

Priority Substances List
Assessment Report

Xylenes

Government of Canada
Environment Canada
Health Canada

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Synopsis

In Canada, xylenes are produced from the catalytic reforming of petroleum and as by-products of the cracking of crude and heavy oil. Each year, an estimated 2 600 kilotonnes is consumed in Canada as a component of gasoline and 145 kilotonnes of purified xylenes for other uses, including as solvents and as chemical feedstock. Xylenes are released into the air principally from their use as solvents and from transportation sources, and into soil and water through spills and leakage of petroleum and other chemical products. These releases have resulted in the presence of measurable concentrations of xylenes in air, water, and soil in Canada although xylenes do not persist in any of these media.

Although most xylenes are released into the air, concentrations to which wildlife are exposed are at least 1 000 times less than the effects threshold estimated for inhalation of xylenes by mammals. Concentrations in ambient air are at least 1 million times less than the effects threshold recorded for plants. Concentrations of xylenes in surface water are at least 100 times less than the effects threshold estimated for the most sensitive aquatic species.

Xylenes are not expected to be associated with global warming or with the depletion of stratospheric ozone because they do not persist in the atmosphere, and because of their limited absorption of infrared radiation and their non-halogenated nature.

Based on data on concentrations of xylenes in ambient air, indoor air, drinking water, and at self-serve gasoline stations, the total average daily intake of xylenes has been estimated for various age groups in the general population. Although data on concentrations of xylenes in foodstuffs were inadequate, it is likely that intake from this source is negligible compared to that which is inhaled. The estimated total average daily intake of xylenes is less (by 15 to 45 times) than the tolerable daily intake derived on the basis of studies in laboratory species. The tolerable daily intake is the intake which it is believed that a person can be exposed to daily, over a lifetime, without harmful effect.

Based on these considerations, it has been concluded that xylenes are not entering the environment in quantities or under conditions that may be harmful to the environment, or that may constitute a danger to the environment on which human life depends, or to human life or health.

1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the Minister of the Environment and the Minister of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are “toxic” as defined in section 11 of the Act which states:

“ . . . a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions

(a) having or that may have an immediate or long-term harmful effect on the environment;

(b) constituting or that may constitute a danger to the environment on which human life depends; or

(c) constituting or that may constitute a danger in Canada to human life or health.”

Substances that are assessed as “toxic” according to section 11 may be placed on Schedule I of the Act, and considered for possible development of regulations, guidelines, or codes of practice to control any aspect of their life-cycle, from the research and development stage through manufacture, use, storage, transport, and disposal.

The assessment of whether xylenes are “toxic”, as defined in CEPA, was based on the determination of whether they **enter** or are likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota at levels that could cause adverse **effects**.

For the assessment of data other than those considered to be critical for the determination of whether xylenes are “toxic” under the Act, evaluations such as those of the U.S. Environmental Protection Agency (U.S. EPA, 1985), the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 1990), and a background report prepared by M.A. Moss of Dalhousie University (1990) were consulted. The Canadian Petroleum Products Institute provided two reports on exposure to motor gasoline hydrocarbon vapours at service stations (PACE, 1987, 1989). To identify literature not included in previous reviews, the following on-line commercial and government databases were searched: HSDB, ENVIROLINE, EMBASE, MEDLINE,

TOXLINE, TOXLIT, RTECS, Chemical Abstracts, Current Contents, and NTIS (1980 to 1989). Then, a search of CHEMID, RTECS, TOXLINE, and TOXLIT (1989 to June 1991) was conducted to identify data relevant to assessment of effects on human health. BIOSIS and Chemical Abstracts (January 1986 to December 1992) were searched for further data relevant to the environmental assessment. Although much of the research on xylenes has been conducted outside of Canada, where possible, Canadian data on sources, use patterns, fate, and effects of xylenes on the environment were emphasized.

Data relevant to the assessment of whether xylenes are “toxic” to human health, obtained after the completion of the health-related sections of this report (June 1991), were not considered for inclusion. Similarly, data relevant to the assessment of whether xylenes are “toxic” to the environment, obtained after the completion of these sections of the report (December 1992), have not been incorporated.

Although review articles were consulted where considered appropriate, all original studies that form the basis for determining whether xylenes are “toxic” under CEPA have been critically evaluated by the following staff of Health Canada (human exposure and effects on human health) and Environment Canada (entry, environmental exposure, and effects on the environment):

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This report presents a synopsis that will appear in the *Canada Gazette*. Section 2.0 presents an extended summary of the technical information that is critical to the assessment. Section 3.0 presents the assessment of whether xylenes are “toxic”, as defined under CEPA. Supporting Documentation, in which the technical information is presented in greater detail, has also been prepared and is available upon request. The effects of photochemical reaction products of xylenes are not addressed here but are considered in the Federal/Provincial Management Plan for nitrogen oxides (NO_x) and volatile organic compounds (VOCs) [CCME, 1990].

The health-related sections of this report were circulated and underwent external peer review by CanTox Inc. Canada (Supporting Documentation only), and the British Industrial Biological Research Association Toxicology International, Great Britain. The sections were then approved by the Standards and Guidelines Rulings Committee

of the Bureau of Chemical Hazards of Health Canada. As part of the review and approvals process established by Environment Canada for its contribution to these reports, the environmental sections of the Assessment Report and Supporting Documentation were reviewed externally by the following: D.A. Birkholz (Enviro-Test Laboratories, Edmonton), A. Bollo Kamara (Alberta Environment, Edmonton), I. Guay (Ministère de l'Environnement du Québec, Sainte-Foy), R. Lafleur (Canadian Petroleum Products Institute, Ottawa), J.F. Payne (Department of Fisheries and Oceans, St. John's), D. Singleton (National Research Council, Ottawa), and E.J. Williams (Shell Canada Ltd., Calgary). The final Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Copies of this Assessment Report and the unpublished Supporting Documentation are available upon request from:

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2.0 Summary of Information Critical to Assessment of “Toxic”

2.1 Identity, Properties, Production and Uses

Xylenes are monocyclic aromatic compounds with two methyl groups attached to the benzene ring [molecular formula $C_6H_4(CH_3)_2$]. There are three isomers of xylenes: *ortho*- or *o*-xylene (1,2-dimethylbenzene), *meta*- or *m*-xylene (1,3-dimethylbenzene), and *para*- or *p*-xylene (1,4-dimethylbenzene). Xylenes are clear, colourless, volatile liquids with a strong, aromatic odour. They have relatively high vapour pressures (1 100 to 1 170 Pa at 25°C), moderate solubilities in water (160 to 220 mg/L at 25°C), and moderately low octanol/water partition coefficients (log K_{ow} of 3.15 to 3.20) [Mackay *et al.*, 1992]. Xylenes do not absorb ultraviolet light of wavelengths greater than 260 nm (NRC, 1980), and only weakly absorb infrared radiation at wavelengths of 7 to 13 μm (Sadtler Research Laboratories, 1982). Gases involved in enhanced global warming strongly absorb radiation of wavelengths of 7 to 13 μm , enabling them to trap and re-radiate a portion of the earth’s thermal radiation (Wang *et al.*, 1976; Ramanathan *et al.*, 1985).

