Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Styrene

Government of Canada
Environment Canada
Health Canada

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Synopsis

Approximately 700 kilotonnes of styrene are produced annually in Canada, of which nearly two thirds are exported. Styrene is used domestically in the production of a number of polymers and resins and is released into the Canadian environment, principally into the atmosphere. Although it does not persist in environmental media, measurable concentrations have been reported in ambient air, indoor air and water in Canada, and in some industrial and municipal effluents.

The maximum concentration of styrene measured in air from a rural site in Canada is over 800 times less than the effects threshold estimated for wild mammals exposed by inhalation. Data were insufficient, however, to estimate the possibly significant contribution of other media to the total intake of wildlife. Furthermore, the data identified on effects on aquatic biota were inadequate for assessment.

Styrene has a short atmospheric half-life, and is present at very low concentrations in the atmosphere. Thus, it is not expected to contribute significantly to depletion of stratospheric ozone or to global warming.

Based on data on concentrations in ambient and indoor air, food, drinking water and soil, the average total daily intakes of styrene for various age groups in the general human population have been estimated. Tolerable daily intakes for styrene have been derived based on the effects observed at the lowest levels in laboratory animals (those on the developing foetus) following inhalation and ingestion. (The tolerable daily intake is the dose to which it is considered that humans may be exposed daily over their lifetime without deleterious effect.) The estimated average total daily intake of styrene by various age groups in the Canadian general population is from 50 to 600 times less than these tolerable daily intakes.

Based on these considerations, it has been concluded that the available information is insufficient to determine whether styrene is entering the environment in quantities or under conditions that may be harmful to the environment. It has, however, been concluded that styrene is not entering the environment in quantities or under conditions 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 Ministers of the Environment and 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 assessed to be "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 ultimate disposal.

The assessment of whether styrene is "toxic" as defined under CEPA, was based on the determination of whether it enters or is 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. The effects of photochemical reaction products of styrene are not addressed in this Assessment Report but are considered in the Federal/Provincial Management Plan for nitrogen oxides (NO_x) and volatile organic compounds (VOCs) [CCME, 1990].

Data relevant to the environmental assessment of styrene were compiled in a review prepared for Environment Canada under contract by Ecological Services for Planning Ltd., Guelph, Ontario. Information cited in this review was identified through on-line searches of the following commercial databases: AGRICOLA, AQUIRE, BIOSIS, CESARS, CHEMFATE, CHEMINFO, ENVIRODAT, ENVIROFATE, HSDB, PHYTOTOX, RTECS and TOXLINE. The on-line searches were conducted in June 1991, and covered the literature published during the period between January 1985

and June 1991. Additional information was subsequently identified during the preparation of this assessment report from more recent review articles and from searches of other commercial databases, conducted in February 1992 (Pollution Abstracts and Chemical Abstracts).

For the health-related sections of this report, a background review was prepared under contract by Mann, Benford and Grasso of the Robens Institute of Health and Safety, University of Surrey, Guildford, Surrey, U.K., in November 1991. A literature survey was conducted by the contractor based on existing reviews of the toxicity of styrene (IARC, 1979, 1985, 1987; HSE, 1981; NIOSH, 1983; IPCS, 1983; U.S. EPA, 1988, 1989; Bond, 1989; Barale, 1991; Brown, 1991), supplemented by on-line searches for the years 1990 and 1991 (search completed on July 1, 1991).

To identify the toxicological data relevant to the assessment of the effects of styrene on human health, literature searches of the following databases were conducted: HSDB, RTECS, IRIS (search done in February 1991) and CCRIS (search done in May 1992). The name and registry number were searched in the TOXLINE (1981 to present) databases, and the TOXLIT (1981 to present) databases. All 1991 references were provided from TOXLINE and TOXLIT, in November 1991. In May 1992, TOXLINE was searched again for review articles; only those references published after 1987 were retrieved. As well, in May 1992, articles from the NTIS subfile that contained styrene as a key word were retrieved. In September 1991, MEDLINE was searched and articles dating back to 1990 indexed with the linked term styrene and pharmacokinetics were reviewed. NTIS and BIOSIS (dating back to 1985) were also searched. Additional relevant articles were identified during external peer review.

To identify data relevant to the estimation of exposure of the general population to styrene, literature searches were conducted in the following databases: Environmental Bibliography, ENVIROLINE, Pollution Abstracts, Chemical Exposure Database, Chemical Safety Newsbase and the Federal Register. The Canadian databases ELIAS, AQUAREF, MICROLOG and CODOC/GDOC were searched for all references to styrene. CISTIMON was also searched for references to styrene. Information on exposure is also included in some of the toxicological sources noted above, especially HSDB and TOXLINE. These sources were supplemented with manual searches of Current Contents throughout 1991 and 1992.

Additional relevant information was obtained from the Canadian Chemical Producers' Association and the Drinking Water Surveillance Program of the Ontario Ministry of the Environment.

