Threshold Concentration – continuous exposure (daily lifetime) (Massachusetts DEP)
ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
CalEPA	California Environmental Protection Agency
CAPCOA	California Air Pollution Control Officers Association
CAS	Chemical Abstracts Service
CCME	Canadian Council of Ministers of the Environment
CEIL	Ceiling Value
CEPA	Canadian Environmental Protection Act
DEC	Department of Environmental Conservation (*e.g.*, New York)
DENR	Department of Environment and Natural Resources (*e.g.*, North Carolina)
DEP	Department of Environmental Protection (*e.g.*, Massachusetts, New Jersey)
DES	Department of Environmental Services (*e.g.*, New Hampshire)
DEQ	Department of Environmental Quality (*e.g.*, Michigan, Louisiana, Oklahoma
DOE	Department of Environment or Department of Ecology (*e.g.*, Washington)
ENEV	Estimated No-Effects Value
EPA	Environmental Protection Agency (*e.g.*, Ohio)
ESL	Effects Screening Level
GLC	Ground Level Concentration
GV	Guideline Value
HAAS	Hazardous Ambient Air Standard
HEAST	Health Effects Assessment Summary Tables
HEC	Human Equivalent Concentration
HRV	Health Risk Value
IARC	International Agency for Research on Cancer
IHRV	Inhalation Risk Value
IRIS	Integrated Risk Information System
IRSL	Initial Risk Screening Level
ITSL	Interim Threshold Screening Level
LC50	Median Lethal Concentration
LD50	Median Lethal Dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEC	Lowest-Observed-Effect Concentration
LOEL	Lowest-Observed-Effect Level
MAAC	Maximum Acceptable Ambient Air Concentration

MAAQC	Maximum Annual Air Quality Criteria
MAC	Maximum Acceptable Concentration
MACT	Maximum Achievable Control Technology
MAGLC	Maximum Acceptable Ground-Level Concentration
MAQC	Maximum Air Quality Criteria
MDH	Minnesota Department of Health
MHRV	Multimedia Health Risk Value
MIC	Maximum Immission Concentration (Netherlands)
MPR	Maximum Permissible Risk Level
MRL	Minimal Risk Level
MTLC	Maximum Tolerable Level Concentration
NAAQO	National Ambient Air Quality Objective
NIEHS	National Institute of Environmental Health Sciences (USA)
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
NPRI	National Pollutant Release Inventory
NRCC	Natural Resource Conservation Commission
NTP	National Toxicology Program (USA)
OEHHA	Office of Environmental Health Hazard Assessment (California EPA)
OEL	Occupational Exposure Limit
OMOE	Ontario Ministry of Environment
OSHA	Occupational Safety and Health Association
PEL	Permissible Exposure Limit
PM	Particulate Matter
POI	Point of Impingement
PSL	Priority Substance List
PSL1	First Priority Substances List (Canada)
PSL2	Second Priority Substances List (Canada)
RD50	Median Respiration Rate Decrease
REL	Either Reference Exposure Limit as used by the California EPA or Recommended Exposure Limit used by both NIOSH and ATSDR
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Netherlands Research for Man and Environment
RM	Risk Management
RTECS	Registry of Toxic Effects of Chemical Substances
SGC	Short-term Guideline Concentration
SRSL	Secondary Risk Screening Level
STEL	Short-term Exposure Limit
TAPG	Toxic Air Pollutant Guideline
T-BACT	Best Available Control Technology for Toxics
TC	Tolerable Concentration
TCA	Tolerable Air Concentration

TC01	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 1% increase in incidence or mortality due to tumours
TC05	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 5% increase in incidence or mortality due to tumours
TD05	Tumorigenic Dose - the total intake of a contaminant generally associated with a 5% increase in incidence or mortality due to tumours
TEL	Threshold Effects Exposure Level
TLV	Threshold Limit Value
TNRCC	Texas Natural Resource Commission
TWA	Time-Weighted-Average
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization

ppm	parts per million
ppb	parts per billion
mg	a milligram, one thousandth of a gram
µg	a microgram, one millionth of a gram
ng	a nanogram, one billionth of a gram

SUMMARY

Xylenes are monocyclic aromatic compounds with two methyl groups attached to the benzene ring. Xylenes exist in three isomeric forms *ortho*- or *o*-xylene, *meta*- or *m*-xylene and *para*-xylene or *p*-xylene. Xylenes are clear, colourless, volatile, flammable liquids under standard conditions.

Xylenes are a naturally occurring minor component of all petroleum products. Also, they are formed during combustion of organic materials; thus forest, grass and other biomass fires will release xylenes to the atmosphere. They also are present in volcanic gases. Anthropogenic xylenes are primarily produced *via* the catalytic reforming of petroleum and as by-products of the cracking of crude and heavy oil. The major use of xylenes is as an additive to gasoline during blending to enhance the fuel's octane rating. Xylenes are widely used as solvents in paints, varnishes and other coatings, pesticide formulations, vitamins, pharmaceuticals, printing inks, dyes, adhesives, sealants, cleaning agents, degreasing agents, paint removers, for chemical extractions and as feedstocks in chemical manufacturing.

Most xylenes released to the environment will occur in the atmosphere and volatilization is the dominant environmental fate process. In the ambient atmosphere, xylenes are expected to exist solely in the vapour phase. Xylenes are degraded in the atmosphere primarily by reaction with photochemically-produced hydroxyl radicals, with an estimated atmospheric lifetime of about 0.5 to 2 days. Xylenes' susceptibility to photochemical oxidation in the troposphere is to the extent that they may contribute to photochemical smog formation.

The major sectors in Alberta that release xylenes to air are the oil and gas sector (including oil sands operations, gas plants and petroleum refineries), cement manufacturing, fabricated metal products manufacturing and aluminum product manufacturing. Depending on the facility, fugitive emissions, stack emissions and releases during storage and handling can all be significant sources of xylenes to the atmosphere.

Xylenes are rapidly and extensively absorbed by the inhalation route. Following absorption, xylene is quickly distributed throughout the body. Xylene accumulates preferentially in lipid-rich tissues such as adipose tissue, brain, liver and kidneys. In the body, considerable and rapid metabolism of xylenes occurs, with the liver being the primary site of metabolism. Xylene isomers are primarily metabolized by oxidation of a methyl group, followed by conjugation with glycine to yield methylhippuric acid. This is the major metabolic pathway for xylenes in humans and animals. In humans, about 95% of the inhaled dose is excreted in the urine, with roughly 5% excreted unchanged in exhaled air. Of the urinary metabolites, more than 90% consists of methylhippuric acid.

The major symptoms of acute human exposure to xylenes include: irritation of the nose, throat and eyes and central nervous system (CNS) effects such as headache, nausea, dizziness, difficulty concentrating, impaired memory, slurred speech, ataxia, fatigue, agitation, confusion, tremors, labored breathing, impaired reaction time, alterations in equilibrium and body balance and sensitivity to noise. In experimental animals, CNS toxicity is a sensitive effect of inhalation exposure to xylenes. Commonly reported signs of CNS neurotoxicity in experimental animals as

a result of acute inhalation exposure to xylene isomers include: narcosis, prostration, incoordination, tremors, muscular spasms, laboured breathing, behavioural changes, hyper-reactivity to stimuli, altered visual evoked potentials, elevated auditory thresholds, hearing loss, decreased acetylcholine in midbrain and norepinephrine in hypothalamus (which suggests effects on motor control, sleep and memory maintenance). Other symptoms of acute xylene exposure in experimental animals include irritation of the respiratory tract, pulmonary edema, pulmonary hemorrhage and pulmonary inflammation. Acute effects are most pronounced at high exposure levels (in excess of 1,000 ppm; 4,350 mg/m^3). Subtler effects occur at lower concentrations.

Neurological effects and irritation of the eyes and respiratory tract are the most commonly reported symptoms following subchronic and chronic inhalation exposure to xylenes. Persistent neurological impairment of the CNS is the most commonly reported and sensitive effect of subchronic or chronic inhalation exposure for experimental animals. In subchronic and chronic studies, measurable effects in several neurobehavioral endpoints begin at concentrations as low as 100 ppm (435 mg/m^3) and manifest themselves before other toxic endpoints.

While a large number of studies have examined the potential developmental effects of inhaled xylenes in animals, adverse effects have been reported only at exposure levels greater than those at which neurological effects occur. The most significant effects on developmental endpoints were decreased fetal body weight or fetal survival in rats at xylene isomer doses of 350 or 700 ppm (Ungváry *et al.*, 1980) or at a mixed xylenes concentration of 780 ppm (Ungváry and Tátrai, 1985) and increased abortions in rabbits exposed to 230 ppm (Ungváry and Tátrai, 1985).

Although the carcinogenicity evidence for xylenes is limited and inconclusive, it does suggest a lack of carcinogenic activity. There appears to be sufficient evidence to conclude that xylenes are not mutagenic or genotoxic.

While differences in the toxicity of the xylene isomers have been detected in a number of studies, no consistent pattern following inhalation exposure has been identified.

Current occupational exposure limits for xylenes derived by ACGIH, NIOSH and OSHA are all based on human studies where irritant effects (ocular and upper respiratory) were demonstrated at air concentrations of 200 ppm (870 mg/m^3). The current ACGIH TLV-TWA, OSHA PEL-TWA and NIOSH REL values are all 100 ppm (435 mg/m^3).

Available ambient air quality guidelines are derived from a number of different sources, including various toxicological and epidemiological studies, the ACGIH TLV-TWA and odour threshold values, all adjusted with various modifying and uncertainty factors. Reported odour thresholds for xylenes are highly variable and have been reported to range from 0.07 to 40 ppm (0.3 to 174 mg/m^3). All existing air quality guidelines appear to be adequately protective of human health. In addition, given the available data on the environmental fate, transport and effects of xylenes, these compounds are not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns.

1.0 INTRODUCTION

Alberta Environment (AENV) establishes Ambient Air Quality Objectives under Section 14 of the Environmental Protection and Enhancement Act (EPEA). These guidelines are part of the Alberta Air Quality Management System (AENV, 2000a).

The concept of whether or not ambient air quality in Alberta is acceptable from a health perspective is addressed in part by Alberta's Ambient Air Quality Objectives (AAQO). Ambient air concentrations considered "acceptable" (*i.e.,* AAQOs) typically consider a number of factors, including physical-chemical properties, sources, effects on human and environmental health, air monitoring techniques and ambient air guidelines derived by other jurisdictions within Canada, the United States, various other countries and multi-country organizations (*e.g.,* World Health Organization).

The main objective of this assessment report is to provide a review of scientific and technical information to assist in evaluating the basis and background for an AAQO for xylenes. The following aspects were examined as part of this review:

- Physical and chemical properties
- Existing and potential natural and anthropogenic emissions sources in Alberta
- Effects on humans, animals and vegetation
- Monitoring techniques
- Ambient air guidelines in other Canadian jurisdictions, United States, European Union and Australia and the basis for their development and use

Key physical and chemical properties that govern the fate and behaviour of xylenes in the environment are reviewed and presented in this assessment report. Existing and potential natural and anthropogenic sources of xylene air emissions in Alberta are also reviewed and presented in this report. This included information obtained from Environment Canada's National Pollutant Release Inventory (NPRI) and the National Air Pollution Surveillance Network (NAPS Network).

Scientific information regarding the toxic effects of xylenes on humans and animals is reported in a number of sources, including toxicological and epidemiological studies published in peer-reviewed journals and detailed regulatory agency reviews such as those published by the International Agency for Research on Cancer (IARC), World Health Organization (WHO), U.S. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency's (U.S. EPA) Integrated Risk Information System (IRIS) and Toxicological Profiles and Canadian Priority Substances List Reports under the Canadian Environmental Protection Act (CEPA 1999). There is also a recent air quality guideline scientific support document for xylenes from the Ontario Ministry of the Environment (OMOE, 2001). All these sources provide valuable information for understanding the potential human and environmental health effects of xylenes. Key information from these sources regarding the effects of airborne concentrations of xylenes on humans, animals, plants and the environment is summarized in this report.

Air monitoring and measuring techniques for xylenes in air are well documented in the peer-reviewed scientific and regulatory agency literature. Several widely used and accepted air monitoring reference methods exist for xylenes that have been developed, tested and reported by such agencies as U.S. EPA, U.S. National Institute of Occupational Safety and Health (NIOSH) and U.S. Occupational Safety and Health Administration (OSHA). These methods and techniques are summarized in this report.

2.0 GENERAL SUBSTANCE INFORMATION

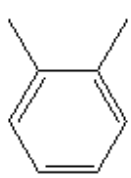
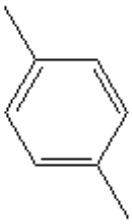
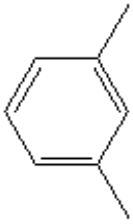
Xylenes are monocyclic aromatic compounds with two methyl groups attached to the benzene ring (CEPA, 1993). Xylenes exist in three isomeric forms *ortho*- or *o*-xylene, *meta*- or *m*-xylene and *para*-xylene or *p*-xylene. The technical or commercial product, "mixed xylenes", consists of about 40 to 70% *m*-xylene, 20% *o*-xylene, 20% *p*-xylene and 20% ethylbenzene (WHO, 1997; ATSDR, 1995). The exact composition of mixed xylenes depends on the source and the manufacturing method used. Ethylbenzene is commonly present in mixed xylenes formulations. Most of the environmental and occupational exposure and toxicological studies have been conducted on mixed xylenes, which as noted, contain ethylbenzene and often minor amounts of toluene, phenol, thiophene, pyridine and C9 aromatics (U.S. EPA, 2003; ATSDR, 1995). In the past mixed xylenes contained benzene in varying amounts; however, current formulations are relatively free (less than 0.001%) of benzene contamination (Gosselin *et al.,* 1984; Riihimaki and Hanninen, 1987).

Xylenes are clear, colourless, volatile liquids under standard conditions (CEPA, 1993; Ellenhorn and Barceloux, 1988; HSDB, 2003; NTP, 2001; Verschueren, 1983; WHO, 1997). The odour of xylenes is commonly described as either sweet (AIHA, 1989; Verschueren, 1983) or aromatic (CEPA, 1993; Ellenhorn and Barceloux, 1988; Mackison *et al.*, 1981; WHO, 1997). Xylenes are relatively insoluble in water and are highly soluble in organic solvents such as ethanol, diethyl ether, acetone and benzene (Budavari *et al.*, 1996; NTP, 2001; WHO, 1997). Xylenes are not compatible with strong oxidizers such as chlorine, bromine and fluorene (DHSS, 1998; NTP, 2001). Xylenes also will attack some forms of plastics, rubbers and coatings (NTP, 2001). Xylene isomers are flammable liquids at room temperature and standard atmospheric pressure (Ellenhorn and Barceloux, 1988; NTP, 2001).

Table 1 provides a list of common synonyms, trade names and identification numbers for xylenes.

Xylenes are a naturally occurring minor component of all petroleum products (CEPA, 1993; HSDB, 2003). Xylenes are primarily produced *via* the catalytic reforming of petroleum and as by-products of the cracking of crude and heavy oil (CEPA, 1993). Mixed xylenes may also be manufactured from coal tar, which yields a mixture of approximately 45 to 70% *m*-xylene, 23% *p*-xylene, l0 to 15% *o*-xylene and 6 to 10% ethylbenzene (HSDB, 2003). Other xylene production processes include gasoline pyrolysis, disproportionation of toluene and recovery from coke-oven light oil (ATSDR, 1995). Individual xylene isomers are produced from mixed xylenes, using such methods as crystallization, fractionation, distillation, isomerization, solvent extraction, complexing with hydrofluoric acid and boron trifluoride or adsorption (HSDB, 2003; ATSDR, 1995).

Table 1 Identification of Xylenes

	Value
Formula	C_8H_{10}
Structure	 *ortho*-xylene  *meta*-xylene  *para*-xylene
CAS Registry Number	1330-20-7 (mixture) 108-38-3 (*m*-isomer) 95-47-6 (*o*-isomer) 106-42-3 (*p*-isomer)
RTECS Number	ZE210000
UN Number	UN1307
Common Synonyms	1,2-Dimethylbenzene (*o*-isomer); 1,3-Dimethylbenzene (*m*-isomer); 1,4-Dimethylbenzene (*p*-isomer); Dimethylbenzene; Xylol; Methyltoluene
Tradenames	AI3-02209-X Caswell No. 906 EPA Pesticide Chemical Code 086802 EPA hazardous waste U239 IMO 3.2 NCI CO7272 VIOLET 3

Xylene is primarily used as an additive to gasoline during blending to enhance the fuel's octane rating (CEPA, 1993; ATSDR, 1995; WHO, 1997). Xylenes also are widely used as solvents in paints, varnishes and other coatings, pesticide formulations, vitamins, pharmaceuticals, printing inks, dyes, adhesives, sealants, cleaning agents, degreasing agents, paint removers and for chemical extractions (Budavari *et al.*, 1996; CEPA, 1993). Xylenes are used as feedstocks or intermediates in the production of benzoic acid, *m*-toluic acid, phthalic anhydride, isophthalic and terephthalic acids and their dimethyl esters, isophthalonitrile, phthalonitrile, 4,4-(trifluoro-1-(trifluoromethyl)ethylidene), diphthalic anhydride (for polyamide polymers) and in polyester manufacturing (Budavari *et al.*, 1996; CEPA, 1993).

In Canada in 1990, 514 kilotonnes were produced and 5 kilotonnes were imported (CEPA, 1993). There are presently no commercial xylene production facilities in Alberta.

2.1 Physical, Chemical and Biological Properties

The physical and chemical properties of xylenes are summarized in Table 2.

Table 2 Physical and Chemical Properties of Xylenes

		Reference
Molecular Weight:	106.16 g/mol	Budavari *et al*., 1996; WHO, 1997
Physical State:	Liquid	Budavari *et al*., 1996; CEPA, 1993; Ellenhorn and Barceloux, 1988; NTP, 2001; WHO, 1997
Melting Point:		
Mixed xylenes	No data	ATSDR, 1995
o-Xylene	-25°C	Budavari *et al*., 1996; HSDB, 2003; Verschueren, 1983
	-25.2°C	WHO, 1997
m-Xylene	-47.9°C	WHO, 1997
	-47.87°C	NTP, 2001; HSDB, 2003
p-Xylene	13°C	Verschueren, 1983
	13.3°C	WHO, 1997; HSDB, 2003
Boiling Point:		
Mixed xylene	138.5°C	Sax and Lewis, 1989
	137 to 140°C	Budavari *et al*., 1996; NTP, 2001
o-Xylene	144.4°C	HSDB, 2003; WHO, 1997
m-Xylene	139.1°C	HSDB, 2003; WHO, 1997
	139.4°C	Budavari *et al*., 1996
p-Xylene	138.3°C	WHO, 1997
	138.37°C	HSDB, 2003
Specific Gravity (liquid):		
Mixed xylene	0.86 at 20°C	NTP, 2001
	0.864 at 20°C	Clayton and Clayton, 1994
o-Xylene	0.88	Verschueren, 1983
m-Xylene	0.864 at 20°C	Verschueren, 1983
p-Xylene	0.86 at 20°C	Verschueren, 1983
Specific Gravity (gas; air=1):		
Mixed xylene	3.7	NTP, 2001
Vapour Pressure:		
Mixed xylene	0.896 kPa at 21°C	NTP, 2001
	1.07 kPa at 25°C	HSDB, 2003
	1.33 kPa at 28°C	NTP, 2001
o-Xylene	0.66 kPa at 20°C	WHO, 1997; Verschueren, 1983
	0.88 kPa at 25°C	HSDB, 2003
	1.2 kPa at 30°C	Verschueren, 1983
m-Xylene	0.79 kPa at 20°C	WHO, 1997; Verschueren, 1983
	1.12 kPa at 25°C	HSDB, 2003
	1.47 kPa at 30°C	Verschueren, 1983

		Reference
p-Xylene	0.86 kPa at 20°C	WHO, 1997; Verschueren, 1983
	1.18 kPa at 25°C	HSDB, 2003
	1.6 kPa at 30°C	Verschueren, 1983
Solubility in Water:		
Mixed xylene	130 mg/L	ATSDR, 1995
o-Xylene	142 mg/L	WHO, 1997
	178 mg/L	ATSDR, 1995
m-Xylene	146 mg/L	WHO, 1997; ATSDR, 1995
p-Xylene	185 mg/L	WHO, 1997; ATSDR, 1995
Solubility in organic solvents:		
Mixed xylene	Very soluble in alcohol and ether	ATSDR, 1995
o-Xylene	Miscible with acetone, benzene and ether	ATSDR, 1995
m-Xylene	Miscible with alcohol, ether and other organic solvents	ATSDR, 1995
p-Xylene	Soluble in alcohol, ether and other organic solvents	ATSDR, 1995
Henry's Law Constant:		
Mixed xylene	No data	ATSDR, 1995
o-Xylene	0.00519 atm.m^3/mol	ATSDR, 1995
m-Xylene	0.00766 atm.m^3/mol	ATSDR, 1995
p-Xylene	0.00766 atm.m^3/mol	ATSDR, 1995
Octanol Water Partitioning Coefficient (log K_{ow}):		
Mixed xylene	No data	No data
o-Xylene	2.77	Verschueren, 1983
	3.12	WHO, 1997; HSDB, 2003
m-Xylene	3.2	WHO, 1997; HSDB, 2003; Verschueren, 1983
p-Xylene	3.15	WHO, 1997; HSDB, 2003; Verschueren, 1983
Octanol Carbon Partitioning Coefficient (log K_{oc}):		
Mixed xylene	No data	ATSDR, 1995
o-Xylene	2.11	ATSDR, 1995
m-Xylene	2.22	ATSDR, 1995
p-Xylene	2.31	ATSDR, 1995
Flash Point (closed cup):		
Mixed xylene	25°C	Budavari *et al*., 1996
	25.6°C	NTP, 2001
o-Xylene	17°C	Budavari *et al*., 1996
	17.2°C	HSDB, 2003
	30°C	WHO, 1997
m-Xylene	25°C	Budavari *et al*., 1996; WHO, 1997; HSDB, 2003
p-Xylene	25°C	Budavari *et al*., 1996; WHO, 1997; HSDB, 2003

		Reference
Explosive Limits:		
Mixed xylene	1.0% to 7.0%	NTP, 2001
o-Xylene	1.0% to 6%	WHO, 1997
m-Xylene	1.1% to 7%	WHO, 1997
p-Xylene	1.1% to 9%	WHO, 1997
Autoignition Temperature:		
Mixed xylene	466°C	NTP, 2001
o-Xylene	465°C	WHO, 1997
m-Xylene	525°C	WHO, 1997
p-Xylene	525°C	WHO, 1997
Odour Threshold:		
Mixed xylene	1.0 ppm	Budavari *et al*., 1996
	0.07 – 40 ppm	Carpenter *et al.*, 1975; Ruth, 1986
o-Xylene	0.17 ppm	Budavari *et al*., 1996
	0.08 ppm	ATSDR, 1995
m-Xylene	0.37 ppm	Budavari *et al*., 1996
p-Xylene	0.47 ppm	Budavari *et al*., 1996
Bioconcentration Factor in Fish	20	HSDB, 2003
	80	CEPA, 1993
Conversion Factors for Vapour (at 25°C and 101.3 kPa)	1 ppm = 4.35 mg/m^3 1 mg/m^3 = 0.23 ppm	WHO, 1997

2.2 Environmental Fate

The environmental fate of xylenes is summarized in Table 3. Fugacity predictions indicate that most xylenes released to the environment will occur in the atmosphere (Mackay *et al.*, 1992) and that volatilization is the dominant fate process.

In the ambient atmosphere, xylenes are expected to exist solely in the vapour phase due to the relatively high vapour pressures and low to moderate water solubilities of these substances (CEPA, 1993; HSDB, 2003). Xylenes are degraded in the atmosphere primarily by reaction with photochemically-produced hydroxyl radicals, with an estimated atmospheric lifetime of about 0.5 to 2 days (HSDB, 2003; Grosjean, 1991; CEPA, 1993). Direct photolysis is not expected to occur because xylenes do not significantly absorb light at wavelengths greater than 290 nm (Jori *et al.*, 1986).

Photooxidation by reaction with ozone or peroxy radicals is believed to be insignificant relative to reaction with atmospheric hydroxyl radicals (ATSDR, 1995). Photooxidation in the presence of nitrate radicals may be a significant fate process at night. The following half-lives for the reaction of xylene with nitrate radicals at night have been estimated: *o*-xylene: 15 to 89 days; *m*-xylene: 23 to 194 days; and *p*-xylene: 13 to 107 days (WHO, 1997). While these half-lives are

Table 3 Environmental Fate of Xylenes (based on CEPA, 1993; HSDB, 2003; Howard *et al.*, 1991)

		Half-life
Water	Loss by volatilization and aerobic and anaerobic biodegradation; moderate adsorption to sediment or suspended particulate matter; low potential for bioconcentration in aquatic organisms; hydrolysis is negligible	*Volatilization*: 3 hours (model river) and 99 hours (model lake) *Aerobic biodegradation*: 7 hours to 28 days *Anaerobic biodegradation:* 28 days to 180 days
Soil	Loss *via* volatilization from dry and moist soils and biodegradation; moderate to high mobility; potential for leaching; hydrolysis, photolysis and oxidation are negligible	*Aqueous aerobic biodegradation*: one minute to 2.2 days
Air	Exists solely as a vapour; degradation *via* reaction with hydroxyl radicals; photolysis is negligible	*Photochemical reactions with hydroxyl radicals*: one to two days

much longer than those for the daylight reaction with hydroxyl radicals, atmospheric night time removal of xylenes could be significant, especially in airsheds with nitrogen oxide pollution. Photooxidation reactions with xylenes yield such products as tolualdehydes, glyoxal, methyl glyoxal, methylbenzylnitrates, dimethylphenols, nitroxylenes, formaldehyde, acetaldehyde, acetyl nitrate, peroxyacetylnitrate, as well as carbon dioxide and water (Bandow and Washida 1985; Darnall *et al.*, 1979; Shepson *et al.*, 1984; Tagaki *et al.*, 1980; Guisti *et al.*, 1974; CEPA, 1993; ATSDR, 1995). Xylenes also participate in ancillary photooxidation reactions including the conversion of nitric oxide to nitrogen dioxide, with *m*-xylene being the most reactive isomer (Altshuller *et al.*, 1962; Kopcyznski, 1964).