Xylenes can be identified and quantified using routine chromatographic techniques. While *o*-xylene is recognized as a distinct product in chemical analyses, the *m*- and *p*- isomers are generally not separated during most routine analyses. Therefore, results of analyses of xylenes in environmental samples are usually presented as the concentration of the *o*- isomer and the total concentration of the combined *m*- and *p*-isomers. In this report, the term xylenes refers to the mixture of all three isomers.

Most xylenes are produced by the catalytic reforming of petroleum and as by-products of the cracking of crude and heavy oil. Minor amounts are produced from coal-derived coke oven light oil (Fishbein, 1985). Commercial xylenes from petroleum sources contain approximately 20% *o*-xylene, 44% *m*-xylene, 20% *p*-xylene, and 15% ethylbenzene. Xylenes derived from coal-tar contain approximately 10 to 15% *o*-xylene, 45 to 70% *m*-xylene, 28% *p*-xylene, and 6 to 10% ethylbenzene (Low *et al.*, 1989).

In 1990, 514 kilotonnes (kt) of isolated (purified) xylenes were produced in Canada and 5 kt were imported, for a total Canadian supply of 519 kt (Corpus Information Services, 1991). Of these, 186 kt were exported, resulting in a total domestic consumption of 333 kt of isolated xylenes. Xylenes are currently produced at the following locations: four plants in the Sarnia/Corunna area, in Ontario; one plant in Hamilton, Ontario; and one plant in Montréal, Quebec. Canada’s production capacity for isolated xylenes is under 790 kt/year. In Canada, the major end-use for isolated xylenes is as an octane enhancer in gasoline; 188 kt were consumed for this use in

1990. A further 58 kt were used as solvents (Corpus Information Services, 1991) in such products as paints, varnishes and other coatings, pesticide formulations, printing inks, dyes, adhesives and sealants, cleaning agents, degreasing agents, paint removers, and for chemical extractions (Levelton and Associates Ltd., 1990). About 87 kt of isolated xylenes were used for other purposes in 1990, predominantly as feedstock for the plastics industry.

In addition, xylenes are a natural minor component of petroleum (Kirk *et al.*, 1983). Over 90% of xylenes present in gasoline in Canada occur as a result of cracking and reforming during the normal petroleum refining process. Additional isolated xylenes may be added to gasoline during blending to increase the octane rating. An estimated 34 000 megalitres of gasoline are sold annually in Canada (Oilweek, 1988). Based on an average content of xylenes in gasolines of about 10.5% by weight (Alberta Research Council, 1992), 2 600 kt of xylenes are estimated to be in the gasoline sold annually in Canada, including the approximately 188 kt added during blending. Most of the xylenes in gasoline are burned during normal engine operation.

Therefore, the total consumption of xylenes in Canada in 1990 is estimated to be 2 745 kt. This number is based on an estimated 2 600 kt of xylenes in gasoline and 145 kt of isolated xylenes used for purposes other than gasoline blending.

2.2 Entry into the Environment

Since xylenes are a natural minor component of crude oil and coal distillates (Kirk *et al.*, 1983), they may be introduced into the ground through petroleum seepage and weathering of exposed coal-containing strata, and into groundwater from petroliferous rocks (Hunt, 1979). The magnitude of such releases to the environment is unknown (U.S. EPA, 1987). Concentrations of xylenes of 21 µg/L *o*-xylene and 50 µg/L *m*- and *p*-xylenes were measured in eight test wells near Belleville, Ontario. Xylenes were present most likely as a result of natural contamination from bituminous deposits (Slaine and Barker, 1990).

Estimated atmospheric releases of xylenes in Canada are summarized in Table 2.1. Total yearly releases are estimated to be 96 kt: solvents account for an estimated 58% of the total releases, and transportation sources account for an estimated 39% of total releases of which an estimated 32% is released from light-duty automobiles.

Total emissions of xylenes into the atmosphere are expected to decline in the future, mainly because of the planned reduction of emissions of volatile organic compounds (VOCs) from light-duty vehicles, and the efforts to reduce VOC emissions from a variety of other sources for purposes of ground-level ozone control (CCME, 1990). Emissions of xylenes from light-duty vehicles have been reduced since the early 1970s (Lonneman *et al.*, 1986; Sigsby *et al.*, 1987).

Table 2.1
Estimated Major Atmospheric Releases of Xylenes in Canada

Sources	Estimated Atmospheric Releases (kilotonnes/year)	% of Total Estimated Atmospheric Releases	References
Industrial Processes			
Petroleum Production	1.6	1.7	CCME, 1990; Jaques, 1990; Scheff <i>et al.</i> , 1989
Xylenes and Other Chemical Production	0.5	0.5	CCME, 1990; Jaques, 1990
(Subtotal)	(2.1)	(2.2)	
Solvent Sources			
Paints and Coatings	42.0	43.8	Levelton and Associates Ltd., 1990
Inks	1.0	1.0	Levelton and Associates Ltd., 1990
Adhesives	2.0	2.1	Levelton and Associates Ltd., 1990
Pesticides	3.0	3.1	Levelton and Associates Ltd., 1990
Other	8.0	8.3	Levelton and Associates Ltd., 1990
(Subtotal)	(56.0)	(58.3)	
Transportation Sources			
Light-duty Vehicles	30.6	31.8	Sigsby <i>et al.</i> , 1987; Jaques, 1990
Heavy-duty Vehicles	2.4	2.5	Sigsby <i>et al.</i> , 1987; Jaques, 1990
Marine/Air/Rail	1.8	1.9	Sigsby <i>et al.</i> , 1987; Jaques, 1990
Off-road	2.2	2.3	Sigsby <i>et al.</i> , 1987; Jaques, 1990
Gasoline Marketing and Storage	0.7	0.7	Sigsby <i>et al.</i> , 1987; Jaques, 1990
(Subtotal)	(37.7)	(39.2)	
Total	95.8	100	

Xylenes enter water from the discharge of industrial and municipal effluents. Data on total environmental loadings from such sources are not available. In Ontario, xylenes were detected in effluents from a variety of industrial and municipal sources. The highest mean concentrations of xylenes in effluents released into surface water were 2.2 µg/L *o*-xylene in storm-water effluent from petroleum refineries (OME, 1990), and 3.3 µg/L *m*- and *p*-xylenes combined in effluents from a coke plant (OME, 1991).