Review articles were consulted where appropriate; however, all original studies that form the basis for determining whether styrene is "toxic" under CEPA have been critically evaluated. The following staff of Environment Canada and of Health Canada contributed to the preparation of this report:

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In this report, a synopsis that will appear in the *Canada Gazette* is presented. Section 2 is an extended summary of the technical information that is critical to the assessment. The assessment of whether styrene is "toxic" under CEPA is presented in Section 3.

As part of the review and approvals process established by Environment Canada, the environmental sections of this Assessment Report and Supporting Documentation were peer reviewed by Mr. Norman Bazinet (Ontario Ministry of the Environment, Toronto, Ontario), Dr. Otto Meresz (Ontario Ministry of the Environment, Rexdale, Ontario), Dr. Arthur Niimi (Department of Fisheries and Oceans, Burlington, Ontario) and Dr. Douglas Spry (Ontario Ministry of the Environment, Toronto, Ontario). Sections related to the effects on human health were peer reviewed by Dr. Jack Siemiatycki (Institut Armand-Frappier, Université du Québec, Laval-des-Rapides, Quebec), Dr. Ron Miller (The Dow Chemical Company, Midland, Michigan—Supporting Documentation only), Dr. Don Johnston and Dr. Flora Ratpan (Novacor Chemicals, Calgary, Alberta—Supporting Documentation only), and BIBRA Toxicology International. The health-related sections were subsequently approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada. The entire Assessment Report was reviewed and approved by Environment Canada/Health Canada CEPA Management Committee.

Copies of this Assessment Report and of 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

Styrene is a monoaromatic hydrocarbon (CAS No. 100-42-5). Synonyms for styrene include vinylbenzene, vinylbenzol, phenylethylene, styrolene, styrol, styrole, ethenylbenzene, cinnamene, cinnamenol and cinnamol (Bond, 1989; Sax and Lewis, 1989; CCOHS, 1990). The structural formula of styrene is $C_6H_5CH = CH_2$. Styrene is a colourless liquid at room temperature, with a vapour pressure of 667 Pa @ 20°C (Verschueren, 1983), a water solubility of 300 mg/L @ 20°C (Verschueren, 1983), a log octanol/water partition coefficient of 2.95 (U.S. EPA, 1984), an estimated organic carbon partition coefficient (K_{oc}) using the method proposed by Mackay *et al.* (1992) of approximately 370, and a Henry's Law Constant of 284.72 Pa-m^3/mol (Howard, 1989). In air, 1 ppm styrene equals 4.33 mg/m^3 (Verschueren, 1983). Styrene absorbs infrared radiation in the 7 to 13 μm wavelength region (Sadtler Research Laboratories, 1982).

Analysis of styrene in air generally includes preconcentration in a cryogenic trap and detection by gas chromatography with a flame ionization or electron capture detector (detection limits range from 0.05 to 0.1 μg/m^3) [Dann, 1991]. Styrene in surface water has also been analyzed by a purge-and-trap technique with gas chromatography/mass spectrometry (detection limit 0.1 μg/L) [Otson, 1987].

In 1990, Canadian production of styrene was reported to total 718 kt/year; of this amount approximately 490 kt were exported while negligible amounts of styrene were imported (Camford Information Services, 1991a). Industrial uses of styrene in Canada include the manufacture of polystyrene (147 kt/year), styrene-butadiene (SB) latex preparations (34 kt/year), acrylonitrile-butadiene-styrene (ABS) resins (28 kt/year), unsaturated polyester resins (11 kt/year) and SB rubber (5 kt/year). End uses of styrene or styrene-containing materials include foam materials, synthetic rubber products such as automobile tires, plastics, waxes, paints and varnishes, adhesives, metal cleaners and fibrous glass products (Howard, 1989; Camford Information Services, 1991a, 1991b).

2.2 Entry into the Environment

Styrene can be released into the Canadian environment from any stage in its production, storage, transport, use and disposal. The substance can also be released from similar activities involving styrene-containing materials.

There are three plants in Canada producing styrene – two in Ontario and one in Alberta (Environment Canada, 1990). Of the seven polyester production plants in Canada, three are located in Ontario, three in Quebec and one in Alberta. Plants producing other derivatives of styrene, such as acrylonitrile-butadiene-styrene (ABS) resin, styrene-butadiene (SB) rubbers and latex preparations, polyester resins and plastics, are mostly located in Quebec and Ontario, with a few located in Alberta, British Columbia and Nova Scotia.

Data on emissions of styrene in Canada are limited. Estimates based on available emission factors for various industrial activities are summarized in Table 1.

Table 1
Summary of Estimated Emissions of Styrene Resulting from Industrial Activities in Canada (tonnes/year).

Styrene production plants	64[1]
Polystyrene production plants	272[2]
ABS resins, SB rubbers and SB latex products plants	217[2]
Unsaturated polyester plants (Reinforced plastics industry)	1 000[3]
Plastic processing plants	8[2]
Total	1 561

1. Environment Canada (1990)
2. Estimated using emission factors presented in U.S. EPA (1990)
3. Edgecombe (1989)

Under the Municipal and Industrial Strategy for Abatement (MISA) program of the Ontario Ministry of the Environment, styrene was detected in the effluent of six industrial sites from the "Organic Chemical Manufacturing sector" (OME, 1992). The highest average concentration of styrene reported for the period October 1979 to September 1990 was 71.1 µg/L; this represents a loading value of 0.511 kg/day for this source.