Xylenes are sufficiently susceptible to photochemical oxidation in the troposphere such that they may contribute to photochemical smog formation. Derwent and Jenkin (1990) calculated Photochemical Ozone Creation Potentials (POCP) for xylenes of 41 (*o*-xylene), 78 (*m*-xylene) and 63 (*p*-xylene). The POCP reflects the ability of a substance to form ground level ozone and are calculated relative to ethylene (a chemical that is thought to be important in ground-level ozone formation and which is assigned a POCP of 100).

Neither wet nor dry deposition is thought to be an important fate process for xylenes. Due to its low water solubility, only a very small proportion of xylene is likely to be removed from the atmosphere by wet deposition. This is supported by observations of very low or non-detectable levels in rainwater samples (WHO, 1997).

Xylenes are expected to exhibit moderate to high mobility in soil based on their partition coefficients (CEPA, 1993; HSDB, 2003). Xylenes tend to sorb to organic carbon in soils but may leach through soils that are low in organic carbon content and moisture content. A general increasing trend for the relative retention of xylene in soil with increasing soil organic matter has been observed (Green *et al.*, 1981; Kango and Quinn 1989; Seip *et al.*, 1986); however, the presence of other organic pollutants may result in competition for sorption sites and may increase the leaching of xylenes through the soil profile (Stuart *et al.,* 1991). Xylenes are expected to volatilize rapidly from moist and dry soil surfaces with an estimated half-life for all three

isomers ranging from one-minute to 2.2 days (CEPA, 1993). Volatilization is the dominant fate process in soil. Hydrolysis, photolysis and oxidization are not expected to be significant in soils (CEPA, 1993).

For xylenes that do not volatilize or leach to groundwater, photo-induced oxidation may be an important transformation process. Jori *et al.* (1986) estimated a half-life for the photooxidation of xylene in soils of 24.1 hours in a closed system laboratory experiment. However, the significance of this fate process under field conditions has not been established.

In subsurface soil, biodegradation is considered to be the only significant environmental fate process for xylenes and is believed to occur slowly. Overall, biodegradation is an important environmental fate process for xylenes not just in subsurface soil, but in surface soil, groundwater, surface water and sediments, under aerobic conditions and also may degrade under anaerobic denitrifying conditions (CEPA, 1993; HSDB, 2003; WHO, 1997). *o*-Xylene has been found to be the most resistant isomer to biodegradation (WHO, 1997). However, the relative importance of xylene biodegradation is a function of site-specific conditions. Xylenes often are noted to be poorly biodegraded in groundwater, which is believed to be due to lack of suitable substrates for co-metabolism, low oxygen levels and limited nutrients (Jorgensen and Aamand, 1991; Jenkins *et al.*, 1993; Morgan *et al.*, 1993).

In surface waters, volatilization is the dominant fate process for xylenes. While biodegradation in water also occurs to some extent, it is likely of lesser significance as the estimated half-life for biodegradation of xylene in water (247.5 hours; Jori *et al.*, 1986) is considerably greater than the half-life predicted for volatilization (5.6 hours; Mackay and Leinonen, 1975). Other reported half-lives for biodegradation in water range from seven to 28 days under aerobic conditions and between 28 and 360 days under anaerobic conditions (Howard *et al.*, 1991). An estimated half-life for volatilization from water surfaces for a model river was 3 hours and 99 hours for a model lake (HSDB, 2003). Oxidation and hydrolysis reactions are not expected to be significant transformation processes for xylene in water (ATSDR, 1995; HSDB, 2003). Aqueous solutions of xylenes have been reported to undergo photooxidation in the presence of hydroxyl radical donors in water, such as hydrogen peroxide, titanium dioxide and humic substances (ATSDR, 1995). Reported half-lives for these reactions in water range from 0.2 to 9.1 hours; however, the relative importance of aqueous photooxidation will depend on site-specific conditions (Beyerle-Pfnur *et al.*, 1989). Degradation products of this reaction include tolualdehyde and methyl benzyl alcohols (Beyerle-Pfnur *et al.*, 1989). Xylenes exhibit moderate adsorption to sediments and suspended particulate matter.

The potential for significant bioconcentration and bioaccumulation of xylenes is low (CEPA, 1993; HSDB, 2003; WHO, 1997; ATSDR, 1995; CEPA, 1993). Reported bioconcentration factors (BCFs) for xylenes in aquatic fish and invertebrates range from six to 177 (CEPA, 1993). BCFs are slightly higher in algae. For example, Herman *et al.* (1991) reported BCFs in *Selenastrum capricornutum* of 257, 251 and 218 for *p*-, *m*- and *o*-xylenes, respectively.

3.0 EMISSION SOURCES, INVENTORIES AND AMBIENT AIR CONCENTRATIONS

3.1 Natural Sources

Xylenes are naturally occurring components of crude oil and natural gas (CEPA, 1993). They are formed during combustion of organic materials; thus forest, grass and other biomass fires will release xylenes to the atmosphere. In addition, xylenes are present in volcanic gases (Isidorov *et al.*, 1990).

3.2 Anthropogenic Sources and Emissions Inventory

3.2.1 Industrial

Production processes, as well as industrial, commercial and domestic sources and uses of xylenes were described in Section 2.0.

A total of 110 industrial facilities in Alberta reported data regarding on-site releases of xylenes to the 2001 National Pollutant Release Inventory (NPRI) database. Most of the environmental releases were to the atmosphere with some facilities in Alberta also releasing xylenes to land. For example, the Petro-Canada Refinery in Edmonton reported 10.92 tonnes released to land of the total 15.01 tonnes released to the environment (4.09 tonnes were released to air) (NPRI, 2001). In addition, Devon Canada Corporation's Wapiti gas plant in Grande Prairie reported 15.7 tonnes released to land out of 21.33 tonnes released to the environment (5.63 tonnes were released to air) (NPRI, 2001).

Table 4 provides a summary of the on-site releases for the top 10 facilities in Alberta that released xylenes to air for the 2001 reporting year. Table 5 provides details on the air emissions for these facilities. The major sectors in Alberta that release xylenes to air are the oil and gas sector (including oil sands operations, gas plants and petroleum refineries), cement manufacturing, fabricated metal products manufacturing and aluminum product manufacturing. Depending on the facility, fugitive emissions, stack emissions and releases during storage and handling can all be significant sources of xylenes to the atmosphere (See Table 5).

3.2.2 Ambient Air Concentrations in Alberta

Alberta Environment has conducted a number of air quality monitoring surveys over the past several years in various regions of Alberta. Some of these surveys have reported ambient air concentrations of xylenes. For example, a survey conducted from October 2000 to June 2001 in the Whitemud Drive area of Edmonton reported that one-hour average ambient air concentrations of xylenes ranged from <5 to 22 $\mu g/m^3$ (AENV, 2002a). A VOC survey in the Fort Saskatchewan/Redwater area (AENV, 2003) conducted over May 2001 to February 2002 reported one-hour average xylene isomer air concentrations in the range of 0.08 to 2.33 $\mu g/m^3$ (average = 0.64 $\mu g/m^3$) for *m*, *p*-xylene and from 0.04 to 0.88 $\mu g/m^3$ (average = 0.23 $\mu g/m^3$) for

Table 4 Total On-site Releases (tonnes/year) of Xylenes in Alberta (Ten Largest Contributors) According to NPRI, 2001

			Total Releases (tonnes/year)			
						Total
2274	Syncrude Canada Ltd. - Mildred Lake Plant Site	Fort McMurray	477.44	0	0	477.44
2230	Suncor Energy Inc. - Suncor Energy Inc. Oil Sands	Fort McMurray	204.83	0	0	204.83
4946	Canam Steel Works – Calgary	Calgary	104.40	0	0	104.40
5291	Lafarge Canada Inc - Exshaw Plant	Exshaw	47.65	0	0	47.65
3219	APEL Extrusions Limited	Calgary	28.0	0	0	28.0
2960	Shell Canada Products - Shell Scotford Refinery	Fort Saskatchewan	17.80	1.14	0	18.94
1541	Kawneer Company Canada Limited – Lethbridge	Lethbridge	17.34	0	0	17.34
4152	BP Canada Energy Company - West Pembina Gas Plant	Location not specified in NPRI, 2001	15.68	0	0	15.68
3707	Imperial Oil - Strathcona Refinery	Edmonton	13.22	2.18	0	15.40
1372	Keyspan Energy Canada - Rimbey Gas Plant	Rimbey	7.99	0	0	7.99

Table 5 Air Emissions of Xylenes (tonnes/year) for Ten Largest Contributors in Alberta According to NPRI, 2001

			Air Emissions (tonnes/year)					
								Total
2274	Syncrude Canada Ltd. - Mildred Lake Plant Site	Fort McMurray	1.41	7.27	468.75	0	0	477.44
2230	Suncor Energy Inc. - Suncor Energy Inc. Oil Sands	Fort McMurray	1.03	1.50	202.30	0	0	204.83
4946	Canam Steel Works - Calgary	Calgary	26.10	0	78.30	0	0	104.40
5291	Lafarge Canada Inc - Exshaw Plant	Exshaw	47.65	0	0	0	0	47.65
3219	APEL Extrusions Limited	Calgary	28.0	0	0	0	0	28.0
2960	Shell Canada Products - Shell Scotford Refinery	Fort Saskatchewan	0	3.12	14.69	0	0	17.80
1541	Kawneer Company Canada Limited - Lethbridge	Lethbridge	17.34	0	0	0	0	17.34
4152	BP Canada Energy Company - West Pembina Gas Plant	Location not specified in NPRI, 2001	15.68	0	0	0	0	15.68
3707	Imperial Oil - Strathcona Refinery	Edmonton	0.19	8.26	4.73	0	0.05	13.22
1372	Keyspan Energy Canada - Rimbey Gas Plant	Rimbey	0	0.14	7.85	0	0	7.99

o-xylene. A survey conducted in the Town of Banff in November 2002 reported one-hour average *m*, *p*-xylene isomer concentrations on two sampling days of 1.82 and 2.91 μg/m^3; *o*-xylene concentrations were 0.69 and 1.08 μg/m^3 on these two sampling days (AENV, 2002b). One-hour average xylene concentrations were non-detectable in an air monitoring survey conducted in the Carstairs/Crossfield Area between December 1999 and March 2000 (AENV, 2000b). A study of VOC air concentrations was conducted in the County of Grande Prairie between 1998 and 2000 (AENV, 2001). At a regional background location (Beaverlodge Agriculture Research Farm), 24-hour average xylene air concentrations ranged from <0.2 to 1.9 μg/m^3. Xylene air concentrations were measured at stations near a number of gas plants, batteries and well sites as well. One-hour average xylene concentrations were reported to range from <4.2 to 114.7 μg/m^3. Twenty-four hour average xylene air concentrations were reported to range from <0.3 to 30.0 μg/m^3.

4.0 EFFECTS ON HUMANS AND ECOLOGICAL RECEPTORS

4.1 Humans and Experimental Animals

The following toxicological review of xylenes is focused primarily on the inhalation route of exposure, as this is the predominant route of human exposure to xylenes in air. Data on other exposure routes are included in this review only where considered relevant or where inhalation exposure data are lacking. Where sufficient data are available, human studies are emphasized in this section. However, relevant experimental animal studies are included where human data are either lacking or inadequate.

For xylenes, it is important to recognize that many early toxicology studies used technical grade xylenes, which contained unquantified but likely substantial amounts of benzene. Thus, observations of haematological effects in these older studies are not believed to have been caused by xylenes, but were feasibly due to the presence of benzene in the technical grade xylene mixtures (ACGIH, 1992).

4.1.1 Overview of Toxicokinetics of Xylenes

Absorption

Numerous studies in both humans and animals have demonstrated that xylenes are rapidly and extensively absorbed by the inhalation route. Overall, it appears that approximately 60% of inspired xylene is absorbed in the lungs, with the remaining 40% expired in exhaled air.

Absorption of xylenes in the lungs appears to occur in two phases: the first phase is short and occurs within 15 minutes of the onset of exposure; the second phase is approximately one hour in duration and represents the establishment of equilibrium between the inhaled xylene and blood xylene concentrations (ATSDR, 1995).

Many studies have measured the retention of xylene in the lungs following inhalation exposure. Only the retained xylene is available for absorption into the systemic circulation. In studies with human volunteers, retention of the three isomers was similar and averaged 63.6% (Sedivec and Flek, 1976b). Other authors have estimated that 49.8% to 87% of inhaled xylene is retained in the lungs (David *et al.*, 1979; Ogata *et al.*, 1970; Riihimaki and Pfaffli, 1978; Riihimaki and Savolainen, 1980; Wallen *et al.*, 1985). Physical exertion and increased air concentrations can both increase the amount of xylene that is retained and subsequently absorbed (Astrand *et al.*, 1978; Riihimaki *et al.*, 1979). Astrand *et al.* (1978) noted that retention efficiency decreases as exposure duration increases. Senczuk and Orlowski (1978) noted that the retention of *m*-xylene in the lung varied with the air concentration and duration of exposure. These authors conducted three measurements each on 10 healthy volunteers (five men and five women) between the ages of 17 and 33 years. The subjects were exposed to *m*-xylene vapour in an inhalation chamber at three concentrations (100, 300 and 600 mg/m^3) for eight hours with two half-hour breaks. At 300 mg/m^3, retention decreased from 83% at the start of the study to 67% at the end of the exposure period (mean = 75%). At 600 mg/m^3, retention decreased from 78% at the start to 65% (mean = 71%) at the end. At 100 mg/m^3, the retention rate was 87% at the start and 84% at the end.

Sato and Nakajima (1979) reported that blood/air partition coefficients for the three xylene isomers ranged from 26.4 to 37.6, indicating that xylene entering the body would be readily absorbed into the bloodstream.

In pregnant mice, approximately 30% of an administered inhalation dose of 600 ppm (2,610 mg/m^3) *p*-xylene was absorbed following a 10-minute exposure period (Ghantous and Danielsson, 1986).

Distribution

Following absorption, xylene is rapidly distributed throughout the body. The majority (90%) of the xylene in blood is bound to serum proteins with about 10 to 15% associated with protein-free serum (Riihimaki *et al.*, 1979). Xylene accumulates preferentially in lipid-rich tissues such as adipose tissue, brain, liver and kidneys. Riihimäki and Savolainen (1980) found that 10 to 20% of absorbed xylene was distributed to adipose tissue.

The level of xylene stored in body fat may decrease as exposure continues, due to an increase in induced metabolism (Savolainen *et al.*, 1979). These authors found that levels of *m*-xylene in the perirenal fat of rats exposed to 300 ppm (1,305 mg/m^3) technical xylene decreased from 67.6 to 36.6 µg/g tissue as exposure duration increased from 5 to 18 weeks.

Both *p*-xylene and *o*-xylene have been shown to readily cross the placenta and distribute to amniotic fluid and embryonic and fetal tissues (Ghantous and Danielsson, 1986; Ungvary *et al.*, 1980). However, the level detected in fetal tissues (brain, liver, lung and kidney), which are relatively low in lipids, was only 2% of that detected in the maternal brain tissue, which contains much higher amounts of lipids (Ghantous and Danielsson, 1986).

Carlsson (1981) determined tissue concentrations of *m*-xylene in male rats following inhalation exposure to 48 ppm (209 mg/m^3) radiolabeled *p*-xylene for one, two, four or eight hours. The greatest concentration of combined xylenes and its metabolites was found in the kidneys immediately following the four-hour exposure, with the next highest concentration found in the subcutaneous fat. The concentration in the subcutaneous fat continued to increase, reaching peak concentration following the eight-hour exposure. Concentrations of xylenes and metabolites in the cerebellum, cerebrum, muscles, spleen and lungs paralleled the concentrations of xylenes in the arterial blood throughout the entire exposure period.

Bergman (1983) investigated the distribution of radiolabeled *m*-xylene in mice using low temperature, whole-body autoradiography and found high radioactivity levels in the body fat, bone marrow, white matter of the brain, spinal cord, spinal nerves, liver and kidney immediately following inhalation exposure. High levels of metabolites were detected in the blood, liver, lung, kidney and adrenal medulla. No radioactivity was detected in the body by 48 hours post-exposure.

Metabolism

Considerable and rapid metabolism of xylenes occurs following absorption, with the liver being the primary site of metabolism. In humans exposed by inhalation, the loss of xylene from the blood has been shown to follow a biphasic, first-order kinetic pattern with half-lives of about 0.5 to one hour in the first phase and 20 to 30 hours in the second phase (U.S. EPA, 2003).

Xylene isomers are principally metabolized by oxidation of a methyl group, followed by conjugation with glycine to yield methylhippuric acid (ATSDR, 1995; WHO, 1997; U.S. EPA, 2003). Mixed function oxidases in the liver are involved in the oxidation step. Toluic acids (methylbenzoic acids) are the products of methyl group oxidation. These toluic acids then conjugate with glycine to form methylhippuric acids that are excreted into the urine (ATSDR, 1995; WHO, 1997; U.S. EPA, 2003). This is the major metabolic pathway for xylenes in both humans and animals.

Minor metabolic pathways include the elimination of unchanged xylenes in exhaled air and in urine and the urinary elimination of methylbenzyl alcohols, *o*-toluylglucuronides (*o*-toluic acid glucuronide), xylene mercapturic acid and xylenols (dimethylphenols) (ATSDR, 1995). Aromatic hydroxylation of xylene to xylenol occurs to a limited extent in humans (ATSDR, 1995).

Metabolism in animals is qualitatively similar to that in humans, except glucuronide conjugates make up a larger proportion of the urinary excretion products (ATSDR, 1995). In addition, the metabolite, methylbenzaldehyde has been detected in animals but not humans. Methylbenzaldehyde is a toxic metabolite of xylene in rats and rabbits (Carlone and Fouts, 1974; Patel *et al.*, 1978; Smith *et al.*, 1982) that can damage lung tissue due to its selective inactivation of enzymes involved in microsomal electron transport (*e.g.*, mixed function oxidases, cytochrome P-450). Minor quantities of methylbenzyl alcohols and xylenols have also been detected in the urine of experimental animals administered xylenes (Ogata *et al.*, 1979; Turkall *et al.*, 1992; van Doorn *et al.*, 1980). Studies in animals have also shown that the metabolism of xylene may be influenced by prior exposures. Elovaara *et al.* (1989) found that pre-treatment of rats with *m*-xylene increased the percentage of methylhippuric acid and thioethers in the urine by approximately 10%.

Some researchers have speculated that the differences in xylene metabolism observed between humans and animals may, in part, be due to differences in the size of the doses received by humans and animals in experimental studies (David *et al.*, 1979; Ogata *et al.*, 1979; van Doorn *et al.*, 1980). The formation of glucuronic acid derivatives by animals may occur when the organism can no longer conjugate all acids with glycine (Ogata *et al.*, 1979; Sedivec and Flek, 1976b; van Doorn *et al.*, 1980).

If this occurs, other elimination pathways may be activated, such as conjugation with glucuronic acid or aromatic hydroxylation to form xylenols. The capacity of the methyl group oxidation reaction is not known (ATSDR, 1995).

In human studies, it has been reported that virtually all (90 to 95%) of absorbed xylenes are excreted as methylhippuric acid in the urine, with the remainder lost as unmetabolized xylene in

expired air (Riihimäki and Savolainen, 1980; Sedivec and Fleck, 1976a; Ogata *et al.*, 1980; Senczuk and Orlowski, 1978; Astrand *et al.*, 1978).

Elimination and Excretion

As mentioned, in humans exposed to xylene, about 95% of the absorbed dose is excreted in the urine, with roughly 5% excreted unchanged in exhaled air. Of the urinary metabolites, more than 90% consists of methylhippuric acid, with minor amounts of xylenol, methylbenzyl alcohol, glucuronic acid conjugates and unchanged xylenes also being reported (ATSDR, 1995).

The elimination of xylenes occurs rapidly in most tissues but is slower from muscle and adipose tissue (ATSDR, 1995). Significant quantities of metabolites can be detected in urine within two hours of inhalation. Sedivec and Flek (1976a) tracked the course of excretion of methylhippuric acid following inhalation exposure in human volunteers. Methylhippuric acid was detected in urine by two hours following the onset of exposure. Urinary concentrations increased during exposure. Following a two-hour post-exposure sampling period, the amount of methylhippuric acid in urine decreased rapidly, but it remained detectable in the urine for four to five days following cessation of exposure.

There appears to be no saturation of xylene metabolism, as the excretion of methylhippuric acid appears to correspond very closely to estimated xylene uptake less expired xylene (Riihimaki *et al.*, 1979). Other studies also report that urinary excretion of methylhippuric acid correlates well with airborne exposure levels (Kawai *et al.*, 1992; Lapare *et al.*, 1993; Skender *et al.*, 1993).

Limited information was found on the elimination of xylene metabolites following inhalation exposure in experimental animals. *m*-Methylhippuric acid was detected in the urine of rats exposed for 6 hours to various doses of *m*-xylene (David *et al.*, 1979). However, the authors did not analyze for other urinary metabolites (ATSDR, 1995).

Physiologically-Based Pharmacokinetic (PBPK) Models

Physiologically based pharmacokinetic (PBPK) models for inhalation exposure to xylenes have been developed for both rats (Tardif *et al.*, 1991; 1992; 1993a) and humans (Tardif *et al.*, 1993b, 1995; Haddad *et al.*, 1999). These models consist of five dynamic tissue compartments representing the lung, adipose tissue, slowly perfused tissues, richly perfused tissues and the liver. These particular models are for inhalation only and cannot be used for other exposure routes (U.S. EPA, 2003). The models assume that all metabolism occurs in the liver. The PBPK models developed by Tardif *et al.* (1993a; 1995; 1997) are reported to have been validated (U.S. EPA, 2003). These models have also been applied to mixtures containing xylenes and other aromatic solvents (U.S. EPA, 2003). Further description and discussion of these models can be found in the original papers as well as ATSDR (1995) and U.S. EPA (2003).

Mechanism of Toxic Action

Although a number of theories have been postulated, the mechanisms by which xylenes exert their toxic effect are not entirely understood. The central nervous system (CNS) toxicity of

xylene has been attributed to its high lipid solubility in the neuronal membrane (Desi *et al.*, 1967; Gerarde 1959; Savolainen and Pfaffli, 1980; Tahti 1992). It is believed that xylene disturbs the conformation of proteins in the neuronal membrane that are essential to normal neuronal function. Others have suggested that metabolic intermediates, such as arene oxides or methylbenzaldehyde, may be responsible for the toxic effects of xylene (Savolainen and Pfaffli, 1980). It is believed that these intermediates inhibit microsomal enzymes through binding to microsomal protein and subsequently inactivating the microsomal enzymes (Patel *et al.*, 1978; Smith *et al.*, 1982).

The mechanism for xylene renal toxicity is believed to be related to the formation of reactive metabolites and subsequent irritation or direct membrane fluidization (U.S. EPA 2003). The mechanism of xylene developmental toxicity has not been fully investigated, but appears to be related to decreased levels of progesterone and estradiol (Ungvary *et al.*, 1981). It is believed that the decreased levels of these hormones may be due to increased microsomal enzyme activity and increased hormone catabolism.

Xylenes also have a high potential to interact with numerous other organic substances because the isomers induce microsomal enzymes in the liver (Blanchard and Morris, 1994; Liira *et al.*, 1991). While numerous studies of xylene interaction with other organic solvents and alcohols have been conducted, the results have been mixed and inconclusive and it cannot be predicted with certainty whether interactions will produce additive, synergistic or antagonistic effects (ATSDR, 1995). Vaidyanathan *et al.* (2003) reported that alteration of cytochrome P-450 activity by *m*-xylene can result in increased or decreased toxicity of other organic chemicals and can change the metabolic profiles of these other xenobiotics in co-exposure scenarios in an organ-specific manner.

Biomarkers

Urinary methylhippuric acid is the most commonly used biomarker of exposure for xylenes (ACGIH, 1992). Measurement of xylenes in the blood is limited by the rapid metabolism of xylene. Furthermore, there are few reliable data available on background concentrations of xylene in blood or urine (ATSDR, 1995). There is a strong association between urinary methylhippuric acid concentrations and inhalation exposure to xylene (Daniel *et al.,* 1992; Jonai and Sato, 1988; Kawai *et al.,* 1991). Methylhippuric may be detected in urine within two hours of inhalation exposure (Sedivec and Flek 1976b). As methylhippuric acid is eliminated within one or two days of exposure to xylene, it is only a useful biomarker for recent exposures. No other biomarkers of exposure appear to be used for xylenes (ATSDR, 1995).