The highest maximum concentrations of xylenes were in raw sewage, with concentrations of 570 µg/L *o*-xylene and 1 700 µg/L *m*- and *p*-xylenes combined at one site (OME, 1988).

Xylenes can enter soil and water through spills of petroleum and other chemical products. Based on the reported number, volume, and recovery rates for spills of xylenes (1980 to 1990), and petroleum products (1988) [NATES, 1992], and the assumption that the mean concentration of xylenes in spilled petroleum products is 10%, approximately 600 tonnes per year could have remained in the environment. Also, xylenes can be released to soil from leaking underground storage tanks that contain gasoline, diesel fuel, or heating oil. About 3% to 20% of the estimated 200 000 storage tanks in Canada have the potential to leak (Barker *et al.*, 1989; DOE, 1989). Reliable estimates of the total amounts of xylenes released from storage tanks are not available. Also, xylenes are released into the soil and groundwater at waste disposal sites (Barker, 1987; Lesage *et al.*, 1990, 1991; Pakdel *et al.*, 1992).

The highest concentrations of xylenes in groundwater in Canada have been recorded near waste disposal sites, including beneath landfill sites (from less than 0.2 µg/L to 123 µg/L of *o*-xylene and 0.2 to 191 µg/L *m*- and *p*-xylenes combined; Barker, 1987), near deep injection wells formerly used for the disposal of liquid industrial waste (from 325 to 374 µg/L xylenes at depths of 61 to 192 metres [Lesage *et al.*, 1991]), and near an active industrial chemical waste disposal lagoon (up to 1 700 µg/L *o*-xylene and 3 100 µg/L *m*- and *p*-xylenes combined [Lesage *et al.*, 1990]). Such levels vary considerably, and Pakdel *et al.* (1992) reported similar or considerably lower concentrations at other disposal sites.

About 300 registered pest-control products in Canada contain xylenes (Davis, 1991). Since many of these products are applied to crop foliage or directly to the soil, much of the xylenes in these formulations can be expected to reach the soil surface.

2.3 Exposure-related Information

2.3.1 Fate

Because of the relatively high vapour pressures and moderate water solubilities of xylenes, the atmosphere plays an important role in their distribution and fate (Mackay *et al.*, 1992). Modelling simulations predict that most xylenes released into the environment should be present in the atmosphere (Mackay *et al.*, 1992). Once released into the atmosphere, either directly or by volatilization from other media, xylenes photo-oxidize relatively quickly in a reaction with OH radicals in the presence of nitrogen dioxide to yield tolualdehydes, methyl glyoxal, methylbenzyl nitrates, dimethylphenols, and nitroxylenes, which are themselves degraded further (Finlayson-Pitts and Pitts, 1986; Atkinson, 1990). Though there are other reaction

products, they have not been identified individually (Atkinson *et al.*, 1991). Various tropospheric lifetimes for xylenes have been calculated to range from 0.5 to 1.5 days (Finlayson-Pitts and Pitts, 1986; Güsten *et al.*, 1984; Jori *et al.*, 1986).

Xylenes are rapidly lost from surface water by volatilization. The half-life in still water 1 metre deep has been estimated to be 5.6 hours; it would be shorter in turbulent water (Mackay and Leinonen, 1975). Volatilization rates were calculated for lakes (8 days) and rivers (1 to 2 days) [SRI, 1979] and for streams and rivers (36 minutes to 47 days) [U.S. EPA, 1987], with reported variations due to differences in conditions such as depth and flow rates of streams and rivers. No data are available regarding the fate of xylenes under ice in winter.

Volatilization half-lives, ranging from less than 1 minute to 2.2 days, have been estimated for all three xylene isomers on the soil surface (U.S. EPA, 1987; Anderson *et al.*, 1991). Volatilization should be much slower for xylenes incorporated into soil, with rates decreasing rapidly with soil depth.

Although xylenes are only moderately soluble in water, they may leach through soils to groundwater. Movement through soils is expected to be slowed by the presence of organic matter (Seip *et al.*, 1986), clay (Johnson *et al.*, 1989), and high moisture content (Aurelius and Brown, 1987). However, xylenes have been reported to move through clay soils (Green *et al.*, 1983; Anderson *et al.*, 1985). Based on theoretical considerations and limited data, the xylene isomers are not expected to be hydrolysed, photolyzed or oxidized significantly in soil (U.S. EPA, 1987).

Xylenes are degraded by micro-organisms in soil, groundwater, surface water, and sediments, under both aerobic and anaerobic conditions (Holm *et al.*, 1991; Edwards *et al.*, 1991; Reinhard *et al.*, 1991; Hutchins and Wilson, 1991). Half-lives for biodegradation by unacclimated organisms in water have been estimated to be between 7 and 28 days for each of the three isomers in aerobic systems, and between 180 and 360 days for *o*-xylene and 28 and 112 days for *m*- and *p*-isomers in anaerobic systems (Howard *et al.*, 1991). Micro-organisms can degrade xylenes by oxidation of both the aromatic ring and the methyl substituents, yielding products such as dimethylphenols, methylsalicylic acid, toluic acids, and ring fission products of methylcatechols (Gibson and Subramanian, 1984).

Based on their octanol/water partition coefficients, Jori *et al.* (1986) calculated a bioconcentration factor (BCF) of 80 for xylenes in fathead minnows, using the equation of Veith *et al.* (1979). Values less than 100 generally indicate that a compound is unlikely to bioconcentrate significantly in organisms or biomagnify along food chains (U.S. EPA, 1987). Experimental studies indicate that xylenes are absorbed very rapidly by molluscs and fish but are not bioconcentrated to a significant extent. BCFs of 6 to 177 have been observed in molluscs, eels, and trout (Nunes and Benville,

1979; Ferrario *et al.*, 1985; Ogata and Miyake, 1978; Walsh *et al.*, 1977). In rainbow trout exposed to 0.36 to 1.3 mg/L emulsified xylenes under flow-through conditions for 56 days, the maximum BCFs ranged from 14.0 to 14.7, and there was no increase in the concentrations in the fillets from day 2 to day 56 (Walsh *et al.*, 1977).

2.3.2 Concentrations

Mean concentrations of *o*-xylene in ambient air at 17 Canadian urban or suburban sites in nine cities during 1988 and 1989 ranged from 0.7 to 7.6 $\mu\text{g}/\text{m}^3$, with 24-hour maxima of 3.8 to 23.4 $\mu\text{g}/\text{m}^3$. Mean concentrations of *m*- and *p*-xylenes (combined) ranged from 1.8 to 18.3 $\mu\text{g}/\text{m}^3$, with 24-hour maxima of 10.7 to 47.8 $\mu\text{g}/\text{m}^3$. At a rural site at Walpole Island, Ontario, mean concentrations of *o*-xylene and *m*- and *p*-xylenes (combined) were 0.5 and 1.7 $\mu\text{g}/\text{m}^3$, respectively (Dann and Wang, 1990). The highest combined mean concentration for the 3 isomers at any one urban site in 1989 was 25.9 $\mu\text{g}/\text{m}^3$, while the combined mean concentration for the 3 isomers at the rural site was 2.2 $\mu\text{g}/\text{m}^3$.