As well, styrene was detected in 9 of 274 samples of raw sewage; the mean concentration was 21.4 µg/L (OME, 1988). Styrene was detected in 1 of 51 samples of raw sludge (at a concentration of 6 011 µg/kg wet weight) from Ontario municipal water pollution control plants, and in 2 of 262 samples of primary and secondary effluents (at concentrations of 15 and 13 µg/L) [OME, 1988]. It was not detected in treated sludge from 34 monitored plants. The detection limits for this study were 40 and 3 µg/L in raw sewage and effluents, respectively; the detection limit in sludge was not stated.

Other unquantified sources of styrene include: combustion products from spark-ignition engines, oxy-acetylene flames, cigarettes, pyrolysis and cracking of petroleum derivatives, bituminous-coal and shale-oil tars (Royal Society of Chemistry, 1989); emissions from waste incineration (Junk and Ford, 1980); spills (OME, 1991; NATES, 1992); and natural sources, including by-products of fungal and microbial metabolism (Clifford *et al.*, 1969; Harada and Mino, 1973; Shirai and Hisatsuka, 1979; Sato *et al.*, 1988; Shimada *et al.*, 1992).

2.3 Exposure-related Information

2.3.1 Fate

The major processes affecting the fate of styrene in the environment are photo-oxidation, volatilization and biotransformation. Most industrial emissions containing styrene are released directly to the atmosphere.

Hydroxyl radicals and tropospheric ozone are major reactants that rapidly degrade styrene in the atmosphere (Atkinson *et al.*, 1982; Alexander, 1990). Atmospheric half-lives ranging between 3.5 and 9 hours have been reported (Howard, 1989; Alexander, 1990). Styrene absorbs wavelengths of sunlight reaching the Earth's surface poorly (Alexander, 1990); therefore, degradation of styrene by direct photolysis is unlikely. The physical removal of airborne styrene by processes such as wet and dry deposition is thought to be relatively minor, and long-range transport of styrene is considered insignificant, based on its short atmospheric half-life (Alexander, 1990).

Styrene is rapidly lost from surface waters by volatilization, with reported half-lives for this medium ranging from 1 to 60 hours, depending on depth of the water body and degree of turbulence (Santodonato *et al.*, 1980; Zoeteman *et al.*, 1980; U.S. EPA, 1987a, 1987b; Howard, 1989; Fu and Alexander, 1992). The U.S. EPA (1984) estimated, on the basis of computer models, that half-lives of styrene were 3 days in a pond and 13 days in an oligotrophic lake. Longer half-life values are expected for stagnant deep water where volatilization does not occur (Zoeteman *et al.*, 1980; Alexander, 1990). Under laboratory conditions, Fu and Alexander (1992) demonstrated that the concentration of styrene in open flasks of distilled and lake water declined by about 95%, from 4 mg/L to about 0.2 mg/L, after 24 hours. They attributed this loss to volatilization.

Styrene can be biodegraded quite readily in water under aerobic conditions. The biodegradation half-life of styrene in water was estimated to be less than 5 days (Price *et al.*, 1974). Based on the results of studies in which the rate of mineralization of styrene was proportional to its concentration in water, Fu and Alexander (1992)

suggested that styrene could persist in low concentrations in water. Wilson *et al.* (1983) reported that styrene would degrade more slowly in groundwater than in surface waters.

The half-life for volatilization of styrene from soil surfaces was estimated to be approximately 1 minute, with the rate of volatilization decreasing with increasing depth (U.S. EPA, 1987a). Based on its estimated organic carbon partition coefficient (K_{oc}) of 370, the mobility of styrene in soil is considered to be moderate (McCall *et al.*, 1981). Roberts *et al.* (1980) found the rate of movement of styrene in a sand aquifer to be approximately 80 times slower than that of a non-adsorbing tracer.

A bioconcentration factor (BCF) in fish of 64 was estimated for styrene using the method presented by Veith *et al.* (1979).

2.3.2 Concentrations

Styrene has been detected at low concentrations in ambient air, indoor air and drinking water across Canada, and in surface water in the Great Lakes area. It was also detected but not quantified in biota and sediment in Canada. Styrene has also been detected in a range of foods, although available data are limited. Data on concentrations in the marine environment, groundwater, rain, snow, dry deposition, plants, birds, wild mammals and breast milk were not identified.

In extensive studies of ambient air, levels of styrene were determined in 586 samples taken from 1988 to 1990 at 18 mostly urban sites across Canada. Mean concentrations in 24-h samples ranged from 0.09 to 2.35 $\mu g/m^3$ (limit of detection approximately ≤ 0.1 $\mu g/m^3$) with an overall mean from all sites of 0.59 $\mu g/m^3$. Daily maximum concentrations were highest in industrial areas of Toronto (10.19 $\mu g/m^3$) and Vancouver (34.20 $\mu g/m^3$). The highest concentration of styrene reported in rural air in Canada was 3.2 $\mu g/m^3$, at Walpole Island, Ontario (Dann, 1990).