There are no specific biomarkers of effect that are specific to the biological responses induced by xylenes (ATSDR, 1995). This is because a number of other organic chemicals cause the same or similar effects.

4.1.2 Acute Toxicity

The major symptoms of acute human exposure to xylenes include: irritation of the nose, throat and eyes and CNS effects such as headache, nausea, dizziness, difficulty concentrating, impaired

memory, slurred speech, ataxia, fatigue, agitation, confusion, tremors, labored breathing, impaired reaction time, alterations in equilibrium and body balance and sensitivity to noise (ATSDR, 1995; WHO, 1997; OEHHA, 1999). All these effects appear to be reversible upon cessation of exposure. Isolated instances of unconsciousness, amnesia, brain hemorrhage and epileptic seizure have been associated with short-term exposure to high air concentrations of solvent mixtures containing xylene (Arthur and Cumock, 1982; Goldie, 1960; Martinez *et al.*, 1989; Morley *et al.*, 1970).

Acute human studies are difficult to interpret as exposure conditions are often poorly characterized or the subjects are exposed to other chemicals in addition to xylene.

Overall, acute effects in humans are most pronounced at high exposure levels (*i.e.,* in excess of 1,000 ppm or 4,350 mg/m^3) with lower concentrations producing subtler effects (U.S. EPA, 2003). The available controlled-exposure human studies indicate that concentrations around 100 to 200 ppm (435 to 870 mg/m^3) are close to the threshold level for short-term reversible neurological and irritation effects from xylenes (U.S. EPA, 2003; ATSDR, 1995).

Nose and throat irritation was reported in human volunteers following exposure to mixed xylenes at 200 ppm (870 mg/m^3) for three to five minutes (Nelson *et al.*, 1943).

Human volunteers exposed to *p*-xylene at 100 ppm (435 mg/m^3) for one to 7.5 hours a day for five days reported nose and throat irritation (Hake *et al.*, 1981). These authors also reported that three women exposed to 100 ppm *p*-xylene for one to 7.5 hours a day, for five days showed no effects based on tests of electroencephalography, evoked potentials or cognitive performance, but frequently reported headache and dizziness. In contrast, four men exposed to *p*-xylene at concentrations up to 150 ppm (653 mg/m^3) under the same exposure conditions reported no increase in headaches or dizziness.

No increased reports of nose and throat irritation and no changes in respiratory rate were seen in a study of human subjects exposed to mixed xylenes at a concentration of 396 ppm (1,723 mg/m^3) for 30 minutes (Hastings *et al.*, 1986). In an earlier study, Hastings *et al.* (1984) exposed 50 healthy individuals to 100, 200 or 400 ppm (435, 870 or 1,740 mg/m^3) mixed xylenes for 30 minutes. The proportion of subjects reporting eye irritation was 56% for controls (clean air), 60% at 100 ppm, 70% at 200 ppm and 90% at 400 ppm.

Human volunteers exposed to xylene concentrations in the range of 200 to 400 ppm (870 to 1,740 mg/m^3) for 15 minutes to four hours reported symptoms of irritation (*e.g.*, watering eyes and sore throat) or neurological impairment (*e.g.*, mild nausea, headache, dizziness) (Carpenter *et al.*, 1975; Gamberale *et al.*, 1978). Dizziness was reported by the majority of subjects exposed to 690 ppm (3,000 mg/m^3) mixed xylene for 15 minutes, but in only one of six persons exposed at 460 ppm (2,000 mg/m^3) (Carpenter *et al.*, 1975). Gamberale *et al.* (1978) reported that exposure to 299 ppm (1,301 mg/m^3) mixed xylene for 70 minutes during exercise resulted in impaired short-term memory and reaction time.

Other studies involving single or multiple four-hour exposures of human volunteers to 200 ppm (870 mg/m^3) xylene (*e.g.*, Laine *et al.*, 1993; Savolainen and Linnavuo, 1979; Savolainen *et al.*, 1984) indicated reversible effects on balance and reaction times. A xylene air concentration of

200 ppm, administered to human volunteers for four hours was not found to impair performance in tests of simple reaction time, short term memory and choice reaction time (Olson *et al.*, 1985) or cause changes in visually evoked brain potentials (Seppäläinen *et al.*, 1983) or EEG patterns (Seppäläinen *et al.*, 1991). In contrast, impaired performance on tests of memory and reaction times was reported for subjects exposed to 100 ppm (435 mg/m^3) xylene for four hours (Dudek *et al.*, 1990).

Morley *et al.* (1970) reported a case study of three workers exposed to approximately 10,000 ppm (43,500 mg/m^3) xylene for 19 hours. One subject was dead upon arrival at the hospital. Autopsy of this individual showed severe pulmonary congestion with focal alveolar hemorrhage and acute pulmonary edema, hepatic congestion with swelling and vacuolization of many cells in the centrilobular areas and microscopic petechial hemorrhages in both the grey and white matter of the brain. There was also evidence of axonal neuronal damage, as indicated by swelling and loss of Nissl substance. A second individual was admitted to the hospital unconscious and exhibited only a slight response to painful stimuli. Other symptoms included hypothermia, flushed face and peripheral cyanosis. Medium-grade moist sounds were present in the lungs and a chest x-ray revealed patchy diffuse opacity in both lungs. Five hours following treatment with tracheal aspiration and oxygen, the subject regained consciousness but was amnesic for two to three days. Evidence of renal damage and slight hepatic impairment were also noted in this subject. The third subject recovered consciousness following admission to the hospital. This individual was confused and amnesic, had slurred speech and was ataxic. Within 24 hours of admission, the subject regained consciousness and was alert, with the ataxia disappearing within two days. There was no evidence of renal impairment and only mild hepatic impairment in this subject. Because the workers had been concurrently exposed to other chemicals when the poisoning occurred, ATSDR (1995) notes that the study is inconclusive with regard to the acute toxicity of xylenes.

Goldie (1960) reported a case study where eight painters were exposed to paint containing 80% xylene and 20% methylglycolacetate in a solvent. The workers complained of headache, vertigo, gastric discomfort, dryness of the throat and slight drunkenness after 30 minutes of exposure. After two months of exposure to this paint, one worker (an 18-year old male) exhibited behavior and symptoms indicative of a convulsive seizure, including weakness, dizziness, inability to speak, unconsciousness, eye and head rotation to one side, chewing with no foaming and kicking motions. The subject recovered consciousness 20 minutes after removal from the exposure conditions. Arthur and Curnock (1982) reported another case in which an adolescent worker developed major and minor seizures following the use of a xylene-based glue for building model airplanes. These two case reports are inconclusive for evaluating the acute toxicity of xylenes as neither of these two case reports provided estimates of xylene air concentrations and exposures were not limited to xylene alone (U.S. EPA, 2003).

Klaucke *et al.* (1982) reported an incident where 15 workers who had been exposed by inhalation to xylenes were admitted to a small community hospital. All subjects complained of at least two of the following symptoms: headache, nausea, vomiting, dizziness or vertigo, eye irritation and nose or throat irritation. It was estimated that the workers were exposed to xylene levels as high as 700 ppm (3,045 mg/m^3).

In animal studies, the neurological effects of xylene exposure are more clearly defined than in human studies. CNS toxicity is a critical effect of inhalation exposure to xylenes (U.S. EPA, 2003). Commonly reported signs of CNS neurotoxicity in experimental animals following acute inhalation exposure to xylene isomers include: narcosis, prostration, incoordination, tremors, muscular spasms, laboured breathing, behavioural changes, hyper-reactivity to stimuli, altered visual evoked potentials, elevated auditory thresholds, hearing loss, decreased acetylcholine in midbrain and norepinephrine in hypothalamus (which suggests effects on motor control, sleep and memory maintenance) (ATSDR, 1995). Other symptoms of acute xylene exposure in experimental animals include irritation of the respiratory tract, pulmonary edema, pulmonary hemorrhage and pulmonary inflammation (ATSDR, 1995). It is shown in numerous animal studies that mixed xylenes or individual isomers generally induce a wide variety of hepatic enzymes, as well as increased hepatic cytochrome P-450 content, liver enlargement and other minor hepatic histopathological changes (ATSDR, 1995). However, it is important to recognize that such changes have not been reported to manifest as adverse hepatic effects but rather, reflect the liver's increased metabolic activity that occurs in response to xylene exposure. Such effects are considered adaptive changes rather than adverse health effects.

Overall, it appears that 100 ppm (435 mg/m^3) is an exposure level that produces statistically significant changes in several neurological endpoints in experimental animals (U.S. EPA, 2003).

The four-hour LC50[2] value for mixed xylenes in rats ranged from 6,350 ppm (27,623 mg/m^3; Hine and Zuidema, 1970) to 6,700 ppm (29,145 mg/m^3; Carpenter *et al.*, 1975). The four-hour LC50 value for *p*-xylene in rats was reported to be 4,740 ppm (20,619 mg/m^3; Harper *et al.*, 1975). In mice, six-hour LC50 values for *m*-xylene, *o*-xylene and *p*-xylene were determined to be 5,267 ppm, 4,595 ppm and 3,907 ppm (22,911, 19,988 and 17,000 mg/m^3), respectively (Bonnet *et al.*, 1979). These latter LC50 values suggest that *p*-xylene may be slightly more toxic than the other xylene isomers.

In general, mice appear to be more sensitive than rats to acute xylene inhalation exposure. Cameron *et al.* (1938) reported that no rats died following a 24-hour exposure to 2,010 ppm (8,744 mg/m^3) *m*-xylene, while 6 of 10 mice died under similar exposure conditions. Also, a 24-hour exposure of rats to 3,062 ppm (13,320 mg/m^3) *o*-xylene resulted in a death rate of one in 10, whereas in mice, four of 10 died.

Patel *et al.* (1979) found that serum enzyme activity increased in a manner consistent with hepatocellular damage in rats exposed to 1,000, 1,500 or 2,000 ppm (4,350, 6,525 or 8,700 mg/m^3) of *p*-xylene for four hours.

EC50 values (for effects on operant behaviour in rats) exposed to xylene isomers by inhalation for 30 minutes, showed a relative toxicity order of *o*-xylene > *p*-xylene > *m*-xylene, whereas EC50s for a motor performance test showed a toxicity order of *p*-xylene > *o*-xylene = *m*-xylene (Moser *et al.*, 1985). The minimally effective concentration for disruption of operant performance (lever-pressing behavior) was 1,400 ppm (6,090 mg/m^3) for all isomers, with EC50s of 6,200, 5,200 or 5,600 ppm (26,970, 22,620, 24,360 mg/m^3) for *m*-xylene, *o*-xylene and *p*-xylene, respectively. The minimally effective concentrations for the motor performance test

[2] LC50 refers to the concentration at which 50% of the test animals die (*i.e.,* lethal concentration)

were 3,000 ppm (13,050 mg/m^3) for *m*-xylene and *o*-xylene and 2,000 ppm (8,700 mg/m^3) for *p*-xylene and the EC50 values were 3,790, 3,640 and 2,676 ppm (16,487, 15,834 and 11,641 mg/m^3) for *m*-xylene, *o*-xylene and *p*-xylene, respectively. Overall, there were no consistent, significant differences in the potency of the individual isomers.

Muller and Gref (1984) reported an EC50 (for reduced respiratory rate) of 1,450 ppm (6,308 mg/m^3) for *o*- and *p*-xylene in mice.

Toftgård *et al.* (1983) exposed male Sprague-Dawley rats to 0, 75, 250, 500, 1,000 or 2,000 ppm (0, 326, 1,088, 2,175, 4,350 or 8,700 mg/m^3) xylene for six hours a day, for three to five days. The xylene mixture used in this study contained 2.0% *o*-xylene, 64.5% *m*-xylene, 10.0% *p*-xylene and 23.0% ethylbenzene. Significant effects reported were a dose-dependent increase in the concentration of liver microsomal cytochrome P-450 and a dose-dependent increase in the surface area of smooth endoplasmic reticulum in hepatocytes at the two highest concentrations tested.

Long Evans rats exposed for four hours to 0, 800 or 1,600 ppm (0, 3,480 or 6,960 mg/m^3) *p*-xylene, showed a reduced flash-evoked potential of the visual system at 1,600 ppm (Dyer *et al.*, 1988). Long Evans rats exposed to 1,600 ppm *p*-xylene for four hours showed unsteadiness and fine tremors that disappeared by 30 minutes post-exposure (Bushnell, 1989).

In Long Evans rats exposed to 2,500 ppm (10,875 mg/m^3) of mixed xylenes for six hours a day for five days, testing of auditory function using reflex modification audiometry (RMA) indicated increased RMA thresholds for the mid-frequency tones (*e.g.*, 8, 16 and 24 kHz) but not for higher or lower tones (Crofton *et al.*, 1994). Auditory effects also were reported by Pryor *et al.* (1987). This study found that hearing loss occurred in rats exposed to 1,450 ppm (6,308 mg/m^3) for eight hours. However, exposure to 1,700 ppm (7,395 mg/m^3) for four hours produced no effects on hearing.

Rats exposed to 620, 980 or 1,600 ppm (2,697, 4,263 or 6,960 mg/m^3) xylene for 18 to 20 hours a day for seven days displayed instability, incoordination and narcosis at the two highest concentrations (Batchelor, 1927). Mucous membrane irritation and congestion and cloudy swelling of kidneys were reported at 980 ppm.

Tegeris and Balster (1994) studied the acute neurobehavioural effect of *m*-xylene in mice after 20 minutes of inhalation exposure using a functional observations battery. In the concentration range of 2,000 to 8,000 ppm (8,700 to 34,800 mg/m^3), effects included changes in posture, decreased arousal and rearing, increased ease of handling, disturbances of gait, mobility and righting reflex, decreased forelimb grip strength, increased landing foot splay and impaired psychomotor coordination. The response to various sensory stimuli was also decreased. The acute effects were all short-lived and recovery began within minutes of removal from the exposure chamber.

Molnár *et al.* (1986) studied motility in groups of eight CFY white male rats following exposure by inhalation for four hours to at least six test concentrations each of all three xylene isomers (individual isomer concentrations not provided). Exposure to 130 to 1,500 ppm (566 to 6,525

mg/m^3) *m*-xylene and 400 to 1,500 ppm (1,740 to 6,525 mg/m^3) *p*-xylene resulted in a dose-dependent increase in group motility, whereas exposure to 150 to 1,800 ppm (653 to 7,830 mg/m^3) *o*-xylene resulted in a slight depression. At higher concentrations, activity was decreased in all groups, with the minimum narcotic concentration for the three isomers reported as 2,180 ppm (9,483 mg/m^3) for *o*-xylene, 2,100 ppm (9,135 mg/m^3) for *m*-xylene and 1,940 ppm (8,439 mg/m^3) for *p*-xylene. All three isomers also produced narcosis in rats at a concentration of approximately 2,000 ppm (8,700 mg/m^3).

Korsak *et al.* (1990) reported that *o*-xylene appears to be the most potent isomer with regard to the effect of xylenes on motor performance. These authors exposed groups of 10 male Wistar rats to approximately 3,000 ppm (13,050 mg/m^3) of *o*-, *m*- or *p*-xylene for six hours and measured rotarod performance before exposure and immediately after cessation of exposure. The number of failures per test group were: 19 of 20 for *o*-xylene at an average concentration of 3,027 ppm; six of 20 for *m*-xylene at an average concentration of 3,093 ppm; and one of 20 for *p*-xylene at an average concentration of 3,065 ppm. In a subsequent study with male Wistar rats exposed to 500 to 4,000 ppm (2,175 to 17,400 mg/m^3) for four hours, an EC50 for disturbed rotarod performance of 1,980 ppm (8,613 mg/m^3) was reported for *m*-xylene (Korsak *et al.*, 1993). This study also reported an RD50 (decreased respiratory rate) of 1,360 ppm (5,916 mg/m^3) for *m*-xylene. Other RD50 values reported for xylenes are 2,440 ppm (10,614 mg/m^3) for mixed xylenes for 6 minutes (Korsak *et al.*, 1988) and 1,467 ppm (6,381 mg/m^3) of *o*-xylene for five minutes (De Ceaurriz *et al.*, 1981).

Carpenter *et al.* (1975) reported that exposure to 1,300 ppm (5,655 mg/m^3) of mixed xylene for four hours produced incoordination in rats, which did not persist after exposure ended. No clinical signs of toxicity were noted at 580 ppm (2,523 mg/m^3) for four hours. At 9,900 ppm (43,065 mg/m^3) for four hours a number of rats died and displayed such effects as atelectasis, hemorrhage and edema of the lungs.

Tables 6 and 7 provide a summary of the acute human and experimental animal inhalation toxicity studies with xylenes.

4.1.3 Subchronic and Chronic Toxicity

In humans, neurological effects and irritation of the eyes and respiratory tract are the most commonly reported symptoms following subchronic and chronic inhalation exposure to xylenes (U.S. EPA, 2003). It is important to recognize though that most available human studies failed to adequately report exposure conditions and the subjects were typically simultaneously exposed to other chemicals in addition to xylenes. The main neurological symptoms reported include: headache, nausea, dizziness, difficulty concentrating, impaired memory, slurred speech, ataxia, fatigue, agitation, confusion, tremors, labored breathing and sensitivity to noise (ATSDR, 1995).

Five women occupationally exposed to xylenes for 1.5 to 18 years experienced such symptoms as chronic headache, chest pain, heart palpitations, electrocardiogram abnormalities, dyspnea, cyanosis of the hands, fever, leukopenia, malaise, impaired lung function, decreased ability to work, complete disability and mental confusion (Hipolito, 1980). However, the reported effects may in part be due to exposure to a number of other chemicals (ATSDR, 1995).

Table 6 Summary of Acute Human Toxicity Studies with Xylenes

			Reference
3 to 5 minutes	870 xylenes (mixed)	Nose and throat irritation	Nelson *et al.*, 1943
1 to 7.5 h for 5 d	435 (*p*-xylene)	Nose and throat irritation	Hake *et al.*, 1981
1 to 7.5 h for 5 d	435 (*p*-xylene)	Frequent headaches and dizziness in females	Hake *et al.*, 1981
1 to 7.5 h for 5 d	653 (*p*-xylene)	Males did not report increase in headaches or dizziness	Hake *et al.*, 1981
30 minutes	1,732 xylenes (mixed)	No increase in nose and throat irritation and no changes in respiratory rate	Hastings *et al.*, 1986
30 minutes	435, 870 or 1,740 xylenes (mixed)	Eye irritation 56% in controls, 60% at 435 mg/m^3, 70% at 870 mg/m^3 and 90% at 1,740 mg/m^3	Hastings *et al.*, 1984
15 minutes to 4 h	870 to 1,740 xylenes	Eye and throat irritation or neurological impairment	Carpenter *et al.*, 1975; Gamberale *et al.*, 1978
70 minutes	1,301 xylene (mixed) during exercise	Impaired short-term memory and reaction time	Gamberale *et al.*, 1978
4 h	870 xylene	No effect on short-term memory or reaction time	Olson *et al.*, 1985
4 h	870 xylene	No changes in visually evoked brain potentials	Seppäläinen *et al.*, 1991
4 h	435 xylene	Impaired performance on tests of memory and reaction times	Dudek *et al.*, 1990

Uchida et al. (1993) conducted surveys at factories in China where workers were exposed to solvents in the production of rubber boots, plastic coated wires or in printing. The surveys identified 994 solvent-exposed workers. To identify and quantify solvent exposures, workers were equipped with a diffusive air sampler for an eight-hour shift. A total of 175 xylene-exposed workers (107 men, 68 women) were selected for the study. The xylene isomers accounted for more than 70% of the total solvent exposure (on a ppm basis). The day after the shift, workers underwent a medical examination that included subjective symptoms, clinical signs and quantitative health measurements of hematology, serum biochemistry and urinalysis. Controls consisted of 241 non-exposed workers from the same factories or from factories in the same region. Both exposed and control groups had worked for an average of seven years with no change in the workplace during their working life, were of similar ages and had comparable drinking rates and smoking habits. Workers were exposed to a maximum concentration of

Table 7 Summary of Acute Inhalation Studies with Xylenes in Experimental Animals

				Reference
Rats	6 h/d, 3 to 5 days	0, 326, 1,088, 2,175, 4,350, 8,700 (mixed xylenes and ethylbenzene)	4,350 mg/m^3 and 8,700 mg/m^3 dose-dependant increase in liver microsomal cytochrome P-450 and smooth endoplasmic reticulum in hepatocytes	Toftgård *et al.*, 1983
Rats	4 h	0, 3,480, 6,960 (*p*-xylene)	6,960 mg/m^3 visual effects	Dyer *et al.*, 1988
Rats	4 h	6,960 (*p*-xylene)	Reversible unsteadiness and fine tremors	Bushnell, 1989
Rats	6 h/d for 5 d	10,875 (mixed xylenes)	Auditory effects	Crofton *et al.*, 1994
Rats	8 h	6,308 (mixed xylene)	Hearing loss	Pryor *et al.*, 1987
Rats	4 h	7,395 (mixed xylene)	No hearing effects	Pryor *et al.*, 1987
Rats	18-20 h/d for 7 d	2,697, 4,263, 6,960 (xylene)	4,263 mg/m^3 instability, incoordination and narcosis	Batchelor, 1927
Mice	Not reported; examined effects 20 minutes after exposure	8,700 to 34,800 mg/m^3	Reversible neurobehavioural effects	Tegeris and Balster, 1994
Rats	4 h	5,655 (mixed xylene)	Reversible incoordination	Carpenter *et al.*, 1975

175 ppm total xylenes (761 mg/m^3), with a geometric mean of 14.2 ppm (62 mg/m^3). *m*-Xylene was the most prevalent isomer, accounting for approximately 50% of the xylene exposure, with *p*-xylene at around 30% and *o*-xylene at around 15%. Workers were exposed also to ethylbenzene (geometric mean of 3.4 ppm), toluene (geometric mean of 1.2 ppm) and trace concentrations of n-hexane.

The prevalence of subjective symptoms during the work shift and in the previous three-month period was significantly higher ($p<0.01$) in exposed workers relative to controls. This was the case for both men and women and both sexes combined. During the work shift, eye and nasal irritation, sore throat and a floating sensation were increased among exposed workers of both sexes. In the exposed group, there was also an increased incidence of nausea, nightmares, anxiety, forgetfulness, inability to concentrate, fainting after suddenly standing up, poor appetite, reduced grasping power, reduced muscle power in extremities and rough skin in the previous three month period, in both sexes. When the exposed group was subdivided according to exposure intensity (either 1 to 20 ppm or >21 ppm xylenes), eye irritation, sore throat and a floating sensation showed a concentration related increase for symptoms reported during the work shift, while reduced appetite was the only concentration-dependent symptom reported for the previous three months. There were no significant differences between the exposed and

controls with respect to hematology, clinical biochemistry or urinalysis parameters. It was impossible to identify a no-observable-adverse-effect-level (NOAEL) in this study. This study has several limitations, including lack of reporting on the duration of exposure, co-exposure to other chemicals, an absence of a demonstrated relationship between response and dose or duration and the inherent bias presented by the self-reporting of symptoms (U.S. EPA, 2003).

Overall, the human evidence for persistent effects on the nervous system or other persistent adverse effects from chronic inhalation exposure to xylenes is limited and inadequate; however, HESIS (1986) concluded that concentrations of 100 to 200 ppm (435 to 870 mg/m^3) are associated with nausea and headache; 200 to 500 ppm (870 to 2,175 mg/m^3) with dizziness, irritability, weakness, vomiting and slowed reaction time; 800 to 10,000 ppm (3,480 to 43,500 mg/m^3) with lack of muscle coordination, giddiness, confusion, ringing in the ears and changes in sense of balance; and >10,000 ppm (43,500 mg/m^3) with loss of consciousness.

In experimental animals, persistent neurological impairment of the CNS is the most commonly reported and sensitive effect of subchronic or chronic inhalation exposure to xylenes. Measurable effects in several neurobehavioral endpoints begin at concentrations as low as 100 ppm (435 mg/m^3) and occur before other forms of toxicity occur in other tissues and organs (U.S. EPA, 2003). The major signs of xylene-induced CNS neurotoxicity reported in experimental animal studies include: narcosis, prostration, incoordination, tremors, muscular spasms, labored breathing, behavioral changes, hyper-reactivity to stimuli, altered visual evoked potentials, elevated auditory thresholds, hearing loss and decreased acetylcholine in midbrain and norepinephrine in hypothalamus (ATSDR, 1995). Animal studies also indicate that xylene isomers generally induce a wide variety of hepatic enzymes, as well as increased hepatic cytochrome P-450 content, liver enlargement and other minor hepatic histopathological changes (ATSDR, 1995). These types of changes have not been reported to manifest as adverse hepatic effects but rather, reflect the liver's increased metabolic activity that occurs in response to xylene exposure. Thus, such effects are considered adaptive changes rather than adverse health effects.

Carpenter *et al.* (1975) exposed groups of 25 male rats and four male beagle dogs to air concentrations of 180, 460 or 810 ppm (783, 2,000 or 3,524 mg/m^3) mixed xylenes, for six hours a day, five days per week, for 65 days (rats) or 66 days (dogs). The mixture consisted of (65.0% *m*-xylene, 7.8 % *p*-xylene, 7.6% *o*-xylene and 19.3% ethylbenzene). No treatment-related effects were observed in exposed rats or dogs of any group relative to controls. No difference in the median time to death was noted in rats exposed to xylenes for 65 days when compared with controls. A NOAEL of 810 ppm was identified from this study for both rats and beagle dogs.