The highest concentrations in ambient air have been recorded in the immediate vicinity of gasoline stations in five Canadian cities. The overall average concentrations of xylenes at self-serve stations were 221 $\mu\text{g}/\text{m}^3$ in the winter and 85 $\mu\text{g}/\text{m}^3$ in the summer. Mean concentrations of xylenes in samples at the marketing pumps were 716 $\mu\text{g}/\text{m}^3$ in the winter and 970 $\mu\text{g}/\text{m}^3$ in the summer (PACE, 1987, 1989).

The concentrations of xylenes can be higher in indoor air than in ambient air because of the following: the presence of household products, including solvents for cleaning and paint stripping; building materials; and personal activities, such as smoking. In surveys of approximately 400 homes in New Jersey, North Carolina, and North Dakota (Wallace *et al.*, 1987a), the population-weighted median concentrations in indoor air ranged from 2.3 to 8.0 $\mu\text{g}/\text{m}^3$ *o*-xylene and 6.2 to 22 $\mu\text{g}/\text{m}^3$ *m*- and *p*-xylenes combined. These values were approximately 2 to 10 times higher than the concentrations in outdoor air. Identified data on concentrations of xylenes in indoor air in Canada are restricted to a limited and possibly unrepresentative number of homes in Toronto, with mean levels ranging from 8.5 to 18.2 $\mu\text{g}/\text{m}^3$ *o*-xylene and 25.1 to 31.1 $\mu\text{g}/\text{m}^3$ *m*- and *p*-xylenes combined (Chan *et al.*, 1990), and in Montréal, with maximum concentrations of 34.0 $\mu\text{g}/\text{m}^3$ *o*-xylene and 74.6 $\mu\text{g}/\text{m}^3$ *m*- and *p*-xylenes combined (Otson and Benoit, 1985).

Concentrations of xylenes were not quantifiable in 824 water samples taken from surface water, groundwater wells, and treated drinking water in six Canadian provinces from 1985 to 1988 (detection limit of 0.5 $\mu\text{g}/\text{L}$ for *o*-xylene and for *m*- and *p*-xylenes combined) [NAQUADAT, 1991]. In a survey of samples of raw water for drinking water supplies in the Great Lakes taken between 1982 and 1983, Otson (1987) reported that the concentration of each xylene isomer was generally below the

detection limit of 0.1 µg/L. The mean concentrations of xylenes in Canadian drinking water supplies, at 30 water treatment plants sampled across Canada in 1979, were less than 1 µg/L (the detection limit of the analytical method) [Otson *et al.*, 1982]. In more recent surveys of water supply systems conducted in Ontario in 1987 and in the Atlantic provinces between 1985 and 1987, concentrations of xylenes were generally less than the detection limit of 0.5 µg/L (OME, 1987; DOE, 1989a, 1989b, 1989c, 1989d).

Data on concentrations of xylenes in soils and sediments in Canada have not been identified. In view of the sources and fate of xylenes in the environment, measurable concentrations of xylenes in soil would be expected to occur only near point sources such as spills, leaks, and waste disposal sites, or in areas with natural contamination from bituminous deposits (Section 2.2).

There are few identified quantitative data on concentrations of xylenes in food. Trace concentrations of *o*-xylene have been reported in split peas (0.008 µg/g), lentils (0.003 µg/g), and beans (average concentration: 0.009 µg/g; maximum concentration: 0.025 µg/g) in the United States by Lovegren *et al.* (1979).

Available data on levels of xylenes in human tissues or fluids are limited. Pellizzari *et al.* (1982) reported concentrations of xylenes in mothers' milk, in populations living near chemical manufacturing plants and/or industrial facilities that use xylenes in the United States. Xylenes were detected but not quantified in 8 of a total of 12 samples collected. The detection limit for these analyses was not specified by the authors.

2.4 Effects-related Information

2.4.1 Experimental Animals and In Vitro

The acute toxicity of xylenes is relatively low. For inhalation, reported 4-hour LC₅₀s in rats ranged from 6 350 ppm (27 622 mg/m³) to 6 700 ppm (29 145 mg/m³). In mice, the 6-hour LC₅₀ values for the individual isomers ranged from 3 907 to 5 267 ppm (16 995 to 22 911 mg/m³). The oral LD₅₀s for xylenes (60% *m*-, 14% *p*-, 9% *o*-xylene, and 17% ethylbenzene), administered by gavage in corn oil, were 3.5 g/kg bw in rats and 5.6 and 5.3 g/kg bw, respectively, in male and female mice (NTP, 1986). The organs most notably affected following acute exposure are the lungs, liver, and nervous system.

Repeated short-term exposure to moderate to high concentrations of xylenes causes cardiovascular, hepatic, and neurological effects. The reported lowest-observed-adverse-effect-level (LOAEL) of xylenes (composition unspecified), for effects other than neurological in short-term inhalation studies, was 230 ppm (1 000 mg/m³), which resulted in coronary changes in rats (Morvai *et al.*, 1987). The lowest

no-observed-adverse-effect-level (NOAEL) in short-term studies, in which the individual xylene isomers was administered orally to rats, was 250 mg/kg bw/day (for each of the three individual isomers). This level is based predominantly on decreases in body weight and increases in liver weight observed at higher doses (Condie *et al.*, 1988).

In the limited number of sub-chronic inhalation studies available, the lowest concentration at which effects were observed was 320 ppm (1 400 mg/m³). This was in small groups (n = 6 to 8) of rats continuously exposed to xylenes (composition unspecified) for 90 days. At this concentration, an increase in the liver to body weight ratio was observed following 30 days exposure, but not after inhalation for 90 days (Kyrklund *et al.*, 1987). In another study, there were no effects on body weight increase, and liver and kidney weight (examined in dogs only), haematological parameters, blood chemistry, or upon histopathological examination in rats or beagle dogs exposed to 770, 2 000 or 3 500 mg/m³ xylenes (7.84% *p*-, 65.01% *m*- and 7.63% *o*-xylenes, 19.7% ethylbenzene and 0.14% toluene), 6 hours/day, 5 days/week for 13 weeks (Carpenter *et al.*, 1975). The lowest reported no-observed-effect-level (NOEL) in sub-chronic studies in which xylenes (17.6% *o*-, 62.3% *m*- and *p*-xylenes, and 20% ethylbenzene) were administered orally was 150 mg/kg bw/day, based predominantly on effects on the liver and kidney of rats observed at the next highest dose (750 mg/kg bw/day) [Condie *et al.*, 1988]. The lowest NOEL in a sub-chronic study in two species (gavage in corn oil) conducted by the National Toxicology Program was 500 mg/kg bw/day xylenes (60% *m*-, 14% *p*-, 9% *o*-xylene, and 17% ethylbenzene), based on decreases in growth in rats observed at the next highest dose (1 000 mg/kg bw/day) [NTP, 1986]. The NOAEL in a sub-chronic study in which *m*-xylene was administered orally to rats was 200 mg/kg bw/day; this was the NOEL in a similar study for *p*-xylene (Hazleton Labs, 1988a, 1988b).