The most extensive data on concentrations of styrene in indoor air in Canada are from a national pilot study, conducted in 1991, of 757 single-family dwellings and apartments selected to represent a probability sample of the general population. The 24-h concentrations of styrene across all homes ranged from non-detected (detection limits = 0.48 $\mu g/m^3$) to 128.93 $\mu g/m^3$, and averaged 0.28 $\mu g/m^3$ (Concord Environmental, 1992). Slightly higher (several $\mu g/m^3$) mean levels have been detected in a number of other more limited studies of Canadian residences (Chan *et al.*, 1990; Bell *et al.*, 1991; Otson and Benoit, 1985) in urban and urban-industrial communities. The concentrations in indoor air may reflect releases from such household products as carpet glues and from cigarette smoke (Wallace *et al.*, 1987a, 1987b, 1989), although the contribution of such products to levels in indoor air has not been examined in studies conducted in Canada.

In surveys of Canadian water supplies, styrene is generally present at concentrations of less than 1 µg/L. For example, in the Ontario Drinking Water Surveillance Program, between 1988 and 1990, styrene was detected in 90 of > 3 000 samples from 86 sources of drinking water; mean concentrations in the individual sources in 1990 ranged from not detected (detection limit = 0.050 µg/L) to 0.250 µg/L in treated drinking waters (Lachmaniuk, 1991). Concentrations of styrene in surface waters and municipal water supplies reported in the ENVIRODAT data base for the period 1985 to 1991 were all below the detection limit (0.5 and 1.0 µg/L, respectively) [ENVIRODAT, 1992]. Otson (1987) conducted a survey of raw and treated water from 10 municipalities around the Great Lakes between July 1982 and May 1983, and reported mean concentrations of styrene of ≤ 0.5 µg/L (detection limit = 0.1 µg/L). The maximum concentration measured in raw water during that survey was 1.7 µg/L, in Cornwall (Otson, 1992).

Based on limited data, background concentrations of styrene in soil are very low. In a survey of organic compounds in soils in uncontaminated urban areas west of Toronto, styrene was detected in 3 of 5 soil samples at Port Credit, Ontario at concentrations of up to 0.2 µg/kg (detection limit = 0.05 µg/kg), and was not detected in any of 8 samples from Oakville/Burlington, Ontario (detection limit = 5 to 10 µg/kg) [Golder Associates, 1987].

Data on concentrations of styrene in Canadian sediments are sparse. Samoiloff *et al.* (1983) detected, but could not quantify, styrene in sediments from Tobin Lake, Saskatchewan.

Whole body concentrations of styrene ranging between 15 and 100 µg/kg were measured in "Splake", a cross of brook trout and lake trout, and in walleye (*Stizostedion vitreum*) caught in the St. Clair River (Bonner and Meresz, 1981). Styrene was also detected, but not quantified, in the tissues of several other fish (emerald shiner [*Notropis atherinoides*]; black crappie [*Pomoxis nigromaculatus*]; bluegill [*Lepomis macrochirus*]; pumpkinseed [*Lepomis gibbosus*]; and walleye [*Stizostedion vitreum*]) from the St. Clair River. Edible shellfish from Atlantic Canada contained < 10.0 µg styrene/kg (Zenon, 1989). In both of these reports, it was not indicated whether the results were expressed on a wet weight or a dry weight basis.

Styrene has also been found in a wide range of foods, but is generally present at levels of less than 10 µg/kg. In some instances, its presence is the result of the migration from food packaging manufactured from styrene-based polymers or copolymers. There is also evidence that styrene occurs in some foods as a natural constituent: it has been detected, sometimes at extremely high concentrations, in food products with no apparent source of contamination (TNO, 1992; MRI, 1992). In early Canadian studies of foods packaged in polystyrene, the concentration of styrene monomer in the food containers ranged from 809 to 3 019 mg/kg by weight. The mean content of styrene

monomer in foods ranged from low values in plain yogurt (trace to 13.0 μg/kg; detection limit = 0.73 μg/kg) to the highest values in sour cream (143.3 to 245.9 μg/kg; detection limit = 13.4 μg/kg) [Withey and Collins, 1978]. In a recent Canadian survey of a much wider range of foods, samples of 34 food groups (each a composite of individual food items, combined in approximate proportion to their consumption in the Nutrition Canada Survey), were collected from retail outlets in Windsor in 1992. Styrene was not detected in any of the 34 food groups (which together approximated an average Canadian diet) by purge-and-trap gas chromatography/mass spectrometry (detection limits were 1.0 μg/L for liquids and 0.005 μg/g [5 μg/kg] for solids) [ETL, 1992].