Tátrai and Ungváry (1980) exposed groups of 30 male CFY rats to 0 or 3,500 ppm (15,225 mg/m^3) *o*-xylene for eight hours a day for six weeks. Although there was an increase in food and water consumption, terminal body weight in the exposed group was significantly lower ($p<0.05$) than in controls by the sixth week. Exposed rats also displayed hepatic changes, including increased absolute and relative liver weights, signs of hepatocellular hypertrophy, increased proportion of smooth and rough endoplasmic reticulum, decreased glycogen and increased peroxisomes. The observed changes in organ weight were considered consistent with an adaptive response to organic chemical exposure and probably reflected induction of enzymes in the liver. A lowest-observable-adverse-effect-level of 3,500 ppm *o*-xylene for significant body weight decreases is identified from this study.

Tátrai *et al.* (1981) exposed male CFY rats to 0 or 1,090 ppm (4,742 mg/m^3) *o*-xylene for eight hours a day, seven days per week, for six or 12 months. In the exposed group, increased food and water consumption, decreased body weight gain, increased absolute and relative liver weight and induction of the hepatic mixed-function oxidase system were reported. Histologic and histochemical examinations of the organs, including the liver, were reported to have shown no alterations. Electron microscopy of liver tissue samples revealed moderate proliferation of the smooth endoplasmic reticulum. The hepatic effects observed in this study were not considered adverse. A LOAEL of 1,090 ppm is identified from this study for decreased body weight in male rats with no adverse hepatic changes.

In Sprague-Dawley rats exposed to 0 or 630 ppm (2,741 mg/m^3) mixed xylenes for six hours a day, five days per week for four weeks, exposed animals showed a significant decrease in body weight gain, while the absolute and relative liver weights increased. There was also an increase in hepatic cytochrome P-450. The xylene mixture used in this study contained 2.0% *o*-xylene, 64.5% *m*-xylene, 10.0% *p*-xylene and 23.0% ethylbenzene (Toftgård *et al.*, 1981).

Ungváry (1990) exposed groups of male CFY rats to 0, 140, 350 or 920 ppm (0, 600, 1,500 or 4,000 mg/m^3) xylenes, for eight hours a day, seven days per week for six weeks and then for five days per week for six months. The test mixture contained 10% *o*-xylene, 50% *m*-xylene, 20% *p*-xylene and 20% ethylbenzene. No statistically significant differences in body weights were observed in any of the exposed groups relative to controls. Statistically significant changes were observed in exposed groups at six months (compared with control group values) for increased relative liver weight (17% in the high-dose group only); hypertrophy of the centrilobular zone of the liver (high-dose group only); increased nuclear volume of hepatocytes and proliferation of smooth endoplasmic reticulum (only the high-dose and control groups were compared); increased concentrations of mixed function oxidases (mid- and high-dose groups); and decreased hexobarbital sleeping time (mid- and high-dose groups). In general, it was reported that maximal effects were achieved by the sixth week of exposure and recovery occurred within four weeks following study termination. Ungváry (1990) also exposed CFY rats to 0, 350, 460 or 1,150 ppm (0, 1,500, 2,000 or 5,000 mg/m^3) of the same test mixture for 72 hours and repeatedly exposed male mice, rats and rabbits to 0 or 575 ppm (2,500 mg/m^3) of the test mixture for eight hours a day for six weeks, all of which resulted in similar effects to those reported in the six-month rat study. The authors did not consider the observed hepatic effects to be adverse and identified the highest test concentration (920 ppm) as the NOAEL. However, as the liver effects could be considered biologically relevant, the U.S. EPA (2003) identified a LOAEL of 920 ppm and a NOAEL of 350 ppm from these experiments.

Jenkins *et al.* (1970) conducted inhalation studies on 12 Sprague-Dawley or Long Evans rats, 15 Princeton-derived guinea pigs, two squirrel monkeys and two beagle dogs. In all experiments, the animals were repeatedly exposed to 780 ppm (3,393 mg/m^3) *o*-xylene for eight hours a day five days per week for six weeks. In another component of the study, 14 rats, 15 guinea pigs, two dogs and three monkeys were exposed to 78 ppm (339 mg/m^3) *o*-xylene continuously for 90 to 127 days (while 14 rats, 15 guinea pigs, 10 dogs and 12 monkeys were exposed continuously for 90 to 127 days to clean control air). The reporting of effects in this study was poor, but it was noted that during the 780 ppm study, two rats died on day three, one rat and one monkey

died on day seven and one dog exhibited tremors throughout the exposure period. The causes of death and clinical signs were not reported. No changes in body weights, hematology or histopathology in animals exposed to either 78 or 780 ppm were reported. A LOAEL or NOAEL cannot be determined from this study due to inadequate reporting.

Morvai *et al.* (1987) reported morphological changes in coronary microvessels (increased wall thickness) of rats exposed to 230 ppm (1,000 mg/m^3) mixed xylenes (the composition of isomers was unspecified) for four weeks.

Korsak *et al.* (1992) studied groups of 12 male Wistar rats exposed to 0 or 100 ppm (435 mg/m^3) *m*-xylene for six hours a day five days per week for six months or 1,000 ppm (4,350 mg/m^3) for three months. Rats exposed to *m*-xylene alone exhibited statistically significantly decreased rotarod performance and decreased spontaneous activity, as measured 24 hours after cessation of exposure, relative to controls. The percent failures in the rotarod test were roughly 60% in rats exposed to 1,000 ppm for three months, 35% in rats exposed to 100 ppm for six months and 0% for controls at either time period. The mean spontaneous motor activity in rats exposed to 100 ppm for six months was about 400 movements per hour, compared with about 800 movements per hour for controls. Spontaneous motor activity data for rats in the 1,000 ppm group were not reported. The rotarod test involves placing the subject animals on a rotating rod and evaluating their ability to remain on the rod for a period of two minutes. There were no statistically significant exposure-related changes in body weight, absolute or relative organ weights or clinical chemistry or hematology parameters in rats of the 1,000 ppm group. The only effect noted was decreased differential counts of lymphocytes and increased counts of monocytes. However, total counts of white blood cells were not significantly different in the test groups. A LOAEL of 100 ppm is identified from this study, based on decreased rotarod performance and decreased spontaneous motor activity. A study NOAEL could not be identified.

In a followup study, Korsak *et al.* (1994) exposed groups of 12 male Wistar rats to 0, 50 or 100 ppm (0, 218 or 435 mg/m^3) *m*-xylene for six hours a day five days per week for three months and evaluated similar endpoints as in the earlier Korsak *et al.* (1992) study. No statistically significant exposure-related changes were reported for body weight gain, absolute or relative organ weights, hepatic microsomal monooxygenase activity, lipid peroxidation or levels of triglycerides in the liver. Statistically significant decreases in erythrocyte counts were observed in rats of the 50 ppm and 100 ppm groups. Decreased levels of hemoglobin were also reported in both these groups. In the 100 ppm group, a statistically significant increase in leukocyte numbers was reported. In the 50 and 100 ppm groups, there was decreased rotarod performance which began at one month of exposure and continued until the end of study. Rotarod performance decreases were statistically significant in the 100 ppm group, relative to controls. Rats in the 50 or 100 ppm groups also showed a statistically significant increased sensitivity to pain by the end of the study. A LOAEL of 100 ppm for decreased rotarod performance and increased pain sensitivity and a NOAEL of 50 ppm were identified from this study.

Gralewicz *et al.* (1995) exposed eight-month-old male Wistar rats to 0, 100 or 1,000 ppm (0, 435 or 4,350 mg/m^3) "pure" *m*-xylene, for six hours a day five days per week for three months. One-hour electroencephalograph (EEG) recordings were performed on days 28 and 56 of exposure and on days 14, 28, 56 and 84 post-exposure. The number and duration of spontaneous

neocortical spike and wave discharges from the EEG were considered to be electrophysiological indices of the biological age of the brain. As rats age, spontaneous wave discharges increase in number and become longer. Tests of spatial learning in an eight-arm radial maze were also conducted for a two-week period that began from day 70 to day 83. The researchers identified no statistically significant differences in body weight between the exposed groups and controls and found no effect on the normalized number and cumulative-duration spike and wave discharge variables. The authors suggested that a learning deficit existed in the exposed rats. For example, after five consecutive trials the mean trial durations in each of the exposed groups were about 240 to 250 seconds, compared with a mean of about 150 seconds for the control group. In addition, the exposed groups did not exhibit a significant decrease in omission errors with successive days in the radial arm maze test that was exhibited by the control group. The mean number of omission errors in control rats showed a progressive decrease from about 2.75 on the first trial to 0 on the fourth and fifth successive trials. In contrast, rats in the 100 and 1,000 ppm groups had mean omission errors in the fifth consecutive trial of 1.5 and 2.5, respectively. A LOAEL of 100 ppm, for deficits in radial maze performance, was identified from this study.

In a behavioural study, Gralewicz and Wiaderna (2001) exposed groups of male Wistar rats to 0 or 100 ppm (435 mg/m^3) of *m*-xylene for six hours a day five days per week for four weeks. Radial maze and hot plate test protocols were used in this study. These protocols were the same as those used in Gralewicz *et al.* (1995) and Korsak *et al.* (1992). There were no differences between control and exposed rats in radial maze parameters at any time during the study. Similarly, no differences were observed between groups with respect to open-field activity. The 100 ppm group showed a significantly shorter step-down time (only in a sixth consecutive trial; there were no differences in trials one to five) in the passive avoidance test, as well as significantly greater paw-lick latency in the hot plate behavior test (35 seconds relative to 10 seconds in the controls). A LOAEL of 100 ppm for neurobehavioral effects is identified from this study.

Pryor *et al.* (1987) investigated the ototoxicity of xylenes in rats. Groups of 12 weanling male Fischer 344 rats were exposed to 0, 800, 1,000 or 1,200 ppm (0, 3,480, 4,350 or 5,220 mg/m^3) mixed xylenes, for 14 hours a day for six weeks. The mixture contained 10% *p*-xylene, 80% *m*-xylene and 10% *o*-xylene. All exposed groups showed a dose-dependent increase in behavioral auditory and brainstem auditory-evoked response (BAER) thresholds relative to controls, but only at certain frequencies. Behavioral auditory thresholds were elevated at 12 and 20 kHz in the 800 ppm group; at eight, 12 and 20 kHz in the 1,000 ppm group; and at all frequencies tested in the 1,200 ppm group. BAER thresholds were elevated at 16 kHz in the 800 ppm group; at eight and 16 kHz in the 1,000 ppm group and at four, eight and 16 kHz in the 1,200 ppm group. This study did not evaluate other types of toxicity. Based on increased behavioral auditory and BAER thresholds, a LOAEL of 800 ppm was identified from this study. A study NOAEL could not be determined.

Nylén and Hagman (1994) exposed groups of male Sprague-Dawley rats to 0 or 1,000 ppm (4,350 mg/m^3) xylene, for 18 hours a day, seven days per week for 61 days. The test mixture contained 1.5% *o*-xylene, 65% *m*-xylene, 32% *p*-xylene and 2.5% ethylbenzene. By day two, rats showed significantly decreased body weights and a slight loss in auditory sensitivity

(relative to controls), as measured by auditory brainstem response. Xylene exposure did not affect flash-evoked potentials or nerve and muscle action potentials measured in the rat tails.

In a recent ototoxicity study, Gagnaire *et al.* (2001) exposed groups of male Sprague Dawley rats to 0, 450, 900 or 1,800 ppm (0, 1,958, 3,915 or 7,830 mg/m^3) of *o*-, *m*- or *p*-xylene, for six hours a day, five days per week for 13 weeks. Neither the *o*- or *m*- isomer resulted in detectable changes in audiometric measurements, either during exposure or during an eight-week recovery period. However, exposure to 1,800 ppm of *p*-xylene produced significant decrements in brainstem auditory-evoked potential (at two, four, eight and 16 kHz) and cochleograms (total cell count) throughout the study. Such changes did not occur at 450 or 900 ppm. A NOAEL for *p*-xylene of 450 ppm was identified by the authors, based on the loss of outer hair cells, as observed by light and electron microscopy.

Savolainen *et al.* (1979) exposed groups of 20 male Wistar rats to 0 or 300 ppm (1,305 mg/m^3) xylenes (consisting of 85% *m*-xylene and 15% *o*- and *p*-xylene), for six hours a day, five days per week for five to 18 weeks. The only effects noted were an increase in microsomal superoxide dismutase activity in the brain, increased levels of brain enzymes, changes in axon membranes and a transient decreased preening frequency.

Rosengren *et al.* (1986) exposed groups of four male and four female Mongolian gerbils to xylene at 0, 160 or 320 ppm (0, 696 or 1,392 mg/m^3) for a period of three months followed by a four-month recovery period. In the exposed groups, there were regional increases in brain concentrations of glial fibrillary acidic protein, a main component of astroglial filaments, S-100 protein (found in fibrillary astrocytes) and DNA. The authors believed these findings to be compatible with the presence of astrogliosis. No other effects were reported.

Table 8 summarizes the subchronic and chronic inhalation NOAELs, LOAELs and other endpoints that were reported in the animal studies described above.

Table 8 Summary of Subchronic and Chronic Xylenes Inhalation Toxicology Studies in Experimental Animals

				Reference
Male rats	6 h/d, 5 d/wk for 65 days	783, 2,000, 3,524 (mixed xylenes)	NOAEL: 3,524 mg/m^3	Carpenter *et al.*, 1975
Male dogs	6 h/d, 5 d/wk for 66 days	783, 2,000, 3,524 (mixed xylenes)	NOAEL: 3,524 mg/m^3	Carpenter *et al.*, 1975
Male rats	8 h/d for 6 wks	0 and 15,225 (*o*-xylene)	LOAEL: 15,225 mg/m^3 for significant body weight decrease	Tátrai and Ungváry, 1980
Rats	6 h/d, 5 d/wk for 4 wks	0, 2,741 (mixed xylenes and ethylbenzene)	Significant decrease in body weight gain and increased liver weights	Toftgård *et al.*, 1981
Male rats	8 h/d, 7 d/wk for 6 to 12 months	0, 4,742 (*o*-xylene)	LOAEL: 4,742 mg/m^3 for decreased body weight	Tátrai *et al.*, 1981
Male rats	8 h/d, 7 d/wk for 6 wks then for 5 d/wk for 6 months	0, 600, 1,500, 4,000 (mixed xylenes and ethylbenzene)	NOAEL: 1,500 mg/m^3 LOAEL: 4,000 mg/m^3 for liver effects	Ungváry, 1990
Male rats	6 h/d, 5 d/wk for 6 months 6 h/d, 5 d/wk for 3 months	0, 435 (*m*-xylene) 4,350 (*m*-xylene)	LOAEL: 435 mg/m^3 for decreased rotarod performance and decreased spontaneous motor activity	Korsak *et al.*, 1992
Male rats	6 h/d, 5 d/wk for 3 months	0, 218, 435 (*m*-xylene)	NOAEL: 218 mg/m^3 LOAEL: 435 mg/m^3 for decreased rotarod performance and increased pain sensitivity	Korsak *et al.*, 1994
Male rats	6 h/d, 5 d/wk for 3 months	0, 435, 4,350 (*m*-xylene)	LOAEL: 435 mg/m^3 deficits in radial maze performance	Gralewicz *et al.*, 1995
Male rats	6 h/d, 5 d/wk for 4 wks	0, 435 (*m*-xylene)	LOAEL: 435 mg/m^3 for neurobehavioural effects	Gralewicz and Wiaderna, 2001
Male rats	14 h/d for 6 wks	0, 3,480, 4,350, 5,220 (mixed xylenes)	LOAEL: 3,480 mg/m^3 for hearing loss	Pryor *et al.*, 1987
Male rats	18 h/d, 7 d/wk for 61 days	0 and 4,350 (mixed xylenes and ethylbenzene)	LOAEL: 4,350 mg/m^3 for auditory effects	Nylén and Hagman, 1994
Male rats	6 h/d, 5 d/wk for 13 wks	0, 1,958, 3,915, 7,830 (*m*-, *p*- or *o*-xylene)	NOAEL: 1,958 mg/m^3 (*p*-xylene)	Gagnaire *et al.*, 2001

4.1.4 Developmental and Reproductive Toxicity

Few human studies were identified that investigated the reproductive effects of xylenes following inhalation exposure. There are no available studies on the possible developmental toxicity of inhaled xylenes in humans, but a large number of animal studies have examined standard developmental toxicity endpoints and neurobehavioral endpoints following inhalation exposure to mixed xylenes or individual xylene isomers (U.S. EPA, 2003).

While a large number of studies have examined the potential developmental effects of inhaled xylenes in animals, adverse effects have been reported only at exposure levels greater than those

at which neurological effects occur (U.S. EPA, 2003; ATSDR, 1995). Furthermore, many of the available developmental toxicity studies suffered from a number of limitations that make them difficult to interpret (*e.g.*, unknown or unreported composition of xylene mixtures; insufficient number of dose levels; lack of reported details on both methods and results) (ATSDR, 1995).

Taskinen *et al.* (1986) studied pregnancy outcomes in female workers in eight Finnish pharmaceutical factories between 1973 and 1980. Of 1,795 pregnancies, there were 1,179 deliveries, 142 spontaneous abortions and 474 induced abortions. Rates of spontaneous abortions were found to be similar among women employed during the first trimester of their pregnancy (10.9%) and those workers who were not employed during their first trimester (10.6%). The corresponding rate of spontaneous abortion for all women in the region was 8.5% for the entire study period. In a case-control study of these women, 44 workers who had a spontaneous abortion were matched by age to three workers who had normal births. Information about chemical exposures was collected by questionnaire. Using a logistic analysis of the collected data (which included estrogen exposure, solvent exposure and heavy lifting as variables), a marginally significant odds ratio was found for exposure to four solvents (including xylenes). This study is greatly limited by its lack of quantification of exposure concentrations, concurrent exposures to other chemicals and unbalanced numbers of test subjects versus control subjects.

Taskinen *et al.* (1994) conducted a case-control study of Finnish female laboratory workers employed during the period 1970 to 1986. In this study, 206 women who had spontaneous abortions were matched by age to 329 referent women who had had normal births. Exposure information was again collected by questionnaire. Using a multivariate analysis that included adjustments for employment, smoking, alcohol consumption, parity, previous miscarriages, failed birth control and febrile disease during pregnancy, statistically significant associations were reported for spontaneous abortions and exposure to three out of 20 solvents for which questionnaire information was collected. The odds ratio for xylenes was 3.1.

Axelsson *et al.* (1984) found that pregnancy outcomes were not affected in university laboratory employees exposed to xylenes during the first trimester of pregnancy. There was no difference in miscarriage rate between exposed workers and unexposed controls. Exposure levels were not stated in this study.

Overall, the available studies of inhalation xylene exposure and human reproductive outcomes are of limited usefulness in assessing the potential reproductive toxicity due to numerous study design deficiencies, the fact that the number of spontaneous abortions was small and that all subjects had been exposed to multiple chemicals.

A much larger number of reproductive and developmental toxicity studies have been conducted in experimental animals for xylenes using the inhalation route of exposure. There is a large degree of variation in concentrations of xylene that produce developmental effects and those that do not. ATSDR (1995) suggests this reflects a number of factors that differ between the various studies such as different strains and species of animal, different purity and composition of xylenes tested, different methods of exposure, exposure patterns and durations, *etc.*

Balogh *et al.* (1982) observed an increase in placental weight at xylene air concentrations of 438 and 775 ppm (1,905 and 3,371 mg/m^3). It was suggested that relatively high concentrations of xylenes could limit oxygen delivery to the placenta, which in turn can lead to increased placental weights.

In a one-generation reproductive toxicity study conducted by Bio/dynamics Inc. (1983), groups of male and female CD rats were exposed to 0, 60, 250 or 500 ppm (0, 261, 1,088 or 2,175 mg/m^3) mixed xylenes (groups I, II, III and IV, respectively), for six hours a day, five days per week for 131 days prior to mating. Exposure continued in females on gestation days one to 20 and lactation days five to 20. The test mixture contained 2.4% toluene, 12.8% ethylbenzene, 20.3% *p*-xylene, 44.2% *m*-xylene and 20.4% *o*-xylene. Two additional 500-ppm groups were similarly exposed (F_0 males only - group V; and F_0 females only - group VI). There were no adverse effects reported in F_0 adults. No differences were observed in testes weights or histologic examination of reproductive tissues in xylene-exposed males that were sacrificed after mating, relative to control males. The female mating index in groups III and VI were significantly lower relative to controls, but the decreases were not considered by the authors to be exposure-related as a similar effect was not observed in group IV (500 ppm) and also because the decreases were compared to an abnormally high mating performance in the controls. Male mating index, pregnancy rate and fertility index in all exposed animals were comparable to controls. The highest exposure level in this study, 500 ppm, is identified as a reproductive NOAEL.

The Bio/dynamics Inc. (1983) study involved exposure of one-half of the group I F_0 pregnant dams (controls) and the group IV F_0 pregnant dams (500 ppm group) to mixed xylenes for six hours a day five days per week during a premating period and during gestation. Maternal exposure to 500 ppm mixed xylenes did not adversely affect maternal body weights, food consumption or food utilization. Terminal body weights (corrected for gravid uterine weights) for the exposed females were significantly increased relative to controls, but the increases were not considered to be biologically significant (106% of controls). Absolute kidney weights were also significantly increased in group IV females (110% of controls), but kidney weight: body weight ratios were comparable to those of controls. No statistically significant differences were noted between group IV and group I with respect to mean number of corpora lutea, implantations, live fetuses, mean percentage of live fetuses/implants or fetal sex ratios. Group IV showed an increased mean number of resorption sites and mean percentage of resorptions to implants, but these increases were not statistically significant. No dams displayed whole litter resorption. There were no definitive treatment-related external, visceral or skeletal malformations or variations observed in group IV offspring. The exposed group had a slightly higher incidence of unossified sternebrae and incompletely ossified cervical vertebral transverse processes. Mean fetal body weights on gestational day 21 were marginally but significantly decreased in exposed female fetuses while male fetal weights were comparable to those of controls. This decrease was not considered to be biologically significant by the authors.

From the Bio/dynamics Inc. (1983) study, a NOAEL of 500 ppm was identified for systemic, reproductive, maternal and development toxicity (ATSDR, 1995).

Nylén and Hagman (1994) exposed male SD rats to a xylene-based solvent, at concentrations up to 1,000 ppm (4,350 mg/m^3). The solvent was reported to contain 1.5% *o*-xylene, 65% *m*-xylene,

32% *p*-xylene and 2.5% ethylbenzene. A number of male reproductive tissue variables were not different between exposed and control rats when evaluated at two weeks or 10 months post-exposure. Endpoints evaluated were percentages of intact spermatozoa, percentages of spermatozoa with normal heads and tails, testis weight, ventral prostate weight and noradrenaline concentration in the vas deferens. Exposed rats showed no impairment of fertility when tested 14 months after cessation of exposure. This study identified a NOAEL of 1,000 ppm based on lack of significant testicular effects and impaired fertility in male rats.

Litton Bionetics (1978a) exposed groups of pregnant rats to 0, 100 or 400 ppm (0, 435 or 1,740 mg/m^3) xylene for six hours a day on gestational days six to 15. The xylene mixture contained 52% *m*-xylene, 11% *o*-xylene, 0.31% *p*-xylene and 36% ethylbenzene. Mean body weights and food consumption were not significantly different in exposed dams relative to controls. There were no significant exposure-related changes in the number of live litters, number of implantation sites, number or percentage of litters with resorptions, litters with dead fetuses, mean liver litter size or the average fetal body weight, relative to controls. No exposure-related malformations were observed in fetuses, but there were some skeletal changes indicative of retarded bone ossification noted in the 400 ppm group. The incidence of fetuses with retarded bone ossification was significantly elevated relative to controls in the 400 ppm, but not the 100 ppm group. However, a Wilcoxon Rank Sum test indicated no significant difference between the 400 ppm group and the control group. Based on this finding, the authors could not attribute the difference in retarded bone ossification to xylene exposure. The highest exposure level in this study, 400 ppm, was identified as the NOAEL for maternal and developmental toxicity.

Hudák and Ungváry (1978) exposed groups of pregnant CFY rats to 0 or 230 ppm (1,000 mg/m^3) xylene, for 24 hours a day during gestational days 9 to 14. The test mixture contained 10% *o*-xylene, 50% *m*-xylene, 20% *p*-xylene and 20% ethylbenzene. There were no statistically significant differences in maternal body weights, fetal deaths, mean fetal or placental weights, external, or visceral malformations between the exposed and control groups. Exposed group fetuses showed increases for skeletal anomalies relative to controls that were statistically significant. As the incidence rate was based on the number of affected fetuses rather than the affected litters and as litter-specific information was not provided, interpretation of this finding is confounded by the inability to adjust for possible litter size covariation (U.S. EPA, 2003). A NOAEL of 230 ppm is identified from this study for maternal and developmental toxicity.