The most extensive bioassay of the chronic toxicity and carcinogenicity of xylenes (60% *m*-, 14% *p*-, 9% *o*-xylene, and 17% ethylbenzene) is a study conducted on rats and mice (gavage in corn oil) by the National Toxicology Program (NTP, 1986). In this study, decreased survival (though some deaths were gavage-related) and lower body weights (5 to 8%, considered to be indicative of slight toxicity) were observed in male rats at the highest dose (LOEL = 500 mg/kg bw/day; NOEL = 250 mg/kg bw/day). Male and female mice in the high dose group (1 000 mg/kg bw/day) were hyperactive for 5 to 30 minutes after dosing; there were no other compound-related non-neoplastic effects (NOAEL in mice = 1 000 mg/kg/day). Based on the lack of compound-related neoplastic lesions observed in these 2-year bioassays, it was concluded that there was no evidence of carcinogenicity of xylenes for male or female F344/N rats or B6C3F₁ mice.

Maltoni *et al.* (1985) reported an increase in the total number of Sprague-Dawley rats with malignant tumours at 141 weeks following administration of xylenes (composition unspecified) by gavage in olive oil for 104 weeks. However, because of limitations of the design and documentation of this study, these results are considered suspect.

Xylenes have not induced mutations or increased the frequency of sister chromatid exchange in various short-term *in vitro* bioassays, nor caused chromosomal aberrations *in vivo* or *in vitro* in mammalian or human cell cultures, with the exception of two limited studies as summarized in ATSDR (1990). In one study (Donner *et al.*, 1980), weak mutagenic activity was observed in *Drosophila* exposed to technical grade xylenes containing 18.3% ethylbenzene. In the other study, Myhr *et al.* (1990) reported positive results in a mouse lymphoma L5178Y cell mutation assay in which cells were exposed to xylenes (composition unspecified). These positive results contrast the negative results obtained in a similar investigation conducted by Lebowitz *et al.* (1979).

In inhalation studies conducted to date, xylenes have not been teratogenic, but they have induced fetotoxic effects, sometimes at doses below those which were toxic to the mothers. With the exception of unconfirmed results reported by Mirkova *et al.* (1983), the lowest concentration of xylenes reported to induce fetotoxic effects in the absence of maternal toxicity in available investigations was 500 mg/m³. At this concentration, in a study that was documented incompletely, moderate embryotoxic effects were observed. Researchers noted retardation of skeletal development and of body weight increase in the offspring of rabbits exposed on days 7 to 20 of gestation to xylenes, the composition of which was unspecified (Ungvary and Tatrai, 1985). In rats, maternal toxicity and fetotoxicity were observed following exposure to 250 mg/m³ on days 7 to 15 of pregnancy (Ungvary and Tatrai, 1985). In the study by Mirkova *et al.* (1983), decreased fetal weight, abnormal ossification of the sternum, and impaired formation of the skull were reported when rats were exposed to 50 and 500 mg/m³ on days 1 to 21 of gestation. However, the composition of the mixture administered was not specified, the health of the test animals may have been compromised, and the presence or absence of maternal toxicity was not addressed. In a single identified study in which xylenes (9.1%, 60.2% and 13.6% *o*-, *m*- and *p*-xylenes, respectively, and 17% ethylbenzene) were administered orally by gavage in cottonseed oil to CD-1 mice, fetotoxic effects and malformations were observed, but only at high doses (2 060 mg/kg bw per day) which were toxic to the mothers (Marks *et al.*, 1982).

The lowest concentration of the individual xylene isomers reported to induce embryo- and fetotoxic effects in the absence of maternal toxicity following inhalation in a limited number of available studies is 150 mg/m³. At this concentration, increased

implantational loss and decreased placental weight and retardation in skeletal development of offspring were observed, following continuous exposure of pregnant rats to *p*-xylene on days 7 to 14 of gestation (Ungvary *et al.*, 1980).

In the only identified study of reproductive toxicity (Bio/Dynamics, 1983), there were no treatment-related effects on the following: mating, fertility or pregnancy indices; gestation length; parturition data; litter size; or pup survival. This was a one-generation study in rats exposed to concentrations of up to 2 100 mg/m³ xylenes (20.42% *o*-, 44.2% *m*-, 20.3 % *p*-xylenes, 12.8% ethylbenzene and 2.4% toluene), 6 hours/day for 131 days before mating, and during a 20-day mating period (both sexes), and on days 1 to 20 of gestation and days 5 to 20 of lactation (females). There were some fetotoxic effects at the highest concentration in this study (LOAEL = 2 100 mg/m³, NOAEL = 1 050 mg/m³).

Identified investigations of the neurotoxicity of xylenes in laboratory animals are principally restricted to those in which only biochemical effects in the brain, clinical signs, or behavioural effects were examined. These results often followed exposure to one concentration of xylenes only, the composition of which was often unspecified, or, in a few cases, to the individual isomers. The lowest concentration at which neurobehavioural effects of xylenes were reported, following inhalation, was 113 ppm (492 mg/m³, composition unspecified) for 2 hours, for which Ghosh *et al.* (1987) observed decreases in the reinforcement rate to which tolerance developed in rats. Biochemical effects on the brain, the significance of which is unclear, have been observed at concentrations as low as 50 ppm (218 mg/m³) *m*-xylene, administered for 2 weeks to rats (Savolainen and Pfaffli, 1980).

2.4.2 Humans

The effects of xylenes on humans have been examined in laboratory studies with volunteers and in epidemiological studies of occupationally-exposed populations. There have also been several case reports of neurological effects following exposure to xylenes. In many of the reported epidemiological studies (Angerer and Wulf, 1985; Askergren, 1982; Franchini *et al.*, 1983; Haglund *et al.*, 1980; Kilburn *et al.*, 1985; Mikulski *et al.*, 1972; Seppalainen *et al.*, 1978), workers were exposed to thinners and solvents that also contained high percentages of benzene or toluene and other aromatic or non-aromatic compounds. Therefore, it is not possible in most cases to attribute the observed effects to xylenes alone.