No data on concentrations of styrene in the breast milk of Canadian women were identified. Styrene was present, but not quantified, however, in all 8 samples of breast milk taken from women living in the urban areas of Bridgeville, Pennsylvania, Bayonne, New Jersey, Jersey City, New Jersey and Baton Rouge, Louisiana (Pellizzari *et al.*, 1982).

Tobacco smoke contributes to indoor air levels of styrene and the body burdens of smokers (Wallace *et al.*, 1986, 1987a). No studies of the styrene content of smoke from Canadian cigarettes were identified, but the U.S. Department of Health and Human Services (1989) reported that styrene was present in mainstream cigarette smoke in the amount of 10 μg/cigarette.

2.4 Kinetics and Metabolism

The toxicokinetics of styrene has been reviewed extensively (HSE, 1981; U.S. EPA, 1988; Bond, 1989). In rats exposed via the oral route, and in rats and humans exposed through inhalation, absorption of styrene is rapid and virtually complete. Dermal absorption is not expected to be an important route of exposure in non-occupational settings. In animals exposed by various routes, styrene is distributed initially to well-perfused organs (particularly the kidney, liver, pancreas and brain), and is then cleared rapidly. Subsequent accumulation in adipose tissue occurs in both animals and humans, but does not persist for extended periods. Styrene is transferred to offspring in animals and humans both transplacentally and via the milk of the mother.

Metabolism of styrene is extensive in both animals and humans, and is initially catalysed by microsomal NADPH-cytochrome P450-dependent monooxygenases, generating reactive epoxides. This step is saturable in rats at airborne concentrations of approximately 200 ppm (866 mg/m^3) or intraperitoneal doses of 250 mg/kg bw. The major epoxide, styrene-7,8-oxide, is subsequently hydrolysed to styrene glycol, which is further metabolised to mandelic and phenylglyoxylic acids, the principal urinary metabolites in both animals and man. The major site of styrene metabolism in a variety of species is the liver. Styrene-7,8-oxide has been detected at low levels in the blood of

humans exposed to styrene (Wigaeus *et al.*, 1983; Löf *et al.*, 1986a, 1986b), although recent preliminary findings (from *in vitro* studies in tissue samples from 5 individuals) indicate that humans have a lower capacity to form this compound, and also have a higher capacity to metabolize the epoxide, once formed, than either rats or mice (Mendrala *et al.*, 1993).

Metabolites of styrene are excreted rapidly and almost exclusively in urine in animals and humans exposed to low levels. With levels that saturate metabolism in animals, increased amounts of unchanged styrene are excreted in the expired air. Pharmacokinetic models, which have been developed on the basis of experiments with animals, have been used to predict the toxicokinetics of styrene and styrene-7,8-oxide in humans.

2.5 Effects-related Information

2.5.1 Experimental Animals and In Vitro

A wide range of effects has been reported in experimental animals following exposure to styrene. The emphasis in this summary is on those studies for which the lowest effect levels have been reported.

The acute toxicity of styrene is weak in experimental animals following inhalation or ingestion (U.S. EPA, 1988; Bond, 1989). In short-term or subchronic repeated-dose experiments, the effects that are evident at the lowest levels are those on neurological development following inhalation, and on the immune system following administration by the oral route. Thus, Kishi *et al.* (1992a, 1992b) reported that Wistar rat offspring exposed to airborne styrene *in utero* (60 ppm [260 mg/m^3] for 6 hours/day during days 7 to 21 of gestation) had significantly reduced pup weights at day 1, delayed development of righting reflex and auditory startle reflex, and nonsignificantly decreased levels of serotonin and its metabolite 5-hydroxy-indoleacetic acid (5-HT) in the cerebrum. Exposure to 293 ppm (1 270 mg/m^3) significantly reduced pup body weight and the levels of serotonin and 5-HT, and induced alterations in a wider range of behavioural measures. Shigeta *et al.* (1989) reported that the development of exploratory and avoidance behaviour, as well as the age at which developmental milestones (pinna detachment, incisor eruption) were achieved, was retarded in THA rats by exposure to 50 ppm (217 mg/m^3) styrene, 7 hours/day, 6 days/week from birth to 48 days of age. The same developmental milestones, but not performance in behavioural tests, were also affected at a concentration of 25 ppm (108 mg/m^3). (It is possible, however, that the neonates may not have been at a comparable stage of development at the start of the experiment, as differences in body weight between exposed and control groups were evident on the first day of exposure.) Exposure to 27 to 30 mg/kg bw/day styrene via the oral route for a period of 4 weeks was associated with increased mortality from an oncogenic

virus encephalomyocarditis and a rodent strain of malaria (there was also significantly increased infection from malaria at 18 mg/kg bw/day) [Dogra *et al.*, 1992], and cell-mediated, humoral, and macrophage functional responses were altered in mice exposed to as little as 20 mg/kg bw/day for 5 days (Dogra *et al.*, 1989). However, there has not been confirmation of these immunotoxic effects in longer-term studies by additional investigators.