Ungváry *et al.* (1980) exposed groups of 15 to 30 pregnant CFY rats to 0, 35, 350 or 700 ppm (0, 150, 1,500 or 3,000 mg/m^3) of *o*-, *m*- or *p*-xylene (purity not stated), for 24 hours a day on gestational days seven to 14. Four dams in the 700 ppm *m*-xylene group died. Necropsy revealed hyperaemia and hemorrhage in several organs, pulmonary edema and distention of the gut and urinary bladder. Maternal food consumption was considerably reduced in 350 and 700 ppm *o*-xylene or *p*-xylene groups during the exposure period, but returned to normal when exposure ceased. Maternal body weight gain exhibited a concentration-related decrease during exposure to all three isomers but was comparable to that in the controls, with the exception being the 700 ppm *m*-xylene group, which was significantly lower than controls. Dams exposed to 350 or 700 ppm *o*-xylene showed slightly elevated but statistically significant liver:body weight ratios and an increase in the rough endoplasmic reticulum profile and smooth endoplasmic vesicles relative

to controls. Exposure to 700 ppm *m*-xylene, but not *o*- or *p*-xylene, resulted in a small but statistically significant decreased number of mean implantations per dam relative to controls. The 700 ppm *p*-xylene group showed a marked postimplantation loss and a corresponding decreased mean litter size. Mean fetal body weights were significantly decreased in both the 350 and 700 ppm *o*-xylene groups and in the 700 ppm *p*- and *m*-xylene groups, relative to controls. There also was a corresponding increase in the number of weight-retarded fetuses in these groups. Histochemical analyses of fetuses from the 700 ppm *o*- and *p*-xylene groups revealed decreased staining of alkaline phosphatase in the proximal convoluted tubules and of succinic hydrogenase, acid phosphatase and glucose-6-phosphatase in the renal nephron. Additionally, decreased activities of succinic dehydrogenase and glucose-6-phosphatase were observed in the liver and thymus cells in fetuses of the 700 ppm *m*-, *p*- and *o*-xylene groups. No exposure-related changes were observed following histopathological or electron microscopic evaluation of organs in fetuses. No statistically significant exposure-related changes were reported for external, visceral or skeletal malformations in fetuses of any group exposed to the three xylene isomers. A statistically significant increase in the incidence of fetuses with extra ribs was reported in the 700 ppm *m*-xylene group and the 700 ppm *p*-xylene group, relative to controls. In addition, statistically significant increases in incidences of fetuses with skeletal retardation were observed at 35, 350 and 700 ppm *p*-xylene and at 700 ppm *o*-xylene, relative to controls.

While the data from this study are suggestive of statistically significant increases in the incidences of fetal skeletal retardation or anomalies, interpretation is confounded by the lack of ability to adjust for possible litter size covariation (U.S. EPA, 2003). The U.S. EPA has identified LOAELs and NOAELs from this study as follows. A LOAEL of 700 ppm for *o*-xylene, *p*-xylene or *m*-xylene and a NOAEL of 350 ppm are identified for maternal toxicity (decreased body weight). For *p*-xylene, 700 ppm is identified as a developmental LOAEL and 350 ppm is a NOAEL for postimplantation loss, decreased litter size and decreased fetal body weight. For *m*-xylene, 700 ppm and 350 ppm are a developmental LOAEL and NOAEL, respectively, for decreased fetal body weight. For *o*-xylene, 350 ppm is the developmental LOAEL and 35 ppm is the NOAEL for decreased fetal body weight.

Ungváry and Tátrai (1985) conducted a developmental toxicity study on xylenes using rats, mice and New Zealand rabbits. Groups of pregnant rats were exposed to 0, 60, 440 or 780 ppm (0, 250, 1,900 or 3,400 mg/m^3) xylenes (composition not specified) for 24 hours a day during gestational days seven to 15. Groups of pregnant CFLP mice were exposed to 0, 115 or 230 ppm (0, 500 or 1,000 mg/m^3) mixed xylenes or to 115 ppm (500 mg/m^3) *o*-xylene, *m*-xylene or *p*-xylene for three four-hour periods daily on gestational days six to 15 or seven to 20, respectively. Groups of 10 pregnant New Zealand rabbits were exposed to 0, 115 or 230 ppm mixed xylenes (0, 500 or 1,000 mg/m^3) or 115 ppm *o*-, *m*- or *p*-xylene for 24 hours a day on gestational days seven to 20. In all experiments, maternal toxicity was reported to be moderate and dose-dependent but specifics were not provided. In rats of the 780 ppm mixed xylenes group, there were statistically significant increases (relative to controls) in the proportion of dead or resorbed fetuses, weight-retarded fetuses, skeletal- retarded fetuses and fetuses with an extra rib. In the 60 and 440 ppm groups, there were significantly increased proportions of skeletal-retarded fetuses, relative to controls.

In mice, there were significantly increased proportions of weight- and skeletal retarded fetuses in the 230 ppm group. In mice of the 115 ppm group (*o*-, *m*- or *p*-xylene), there was a significantly increased proportion of skeletal-retarded fetuses relative to controls.

In rabbits of the 230 ppm mixed xylenes group, no live fetuses were produced. Furthermore, three dams died, six aborted and the remaining dam showed total resorption. Another group of eight rabbits also exposed to 230 ppm *p*-xylene produced no live fetuses, one dead dam, and three aborted fetuses. Four showed total resorptions. These findings from the rabbit experiment suggest severe maternal toxicity at 230 ppm. In rabbits of the 115 ppm mixed xylene group, there were no increases (relative to controls) with respect to the percentages of fetuses with skeletal retardation, minor anomalies or skeletal, internal or external malformations. The only effect at this concentration was significantly reduced average female (but not male) fetal body weights. This was not considered biologically significant by the authors. In the 115 ppm group, there were also no significant differences from controls in the number of abortions, number of live fetuses, proportions of dead or resorbed fetuses. There was an increased percentage of dead or resorbed fetuses in the *m*-xylene 115 ppm group.

As with Ungváry *et al.* (1980), interpretation of statistically significant findings for increased incidence of fetuses with retarded skeletal ossification is difficult, given the inability to adjust for possible litter size covariation and the relatively small magnitude of the increased incidences (U.S. EPA, 2003). Maternal toxicity NOAELs or LOAELs for rats and mice cannot be identified due to inadequate reporting of maternal toxicity findings. The U.S. EPA (2003) identified NOAELs and LOAELs from this study as follows. For rats, 780 ppm mixed xylenes is identified as an apparent developmental LOAEL for increased percentage of dead or resorbed fetuses and 440 ppm is the NOAEL. In mice, 230 ppm mixed xylenes is the apparent NOAEL for developmental effects. For mice exposed to *o*-, p or *m*-xylene, a NOAEL of 115 ppm is identified based on effects on fetal survival or fetal malformations or variations. For rabbits, a NOAEL of 115 ppm mixed xylenes is identified as a maternal and developmental NOAEL. For rabbits exposed to *o*-, *p*- or *m*-xylene, a NOAEL of 115 ppm is identified based on effects on fetal survival and fetal malformations or variations.

Hass *et al.* (1995) exposed pregnant rats (Mol:Wist) to 0 or 500 ppm (2,175 mg/m^3) xylenes for six hours a day on gestational days seven through 20. The test mixture contained 19% *o*-xylene, 45% *m*-xylene, 20% *p*-xylene and 15% ethylbenzene. Litters with fewer than six pups were not evaluated in this study. From each litter, two males and two females underwent behavioral testing. For one male and one female from each litter this testing consisted of standard housing for three months post-exposure, then undergoing the Morris water maze test (finding a hidden platform while swimming in a maze). The remaining male and female from each litter were kept in enriched housing (cages contained various toys) and then tested for rotarod, open field and Morris maze performance at about three months of age. It was found that exposure to xylenes did not affect maternal clinical signs, body weight gain or food consumption. There also were no significant differences between control and exposed groups with respect to length of gestation period, number of pups per litter and sex distribution per litter. The litters of the exposed group had a slight decrease in mean birth weight and a trend toward lower body weight during the postnatal followup, but differences were not statistically significant. Absolute brain weights were statistically significantly decreased on postnatal day 28 (when males and females were

pooled), but statistically significant decreases were not observed in absolute or relative brain weights when considering males or females separately or for relative brain weights of males and females combined. The air-righting reflex was significantly delayed by one day in exposed litters. No significant differences were observed between control and exposed groups in open field performance or rotarod performance. Offspring from exposed rats that were raised in the enriched environment showed no difference in the Morris maze test relative to controls. However, offspring from exposed rats that were raised in the standard housing showed a weak trend for increased latency for finding the platform at the beginning of this test. By 16 weeks, exposed offspring took significantly more time to find the platform. Further analysis revealed that this effect was limited to female offspring from the standard housing. In four consecutive trials conducted at 16 weeks, the mean time (*i.e.*, latency) to find the hidden platform was consistently greater in the standard housing exposed females than in the controls.

In a followup study to Hass *et al.* (1995), female offspring from the standard housing conditions also were evaluated at 28 and 52 weeks (Hass *et al.*, 1997). By 28 weeks, there was an increased latency for finding a platform that was moved to a new position in female offspring only, during the first trial of a three-trial testing block. However, the next two trials resulted in similar latencies between exposed and control rats. No other statistically significant differences were observed in the Morris maze test. By 55 weeks post-exposure, there were no statistically significant differences observed between exposed and control groups.

This study is limited by the fact that only one concentration was tested. However, the results suggest that gestational exposure to 500 ppm produces minor adverse effects on neurological development that appear to be reversible. A developmental LOAEL of 500 ppm is identified from this study and 500 ppm can be considered a NOAEL for maternal toxicity.

Hass and Jakobsen (1993) exposed groups of 36 pregnant Wistar rats to 0 or 200 ppm (870 mg/m^3) technical xylene (composition not stated) for six hours a day, during gestational days six to 20. No maternal toxicity was observed. The only significant effect noted in fetuses from exposed dams was an increased incidence of delayed ossification in the skulls. In a postnatal study, significantly decreased rotarod performance was observed in female pups by postnatal days 22 and 23 and in male pups by postnatal day 23. This study is limited in that only one exposure concentration was tested and a limited battery of behavioural tests was used. As such, U.S. EPA (2003) considers that this study is insufficient for identifying a reliable developmental NOAEL or LOAEL.

Rosen *et al.* (1986) exposed pregnant Sprague-Dawley rats to 0, 800 or 1,600 ppm *p*-xylene (0, 3,500 or 7,000 mg/m^3; 99% pure) on gestational days seven through 16. There was no effect on litter size or pup weight, nor was there any effect on CNS development, figure-8 maze activity or growth rate of the pups. The only significant effect was a decrease in maternal body weight gain in the 1,600 ppm group. A maternal toxicity LOAEL of 1,600 ppm is identified from this study based on decreased body weight gain and the NOAEL is 800 ppm. The developmental neurotoxicity NOAEL is 1,600 ppm.

Kükner *et al.* (1997) exposed pregnant Wistar rats to 0 or 2,600 ppm xylenes (0 or 11,300 mg/m^3) (purity and composition not stated) for eight hours a day on gestational days six to 21. Non-pregnant rats were exposed to 2,600 ppm xylenes for the same period and a

control group of pregnant rats inhaling clean air was also evaluated. Increases in liver enzyme activity were reported in the exposed group. Electron microscopy of pregnant and non-pregnant rat liver tissue revealed mitochondria that concentrated near the periphery of hepatocytes, increased lysosomes and expanded smooth endoplasmic reticulum. In fetal livers from the exposed group, there were expanded smooth endoplasmic reticulum, structurally deformed mitochondria and granular endoplasmic reticulum. No structural defects were observed in the kidneys or pancreas of exposed pregnant or non-pregnant rats or fetuses from exposed dams.

Mirkova *et al.* (1983) exposed groups of pregnant white Wistar rats to 0, three, 12 or 110 ppm (0, 14, 53 or 468 mg/m^3) xylene isomers (composition not stated) for six hours a day five days per week, during gestational days one through 21. Pregnancy rates were 29 of 36, 11 of 18, 18 of 27 and 11 of 15 for the 0, three, 12 and 110 ppm groups, respectively. Numerous manifestations of toxicity in mid- and high-dose groups were observed, including a statistically significant increased percentage of post-implantation loss per implantation, a statistically significant decreased fetal body weight and a statistically significant increase in the percentage of hemorrhages in fetuses, relative to controls. The authors also reported an increased incidence of anomalies of the internal organs (including hydrocephalus, microphthalmia, intracerebral hematomas and hemorrhages in the liver) and defects in ossification of the sternum and bones of the skull in fetuses from exposed dams. However, incidence rates for these anomalies were not provided in the study. A statistically significant decrease in pup weight on postnatal days seven and 21 was also reported for the mid- and high-dose groups. As the data from this study are limited by numerous factors, including composition and purity of xylenes not being stated, incomplete description of methods, inadequate litter size for proper fetal evaluations, high incidence of fetal hemorrhages in the control group (which questions the pre-experiment health status of the animals) and incomplete reporting of results, reliable NOAELs or LOAELS for maternal or developmental toxicity cannot be identified from this study (U.S EPA, 2003).

A recent study by Saillenfait *et al.* (2003) exposed pregnant Sprague-Dawley rats to *o*-, *m*-, *p*-xylene and technical xylene at concentrations of 100, 500, 1,000 or 2,000 ppm (435, 2,175, 4,350 or 8,700 mg/m^3), for six hours a day during gestational days six to 20. All test concentrations caused maternal toxicity, as indicated by reduced body weight gain. Decreased corrected weight gain and food consumption were observed in the 1,000 and 2,000 ppm groups and in the 2,000 ppm technical xylene group. There was no evidence of teratogenicity in any of the 2,000 ppm groups. Fetal toxicity, as indicated by significant decreases in fetal body weights, occurred in the 500 ppm group (and higher concentrations) for *o*-xylene and technical xylene and in the 1,000 and 2,000 ppm groups for *m*- and *p*-xylene. A significant increase in the mean percentage of fetuses per litter with skeletal variations was also noted in the 2,000 ppm groups for *o*- and *p*-xylene. A LOAEL of 500 ppm is identified from this study based on decreased fetal body weights (*o*-xylene and technical xylenes) and a developmental NOAEL of 100 ppm is identified also.

Table 9 Summary of Reproductive and Developmental Inhalation Toxicology Studies in Experimental Animals

				Reference
Rats	6 h/d for 131 d prior to mating with continued exposure in ♀on gestation d 1-20 and lactation d 5-20	0, 261, 1,088, 2,175 (mixed xylenes)	NOAEL: 2,175 mg/m^3 reproductive NOAEL	Bio/dynamics Inc., 1983
Male rats	Not reported; evaluated 2 to 10 months post-exposure	4,350 (mixed xylenes and ethylbenzene)	NOAEL: 4,350 based on lack of significant reproductive effects	Nylén and Hagman, 1994
Female rats	6 h/d on gestational d 6-15	0, 435, 1,740 (mixed xylenes and ethylbenzene)	NOAEL: 1,740 mg/m^3 for maternal and developmental toxicity	Litton Bionetics, 1978a
Female rats	24 h/d during gestational d 9-14	0, 1,000 (mixed xylene and ethylbenzene)	NOAEL: 1,000 mg/m^3 for maternal and developmental toxicity	Hudák and Ungváry, 1978
Female rats	24 h/d on gestational d 7-14	0, 150, 1,500, 3,000 (*o*-, *m*- or *p*-xylene)	*m*-, *p*- or *o*-xylene NOAEL: 1,500 mg/m^3 LOAEL: 3,000 mg/m^3 for maternal toxicity *p*-xylene NOAEL: 1,500 mg/m^3 LOAEL: 3,000 mg/m^3 for developmental effects *m*-xylene NOAEL: 1,500 mg/m^3 LOAEL: 3,000 mg/m^3 for developmental effects *o*-xylene NOAEL: 150 mg/m^3 LOAEL: 1,500 mg/m^3 for developmental effects	Ungváry *et al.*, 1980
Female rats	24 h/d on gestational d 7-15	0, 250, 1,900, 3,400 (xylenes)	NOAEL: 1,900 mg/m^3 LOAEL: 3,400 mg/m^3 for developmental effects	Ungváry and Tátrai, 1985
Female mice	Three 4 h periods daily on gestational d 6-15	0, 500, 1,000 (mixed xylenes)	NOAEL: 1,000 mg/m^3 for lack of developmental effects	Ungváry and Tátrai, 1985
	Three 4 h periods daily on gestational d 7-20	500 (*m*-, *p*- or *o*-xylene)	NOAEL: 500 mg/m^3 for lack of developmental effects	
Female rabbits	24 h/d on gestational d 7-20	0, 500, 1,000 (mixed xylenes)	NOAEL: 500 mg/m^3 for lack of maternal and developmental effects	Ungváry and Tátrai, 1985
	24 h/d on gestational d 7-20	500 (*o*-, *m*- or *p*-xylene)	NOAEL: 500 mg/m^3 for lack of developmental effects	

				Reference
Female rats	6 h/d on gestational d 7-20	0, 2,175 (mixed xylenes and ethylbenzene)	NOAEL: 2,175 mg/m^3 for maternal toxicity LOAEL: 2,175 mg/m^3 for developmental effects	Hass *et al.*, 1995; 1997
Female rats	6 h/d on gestational d 7-16	0, 3,500, 7,000 (*p*-xylene)	NOAEL: 7,000 mg/m^3 for developmental neurotoxicity NOAEL: 3,500 mg/m^3 for maternal toxicity LOAEL: 7,000 mg/m^3 for maternal toxicity	Rosen *et al.*, 1986
Female rats	6 h/d on gestational d 6-20	435, 2,175, 4,350, 8,700 (*m*-, *p*-, *o*- and technical xylene)	NOAEL: 435 mg/m^3 developmental LOAEL: 2,175 mg/m^3 based on decreased fetal body weights	Saillenfait *et al.*, 2003

4.1.5 Genotoxicity and Mutagenicity

Limited human data are available regarding the genotoxicity of xylenes following inhalation exposure. No inhalation studies were located regarding the genotoxicity of *m*-xylene, *o*-xylene or *p*-xylene in humans or animals. Overall, the available evaluations of the genotoxic effects of xylenes have consistently provided negative results (U.S. EPA, 2003; ATSDR, 1995).

Five adult healthy white males exposed for seven hours a day for three days to 40 ppm (174 mg/m^3) xylene, on three occasions over two weeks, showed no significant effects on sister-chromatid exchange frequency, cell cycle time or cell mortality in peripheral lymphocytes (Richer *et al.*, 1993). Sister-chromatid exchanges (SCE) in peripheral lymphocyte cultures were studied in two groups of 23 workers who had been exposed for four months to 23 years to mixed xylenes (Pap and Varga, 1987). The exposure levels for the two groups were 11 and 13 ppm (48 and 57 mg/m^3), respectively. There were no differences in SCE frequency, relative to controls. Funes-Cravioto *et al.* (1977) and Haglund *et al.* (1980) reported increased incidence of chromosomal aberrations or sister-chromatid exchange frequencies in exposed workers. However, in both these studies the exposure to xylene (not defined) was accompanied by exposure to other solvents, including ethylbenzene and benzene (WHO, 1997).

Xylenes have been found to be non-mutagenic in bacterial test systems with *Salmonella typhimurium* (Bos *et al.*, 1981; Florin *et al.*, 1980; NTP, 1986) and *Escherichia coli* (McCarroll *et al.*, 1981) or in cultured mouse lymphoma cells (Litton Bionetics, 1978b). Xylenes did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells (Anderson *et al.*, 1990), in cultured human lymphocytes (Gerner-Smidt and Friedrich, 1978) or in rat bone marrow (Litton Bionetics, 1978b). Xylenes also did not induce micronuclei in mouse bone marrow (Mohtashamipur *et al.*, 1985) or sperm head abnormalities in rats (Washington *et al.*, 1983).

Technical grade xylenes, not pure isomers, have been reported to cause a weakly mutagenic effect in *Drosophila* recessive lethal tests (Donner *et al.*, 1980). However, technical xylenes contain considerable amounts of ethylbenzene that may have been responsible for this effect.

In summary, genotoxicity studies on mixed xylenes and the individual isomers have provided consistently negative results in a variety of *in vitro* and *in vivo* assays and test systems using bacteria, yeast, insects, cultured mammalian cells, mice, rats and humans. Thus, there is sufficient evidence to conclude that xylenes are not mutagenic (ATSDR, 1995). There is also limited evidence from bacterial test systems which suggests xylene metabolites, specifically *m*-xylenol, *p*-xylenol, 2,4-dimethylphenol and *o*-methylbenzyl alcohol, are also not mutagenic (ATSDR, 1995).

4.1.6 Carcinogenicity

Data on the carcinogenicity of xylenes following inhalation exposure are limited. While a number of human occupational studies (*e.g.,* Arp *et al.*, 1983; Wilcosky *et al.*, 1984; Spirtas *et al.*, 1991) have suggested possible carcinogenic effects from xylene exposure, there was co-exposure to other chemicals, including benzene in many cases (U.S. EPA, 2003; ATSDR, 1995). This co-exposure is a major confounding variable in these studies that greatly limits interpretation of results. These studies are also limited by small numbers of subjects, low incidence rates, exposure misclassifications, insufficient employment durations and poorly quantified exposure concentrations.

Gérin *et al.* (1998) conducted a population-based case-control study in Montreal, Canada. These authors identified sites of "high" cancer incidence and administered questionnaires to hospitalized individuals being treated for cancer. The questions involved information about the lifestyles and work habits of the patients. This information was used to identify potential exposure to benzene, toluene, xylene and styrene. Exposure was only qualitatively evaluated as low, medium or high. Randomly selected individuals served as controls. An elevated standard mortality rate (SMR) was reported for exposure to "high" concentrations of xylene and cancer of the colon (SMR = 5.8) and rectum (SMR = 2.7), relative to controls. However this study is limited by a small number of cases, poorly defined exposure concentrations, lack of xylene mixture characterization and co-exposure of roughly 88% of cases to toluene and benzene.

No cancer studies in animals exposed by inhalation to xylenes were identified in the available scientific literature. Two oral studies were identified (NTP, 1986; Maltoni *et al.*, 1983; 1985).

NTP (1986) conducted a two year toxicology and carcinogenesis study using F344/N rats and B6C3F1 mice. Rats of each sex were administered 0, 250 or 500 mg/kg mixed xylenes in corn oil by gavage, for five days per week for 103 weeks. Mice of each sex were administered 0, 500 or 1,000 mg/kg xylenes on the same schedule. Body weights of the high dose male rats were 5 to 8% lower than those of controls after week 59. The mean body weights of low dose and control male rats and those of dosed and control female rats were similar. The survival rates of female rats and both sexes of dosed mice were not significantly different from those of the controls. Male rat survival was reduced relative to controls. There was also hyperactivity observed in the high dose mice, beginning after week four and continuing through week 103. There was no observed evidence of neoplastic or non-neoplastic lesions in dosed rats or mice of

either sex, at any site, that were considered to be related to the administration of xylenes. NTP concluded that under the conditions of these two-year gavage studies, there was "no evidence" of carcinogenicity of mixed xylenes in male or female F344/N rats administered 250 or 500 mg/kg or in male or female B6C3F1 mice administered 500 or 1,000 mg/kg. "No evidence" implies studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.

Maltoni et al. (1983; 1985) orally exposed groups of 40 male and 40 female Sprague-Dawley rats to 500 mg/kg mixed xylenes (composition unspecified) in olive oil by gavage, four to five days per week for 104 weeks. Control groups received olive oil only. All rats died by 141 weeks. The percentages of mice that survived treatment were similar in controls and treated groups up to 92 weeks; survival data for the remainder of experiment were not reported. These reports only provided limited information regarding tumour incidences at specific tissue sites, with no information provided on non-neoplastic lesions or tumour pathology. Incidences for thymomas were 1/34 and 0/36 in exposed males and females, compared with 0/45 and 0/49 in controls. Incidences of other hemolymphoreticular neoplasias (not specified) were 4/34 and 3/36 in exposed males and females, compared with 3/45 and 1/45 in controls. Fishers exact tests indicated no significant differences between treated and control rats in the incidences for hemolymphoreticular neoplasias. The authors also reported an increase in the total number of exposed rats with malignant tumours (unspecified type). Incidences were 14/38 and 22/40 for exposed males and females, compared with 11/45 and 10/49 for controls. The exposed female total malignant tumour incidence was significantly increased relative to controls. However, because the reporting of site-specific tumour incidence data and pathology was incomplete, this study is of limited use in evaluating the carcinogenicity of xylenes (U.S. EPA, 2003).

Under the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999a), the available data are considered inadequate for an assessment of the carcinogenic potential of xylenes. Adequate human data on the carcinogenicity of xylenes are not available and the available animal data are inconclusive as to the ability of xylenes to cause a carcinogenic response (U.S. EPA, 2003). Previously, the U.S. EPA categorized xylenes as "D - not classifiable as to human carcinogenicity", based on a lack of appropriate animal bioassays and human studies. Health Canada classifies xylenes as Group IV – probably not carcinogenic to humans (CCME, 2003). IARC (1999) classifies xylenes as Group 3 – not classifiable as to their carcinogenicity in humans, based on inadequate experimental animal and human evidence. The NTP has not classified xylene as to its carcinogenicity.

4.2 Effects on Ecological Receptors

Aquatic Life

Given its volatility, xylene exposures have been difficult to determine in many aquatic toxicity tests that used open test systems. For example, many of the 24 h and 96 h LC50 values are the same or similar, suggesting that most of the xylene had been lost during the test (WHO, 1997). Therefore, care must be taken when interpreting data from open static tests over longer periods than 24 h, especially those based on nominal concentrations.

Overall, xylene has a moderate to low acute toxicity for aquatic organisms.