Transient, mildly adverse effects, such as impairment of body balance, reaction-time performance and equilibrium, have been observed in human volunteers by one group of investigators, following volunteer exposure to xylene concentrations of 100 ppm (435 mg/m³) or greater (Riihimaki and Savolainen, 1980; Savolainen *et al.*, 1980,

1982, 1984, 1985). However, in other studies by the same and different investigators, such effects were not observed at higher concentrations (Savolainen, 1980; Seppalainen *et al.*, 1989).

2.4.3 Ecotoxicology

Information on the acute and chronic toxicity of xylenes was identified for aquatic species from a number of trophic levels and taxa, including algae to fish and amphibians. Data on toxicity to terrestrial and avian species are limited to bacteria and plants. Only the more sensitive responses are noted in this report.

Growth of the alga *Selenastrum capricornutum* was reduced by 50% after 72 hours of exposure to 3.2 to 4.9 mg/L of each of the three xylene isomers (Galassi *et al.*, 1988). Exposure for 30 minutes to 300 mg/L resulted in a 65 to 100% kill of the freshwater macrophytes *Elodea* and *Potamogeton* (Frank *et al.*, 1961).

The most sensitive freshwater organism was the water flea (*Daphnia magna*) with 24-hour LC₅₀s of 1.0 mg/L for *o*-xylene, 3.6 mg/L for *p*-xylene, and 4.7 mg/L for *m*-xylene (Galassi *et al.*, 1988). Among marine organisms, the most sensitive species was the bay shrimp (*Crago franciscorum*) with 96-hour LC₅₀s of 1.1 mg/L for *o*-xylene, 1.7 mg/L for *p*-xylene, and 3.2 mg/L for *m*-xylene (Benville and Korn, 1977).

The most sensitive freshwater fish was the rainbow trout (*Oncorhynchus mykiss*), with 96-hour LC₅₀s of 2.6, 7.6, and 8.4 mg/L for the *p*-, *o*-, and *m*- isomers, respectively (Galassi *et al.*, 1988). The most sensitive marine species tested was the young of the striped bass (*Morone saxatilis*), with 96-hour LC₅₀s of 1.7, 8.0, and 9.7 mg/L for the *p*-, *m*-, and *o*- isomers, respectively (Benville and Korn, 1977).

Among terrestrial plants, exposure of barley to 20 g/m³ of xylenes vapour for 4 hours resulted in 80% injury of leaves within 24 hours, with leaves recovering to 10% injury 4 weeks after exposure (Currier, 1951; Currier and Peoples, 1954).

The 8-day EC₅₀ for growth of *Selenastrum capricornutum* ranged from 3.9 to 4.4 mg/L for each of the three xylene isomers (Herman *et al.*, 1990). Black *et al.* (1982) determined the toxicity of *m*-xylene to the early life stages of the leopard frog (*Rana pipiens*) and rainbow trout. Eggs of each species were exposed continuously to *m*-xylene from within 30 minutes of fertilization (embryos) to 4 days post-hatch (larvae), resulting in total continuous exposures of 9 days for the frog, and 27 days for the trout. The LC₅₀s for continuous exposure were 3.53 mg/L for the frog and 3.77 mg/L for the trout.

3.0 Assessment of “Toxic” under CEPA

3.1 CEPA 11(a): Environment

Xylenes enter the Canadian environment primarily through atmospheric releases, as a result of their use as solvents and their release from transportation sources. Xylenes are released into the soil and groundwater in spills and in leachate from contaminated waste disposal sites, and to surface water through spills and discharge of contaminated effluents. Xylenes do not persist in water or soil because of their high volatility and their biodegradation, nor do they persist in the atmosphere because of their rapid photo-oxidation. Accumulation of xylenes is not expected to be significant in terrestrial or aquatic organisms, and there are no reports indicating significant bioconcentration in organisms or biomagnification in the food chain.

Since xylenes are found primarily in the air, terrestrial wildlife, particularly herbivores that eat plants exposed to atmospheric xylenes, may be among the organisms with the highest overall exposure. Only direct exposure of wildlife to air can be evaluated, since no data are available to estimate concentrations of xylenes in terrestrial plants resulting from atmospheric deposition and plant uptake. Walpole Island is a rural site on the St. Clair River, located in an industrialized region of southern Ontario. Therefore, the site could potentially represent the highest concentration of xylenes in a rural setting. The mean concentration for *o*-, *m*-, and *p*-xylenes combined was 2.2 µg/m³ at Walpole Island in 1989. The highest combined mean concentration for the three isomers at any one urban site in 1989 was 25.9 µg/m³. Dose-dependent maternal toxicity and fetal-skeletal retardation were recorded in rats exposed by inhalation to xylenes (LOEL = 250 mg/m³) [Ungvary and Tatrai, 1985]. Using a factor of 100 to account for differences between species, and to convert a LOAEL to a NOAEL, yields an estimated effects threshold of 2.5 mg/m³. The mean concentration at Walpole Island was at least 1 000 times less than this estimated effects threshold. Therefore, terrestrial mammalian wildlife should not be at risk from direct exposure to xylenes in rural air.

There are insufficient data available to assess wildlife exposure in the aquatic environment or potential effects of xylenes on birds in terrestrial or aquatic environments. However, in view of the environmental fate and concentrations of xylenes, and the considerations outlined above for mammalian wildlife, xylenes are unlikely to affect birds or aquatic mammals.

Concentrations in ambient air are at least 1 million times less than the lowest effect threshold recorded for terrestrial plants (20 g/m³ for barley).

Based on available data, the aquatic organism most sensitive to the effects of xylenes is the water flea (*Daphnia magna*), with 24-hour LC₅₀s of 1.0 mg/L for *o*-xylene, 3.6 mg/L for *p*-xylene, and 4.7 mg/L for *m*-xylene. Dividing these values by 20 to convert the acute thresholds to chronic NOECs for non-persistent, non-bioaccumulative substances, and to account for differences in species sensitivity and extrapolation from laboratory to field effects, yields estimated effects thresholds for long-term exposure of 50 µg/L for *o*-xylene, 180 µg/L for *p*-xylene, and 235 µg/L for *m*-xylene. Concentrations of xylenes in ambient surface water have been reported to be below the detection limits (as high as 0.5 µg/L for *o*-xylene and for *m*- and *p*-xylenes combined). Therefore ambient concentrations are at least 100 times less than the estimated effects threshold for *o*-xylene, and at least 360 to 470 times less than the estimated effects thresholds for *m*- and *p*-xylenes.

Therefore, on the basis of available data, it has been concluded that xylenes are not entering the environment in quantities or under conditions that may be harmful to the environment.

3.2 CEPA 11(b): Environment on which Human Life Depends

Xylenes will not contribute directly to global warming because of the following: their short residence time in the troposphere, their low atmospheric concentrations relative to known greenhouse gases (Jaques, 1992), and their low absorption of radiation within the critical wavelengths between 7 and 13 µm. Unlike substances associated with depletion of stratospheric ozone (Firor, 1990), xylenes do not persist in the atmosphere and are not halogenated. Therefore, they are not expected to contribute to stratospheric ozone depletion.