With higher exposures, a wide range of effects has been observed in rodents exposed to styrene levels of between 150 and 450 ppm (650 to 1 950 mg/m^3) in short-term and subchronic studies, including glutathione depletion in lung and liver (Vainio *et al.*, 1979; Elovaara *et al.*, 1990), microsomal enzyme induction in liver and kidney (Sandell *et al.*, 1978; Vainio *et al.*, 1979), histopathological changes in the respiratory epithelium (Morisset *et al.*, 1979; Ohashi *et al.*, 1985, 1986) and liver (Vainio *et al.*, 1979), effects on the haematopoietic system (Seidel *et al.*, 1990), alterations in the levels of neurochemicals and in the cellular composition of the brain (Savolainen and Pfaffli, 1977; Rosengren and Haglid, 1989), and performance in behavioural testing (Kulig, 1988). In short-term and subchronic studies in which styrene was administered orally or intraperitoneally, exposure to between 100 and 450 mg/kg bw/day altered the activities of metabolizing enzymes in the liver, kidney, and brain of rats (Sandell *et al.*, 1978; Dixit *et al.*, 1982; Srivastava *et al.*, 1982; Das *et al.*, 1981, 1983), induced histopathological changes in the liver of rats and dogs (Quast *et al.*, 1979; Srivastava *et al.*, 1982), and affected several neurological end-points in rats, including levels of neurotransmitters in the brain (Husain *et al.*, 1985), dopaminergic function (Agrawal *et al.*, 1982; Zaidi *et al.*, 1985) and performance in behavioural tests (Zaidi *et al.*, 1985; Husain *et al.*, 1985). (Although Ohashi *et al.* [1985, 1986] reported that exposure to as little as 30 ppm [130 mg/m^3] of styrene for several weeks produced mild ultrastructural changes in the nasal mucosa of rats, the observed alterations were not clearly compound-related, and were of uncertain clinical significance. Similarly, Fujita *et al.* [1987] reported reductions in the activity and concentrations of δ-amino-levulinate dehydratase in the erythrocytes and bone marrow of rats following continuous exposure to 48 ppm [210 mg/m^3] styrene for 1 week; the clinical significance of these results is unclear, however, and there were no effects on body weight and liver weight, the only other end-points examined).

The carcinogenicity of styrene has been examined in rats exposed by various routes, and in studies in mice following oral administration. The following discussion is limited principally to those studies that involved an adequate number of animals exposed to styrene for a sufficient length of time. Even these studies have limitations that preclude firm conclusions being drawn with respect to the carcinogenicity of styrene.

Jersey *et al.* (1978) reported that in groups of 84 to 86 Sprague-Dawley rats of both sexes exposed to 600 and 1 000 ppm (2 600 and 4 330 mg/m^3) for 6 hours/day, 5 days/week for 78 to 89 weeks via inhalation, the incidence of leukaemias and lymphosarcomas combined was significantly increased in exposed females compared to historical controls, but not to their concurrent controls; however, it is currently considered inappropriate to combine leukaemias and lymphomas (McConnell *et al.*, 1986), and the incidences of the individual malignancies were not significantly increased. An increased incidence of mammary carcinomas in females was reported, but did not appear to be compound-related, as it was observed only at the low concentration. There were no significant compound-related increases in tumour incidence in males, although these may have been masked by high mortality from murine viral pneumonia in the control and high-dose groups (Jersey *et al.*, 1978).

In a somewhat smaller inhalation study of groups of 30 Sprague-Dawley rats of both sexes exposed to lower concentrations of styrene (up to 300 ppm, or 1 300 mg/m^3, 4 hours/day, 5 days/week for 52 weeks) [Conti *et al.*, 1988], there was an increase in the incidence of malignant mammary tumours in all groups of styrene-exposed female rats, but no clear dose-response relationship. It is not possible to assess whether these tumours were associated with exposure to styrene based on the information included in the report of this inadequately documented study, in which the results of a large number of studies with several compounds were summarized.

NCI (1979) investigated the carcinogenicity of styrene via the oral route in groups of 50 Fischer 344 rats of both sexes with long-term exposure to 500, 1 000 or 2 000 mg/kg bw/day, 5 days per week for 104 to 105 weeks. There were no significant differences in tumour incidence at any site between exposed and control rats. A distinct lack of neoplasia in the high-dose rats was attributed to the early mortality at this dose. The significance of this study is further limited by the small number of controls (20) used.

The incidence of lung tumours has been increased marginally in mice following administration of styrene by gavage in two studies. In one of these investigations (NCI, 1979), groups of 50 B6C3F$_1$ mice of each sex were exposed to 150 or 300 mg/kg bw styrene, 5 days/week for 78 weeks. There was a significant increase in the incidence of lung adenomas and carcinomas combined in the high-dose males when compared to the concurrent controls, but not to untreated historical controls. Interpretation of this study is limited by the small number (20) of concurrent controls. The authors questioned the significance of this increase, noting the unusual absence of these tumours in the concurrent controls; however, none was also observed in a larger group of 40 historical vehicle controls.