Bringmann and Kühn (1977) exposed the green alga, *Scenedesmus quadricauda* for eight days to xylene. Reduction in cell multiplication at concentrations > 200 mg/L were reported. Brooks *et al.* (1977) studied the effect of xylene on photosynthesis in a mixed ocean culture of phytoplankton. It was found that exposure to 3 mg/L xylene for eight hours caused a 50% reduction in photosynthesis.

Galassi *et al.* (1988) used a closed static system to prevent loss of xylenes by volatilization and calculated the 72 h EC50 for growth inhibition in the alga, *Selenastrum capricornutum* to be 4.7, 4.9 and 3.2 mg/L for the ortho, meta and para isomers, respectively. Similar results were obtained by Herman *et al.* (1990). Using the same species of alga, they obtained eight day EC50 values for growth inhibition of 4.2, 3.9 and 4.4 mg/L for the ortho, meta and para isomers, respectively. Sheedy *et al.* (1991) reported a 14 day EC50 for growth inhibition of *Selenastrum capricornutum* of 72 mg/L for xylene.

Hutchinson *et al.* (1980) exposed the alga, *Chlamydomonas angulosa* and *Chlorella vulgaris* to *p*-xylene for three hours and reported EC50 values for inhibition of photosynthesis of 5.7 and 105.1 mg/L for the two species, respectively. Dunstan *et al.* (1975) exposed marine microalgae, the diatom, *Skeletonema costatum*, the dinoflagellate *Amphidinium carterae*, the coccolithophorid *Cricosphaera* and the green flagellate *Dunaliella tertiolecta*, to xylene for three days. A xylene concentration of 10 mg/L inhibited the growth of all species.

In freshwater aquatic invertebrates, LC50's based on measured water concentrations are reported to range from 1 mg/L *o*-xylene in a 24 h *Daphnia magna* test to >22.4 mg/L *o*-xylene in the snail, *Aplexa hypnorum* (96 h test) (WHO, 1997; Galassi *et al.*, 1988; Holcombe *et al.*, 1987).

In freshwater fish, LC50's based on measured water concentrations are reported to range from 2.6 mg/L *p*-xylene in a 96 h static test with rainbow trout to 30.6 mg/L (isomer not stated) in goldfish (24 h flowthrough test) (Galassi *et al.*, 1988; Weber *et al.*, 1975; WHO, 1997).

Terrestrial Invertebrates/Microorganisms

Walton *et al.* (1989) studied the effect of *p*-xylene on the microbial respiration of two soil types, a silt loam (1.49% organic carbon) and a sandy loam (0.66% organic carbon). The chemical was applied at a rate of 1,000 µg/g (dry weight). Microbial respiration of the silt loam was unaffected. In the sandy loam, respiration initially decreased and then increased, but returned to control levels within the six-day exposure period.

Anderson *et al.* (1991) reported that 100 mg/kg of *p*-xylene in soil was not toxic to soil microbes.

Environment Canada (1995) reported that the earthworm, *Eisenia foetida*, experienced 25% mortality at 56 mg/kg xylenes in soil. ESG (2002) reported an LC25 of 733 mg/kg for xylenes in a collembolan and an earthworm NOEC and LOEC of 8 and 78 mg/kg, respectively, all in coarse soil. In fine soils, Komex (2002) reported an LC25 of 835 mg/kg for a collembolan and a geometric mean of earthworm NOEC and LOEC values of 25 mg/kg.

Birds

Hill and Camardese (1986) exposed Japanese quail (*Coturnix coturnix japonica*) to xylene in a 5 day dietary toxicity test. The LC50 was found to be greater than 20,000 mg/kg diet. No overt signs of toxicity occurred at 5,000 mg/kg.

Plants

Barley exposed to 20,000 mg/m^3 of xylenes vapour for four hours displayed 80% injury of leaves within 24 hours (Currier, 1951; Currier and Peoples, 1954).

Environment Canada (1995) reported LOECs for seedling emergence in radishes and lettuce of 32 and 5 mg/kg, respectively. However, these data were considered suspect due to xylene volatility and problems with its recovery from soil. ESG (2002) used more advanced plant bioassay techniques that minimized loss *via* volatilization and that involved 14 day exposures ion both coarse and fine soils. In coarse soil, an IC25 of 421 mg/kg for reduction in alfalfa shoot dry mass was reported. For northern wheat grass, an IC25 of 90 mg/kg was reported for reduction of root wet mass. In fine soils, the IC25 values in alfalfa and wheatgrass were estimated to be 92 mg/kg (reduced shoot dry mass) and 241 mg/kg (reduced root length), respectively (Komex, 2002).

Other Environmental Effects

Based on the available data on the environmental fate, transport and effects of xylenes, these compounds are not expected to affect the physical properties of the atmosphere, contribute to global warming (as xylenes do not strongly absorb infrared radiation (CEPA, 1993), deplete stratospheric ozone or alter precipitation patterns.

Xylenes are sufficiently susceptible to photochemical oxidation in the troposphere such that they may contribute to photochemical smog formation. Derwent and Jenkin (1990) calculated Photochemical Ozone Creation Potentials (POCP) for xylenes of 41 (*o*-xylene), 78 (*m*-xylene) and 63 (*p*-xylene). The POCP reflects the ability of a substance to form ground level ozone and are calculated relative to ethylene (a chemical that is thought to be important in ground-level ozone formation and which is assigned a POCP of 100).

Summary

The major symptoms of acute human exposure to xylenes include: irritation of the nose, throat and eyes and central nervous system effects such as headache, nausea, dizziness, difficulty concentrating, impaired memory, slurred speech, ataxia, fatigue, agitation, confusion, tremors, labored breathing, impaired reaction time, alterations in equilibrium and body balance and sensitivity to noise. In experimental animals, central nervous system (CNS) toxicity is a sensitive effect of inhalation exposure to xylenes. Commonly reported signs of CNS neurotoxicity in experimental animals following acute inhalation exposure to xylene isomers include: narcosis, prostration, incoordination, tremors, muscular spasms, laboured breathing, behavioural changes, hyper-reactivity to stimuli, altered visual evoked potentials, elevated

auditory thresholds, hearing loss, decreased acetylcholine in midbrain and norepinephrine in hypothalamus (which suggests effects on motor control, sleep and memory maintenance). Other symptoms of acute xylene exposure in experimental animals include irritation of the respiratory tract, pulmonary edema, pulmonary hemorrhage and pulmonary inflammation. Neurological effects and irritation of the eyes and respiratory tract are the most commonly reported symptoms following subchronic and chronic inhalation exposure to xylenes. In experimental animals, persistent neurological impairment of the central nervous system is the most commonly reported and sensitive effect of subchronic or chronic inhalation exposure to xylenes. In subchronic and chronic studies, measurable effects in several neurobehavioral endpoints begin at concentrations as low as 100 ppm (435 mg/m^3) and occur before other forms of toxicity occur in other tissues and organs. Acute effects are most pronounced at high exposure levels (in excess of 1,000 ppm; 4,350 mg/m^3). At lower concentrations, more subtle effects may occur. The most significant effects on developmental endpoints were decreased fetal body weight or fetal survival in rats at xylene isomer doses of 350 or 700 ppm (Ungváry *et al.*, 1980) or at mixed xylenes concentration of 780 ppm (Ungváry and Tátrai, 1985) and increased abortions in rabbits exposed to 230 ppm (Ungváry and Tátrai, 1985). All these effects occur at concentrations above those at which neurobehavioral effects occur in experimental animals.

The carcinogenicity evidence for xylenes is limited and inconclusive, but suggests a lack of carcinogenic activity. There appears to be sufficient evidence to conclude that xylenes are not mutagenic or genotoxic, which supports the premise that xylenes are not carcinogens. While differences in the toxicity of the xylene isomers have been detected in a number of studies, no consistent pattern following inhalation exposure has been identified (U.S. EPA, 2003).

Based on a review of current and/or ongoing research and/or assessment activities or programs overseen by Health Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME), U.S. National Toxicology Program (NTP), U.S. National Institute of Health CRISP Database, U.S. National Institutes of Environmental Health Sciences (NIEHS), various U.S. EPA offices and programs (*e.g.*, TSCA, Science Advisory Board reports, etc.), Chemical Industries Institute of Toxicology (CIIT), Toxicology Excellence for Risk Assessment (TERA), World Health Organization (WHO), Agency for Toxic Substances and Disease Registry (ATSDR) and Health Effects Institute (HEI), there appear to be a number of current or ongoing studies or reviews related to xylenes toxicology under the direction of these agencies and institutes. For example, U.S. EPA IRIS revised the RfC for xylenes in 2003. The NIH CRISP (2004) database lists ongoing research activities related to feto-maternal pharmacokinetics.

5.0 AMBIENT MONITORING METHODS

This section assesses the various air monitoring methodologies to measure xylenes in ambient air and describes their advantages and disadvantages.

5.1 Background

5.1.1 Introduction

Air monitoring is used to determine the concentrations of chemical species in the atmosphere. For any single chemical species, there are typically several methods that can be used, with varying detection levels, sampling periods/frequencies and operational levels-of-effort. Specific air monitoring methods include continuous, integrated passive, grab sampling and integrated active (Lodge, 1988). Many factors must be considered in selecting the best approach based on the overall objectives of the monitoring program. Considerations include minimum detection levels, measurement precision, averaging period and cost.

5.1.2 General Monitoring Approaches

In continuous monitors, a sample of air is drawn past a fast response detector using a pump. The detector produces an electrical signal that is proportional to the concentration of a specific chemical compound. Hourly average concentration information can be recorded by a digital data collection system (*i.e.*, a computer) or other storage medium (chart recorder).

In integrated passive sampling, a reactive surface in a controlled diffusion path is exposed for a nominal period ranging from 24 hours to one-month. The reactive surface is analyzed in a chemical laboratory to determine the concentration of the captured compounds. The method is termed passive because pumps are not drawing an air sample past a detector or through a collection medium.

In grab sampling, a whole air sample is collected in a non-reactive steel canister or plastic bag. The air sample is then analyzed in a laboratory to determine the concentration of the compounds in the air sample. Grab samples typically represent samples collected over the course of a few minutes to several hours.

In integrated active sampling, a known volume of air is drawn through a column filled with an absorbent material (for gases) or a collection filter (for particles) using a pump. These absorbent columns or filters are then analyzed in a laboratory to determine the concentrations of the collected compounds. Integrated samples are typically collected once every six days for a 24-hour period.

Integrated samplers require a sorbent to entrap the chemical species being sampled. The selection of the sorbent will depend on the specific compounds being sampled. Commonly used sorbents include, but are not limited to, Tenax, XAD-2, activated charcoal, Carbotrap C, Anasorb 747, Carbosieve or a multi-stage combination using more than one sorbent. Dewulf and Langenhove (1997) describe four criteria that can be used in the selection of an appropriate sorbent. First, it is important that the sampled compounds do not breakthrough the sorbent and

that the specific retention volume of the sorbent is known. Secondly, the sorbent cannot influence the sample by causing unwanted reactions with the sample. Thirdly, it is imperative that the sorbent not be contaminated prior to and after the sampling process. Lastly, the retention of water on the sorbent should be small to avoid any interference with the laboratory analysis of the sample.

5.1.3 Laboratory Analysis

Collected samples (grab sampling) or sample media (integrated sampling) are analyzed to determine the respective concentrations. The most common process uses a gas chromatograph (GC) coupled to an appropriate detector. The GC process requires the sample to be placed in a heated chamber and purged with inert gas (*e.g.* helium) to separate and transfer the VOC sample from the sorbent, through a cold trap, onto the front of the GC column, which is initially at a low temperature. The GC column is heated to elute individual compounds based on their retention time (Lodge, 1988). The GC is usually coupled to an appropriate detector. Based on the required specificity and sensitivity of the application, there are several specific and non-specific detectors that can be used.

Non-specific detectors include the nitrogen-phosphorous detector (NPD), the flame ionization detector (FID), the electron capture detector (ECD) and the photo-ionization detector (PID) (U.S. EPA, 1999b). These detectors are generally less costly per analysis than specific detectors and can be more sensitive for specific classes of compounds. For example, if multiple halogenated compounds are targeted, the ECD would provide more accurate identification. The non-specific detectors are coupled to the GC and individual compounds are identified by their retention time. The downside of using non-specific detectors is that they are prone to greater margins of error since they rely on retention times alone for compound identification. Also, there is a chance that interference can occur due to non-targeted compounds (U.S. EPA, 1999b).

Specific detectors include the linear quadrupole mass spectrometer (MS) and the ion trap detector. Both of these detectors are mass spectrometers. The mass spectra for individual peaks in the ion chromatogram are analyzed for the fragmented mass patterns of the primary and secondary ions. These fragmentations are compared to known spectra observed under like conditions. Based on the GC retention time and the mass spectral characteristics, each VOC in the sample can be determined.

Mass spectrometry is a more accurate method of determining specific compounds in ambient air samples because of their range of precision and simple identification process. Although the non-specific detectors have some advantages such as lower cost and higher sensitivity, the U.S. EPA (1999c) stresses that mass spectrometry is considered a more definitive identification technique and reduces the chances of misidentification.

5.1.4 Information Sources

Standardized air monitoring methods are documented by the U.S. Environmental Protection Agency (U.S. EPA), the Occupational Safety and Health Administration (OSHA) and the National Institute of Occupational Safety and Health (NIOSH). These agencies provide detailed approaches required to adequately measure hazardous air pollutants (HAPs) in ambient and

workplace air using a variety of air monitors and analysis techniques. Other information sources (*e.g.* technical journals, conference proceedings) were also reviewed to explore other air monitoring technologies, as well as new or emerging technologies.

5.1.4.1 U.S. EPA

The U.S. EPA has developed several air toxics methodologies for sampling VOC in ambient air. Detailed descriptions of these methods are available on the U.S. EPA Technology Transfer Network (TTN) – Ambient Monitoring Technology Information Center (AMTIC). The following U.S. EPA air toxics methods can be used to sample xylene:

- Method TO-1: Method for the determination of volatile organic compounds in ambient air using Tenax adsorption and gas chromatography/mass spectrometry (GC/MS) (U.S. EPA, 1984).
- Compendium Method TO-14A: Determination of volatile organic compounds in ambient air using specially prepared canisters with subsequent analysis by gas chromatography (GC) (U.S. EPA, 1999b).
- Compendium Method TO-15A: Determination of volatile organic compounds in air collected in specially-prepared canisters and analyzed by gas chromatography/mass spectrometry (GC/MS) (U.S. EPA, 1999c).
- Compendium Method TO-17: Determination of volatile organic compounds in ambient air using active sampling onto sorbent tubes (U.S. EPA, 1999d).
- The following method provides alternative monitoring techniques that are specific to point source monitoring:
- Method 0030: Volatile Organic Sampling Train (VOST) (U.S. EPA, 1986).

Each of these methodologies can be applied to a range of VOC as determined by previously successful trials conducted by the U.S. EPA. All five methods can be used to sample and analyze xylene. The following sections describe each U.S. EPA method.

U.S. EPA Method TO-1

Method TO-1 is limited to non-polar organic compounds that have a boiling point between 80° and 200°C. The U.S. EPA provides a list of compounds that can be sampled using this method, as not all non-polar organic compounds within that boiling range can be determined. Xylene is among those compounds that can be determined.

This method uses sorbent tubes to trap VOC in ambient air. The ambient air to be sampled is drawn through a chamber containing Tenax (poly 2,6-Diphenyl phenylene oxide) sorbent. The xylene adheres to the Tenax sorbent while other highly volatile organic compounds and most inorganic components pass through the chamber. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Compendium Method TO-14A

Method TO-14A provides procedures for sampling VOC in pressurized (above atmospheric pressure) and subatmospheric pressure (below atmospheric pressure) canisters. Originally, this method was based on the collection of whole ambient samples using SUMMA passivated stainless steel canisters but can now be applied to other types of canisters. It can be applied to ambient concentrations of VOC above 0.5 ppbv and will usually require a sample size on the order of one litre. The U.S. EPA provides a list of compounds that can be sampled based on their storage capability in canisters. Xylene is among those compounds that can be determined.

This method uses an empty canister and pump-ventilated sample line for sample collection. For pressurized sampling, an additional pump to pressurize the canister is required. The ambient air sample is drawn through a sampling train, which is made up of components that regulate the rate and length of sampling, into the specially prepared passivated canister. The sample is transferred to a laboratory for analysis with a GC coupled to one of many GC detectors described in Section 5.1.4.

U.S. EPA Compendium Method TO-15A

Method TO-15A is an extension of the sampling method TO-14A. This method is more generalized but provides better definitions for VOC sampling methods. The set of compounds that can be sampled using the specially prepared canisters is a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act and includes xylene. This list includes more compounds than are described in Method TO-14A. The only means of laboratory analysis for this method is by GC/MS. Further, method TO-15A includes more detailed guidelines for quality control, mainly internal analytical standards and frequent verification of analytical performance.

U.S. EPA Compendium Method TO-17

Method TO-17 is a thermal desorption based ambient air monitoring method for VOC and is applicable for 0.5 and 0.25 ppbv ambient concentration levels. The U.S. EPA provides a list of compounds for which this method can be used based on sampling performance. These compounds, which are the same as those that can be sampled using TO-15A, are a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act. Xylene is among those compounds that can be determined.

This method uses single or multi sorbents packed in tubes in order of increasing sorbent strength, allowing for a wide volatility range of VOC to be sampled. Using multi-sorbent tubes, compounds with higher molecular weights are retained first and compounds with lower molecular weights last. If a single sorbent is being used, it should be specific to the target compound. Because of the specificity of certain sorbents, the thermal desorption process is very efficient.

The sample is drawn through a tube containing the selected sorbents. The xylene adsorbs to the sorbents while unwanted VOC and most other inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Method 0030

Method 0030 was developed for sampling volatile principal organic hazardous constituents (POHC) from the stack gas effluents of hazardous waste incinerators. Alberta Environment has developed a similar stack sampling code (AENV, 1995) that describes in detail methods for sampling VOC (method 25) in stack gas effluent. Volatile POHC are compounds with boiling points that are less than 100°C. The U.S. EPA provides a list of compounds for which this method can be used. Xylene is among those compounds that can be determined.

This method employs a 20 litre sample stack gas effluent which contains volatile POHC. Using a glass-lined probe and a volatile organic sampling train (VOST), the gas is withdrawn at a rate of 1 L/min. The stream is then cooled to 20°C as it passes through a water-cooled condenser. The volatile POHC are collected on a pair of resin traps. The first trap contains Tenax (see U.S EPA Method TO-1) while the second contains a mixture of Tenax and petroleum-based charcoal. Up to six pairs of sorbent traps can be used to collect the volatile POHC over a period of 2 hours. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

5.1.4.2 NIOSH

NIOSH has developed several air toxics methodologies for sampling VOC in workplace air. Detailed descriptions of these methods are contained in the NIOSH Manual of Analytical Methods (NMAM). It should be noted that the NMAM was intended to achieve consistent industrial hygiene analyses and was not designed specifically for ambient air. The following NIOSH analytical method can be used to sample xylene:

- NIOSH Manual of Analytical Methods, Fourth Edition, Method 1501: Hydrocarbons, Aromatic (NIOSH, 1994a,b).

According to NMAM, Method 1501 is the only method that can be used to sample and analyze xylene. The following section describes method 1501.

NIOSH Method 1501

Method 1501 employs an activated charcoal based solid sorbent tube, which is a commonly used sorbent because of its reactive surface which promotes higher adsorptive capacity. It also has a very high area to weight ratio which allows for higher sampling capacity.

The sample is drawn through a tube containing the activated charcoal sorbent. The xylene would adsorb to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

5.1.4.3 OSHA

OSHA has developed several air toxics methodologies for sampling VOCs in ambient air. Detailed descriptions of these methods are available from the Directorate of Science, Technology and Medicine (DSTM): Salt Lake Technical Center (SLTC). It should be noted that these methods were intended to provide a uniform and practical means for evaluating workplace air quality and were not designed specifically for ambient air. The following OSHA analytical methods can be used to sample xylene:

- OSHA Sampling and Analytical Methods Organic Method 7: Organic Vapors (OSHA, 2000).
- OSHA Sampling and Analytical Methods Organic Method 1002: Xylene (*o*-, *m*-, *p*-isomers) and Xylene (OSHA, 1999).

Organic Method 7 can be applied to a range of organic compounds whereas Organic Method 1002 is limited to xylene. Organic Method 7 is a general sampling method and provides a list of compounds that can be determined. OSHA usually provides sampling methods for individual and grouped compounds. For example, Method 111 describes a specific sampling method for xylene. The following sections describe both OSHA methods.

OSHA Method 7

Method 7 is a general organic vapour sampling methodology. It uses an activated charcoal based solid sorbent tube similar to that described in NIOSH Method 1,500. Activated charcoal (prepared from coconut shells) is a commonly used sorbent because its reactive surface promotes higher adsorptive capacity. It also has a very high area to weight ratio that allows for higher sampling capacity.

The sample is drawn through a tube containing activated charcoal sorbent. The xylene adsorbs to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

OSHA Method 1002

Method 1002 is limited to xylene (*o*-, *m*-, *p*-isomers) and there are two possible sampling techniques described in this method. The first method is the same as Method 7; using an activated charcoal sorbent as the collection medium. A second method for xylene is diffusive sampling. This is a passive sampling technique using the SKC 575-002 passive sampler.

The SKC 575-002 passive sampler is a very small sampler that can be affixed to a worker's collar. Since OSHA is primarily interested with workplace safety, they suggest that the monitor should be placed near the breathing area (*i.e.* mouth and nose). The air to be sampled is drawn through a mesh screen and through the desorption solvent chamber. The sorbent used by this sampler is called Anasorb 747 and is a synthetic carbon, which can be used for a larger array of

compounds than the coconut charcoal used in the sorbent tubes described in OSHA method 7. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

5.1.4.4 Alternative and Emerging Technologies

The combination of the U.S. EPA, NIOSH and OSHA ambient air sampling methods provides a broad scope of approaches. The sampling methods described in this section are designed for use over an 8-h to 24-h period. There are, however, other notable methods of sampling xylene that have been used in the past for specific applications.

Kuo *et al.* (2000) sampled the road-side concentrations of certain VOC including xylene in Taichung, Taiwan. Their methodology was a similar approach as U.S. EPA Compendium TO-17, NIOSH method 1501 and OSHA method 7. A small stainless steel tube containing a Carbopack B sorbent and a low-flow sampling pump was attached to the collar of motorists. A GC coupled to a MS was used for analysis of samples.

Uchiyama *et al.* (1999) successfully used a modified diffusion sampler with thermal desorption for analysis since higher sensitivity was required for their application. The diffusive sampler used either Carboxen or Carbotrap B sorbents to collect VOC through the molecular diffusion and collection. A GC coupled to a MS was used for analysis of samples.

Leibrock and Slemr (1997) conducted a fairly unique, yet effective, sampling technique without the use of a sorbent. Their sampler design employed two cryogenic sampling traps that would remove compounds from the ambient air being drawn into the sampler dependant on their temperature resistance. A GC coupled to a MS was used for analysis of samples.

Environment Canada has used SUMMA canisters based on the U.S. EPA Compendium TO-14A to measure for urban pollutants. This method has also been used in Edmonton, Alberta (Cheng *et al.*, 1997) to measure the concentration of VOC (including xylene) in ambient air.

For long-term exposure trends, passive diffusion monitors such 3M 3,500 Organic Vapor Monitors have been used. Usually, these monitors are exposed for 7 to 24 days and returned to a laboratory for analysis. In a recent animal health study, these monitors were used to measure VOC concentrations in rural Alberta, Saskatchewan and British Columbia.

As new and emerging technologies are developed, agencies such as the U.S. EPA provide information to users ensuring that the best available environmental practices are upheld.

6.0 EXISTING AMBIENT GUIDELINES

Current recommended or proposed xylenes ambient air quality guidelines from selected regulatory agencies in Canada (other than Alberta), the United States and elsewhere are summarized in Table 10. Appendix A contains further information on each of these existing guideline values.

In general, all jurisdictions reviewed have common uses for their ambient air quality guidelines, including:

- Reviewing permit applications for air emission sources
- Investigating accidental releases or community complaints about adverse air quality for the purpose of determining follow-up or enforcement activity
- Conducting health risk assessments of industrial facilities and airsheds
- Monitoring and controlling ambient air quality

The development of ambient air quality guidelines is driven by numerous societal and scientific issues, which require consideration of numerous factors such as aesthetics, property damage, toxicology and ecology. Odour, for example, is an issue of aesthetics and for chemicals with particularly distasteful odours, guideline values may be driven by odour thresholds, while for airborne chemicals that are corrosive, damage to structures may be a key consideration.

In terms of toxicology, air quality guidelines typically consider basic toxicological principles, which dictate that the response of an organism is a function of the magnitude of the dose and the duration over which the dose is received. The nature of the response of organisms (*i.e.,* the target tissues or organs and the toxicological endpoints) is another important consideration. For example, chemicals that act as primary respiratory irritants may have guidelines developed that are protective of these types of effects. Where toxicity concerns relate to non-respiratory targets (*e.g.,* liver or kidney) or to toxicological endpoints of late onset (*e.g.,* cancer, reproductive), air quality guidelines may be established to be protective of these types of effects. Chemicals that have multiple toxicological endpoints in more than one tissue or organ may have guidelines developed that are protective of the most sensitive toxic effects. Another consideration is the estimated or actual degree of exposure of key receptors to the air pollutant, particularly receptor groups that may exhibit sensitivity to the air pollutant (*e.g.*, elderly, asthmatics, children, *etc.*). Other important considerations in establishing an air quality guideline include the available technologies (and their costs) for routinely or periodically monitoring for the pollutant in air, and the availability and technical feasibility of approaches for estimating ambient ground-level air concentrations, in order to compare to air quality guidelines.