Therefore, on the basis of available data, it has been concluded that xylenes are not entering the environment in quantities or under conditions that may constitute a danger to the environment on which human life depends.

3.3 CEPA 11(c): Human Life or Health

Population Exposure

The general population's estimated daily intake of xylenes is presented in Table 3.1. In the table, the sources of exposure are, in order of their relative contribution: indoor air, ambient air, air at self-serve gasoline stations, and water. Available data on concentrations of xylenes in foodstuffs were insufficient to estimate intake. However, based on consideration of physical-chemical properties, it is likely that dietary intake is minimal, compared to the sources considered here.

Table 3.1
Estimates of the Intake of Xylenes for Canadians

Substrate/Medium ^a	Estimated Intake				
	Micrograms per Kilogram of Body Weight per Day				
	0 to 0.5 yr ^b	0.5 to 4 yr ^c	5 to 11 yr ^d	12 to 19 yr ^e	20 to 70 yr ^f
Ambient Air	0.2 to	0.3 to	0.3 to	0.2 to	0.2 to
(Urban)	2.2	2.9	3.4	2.5	2.5
(Rural)	0.2	0.2	0.3	0.2	0.2
Indoor Air	2.8 to	3.8 to	4.4 to	3.3 to	3.3 to
	3.7	5.0	5.7	4.3	4.3
Drinking Water	0	< 0.03	< 0.02	< 0.01	< 0.01
Self-serve Gasoline Station					
(Summer	0.2 to	0.2 to	0.3 to	0.2 to	0.2 to
and Winter)	0.3	0.3	0.4	0.3	0.3
Total Estimated Intake	3.2 to 6.2	4.3 to 8.2	5.0 to 9.5	3.7 to 7.1	3.7 to 7.1
Cigarette Smoking				< 0.01 to	< 0.01 to
(Mainstream)	–	–	–	10.0	13.8
(Sidestream)	1.8	2.4	2.8	2.1	2.1

- a. Mean concentrations of xylenes in ambient air are 2.5 to 25.9 and 2.2 $\mu\text{g}/\text{m}^3$ for urban and rural locations, respectively (Dann and Wang, 1990); mean concentrations in indoor air in the homes of non-smokers in various seasons are 14 to 18.2 $\mu\text{g}/\text{m}^3$ (Wallace and Pellizzari, 1986; Wallace *et al.*, 1987b). It is assumed that people generally spend 7 hours outdoors and 17 hours indoors (NHW, 1989). Mean concentrations in drinking water are generally < 0.5 $\mu\text{g}/\text{L}$ (Otson *et al.*, 1982; OME, 1987; DOE, 1989a, 1989b, 1989c, 1989d). For self-serve gasoline stations, the mean airborne concentrations are 716 $\mu\text{g}/\text{m}^3$ in winter and 973 $\mu\text{g}/\text{m}^3$ in summer, respectively (PACE, 1987, 1989). It is also assumed that the average person spends 10 minutes (0.02 hour) per week at the gas station. Cigarettes are estimated to contain < 0.01 to 38 μg xylenes/cigarette for ultra-low tar and high tar cigarettes, respectively, in the mainstream smoke (Higgins *et al.*, 1983); it is assumed that adults aged 20 to 70 years smoke 25 cigarettes per day and those aged 12 to 19 years smoke 15 cigarettes per day. The intake from sidestream smoke is estimated based on the difference in concentrations of xylenes between homes with smokers and those with non-smokers in the winter (i.e., 8.9 $\mu\text{g}/\text{m}^3$) [Wallace and Pellizzari, 1986; Wallace *et al.*, 1987b] and the assumption that people spend 17 hours indoors (NHW, 1989); data were insufficient to estimate intake from food or from soil.
- b. Weighs 7 kg, breathes 2 m^3 air, and drinks 0 L water daily (EHD, 1991).
- c. Weighs 13 kg, breathes 5 m^3 air, and drinks 0.8 L water daily (EHD, 1991).
- d. Weighs 27 kg, breathes 12 m^3 air, and drinks 0.9 L water daily (EHD, 1991).
- e. Weighs 57 kg, breathes 19 m^3 air, and drinks 1.3 L water daily (EHD, 1991).
- f. Weighs 69 kg, breathes 23 m^3 air, and drinks 1.5 L water daily (EHD, 1991).

The estimated total average daily intake of xylenes for the various age groups in the general population ranges from 3.2 to 9.5 µg/kg bw/day. Smokers who smoke 20 cigarettes per day may increase their total intake of xylenes by < 0.01 to 13.8 µg/kg bw/day.

Effects

Technical grade xylenes, which are used commercially, contain ethylbenzene and all three isomers of xylene. In the majority of toxicological studies conducted to date, experimental animals have been exposed to this mixture rather than to the individual isomers. Also, in epidemiological studies, workers have been exposed to technical grade xylenes and other solvents. Therefore, available data are insufficient to assess the health risks associated with exposure to the individual xylene isomers. Moreover, in the general environment, the population is more likely to be exposed to xylenes than to the individual isomers. For the above reasons, the following discussion addresses principally the ternary mixture of xylenes.

Epidemiological studies are limited to a few investigations of small populations of workers exposed to thinners and solvents that contain xylenes, high percentages of benzene or toluene, and other aromatic and non-aromatic compounds. Because of the limited power of these studies and possible confounding by accompanying exposure to other substances, which may have contributed to observed effects, available epidemiological data are inadequate to assess the health risks (including carcinogenicity) of xylenes in humans.

Xylenes have not been carcinogenic following oral administration to rats and mice in a well-conducted bioassay (NTP, 1986). However, results of another carcinogenesis bioassay by the oral route (Maltoni *et al.*, 1985) are not considered to contribute meaningfully to the weight of evidence for carcinogenicity because of the study's limitations. The weight of available evidence also indicates that xylenes are not genotoxic. Xylenes have been classified, therefore, in Group IV (probably not carcinogenic to humans) of the classification scheme, developed by the Bureau of Chemical Hazards for use in the derivation of the *Guidelines for Canadian Drinking Water Quality* (EHD, 1989).

For compounds classified in Group IV, a tolerable daily intake (TDI) is derived on the basis of a NO(A)EL or LO(A)EL in humans or animal species, in studies conducted by the most relevant route of exposure, divided by an uncertainty factor. For xylenes, studies in which volunteers have been exposed are limited principally to those involving short-term repeated exposure of a limited number of subjects to 100 ppm (435 mg/m³) *m*-xylene or greater (Riihimaki and Savolainen, 1980; Savolainen, 1980; Savolainen *et al.*, 1980, 1982, 1984, 1985; Seppalainen *et al.*, 1989). Due to these limitations of the available studies in volunteers and the epidemiological studies

mentioned (i.e., the limited power to detect effects and confounding by concomitant exposure to other substances), available data are considered insufficient for development of a TDI on the basis of studies in humans.