An increased incidence in lung adenomas and carcinomas combined was also reported by Ponomarkov and Tomatis (1978) in groups of 45 male and 39 female 0_{20} mice progeny exposed to styrene *in utero* (dams received 1 350 mg/kg bw by gavage on day 17 of gestation), and then by gavage to the same dose weekly for 16 weeks after weaning; this exposure is considered to have exceeded the maximum tolerated dose. The increase was significant in both sexes compared to vehicle controls, and in females compared to untreated controls. Lung tumours reportedly developed earlier in styrene-exposed mice, but it may be that exposed animals, many of which died early in the experiment, were simply being examined earlier than the controls. Interpretation of this experiment is also limited by the fact that the data were not analyzed by litter.

Forestomach papillomas and carcinomas have been consistently observed in rats and mice following oral exposure to styrene-7,8-oxide, the putative genotoxic and carcinogenic metabolite of styrene in mammals (Maltoni *et al.*, 1979; Ponomarkov *et al.*, 1984; Lijinsky, 1986; Conti *et al.*, 1988). The relevance of these findings to humans is uncertain, however; the neoplasms were accompanied by squamous cell hyperplasia and/or hyperkeratosis of the forestomach, suggesting that these tumours may have been associated with tissue damage at the high doses employed in these studies. Mechanistic studies of these neoplasia, including DNA-binding and cellular proliferation, were under way at the time of completion of this assessment (Science and Technology Task Group of the Styrene Information Research Center, 1991).

The genotoxicity of styrene has been examined in a number of *in vitro* and *in vivo* assays and has been recently reviewed by Barale (1991) and Preston (1990a, 1990b). In the absence of metabolic activation, styrene has not been genotoxic in *in vitro* assays for gene mutation (bacterial and mammalian systems), clastogenicity or DNA damage. (This contrasts with the clear genotoxic activity in these assays of the primary metabolite of styrene, styrene-7,8-oxide, and indicates that any genotoxic activity of styrene will be dependent upon appropriate metabolic activation.) With metabolic activation, styrene has been either weakly, or not, mutagenic, likely reflecting variations in the balance between the production and inactivation of metabolically activated species. Despite some inconsistency in results, styrene should be considered an *in vitro* clastogen capable of inducing chromosomal aberrations and micronuclei in mammalian-cell systems. In addition, styrene has been shown to induce sister chromatid exchanges (SCE) in Chinese hamster ovary cells in the presence of metabolic activation and to bind DNA and induce DNA repair in isolated rat hepatocytes.

In *in vivo* tests, styrene induced SCE and chromosomal aberrations in bone marrow cells, and SCE in splenocytes, regenerating liver cells and alveolar macrophages of mice following inhalation exposure. Intraperitoneal injection of styrene increased the levels of SCE and micronuclei in bone-marrow cells of mice, and of SCE in splenocytes of mice and rats. No conclusions can be drawn regarding the genotoxic

activity of styrene in mice following acute or subchronic oral administration, since both of the available studies were flawed (Loprieno *et al.*, 1978; Sbrana *et al.*, 1983). Styrene has also been weakly active in sperm morphology assays in rats and mice treated by intraperitoneal injection, supporting the conclusion that styrene is genotoxic *in vivo*.

In the most comprehensive reproduction study (Beliles *et al.*, 1985), the reproductive system of male rats was not affected by chronic exposure to 14 mg/kg bw/day styrene in drinking water, although in other studies, testicular histopathology and biochemistry, and sperm count, have been affected at higher doses; however, Beliles *et al.* (1985) observed that pup survival or weight was slightly reduced at some times in each of three generations exposed to styrene (250 ppm [mg/L] in drinking water [14 and 21 mg/kg bw/day for males and females, respectively]) over the lifespan. The no-observed-effect-level (NOEL) in this study was 125 mg/L in drinking water (7.7 and 12 mg/kg bw/day for males and females, respectively).

The results of most available studies do not indicate that styrene is a developmental toxicant at concentrations or doses less than those that are maternally toxic; however, in one study rat pups exposed to airborne styrene *in utero* had reduced body weights and slight alterations in behaviour and neurotransmitter levels in brain at airborne concentrations [60 and 293 ppm (260 and 1 300 mg/m^3) for 6 hours/day on days 7 to 21 of gestation] that did not affect the dams (Kishi *et al.*, 1992a, 1992b).

2.5.2 Humans

Irritation, prenarcotic symptoms, and altered coordination have been commonly reported in workers and volunteers exposed to between 10 and 100 ppm (43 to 433 mg/m^3) and more styrene in air. There are also indications of increased prevalence of abnormal EEG patterns, reduced peripheral nerve conduction velocity (especially in sensory nerves) and effects on the neuroendocrine system in workers exposed to atmospheric concentrations of 50 to 100 ppm (217 to 433 mg/m^3) styrene (Seppäläinen and Härkönen, 1976; Rosén *et al.*, 1978; Mutti *et al.*, 1984a; Cherry and Gautrin, 1990; Murata *et al.*, 1991). In neuropsychological studies, the principal observations are a slowing of reaction time, especially in workers who have been exposed for more than a few weeks to concentrations of styrene of 50 to 100 ppm (217 to 433 mg/m^3) [Gamberale *et al.*, 1976; Cherry *et al.*, 1980, 1981; Cherry and Gautrin, 1990]. More subtle effects, such as reductions in visuomotor accuracy and verbal learning skills, and subclinical effects on colour vision, appear to occur at lower concentrations (i.e., 25 to 50 ppm [108 to 217 mg/m^3]) in some studies (Härkonen, 1978; Mutti *et al.*, 1984b; Gobba *et al.*, 1991; Fallas *et al.*, 1992), although the extent of historical exposures and exposures to other substances is uncertain. The neurological effects observed are characteristic of occupational exposure to other