The three most common approaches by which ambient air quality guidelines are developed are as follows:

1. Using an occupational exposure level (OEL) and dividing it by safety or uncertainty factor and amortizing for continuous exposure. These factors are intended to account for differences between eight-hour exposures in the workplace and continuous 24-hour environmental exposures, increased susceptibility of individuals in the general population

versus the relatively healthy worker and uncertainties in the margin of safety provided in an occupational exposure limit. It should be recognized however, that the use of OEL values has its limitations. For example:

- OELs are based on human effects information in industrial settings and may not accurately reflect ambient environmental exposure situations.
- OELs are derived to be protective of workers who are typically considered in good health and within the age range of 18 to 65 years. Such individuals are potentially less sensitive and/or susceptible to the effects of airborne pollutants than members of the general population. Among the general populations, there may be subpopulations or individuals that are more sensitive or susceptible to the effects of an airborne pollutant (*e.g.*, elderly, young children, asthmatics, people with pre-existing respiratory conditions, etc.)
- Worker exposures are typically based on a normal work schedule (eight hours per day, five days per week). For this work schedule, there are two days per week (weekends) in which the body may eliminate much of the accumulated substances before the next workweek begins. However, for individuals continuously exposed to an air pollutant in the ambient environment, there is no similar period during which no exposure occurs.
- For these reasons, agencies using OELs as the basis for ambient air quality guidelines typically adjust OELs by applying safety or uncertainty factors.

2. Threshold chemical risk assessment procedures: Used for chemicals that are not believed to act as carcinogens and that exhibit a clear toxicity threshold. In this approach, a NOAEL or LOAEL from a suitable animal or human study is divided by a series of uncertainty factors that account for issues such as: differences between animals and humans, sensitive individuals, use of a LOAEL instead of a NOAEL and for extrapolation from subchronic to chronic exposure durations.

3. Non-threshold chemical risk assessment procedures: Used for substances believed act as carcinogens. Cancer potency estimates, slope factors, tumorigenic potency values, etc. are used to establish ambient air levels based on acceptable levels of incremental lifetime cancer risk, such as one in 100,000. These acceptable levels are established by regulatory agencies.

Finally, the potential ecological impacts of airborne chemicals are also important considerations in the guideline-setting process. Although a chemical may have no direct impact on human health or property, transfer of the chemical from the air to the terrestrial and aquatic environments by dry or wet deposition could have ecological impacts, depending on the physical and chemical properties of the substance.

Current occupational exposure limits for xylenes derived by ACGIH, NIOSH and OSHA are all based on human studies where irritant effects (ocular and upper respiratory) were demonstrated at air concentrations of 200 ppm (870 mg/m^3) (Carpenter *et al.*, 1975). An air concentration of 100 ppm (435 mg/m^3) was considered satisfactory in Nelson *et al.* (1943). The current ACGIH TLV-TWA, OSHA PEL-TWA and NIOSH REL values are all 100 ppm (435 mg/m^3). Short-term or ceiling exposure levels have also been established for xylenes by these agencies. The current STEL values from ACGIH, OSHA and NIOSH are all 150 ppm (653 mg/m^3). All values are recommended for both individual xylene isomers and mixed isomers. At concentrations at or

below these occupational limits, it is believed that irritant effects will be minimal and that neither significant narcosis nor chronic injury will result from continued occupational exposure (ACGIH, 1992). Occupational exposure limits from other countries are similar (ACGIH, 1992). For example, Germany and the United Kingdom (U.K.) use a threshold value of 100 ppm (435 mg/m^3). Australia and Sweden use 80 ppm (348 mg/m^3) as a threshold limit. For short-term values, Australia and the U.K. use 150 ppm (653 mg/m^3), Germany uses 200 ppm (870 mg/m^3) and Sweden uses 100 ppm (435 mg/m^3).

NIOSH (2003) reports an immediately-dangerous-to-life-and-health (IDLH) value of 900 ppm (3,915 mg/m^3). The IDLH is based on acute inhalation toxicity data in animals. NIOSH also notes that this value would have otherwise been selected for safety considerations (*i.e.*, being 10% of the lower explosive limit of 0.9% for *o*-xylene). This value does not represent an appropriate basis for establishing an ambient air quality guideline.

The U.S. EPA, ATSDR, CalEPA OEHHA, Health Canada, the WHO and RIVM have derived health-based airborne ambient exposure limits for xylenes. These limits are described below.

The U.S. EPA (2003) RfC for xylenes is 0.1 mg/m^3. The subchronic study by Korsak *et al.* (1994) was selected as the principal study and neurological effects (impaired motor coordination) were the critical effects. A NOAEL of 50 ppm and a LOAEL of 100 ppm were identified for decreased rotarod performance from the principal study. The NOAEL of 50 ppm (217 mg/m^3) was duration adjusted as follows: [217 mg/m^3 x 5/7 x 6/24] and then converted to a human equivalent concentration (HEC), as follows: duration-adjusted NOAEL x the ratio of animal to human blood/air partition coefficients reported in Tardif *et al.* (1995) and (Tardif *et al.*, 1993a). A NOAEL (HEC) of 39 mg/m^3 was the result. A total uncertainty factor of 300 was applied to this NOAEL (HEC) to derive the RfC (3 to account for laboratory animal-to-human interspecies differences; 10 for intraspecies uncertainty; 3 for extrapolation from subchronic to chronic duration; and 3 for uncertainties in the database). The U.S. EPA (2003) also used validated PBPK models for xylene inhalation in rats and humans (*e.g.*, Haddad *et al.*, 1999; Tardif *et al.*, 1991; 1992; 1993a,b; 1995) to derive a NOAEL for comparison to the NOAEL (HEC). PBPK modelling was found to support the NOAEL (HEC) of 39 mg/m^3 that was calculated by standard inhalation dosimetric methods.

ATSDR (1995) derived a mixed xylenes MRL of 1 ppm (4.35 mg/m^3) for an acute-duration inhalation exposure (14 days or less). The MRL is based on increased reaction times that were observed in 10 male volunteers exposed to xylenes at 100 ppm (435 mg/m^3) for 4 hours (Dudek *et al.*, 1990). ATSDR (1995) derived an MRL of 0.7 ppm (3.04 mg/m^3) for intermediate-duration inhalation exposure (15 to 364 days) to mixed xylene. This MRL is based on reduced rotarod performance of offspring from rats exposed to 200 ppm (870 mg/m^3) technical grade xylene for 6 hours a day on gestational days 4 through 20 (Hass and Jakobsen, 1993). ATSDR (1995) also derived a chronic MRL of 0.1 ppm (0.435 mg/m^3) for mixed xylenes. This MRL is based on an increase in subjective symptoms including anxiety, forgetfulness, inability to concentrate, eye and nasal irritation, dizziness and sore throats reported by workers exposed to xylenes for an average of 7 years at a geometric mean TWA concentration of 14 ppm (Uchida *et al.*, 1993).

OEHHA (1999) derived an acute 1hour REL of 22 mg/m³ for mixed xylenes. This REL was based on the human study by Hastings *et al.*, 1984 (with support from Carpenter *et al.*, 1975; Nelson *et al.*, 1943). The critical effects were subjective reports of eye, nose and throat irritation. A LOAEL of 860 mg/m^3 and a NOAEL of 430 mg/m^3 (100 ppm) were identified from the Hastings *et al.* (1984) study. The NOAEL was converted to a 1-hour concentration of 50 ppm and a 10-fold uncertainty factor (for intraspecies differences in sensitivity) was applied to yield the acute REL of 5 ppm (22 mg/m^3).

The OEHHA (2003) derived a chronic REL of 0.7 mg/m^3 for mixed xylenes and individual xylene isomers. This REL was based on the study by Uchida *et al.* (1993) where the critical effects were an increased prevalence of eye irritation, sore throat, floating sensation and poor appetite in exposed workers. A LOAEL of 14.2 ppm was identified from this study. This LOAEL was duration-adjusted as follows: [14.2 x 10/20 x 5/7], to yield an adjusted LOAEL of 5.1 ppm. A cumulative uncertainty factor of 30 was then applied to this adjusted LOAEL (3 for use of a LOAEL; 10 for intraspecies uncertainty) to yield the REL of 0.2 ppm (0.7 mg/m^3).

Health Canada (Meek and Chan, 1994) derived a provisional tolerable concentration (TC) for xylenes of 0.18 mg/m^3. This TC is based on the lowest LOEL (250 mg/m^3) identified for meaningful developmental effects in the study by Ungvary and Tatrai (1985). The LOAEL was adjusted for the ratio of inhalation volume to body weight of rats [(0.11 m^3/day) / 0.35 kg] to humans aged 5 to 11 years [(12 m^3/day) / 27 kg]. An uncertainty factor of 1,000 was then applied [10 for intraspecies variation; 10 for interspecies variation; 10 for use of a LOEL rather than a NOEL].

RIVM (1999) derived a tolerable concentration in air (TCA) of 0.87 mg/m^3 based on a LOAEL of 870 mg/m^3 for developmental toxicity in rats reported in Hass and Jakobsen (1993). An uncertainty factor of 1,000 (10 each for intra-, inter-species variability and use of a LOAEL over a NOAEL) was applied to the LOAEL to yield the TCA (TERA-ITER, 2004).

The WHO (1997) derived a 24-hour guideline value for xylenes of 4.8 mg/m^3. This value is based on a NOAEL of 304 mg/m^3 for central nervous system effects in humans reported in Anshelm Olson *et al.* (1985). The WHO applied an uncertainty factor of 60 (10 for inter-individual variation; 6 for exposure duration adjustment) to this NOAEL to derive the 24 hour guideline value. The WHO (1997) also derived an annual guideline value of 0.87 mg/m^3. The annual guideline value is based on a LOAEL of 870 mg/m^3 for developmental neurotoxicity in rats reported in Hass and Jakobsen (1993). The WHO applied an uncertainty factor of 1,000 (10 for use of a LOAEL rather than a NOAEL; 10 for interspecies variation; 10 for inter-individual variation) to this LOAEL to derive the annual guideline value.

The guidelines presented below in Table 10 are derived from a number of different sources, including various toxicological and epidemiological studies, the ACGIH TLV-TWA and odour threshold values, all adjusted with various modifying and uncertainty factors). In the available documentation from some agencies, the basis behind the air quality guideline is not clearly specified. Further information on the scientific basis for these guidelines, the application of uncertainty factors and the practical application of these guidelines by the respective agencies, is provided in Appendix A.

Table 10 Summary of Existing Air Quality Guidelines for Xylenes

				Date of Guideline[a]
California Environmental Protection Agency, Office of Environmental Health Hazard Assessment	Acute REL (1 h)	22	Hastings *et al.*, 1984	1999
	Chronic REL (continuous lifetime daily exposure)	0.7	Uchida *et al.*, 1993	2002
Health Canada	Provisional TC (continuous lifetime daily exposure)	0.18	Ungvary and Tatrai, 1985	1996
Louisiana Department of Environmental Quality	AAS (8 h)	10.3	Not provided in available documentation	2003
Massachusetts Department of Environmental Protection	TEL (24 h)	0.012	ACGIH TLV-TWA of 100 ppm	1995
	AAL (annual)	0.012	Based on the TEL	
	ATC (continuous lifetime daily exposure)	0.06	5 times the TEL	
Michigan Department of Environmental Quality	ITSL (24 h)	0.1	Based on U.S. EPA RfC of 0.1 mg/m^3	2003
Minnesota Department of Health	HRV (1 h)	43	Not provided in available documentation	2003
Netherlands Research for Man and Environment (RIVM)	TCA (continuous lifetime daily exposure)	0.87	Hass and Jakobsen, 1993	2001
Newfoundland and Labrador Department of the Environment	AQS (24 h)	2.3	Not provided in available documentation	2003
	POI (1 h)	1.9	Not provided in available documentation	
New Hampshire Department of Environmental Services	AAL (24 h)	1.55	ACGIH TLV-TWA of 100 ppm	1997
	AAL (annual)	1.03	ACGIH TLV-TWA of 100 ppm	
New Jersey Department of Environmental Protection	Short term RfC (1 h)	22	CalEPA-OEHHA, 1999 acute REL	2003
	RfC (continuous lifetime daily exposure)	0.1	Based on U.S. EPA RfC of 0.1 mg/m^3	2003
New York State Department of Environmental Conservation	SGC (1 h)	4.3	Not provided in available documentation	2000
	AGC (continuous lifetime daily exposure)	0.7	Not provided in available documentation	
North Carolina Department of	TAPG (1 h)	65	Not provided in available documentation	2001

				Date of Guideline[a]
Environment and Natural Resources	TAPG (24 h)	2.7	Not provided in available documentation	
Oklahoma Department of Environmental Quality	MAAC (24 h)	43.43	ACGIH TLV-TWA of 100 ppm	2003
Ontario Ministry of Environment and Energy	AAQC (24 h)	2.3	odour effects; specific basis not provided in available documentation	2001
	POI (1/2 h)	2.3	odour effects; specific basis not provided in available documentation	
Quebec Ministry of the Environment	MAQC (15 minute)	1.5	odour threshold reported by American Industrial Hygiene Association	2002
	MAAQC (continuous lifetime daily exposure)	1.0	U.S. EPA oral RfD of 2 mg/kg/day for xylenes	
Texas Natural Resource Conservation Commission	Short- term ESL (1 h)	3.7	odour nuisance potential	2003
	Long-term ESL (annual)	0.37	odour nuisance potential	
U.S. Agency for Toxic Substances and Disease Registry	Acute MRL (1-14 d)	4.34	Dudek *et al.*, 1990	1995
	Intermediate MRL (15-364 d)	3.04	Hass and Jakobsen, 1993	
	Chronic MRL (≥365 d)	0.434	Uchida *et al.*, 1993	
U.S. Environmental Protection Agency, Integrated Risk Information System (IRIS)	RfC (continuous lifetime daily exposure)	0.1	Korsak *et al.*, 1994	2003
Vermont Agency of Natural Resources	Chronic HAAS (annual)	1.04	ACGIH TLV-TWA of 100 ppm	2001
Washington Department of Ecology	ASIL (24 h)	1.5	ACGIH TLV-TWA of 100 ppm	1998
World Health Organization	GV (24 h)	4.8	Anshelm Olson, 1985	1999
	GV (annual)	0.87	Hass and Jakobsen, 1993	

a Date guideline was either promulgated or date of last review/revision by agency.

The air quality guideline values used by the jurisdictions listed in Table 10 can be split into short-term and long-term values. Short-term ambient air guidelines for xylenes include 15-minute, half-hour, one-hour, eight-hour, 24-hour and one to 14 day averaging periods. Ontario is the only jurisdiction with a half-hour limit (2.3 mg/m^3) and Quebec is the only jurisdiction with a 15 minute limit (1.5 mg/m^3). One-hour limits exist in California, Minnesota, Newfoundland and Labrador, New Jersey, New York, North Carolina and Texas. The lowest one-hour guideline is

1.9 mg/m^3 (Newfoundland and Labrador POI limit), while the highest is 65 mg/m^3 (North Carolina). Louisiana cites an 8 hour limit of 10.3 mg/m^3. Twenty-four hour guidelines exist in Massachusetts, Michigan, Newfoundland and Labrador, New Hampshire, North Carolina, Oklahoma, Ontario and Washington and from the World Health Organization (WHO). These 24-hour guideline values range from 0.012 mg/m^3 (Massachusetts) to 43.4 mg/m^3 (Oklahoma). Long-term air quality guidelines in the jurisdictions reviewed are generally listed as annual ambient limits or are stipulated for continuous lifetime daily exposure. Long term limits exist within California, Health Canada, Massachusetts, the Netherlands, New Hampshire, New Jersey, New York, Quebec, Texas, the U.S. EPA, Vermont and the World Health Organization. These values range from 0.012 mg/m^3 (Massachusetts) to 1.04 mg/m^3 (Vermont). ATSDR (1995) developed acute, intermediate and chronic minimal risk levels of 4.34 mg/m^3 (1 to 14 days), 3.04 mg/m^3 (15 to 364 days) and 0.434 mg/m^3 ($\geq$365 days).

It should be noted that the considerable variability observed between guidelines is primarily the result of differences in the approaches used in their derivation. While there is generally good agreement with respect to the choice of toxicological studies and data used as the basis for the guidelines, all jurisdictions use different averaging periods and apply unique sets of uncertainty and modifying factors and assumptions in guideline development. The decision to use a particular approach involves policy decisions in addition to scientific considerations.

7.0 DISCUSSION

Xylenes are not corrosive, but will attack some forms of plastics, rubbers and coatings (NTP, 2001). While xylenes are highly flammable, this is a safety issue that is separate and distinct from health-based air quality guideline development.

The carcinogenicity evidence for xylenes is limited and inconclusive, but suggests a lack of carcinogenic activity. There appears to be sufficient evidence to conclude that xylenes are not mutagenic or genotoxic, which supports the premise that xylenes are not carcinogens. Under the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999a), the available data are considered inadequate for an assessment of the carcinogenic potential of xylenes. Adequate human data on the carcinogenicity of xylenes are not available and the available animal data are inconclusive as to the ability of xylenes to cause a carcinogenic response (U.S. EPA, 2003). Previously, the U.S. EPA categorized xylenes as "D - not classifiable as to human carcinogenicity", based on a lack of appropriate animal bioassays and human studies. Health Canada classifies xylenes as Group IV – probably not carcinogenic to humans (CCME, 2003). IARC (1999) classifies xylenes as Group 3 – not classifiable as to their carcinogenicity in humans, based on inadequate experimental animal and human evidence. The NTP has not classified xylene as to its carcinogenicity. There are currently no existing ambient air quality guidelines or other health-based airborne exposure limits that are based on carcinogenic effects of xylenes. Based on these considerations, toxicological considerations for xylenes should focus on non-cancer endpoints following acute and chronic exposure.

Review of the physical chemical properties (Section 2.0) and the toxicology (Section 4.0) of xylenes indicate several key benchmark air concentrations that should be considered in establishing an ambient air quality guideline. First, odour thresholds for xylenes are highly variable and have been reported to range from 0.07 to 40 ppm (0.3 to 174 mg/m^3; Budavari *et al*., 1996; Carpenter *et al.*, 1975; Ruth, 1986; ATSDR, 1995).

The major symptoms of acute human exposure to xylenes include: irritation of the nose, throat and eyes and central nervous system effects such as headache, nausea, dizziness, difficulty concentrating, impaired memory, slurred speech, ataxia, fatigue, agitation, confusion, tremors, labored breathing, impaired reaction time, alterations in equilibrium and body balance and sensitivity to noise. In experimental animals, central nervous system (CNS) toxicity is a sensitive effect of inhalation exposure to xylenes. Commonly reported signs of CNS neurotoxicity in experimental animals following acute inhalation exposure to xylene isomers include: narcosis, prostration, incoordination, tremors, muscular spasms, laboured breathing, behavioural changes, hyper-reactivity to stimuli, altered visual evoked potentials, elevated auditory thresholds, hearing loss, decreased acetylcholine in midbrain and norepinephrine in hypothalamus (which suggests effects on motor control, sleep and memory maintenance). Other symptoms of acute xylene exposure in experimental animals include irritation of the respiratory tract, pulmonary edema, pulmonary hemorrhage and pulmonary inflammation. Acute effects are most pronounced at high exposure levels (in excess of 1,000 ppm; 4,350 mg/m^3).

Neurological effects and irritation of the eyes and respiratory tract are the most commonly reported symptoms following subchronic and chronic inhalation exposure to xylenes. In

experimental animals, persistent neurological impairment of the central nervous system is the most commonly reported and sensitive effect of subchronic or chronic inhalation exposure to xylenes. In subchronic and chronic studies, measurable effects in several neurobehavioral endpoints begin at concentrations as low as 100 ppm (435 mg/m^3) and occur before other forms of toxicity occur in other tissues and organs. At lower concentrations, more subtle effects may occur. The most significant effects on developmental endpoints were decreased fetal body weight or fetal survival in rats at xylene isomer doses of 350 or 700 ppm (Ungváry *et al.*, 1980) or at mixed xylenes concentration of 780 ppm (Ungváry and Tátrai, 1985) and increased abortions in rabbits exposed to 230 ppm (Ungváry and Tátrai, 1985). These developmental effects all occur at concentrations above those at which neurobehavioral effects occur in experimental animals

Current occupational exposure limits for xylenes derived by ACGIH, NIOSH and OSHA are all based on human studies where irritant effects (ocular and upper respiratory) were demonstrated at air concentrations of 200 ppm (870 mg/m^3) (Carpenter *et al.*, 1975). An air concentration of 100 ppm (435 mg/m^3) was considered satisfactory in Nelson *et al.* (1943). The current ACGIH TLV-TWA, OSHA PEL-TWA and NIOSH REL values are all 100 ppm (435 mg/m^3).

While differences in the toxicity of the xylene isomers have been detected in a number of studies, no consistent pattern following inhalation exposure has been identified (U.S. EPA, 2003). As such, there is no basis upon which to assume xylene isomers differ substantially in their toxic potency.

All of the short-term guideline values summarized in Table 10 are considerably lower than the apparent human irritation threshold of 100 ppm (435 mg/m^3). Therefore, all these values appear to be adequately protective of human health over their respective averaging periods. All the long-term values in Table 10 are well below the subchronic, chronic, reproductive and developmental NOAEL and LOAEL values reported in the scientific literature. Thus, all the long-term air quality guideline values also appear to be adequately protective of human health.

Most air quality guidelines in Table 10 have the built-in assumption that all human exposure to xylenes occurs *via* inhalation. They do not account for other sources, pathways and routes of xylene exposure. If exposure were apportioned to reflect these, the values presented in Table 10 would decrease in proportion to the magnitude of the exposure from these other sources, pathways and routes. However, two notable exceptions to this are the Massachusetts and Quebec jurisdictions. MDEP (1995) divides its TEL by a factor of five to account for exposure through media other than air based on an assumption that ambient air contributes only 20% of the total exposure. The MAAQC for xylenes in Quebec is adjusted by a factor of 25% to account for the relative contribution of the sources of exposure. None of the other jurisdictions reviewed discuss exposure apportionment with respect to xylenes air quality guidelines in their available documentation.

In addition, none of the agencies with air quality guidelines in Table 10 reported any special consideration of children or other sensitive individuals in air quality guideline development.

Based on the information reviewed, none of the agencies listed in Table 10 specifically acknowledged an ecological component in the development of air quality guidelines for xylenes.

In addition, given the available data on the environmental fate, transport and effects of xylenes, these compounds are not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. However, xylenes are sufficiently susceptible to photochemical oxidation in the troposphere such that they may contribute to photochemical smog formation. Derwent and Jenkin (1990) calculated Photochemical Ozone Creation Potentials (POCP) for xylenes of 41 (*o*-xylene), 78 (*m*-xylene) and 63 (*p*-xylene). The POCP reflects the ability of a substance to form ground level ozone and are calculated relative to ethylene (a chemical that is thought to be important in ground-level ozone formation and which is assigned a POCP of 100).

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APPENDIX A

REVIEW OF AIR QUALITY GUIDELINES FOR XYLENES USED BY AGENCIES IN NORTH AMERICA AND ELSEWHERE

Agency:

California Environmental Protection Agency (Cal EPA), Office of Environmental Health Hazard Assessment (OEHHA)

Guideline Value(s):

Acute reference exposure level (REL) = 22,000 μg/m^3.
Chronic reference exposure level (REL) = 700 μg/m^3.

Averaging Time to Which Guideline Applies:

Acute REL = one-hour averaging time.
Chronic REL = continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

RELs are for use in facility health risk assessments conducted for the AB 2588 Air Toxics "Hot Spots" Program.

Scientific Basis for Guideline Development:

The acute REL was derived from a NOAEL of 430 mg/m^3 for eye and respiratory tract irritation in humans, where critical effects included eye, nose and throat irritation. The Cal EPA adjusted the NOAEL for one-hour exposure and applied an uncertainty factor of 10 to account for intraspecies variation.

The chronic REL was developed from a LOAEL of 14.2 ppm for nervous system and respiratory system effects in humans, where critical effects included eye irritation, sore throat, floating sensation and poor appetite. The Cal EPA converted the LOAEL to an average experimental concentration based on the experimental exposure duration and applied an uncertainty factor of 30 to account for the use of a LOAEL and intraspecies variation.

Status of Guideline (Date of Last Revision or Update):

Acute REL = May 2000.
Chronic REL = September 2002.

Additional Comments:

n/a

References and Supporting Documentation:

California Environmental Protection Agency (Cal EPA). 1999. Acute Toxicity Summary for Xylenes (m, o, *p*-isomers). California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, May 2000. URL: http://www.oehha.org/air/acute_rels/allAcRELs.html (accessed 11 November 2003).

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Agency:

Health Canada

Guideline Value(s):

Tolerable concentration (TC) = 180 μg/m^3 (provisional).

Averaging Time to Which Guideline Applies:

Continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

The government of Canada states that TCs provide a health-based goal to which levels of various pollutants generally indoor or ambient air can be compared. TCs are generally airborne concentrations to which it is believed that a person can continuously be exposed to over a lifetime without deleterious effect.