Inhalation is considered to be the most important route of exposure to xylenes for the general public (see “Population Exposure”). Therefore, a TDI for humans has been derived on the basis of the results of studies in animal species exposed to xylenes by inhalation. The lowest concentration at which meaningful effects (feto-toxic effects in the absence of maternal toxicity) have been observed, following exposure by inhalation to xylenes, is 500 mg/m³ in a limited study¹ (Ungvary and Tatrai, 1985). At this concentration, moderate embryotoxic effects, such as a retardation of body weight increase, were observed in the offspring of rabbits exposed to xylenes of unspecified composition continuously on days 7 to 20 of gestation. However, it should be noted that in the same study, maternal (unspecified) and fetal (skeletal retardation) toxicity were observed in rats exposed during gestation to 250 mg/m³ (the lowest concentration administered), indicating that the rats may be a more sensitive species. The available data do not preclude the possibility that a similar pattern to that observed in rabbits might be observed in rats exposed to lower concentrations.

At similar concentrations (492 mg/m³ for 2 hours), transient neurobehavioural effects in rats have been observed (Ghosh *et al.*, 1987). At slightly lower concentrations (50 ppm, 218 mg/m³ for 2 weeks), biochemical effects on the brain, the significance of which is unclear, have been reported in rats (Savolainen and Pfaffli, 1980). In the longest-term studies of the effects of xylenes following inhalation (i.e., sub-chronic studies), the lowest concentration at which effects (a transient increase in the liver to body weight ratio) were observed, in the limited number of available studies, is 320 ppm (1 400 mg/m³), in small groups of rats continuously exposed to xylenes (composition unspecified; single exposed group) for 90 days (Kyrklund *et al.*, 1987). In another adequate study of a range of end-points, there were no effects in rats or beagle dogs exposed to up to 3 500 mg/m³ xylenes, 6 hours/day, 5 days/week for 13 weeks (Carpenter *et al.*, 1975).

On the basis of these data, the TDI is derived as follows:

$$\begin{aligned} \text{TDI} &= \frac{(250 \text{ mg/m}^3) \times (0.144 \text{ m}^3/\text{day})}{(0.25 \text{ kg}) \times 1\,000} \\ &= 0.144 \text{ mg/kg bw/day (144 } \mu\text{g/kg bw/day);} \end{aligned}$$

where:

250 mg/m³ = the lowest LOEL for meaningful effects reported in a bioassay of adequate quality (though documentation was incomplete) in the most sensitive species (Ungvary and Tatrai, 1985);

1. Documentation of the protocol and results in the published account was incomplete.

- 0.144 m³/day = assumed inhaled air volume of an adult rat (Altman and Dittmer, 1972);
- 0.25 kg = assumed body weight of an adult rat (NIOSH, 1985); and
- 1 000 = uncertainty factor (× 10 for intra-species variation; × 10 for inter-species variation; × 10 for LOEL rather than NOEL [although observed effects at the LOEL were only moderately fetotoxic; documentation was also limited]. No additional factor was incorporated for the limited period of exposure, since fetotoxic effects occur at doses below those which induce adverse effects in sub-chronic and chronic studies).

The lowest concentration of the individual xylene isomers, reported to induce adverse effects in animal species following inhalation, is 150 mg/m³. At this concentration, there were implantational loss and decreased placental weight, and retardation in skeletal development of offspring in the absence of maternal toxicity. The observations followed continuous exposure of pregnant rats to *p*-xylene on days 7 to 14 of gestation (Ungvary *et al.*, 1980). This is only slightly less than the LOEL used above in the derivation of a TDI for xylenes.

The database on effects of long-term exposure to xylenes following ingestion is more complete than for that of inhalation. The lowest reported NOEL in the longest-term study conducted to date in which xylenes have been administered orally (gavage in corn oil) is 250 mg/kg bw/day, based on a 5 to 8% decrease in body weight in male rats observed at the next highest dose (500 mg/kg bw/day) in a 2-year bioassay conducted by the National Toxicology Program (NTP, 1986). The decrease in body weight was considered to be indicative of slight toxicity. Survival was also reduced at 500 mg/kg bw/day in this study, however, some of these deaths were gavage-related. The NOAEL in the only available study of developmental toxicity, in which xylenes were administered orally, was considerably greater than the NOAEL in the NTP bioassay – i.e., 1 030 mg/kg bw/day (Marks *et al.*, 1982). NO(A)ELs for the individual isomers in sub-chronic studies, in which *m*- or *p*-xylene was administered, are slightly less than the NOAEL in the 2-year NTP bioassay – i.e., 200 mg/kg bw/day (Hazleton Labs, 1988a, 1988b). A TDI derived from the studies in which xylenes have been administered orally would be considerably greater than a TDI derived on the basis of inhalation bioassays. For example, a TDI of 1 800 µg/kg bw/day can be calculated by division of the NOEL in male rats in the NTP bioassay (250 mg/kg bw/day), by an uncertainty factor of 100, for intra- and inter-species variation, and converting 5 days per week of dosing to 7 days per week. The more conservative TDI derived above, on the basis of results of studies in which xylenes have been administered by inhalation is, therefore, considered to be protective, based on consideration of results of studies in which the compound was administered orally.

The estimated total average daily intake of xylenes from various sources for different age groups in the Canadian population ranges from 3.2 to 9.5 µg/kg bw/day. These estimated total average daily intakes of xylenes are 15 to 45 times less than the tolerable daily intake derived above on the basis of bioassays in animal species.

Therefore, on the basis of available data, it has been concluded that xylenes are not entering the environment in quantities or under conditions that may constitute a danger in Canada to human life or health.

3.4 Conclusion

On the basis of available data, it has been concluded that xylenes are not entering the environment in quantities or under conditions that may be harmful to the environment, or that may constitute a danger to the environment on which human life depends, or to human life or health.

4.0 Recommendations for Research and Evaluation

Acquisition of additional data in the following areas would permit a more complete evaluation of the effects of xylenes on human health and environmental organisms in Canada. The priority for this work is low.

1. Additional monitoring data, particularly for indoor air, since this appears to be the principal source of exposure for the general population.
2. Quantitative information on the concentrations of xylenes in foodstuffs.
3. The prevalence and extent of natural contamination of groundwater by xylenes.
4. Additional studies of the developmental effects of xylenes and the individual isomers.
5. Better characterization of the delivered dose to the fetus, using physiologically-based pharmacokinetic methods.
6. The effects of chronic exposure to low concentrations of xylenes on growth, survival, and reproduction of sensitive freshwater fish and invertebrates.
7. The concentrations and persistence of xylenes under ice and the potential effects on aquatic biota under such conditions.

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