Scientific Basis for Guideline Development:

Based on the lowest LOEL (250 mg/m^3) identified for meaningful developmental effects in the study by Ungvary and Tatrai (1985). The LOAEL was adjusted for the ratio of inhalation volume to body weight of rats [(0.11 m^3/day) / 0.35 kg] to humans aged 5 to 11 years [(12 m^3/day) / 27 kg]. An uncertainty factor of 1,000 was then applied [10 for intraspecies variation; 10 for interspecies variation; 10 for use of a LOEL rather than a NOEL].

Status of Guideline (Date of Last Revision or Update):

1996.

Additional Comments:

n/a

References and Supporting Documentation:

Health Canada. 1996. Health-Based Tolerable Daily Intakes/ Concentrations and Tumorigenic Doses/ Concentrations for Priority Substances. Government of Canada, Health Canada, Environmental Health Directorate, Health Protection Branch. Ottawa, ON.

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Agency: Louisiana Department of Environmental Quality (DEQ).
Guideline Value(s): Ambient air standard (AAS) = 10,300 μg/m^3.
Averaging Time to Which Guideline Applies: Eight-hour averaging time.
Application / How Guideline is Used by Agency: AASs are used by Louisiana DEQ to review permit applications for stationary sources that emit xylenes to the atmosphere.
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): October 2003.
Additional Comments: Louisiana DEQ classifies xylenes as a suspected human carcinogen and known or suspected human reproductive toxin.
References and Supporting Documentation: Louisiana Department of Environmental Quality (DEQ). 2003. Title 33 Environmental Quality, Part III Air, Chapter 51: Comprehensive Toxic Air Pollutant Emission Control Program. Louisiana Department of Environmental Quality (DEQ). Baton, LA.

Agency:

Massachusetts Department of Environmental Protection (DEP).

Guideline Value(s):

Threshold effects exposure level (TEL) = 11.8 $\mu g/m^3$.
Allowable ambient limit (AAL) = 11.8 $\mu g/m^3$.
Allowable threshold concentration (ATC) = 60 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

TEL = 24-hour averaging time.
AAL = annual averaging time.
ATC = continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

The TEL and AAL guidelines are to be employed in the permitting, compliance and enforcement of the MA DEP air quality program. The primary goal of the TELs and the AALs developed by MA DEP is to protect public health from any air contaminant causing known or potentially deleterious effects. These guidelines were developed without regard to production volume, exposure level, regulatory implication, economic considerations or control technology issues.

Scientific Basis for Guideline Development:

TELs are developed using either an occupational limit or, when a reference concentration (RfC) is published by the U.S. EPA IRIS, an RfC where appropriate and defensible. In the case of xylenes, the TEL is derived from the threshold limit value time weighted average (TLV-TWA) of 100 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. This occupational limit was then adjusted by the MA DEP for occupational to environmental exposure, adult to child receptor, intraspecies variation and for inadequacies or limitations in the toxicity data. An uncertainty factor of 10 was applied to the "adjusted" occupational limit to account for documented developmental/ reproductive effects not accounted for in the occupational limit and then the limit was divided by five to account for exposure through media other than air based on an assumption that ambient air contributes only 20% of the total exposure.

In the case of xylenes, the AAL was based on the TEL of 11.8 $\mu g/m^3$ because the non-threshold effects level was greater than the TEL.

ATCs are roughly equivalent to the U.S. EPA reference concentration (RfC), but are derived from the threshold effects exposure limit (TEL) representing 20% of an allowable exposure. The ATC thus corresponds to five times the TEL. ATCs are an air concentration that would not be expected to result in adverse non-carcinogenic health effects. The ATC is derived considering acute and chronic threshold health endpoints, including reproductive effects.

Status of Guideline (Date of Last Revision or Update):

December 1995.

Additional Comments:

n/a

References and Supporting Documentation:

Massachusetts Department of Environmental Protection (DEP). 1995. Massachusetts Allowable Threshold Concentrations (ATCs). Commonwealth of Massachusetts, Executive Office of Environmental Affairs, Department of Environmental Protection. Boston, MA.

Agency:

Michigan Department of Environmental Quality (DEQ).

Guideline Value(s):

Initial threshold screening level (ITSL) = 100 μg/m^3.

Averaging Time to Which Guideline Applies:

ITSL = 24-hour averaging time.

Application / How Guideline is Used by Agency:

Michigan air toxic rules require that each source must apply the best available control technology for toxics (T-BACT) and that the emissions of the toxic air contaminant cannot result in a maximum ambient concentration that exceeds the applicable health based screening levels (*i.e.*, ITSL, IRSL or SRSL). ITSLs are required for any new or modified emissions source or sources for which a permit to install is requested and which emits a toxic air contaminant.

Scientific Basis for Guideline Development:

The ITSL was based on the reference concentration (RfC) of 100 μg/m^3 for impaired motor coordination established by the U.S. EPA.

Status of Guideline (Date of Last Revision or Update):

March 2003.

Additional Comments:

The Initial Threshold Screening Level (ITSL) is defined as the health based screening level for non-carcinogenic effects of a toxic air contaminant. It is determined by a number of different methods, depending upon the available toxicological data. The rules specify a hierarchy of methods for determining the ITSL. There are two health based screening levels for carcinogenic effects. These include the Initial Risk Screening Level (IRSL), which is defined as an increased cancer risk of one in one million (10-6) and the Secondary Risk Screening Level (SRSL), which is defined as an increased cancer risk of one in one hundred thousand (10-5). The IRSL applies only to the new or modified source subject to the permit application. If the applicant cannot demonstrate that the emissions of the toxic air contaminant meet the IRSL, they may choose to demonstrate compliance with the SRSL, however in this case they must include all sources of that toxic air contaminant emitted from the plant, not just the emission unit being permitted.

References and Supporting Documentation:

Michigan Department of Environmental Quality (DEQ). 2003. Final Screening Level List. Table 2. Michigan Department of Environmental Quality (DEQ). Air Quality Division. URL: http://www.michigan.gov/deq/0,1607,7-135-3310_4105---,00.html (accessed 12 November 2003).

Michigan Department of Environmental Quality (DEQ). 2002. Procedures for Developing Screening Levels. Michigan Department of Environmental Quality (DEQ). Air Quality Division. Lansing, Michigan.

Agency: Minnesota Department of Health (MDH).
Guideline Value(s): Acute health risk value (HRV) = 43,000 μg/m^3.
Averaging Time to Which Guideline Applies: Acute HRVs are comparable to a one-hour averaged concentration of chemicals or defined mixtures of chemicals in air.
Application / How Guideline is Used by Agency: HRVs are used by the MDH and sister agencies such as the Minnesota Pollution Control Agency, to assist in the assessment of potential health risks associated with chemicals in ambient air. HRVs may also be used as one set of criteria for assessing risks in the environmental review process, issuing air permits, risk assessments and other site-specific assessments.
Scientific Basis for Guideline Development: HRVs were derived using the best peer-reviewed science and public health policies available at the time of their development. Uncertainty values were incorporated to ensure that the HRVs present minimal risk to human health. The acute HRV specific to xylenes was based on nervous system effects and eye and respiratory system irritation.
Status of Guideline (Date of Last Revision or Update): August 2003.
Additional Comments: The approaches used to develop HRVs are considered conservative (*i.e.*, by design they err in the direction of protecting public health); thus, the MDH is confident that exposures to chemicals in concentrations at or below the HRVs present minimal risk to human health. In addition, because of MDH's conservative approach, exposures to chemical concentrations above HRVs do not necessarily pose a public health risk.
References and Supporting Documentation: Minnesota Department of Health (MDH). 2003. Health Risk Values for Air. Minnesota Department of Health (MDH), Environmental Health in Minnesota. URL: http://www.health.state.mn.us/divs/ehours a air/hrvtablepr.htm (accessed 12 November 2003).

Agency: Netherlands Research for Man and Environment (RIVM).
Guideline Value(s): Tolerable concentration in air (TCA) = 870 μg/m^3.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: Not provided.
Scientific Basis for Guideline Development: The TCA was based on the LOAEL (no NOAEL determined) of 870 mg/m^3 for developmental neurotoxicity in agreement with the International Programme of Chemical Safety (IPCS) approach. An uncertainty factor of 1,000 was applied by RIVM to account for interspecies and intraspecies differences and for the use of a LOAEL.
Status of Guideline (Date of Last Revision or Update): March 2001.
Additional Comments: TCAs are a type of maximum permissible risk level (MPR) specific to inhalation exposure. MPRs are defined as the amount of a substance (usually a chemical substance) that any human individual can be exposed to daily during full lifetime without significant health risk.
References and Supporting Documentation: Research for Man and Environment (RIVM). 2001. RIVM Report 711701 025 Re-evaluation of Human-toxicological Maximum Permissible Risk Levels. URL: http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf (accessed 13 November 2003).

Agency: Newfoundland and Labrador Air Pollution Control Regulations.
Guideline Value(s): 24-hour air quality standard (AQS) = 2,300 μg/m^3. One-hour point of impingement (POI) = 1,900 μg/m^3.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: The minister under the Executive Council Act uses the values prescribed in the Criteria for Acceptable Air Quality for controlling air quality, where the amount of air contaminants in the atmosphere due to all sources shall not exceed these values (*i.e.*, AQS). Point of impingement values are used as the standard for concentrations of air contaminants from a stationary source at the point of impingement that shall not be exceeded.
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): May 2003.
Additional Comments: n/a
References and Supporting Documentation: Newfoundland and Labrador Air Pollution Control Regulations. 2003. Newfoundland and Labrador Regulation 56/03. Government of Newfoundland and Labrador, Queen's Printer, May 2003.

Agency:

New Hampshire Department of Environmental Services (DES).

Guideline Value(s):

24-hour ambient air limit (AAL) = 1,550 μg/m^3.
Annual ambient air limit (AAL) = 1,033 μg/m^3.

Averaging Time to Which Guideline Applies:

See above.

Application / How Guideline is Used by Agency:

AALs are used by the New Hampshire DES to review permit applications for sources that emit xylenes to the atmosphere. Sources are regulated through a state-wide air permitting system and include any new, modified or existing stationary source, area source or device.

Scientific Basis for Guideline Development:

The 24-hour AAL is derived from the threshold limit value time weighted average (TLV-TWA) of 100 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The New Hampshire DES applied a time adjustment factor of 2.8 and a safety factor of 100 to the TLV-TWA.

The annual AAL is derived from the threshold limit value time weighted average (TLV-TWA) of 100 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The New Hampshire DES adjusted the occupational limit by 4.2 and applied a safety factor of 100 to the TLV-TWA.

Status of Guideline (Date of Last Revision or Update):

March 1997.

Additional Comments:

n/a

References and Supporting Documentation:

New Hampshire Department of Environmental Services (DES). New Hampshire Code of Administrative Rules. Chapter Env-A 1400. Regulated Toxic Air Pollutants. New Hampshire Department of Environmental Services (DES). Concord, NH.

Agency:

New Jersey Department of Environmental Protection (DEP).

Guideline Value(s):

Short-term reference concentration (RfC) = 22,000 μg/m^3.
Reference concentration (RfC) = 100 μg/m^3.

Averaging Time to Which Guideline Applies:

Short-term RfC = one-hour averaging time.
RfC = continuous exposure (daily exposure over a lifetime).

Application / How Guideline is Used by Agency:

RfCs are used by the New Jersey DEP to review permit applications for sources that emit xylenes to the atmosphere.

Scientific Basis for Guideline Development:

The 24-hour RfC is derived from the acute REL of 22,000 μg/m^3 for eye and respiratory tract irritation established by the Cal EPA.

The RfC for xylenes is based on the reference concentration of 100 μg/m^3 for impaired motor coordination established by the U.S. EPA.

Status of Guideline (Date of Last Revision or Update):

April 2003.

Additional Comments:

n/a

References and Supporting Documentation:

New Jersey Department of Environmental Protection (DEP). 2003. Reference Concentrations for Short-Term Inhalation Exposure. New Jersey Department of Environmental Protection (DEP), Division of Air Quality, Bureau of Air Quality Evaluation. April, 2003.

New Jersey Department of Environmental Protection (DEP). 1994. Technical Manual 1003: Guidance on Preparing a Risk Assessment for Air Contaminant Emissions. New Jersey Department of Environmental Protection (DEP), Air Quality Permitting Program, Bureau of Air Quality Evaluation. Revised December 1994.

Agency: New York State Department of Environmental Conservation (DEC).
Guideline Value(s): Short-term guideline concentration (SGC) = 4,300 μg/m^3. Annual guideline concentration (AGC) = 700 μg/m^3.
Averaging Time to Which Guideline Applies: SGC = one-hour averaging time. AGC = continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: SGCs and AGCs are used by the New York State DEC to review permit applications for sources that emit xylenes to the atmosphere.
Scientific Basis for Guideline Development: Both the SGC and the AGC for xylenes were independently derived by the NY State DEC to protect the general population from adverse inhalation exposure at off-site industrial property. The specific scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): July 2000.
Additional Comments: n/a
References and Supporting Documentation: New York State Department of Environmental Conservation (DEC). 2000. DAR – 1 AGC/SGC Tables includes TLVs & STELs for the Year 2000. New York State Department of Environmental Conservation, Division of Air Resources, Bureau of Stationary Sources. Albany, NY.

Agency:

North Carolina Department of Environment and Natural Resources (DENR).

Guideline Value(s):

One-hour toxic air pollutant guideline (TAPG) = 65 mg/m^3 (65,000 $\mu g/m^3$).
24-hour toxic air pollutant guideline (TAPG) = 2.7 mg/m^3 (2,700 $\mu g/m^3$).

Averaging Time to Which Guideline Applies:

See above.

Application / How Guideline is Used by Agency:

TAPGs are used by the North Carolina DENR to review permit applications for sources that emit xylenes to the atmosphere.

Scientific Basis for Guideline Development:

Scientific basis was not provided.

Status of Guideline (Date of Last Revision or Update):

April 2001.

Additional Comments:

n/a

References and Supporting Documentation:

North Carolina Department of Environment and Natural Resources (ENR). 2002. North Carolina Air Quality Rules 15A NCAC 2D (Air Pollution Control Requirements) and 15A NCAC 2Q (Air quality Permit Procedures). Section .1100 – Control of Toxic Air Pollutants. North Carolina Department of Environment and Natural Resources. Raleigh, NC.

Agency: Ohio Environmental Protection Agency (EPA)
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Ohio Environmental Protection Agency (EPA). 2002. Review of New Sources of Air Toxic Emissions. Option A. Ohio Environmental Protection Agency, Division of Air Pollution Control. Columbus, Ohio.

Agency: Oklahoma Department of Environmental Quality (DEQ).
Guideline Value(s): Maximum acceptable ambient air concentration (MAAC) = 43,427 μg/m^3.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: MAACs are used by Oklahoma DEQ to review permit applications of sources that emit xylenes to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour MAAC was based on the threshold limit value time weighted average (TLV-TWA) of 100 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. A safety factor of 10 was incorporated by the Oklahoma DEQ.
Status of Guideline (Date of Last Revision or Update): November 2003.
Additional Comments: n/a
References and Supporting Documentation: Oklahoma Department of Environmental Quality (DEQ). 2003. Total Air Toxics Partial Listing. Oklahoma Department of Environmental Quality. URL: http://www.deq.state.ok.us/AQDnew/toxics/listings/pollutant_query_1.html (accessed 12 November 2003). Oklahoma Department of Environmental Quality (DEQ). Title 252. Department of Environmental Quality Chapter 100. Air Pollution Control. 100:252-41: Control of Emission of Hazardous and Toxic Air Contaminants. Oklahoma Department of Environmental Quality. Oklahoma City, OK.

Agency: Ontario Ministry of Environment and Energy (OMEE).
Guideline Value(s): 24-hour ambient air quality criteria (AAQC) = 2,300 μg/m^3. Half-hour point of impingement (POI) = 2,300 μg/m^3.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: AAQCs are used by OMEE to represent human health or environmental effect-based values not expected to cause adverse effects based on continuous exposure. AAQCs are not used by OMEE to permit stationary sources that emit xylenes into the environment. The 30-minute POI is used by OMEE to review permit applications for stationary sources that emit xylenes to the environment.
Scientific Basis for Guideline Development: The AAQC and the POI for xylenes were both derived based on odour effects, where the odour thresholds range from 300 to 174,000 μg/m^3. The specific scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): May 2001.
Additional Comments: The half-hour POI for xylenes is defined as an air quality standard by OMEE.
References and Supporting Documentation: Ontario Ministry of Environment and Energy (OMEE). 2001. Summary of Point of Impingement Standards, Point of Impingement Guidelines and Ambient Air Quality Criteria (AAQCs). Standards Development Branch, Ontario Ministry of the Environment, September 2001. Ontario Ministry of Environment and Energy (OMEE). 2001. Notice of Decision for Policy ERB Registry Number: "PA00E0020". Standards Development Branch, Ontario Ministry of the Environment, March 2001.

Agency: Quebec Ministry of the Environment.
Guideline Value(s): Maximum 15-minute air quality criteria (MAQC) = 1,500 μg/m^3. Maximum annual air quality criteria (MAAQC) = 1,000 μg/m^3.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: MAQCs and MAAQCs are taken into account in the determination of the allowed quantity of a substance in the ambient air and in the exposure received from drinking water, food or other sources.
Scientific Basis for Guideline Development: The MAAQC for xylenes was based on the reference dose (RfD) of 2 mg/kg-day established by the U.S. EPA. The RfD was converted to an inhalation dose assuming body weight of 18 kg and an inhalation rate of 8.46 m^3/day. The inhalation dose was then adjusted by a factor of 25% to account for the relative contribution of the sources of exposure. The 15 minute MAQC was based on the odour threshold of 1,500 μg/m^3 reported by the American Industrial Hygiene Association (AIHA).
Status of Guideline (Date of Last Revision or Update): May 2002.
Additional Comments: n/a
References and Supporting Documentation: Government of Quebec. 2002. Air Quality Criteria. Government of Quebec, Ministry of the Environment. URL: http://www.menv.gouv.qc.ca/air/criteres/fiches.pdf (accessed 13 November 2003).

Agency: Texas Natural Resource Conservation Commission (TNRCC).
Guideline Value(s): Short-term effects screening level (ESL) = 3,700 μg/m^3. Long-term effects screening level (ESL) = 370 μg/m^3.
Averaging Time to Which Guideline Applies: Short-term ESL = one-hour averaging time. Long-term ESL = annual averaging time.
Application / How Guideline is Used by Agency: ESLs are used to evaluate the potential for effects to occur as a result of exposure to concentrations of constituents in the air. ESLs are based on data concerning health effects, odour nuisance potential, effects with respect to vegetation and corrosion effects. They are not ambient air standards. If predicted or measured airborne levels of a constituent do not exceed the screening level, adverse health or welfare effects would not be expected to result. If ambient levels of constituents in air exceed the screening levels, it does not necessarily indicate a problem, but rather, triggers a more in-depth review.
Scientific Basis for Guideline Development: Both the short-term and long-term ESLs for xylenes were developed based on odour nuisance potential, however the specific scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): October 2003.
Additional Comments: n/a
References and Supporting Documentation: Texas Natural Resource Conservation Commission (TNRCC). 2003. Effects Screening Levels List. URL: http://www.tnrcc.state.tx.us/permitting/tox/esl.html (accessed 13 November 2003).

Agency:

U.S. Agency for Toxic Substances and Disease Registry (ATSDR).

Guideline Value(s):

Acute minimum risk level (MRL) = 1 ppm (4,340 $\mu g/m^3$).
Intermediate minimum risk level (MRL) = 0.7 ppm (3,038 $\mu g/m^3$).
Chronic minimum risk level (MRL) = 0.1 ppm (434 $\mu g/m^3$).

Averaging Time to Which Guideline Applies:

Acute exposure durations are based on exposure durations ranging from one to 14 days.
Intermediate exposure durations are based on exposure durations ranging from 15 to 364 days.
Chronic exposure durations are based on exposure durations equivalent to or greater than 365 days (*i.e.*, one year).

Application / How Guideline is Used by Agency:

MRLs are intended to serve as a screening tool to be used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. MRLs are not intended to define clean-up or action levels for ATSDR or other Agencies.

Scientific Basis for Guideline Development:

The acute MRL was developed from an inhaled exposure concentration of 100 ppm that resulted in neurological effects in humans, which is considered to be near the threshold for adverse effects. The ATSDR applied an uncertainty factor of 100 to this exposure concentration to derive the acute MRL.

The intermediate MRL was derived from the observation of reduced rotarod in offspring from rats exposed to 200 ppm technical grade xylene 6 hours a day on gestation days 4 through 20. No maternal toxicity or effects on reproduction and litter endpoints were observed. The ATSDR applied safety factor of 300 to the exposure concentration to derive the intermediate MRL.

The chronic MRL was based on an increase of subjective symptoms including anxiety, forgetfulness, an inability to concentrate, eye and nose irritation and sore throats reported by workers exposed to xylenes for an average of seven years at a geometric mean TWA concentration of 14 ppm. The ATSDR applied an uncertainty factor of 100 to the exposure concentration to derive the chronic MRL.

Status of Guideline (Date of Last Revision or Update):

August 1995.

Additional Comments:

MRLs are an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects.

References and Supporting Documentation:

U.S. Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Toxicological profile for xylenes. URL: http://www.atsdr.cdc.gov/toxpro2.html (accessed on 11 November 2003).

Agency: U.S. Environmental Protection Agency (EPA).
Guideline Value(s): Reference concentration (RfC) = 100 µg/m^3.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: The RfC was developed for use by the U.S. EPA staff in risk assessments, decision-making and regulatory activities.
Scientific Basis for Guideline Development: The RfC was developed from a NOAEL of 50 ppm based on impaired motor coordination (decreased rotarod performance in a subchronic inhalation study in male rats. The U.S. EPA adjusted the NOAEL to a human equivalent concentration of 39 mg/m^3 and applied a safety factor of 300 was applied to account for animal-to-human interspecies differences, intraspecies variability, extrapolation from subchronic to chronic exposure and to account for data base deficiencies.
Status of Guideline (Date of Last Revision or Update): February 2003.
Additional Comments: U.S. EPA considers the data to be inadequate for an assessment of the carcinogenic potential of xylenes. The Integrated Risk Information System (IRIS) is an electronic database containing information pertaining to human health effects that may result from environmental exposure to a variety of chemicals. IRIS is prepared and maintained by the U.S. Environmental Protection Agency (EPA).
References and Supporting Documentation: U.S. Environmental Protection Agency (EPA). 2003. Integrated Risk Information System (IRIS). URL: http://www.epa.gov/iris/index.html (accessed 11 November 2003).

Agency:

Vermont Agency of Natural Resources (ANR).

Guideline Value(s):

Chronic hazardous ambient air standard (HAAS) = 1,040 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

Annual averaging time.

Application / How Guideline is Used by Agency:

HAASs are used by Vermont ANR to review permit applications for stationary sources that emit xylenes to the atmosphere.

Scientific Basis for Guideline Development:

The annual HAAS is based on the threshold limit value time weighted average (TLV-TWA) of 100 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The Vermont ANR applied a time factor of 4.2 to the TLV-TWA to extrapolate to a continuous level and incorporated a safety factor of 100.

Status of Guideline (Date of Last Revision or Update):

November 2001.

Additional Comments:

The Vermont ANR classified xylenes as a non-carcinogen with potential chronic/system effects due to long-term exposure.

References and Supporting Documentation:

Vermont Agency of Natural Resources (ANR). 2001. Air Pollution Control Regulations, Including Amendments to the Regulations Through: November 29, 2001. Vermont Agency of Natural Resources, Air Pollution Control Division, Department of Environmental Conservation, Agency of Natural Resources. Waterbury, Vermont.

Agency: Washington Department of Ecology (DOE).
Guideline Value(s): Acceptable source impact level (ASIL) = 1,500 μg/m^3.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: ASILs are used Washington DOE to review permit applications for stationary sources that emit xylenes to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour ASIL for xylenes is based on the threshold limit value time weighted average (TLV-TWA) of 100 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The TLV-TWA was adjusted by a factor of 300 to calculate the 24-hour TWA acceptable source impact level.
Status of Guideline (Date of Last Revision or Update): October 1998.
Additional Comments: n/a
References and Supporting Documentation: Washington Department of Ecology (DOE). 1998. Chapter 173-460 WAC. Controls for New Sources of Toxic Air Pollutants. Washington Department of Ecology (DOE). Olympia, WA.

Agency: World Health Organization (WHO).
Guideline Value(s): 24-hour guideline value (GV) = 4,800 μg/m^3. Annual guideline values (GV) = 870 μg/m^3.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: The GVs were developed to provide background information which enables countries to set their national or regional air quality standards in the context of existing environmental, social, economic and cultural conditions.
Scientific Basis for Guideline Development: The 24-hour GV developed for xylenes was based on a NOAEL of 304 mg/m^3 for central nervous system effects in humans. WHO applied an uncertainty factor of 60 to the NOAEL to derive the 24-hour GV. The annual GV was derived from a LOAEL of 870 mg/m^3 for neurotoxicity in rats. WHO applied an uncertainty factor of 1,000 to the LOAEL to derive the annual GV.
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: World Health Organization (WHO). 1999. Air Quality Guidelines. Chapter 3: Health-based Guidelines. World Health Organization, Geneva.