organic solvents such as toluene or white spirit, which does not involve lasting nerve damage, does not lead to progressive impairment of nervous system function and is generally reversible on cessation of exposure.

The potential carcinogenicity of styrene has been investigated in a number of historical cohort and case-control studies in populations exposed to styrene and related chemicals in the manufacture of styrene-butadiene rubber, styrene and/or polystyrene, or fibrous glass products. Mortality from cancers of the lymphatic and haematopoietic system has been of particular interest, based on an early report of a significantly elevated risk ratio for this family of malignancies (4 cases, RR = 6.2, 95% confidence interval (CI) 4.1 to 12.5) among workers in the synthetic rubber plant at a United States tire manufacturing factory (McMichael *et al.*, 1976).

In the most sensitive study, Matanoski *et al.* (1990) reported the mortality experience in a cohort of 12 110 male workers involved in styrene-butadiene polymer production for at least 1 year. The vital status was known for 96.6% of this cohort, who had an average duration of follow-up of 20.8 years. (In addition to styrene and butadiene, compounds to which workers were exposed would potentially have included thiocarbamates, diphenylamines, mercaptans, hydroquinones, extender oils and carbon black.) Mortality from the major causes of death (2 441 deaths in all) and for most cancer sites was generally lower than expected for the general population. Deaths from lymphopoietic cancers were not significantly elevated in the cohort as a whole (55 observed, Standardized Mortality Ratio (SMR) = 0.97, 95% CI 0.73 to 1.26), but occurred more frequently than expected among production workers (19 observed, SMR = 1.46, 95% CI 0.88 to 2.27), a difference due primarily to a significant excess in Black production workers (6 observed, SMR = 5.07, 95% CI 1.87 to 11.07). Significant excesses were observed in the subcategories of leukaemia in Black production workers and in other lymphatic cancers (non-Hodgkin's lymphoma and multiple myeloma) in production workers as a whole. The SMRs were not clearly related to either duration of employment or years since first employment. In a nested case-control study of 59 lymphopoietic cancer cases, there was a significantly increased risk of mortality from leukaemia associated with an index of cumulative exposure to butadiene (26 cases, odds ratio (OR) = 9.36, 95% CI 2.05 to 22.9), and a nonsignificant increase for styrene (OR 3.13, 95% CI = 0.84 to 11.2). There was a significant correlation between log cumulated exposure to butadiene and to styrene; however, based on conditional logistic regression analysis, only butadiene was associated with an increased risk of leukaemia (Matanoski *et al.*, 1989; Santos-Burgoa *et al.*, 1992).

For 2 756 workers in two styrene-butadiene rubber plants in the U.S., Meinhardt *et al.* (1978, 1982) reported that mortality for the cohort as a whole was similar to that for the U.S. general population. (In addition to styrene, the workers were also exposed to butadiene and benzene.) A slight excess of mortality was observed, however, for

cancers of the lymphatic and haematopoietic system (9 observed, SMR = 212, $0.05 < p < 0.10$), and, in the subset of this category, leukaemia and aleukaemia (5 observed, SMR = 278, $0.05 < p < 0.10$) in 600 workers employed during a period when "hot temperature batch polymerization" was used to produce styrene-butadiene rubber.

Bond *et al.* (1992) conducted a historical cohort study of the mortality of 2 904 male workers (99.6% traced, average duration of follow-up = 30.9 years) employed in the development and manufacture of styrene products at United States Dow Chemical plants. When mortality for the cohort (687 deaths in all) was compared to that of a reference group of Michigan-based Dow employees, there was a significant excess of multiple myeloma for the cohort (Observed:Expected (O:E) = 7:2.9, relative risk 2.45, 95% CI 1.07 to 5.65). There was a significant increase in mortality from lymphatic and haematopoietic cancer among workers exposed to an estimated 8-h time-weighted average (TWA) concentration of 1 to 4 ppm styrene and ethylbenzene (O:E = 12:5.1, SMR = 236, 95% CI 122 to 411), but this occurred primarily in workers with less than 5 years exposure. Most of these neoplasms occurred in workers involved in polymerization, colouring and extrusion, who would have been exposed to extrusion fumes, solvents (styrene, ethylbenzene, acrylonitrile) and colourants.

In a study of 622 workers in a styrene-production and polymerization plant in the U.K., among the 34 deaths from all causes, three deaths from non-Hodgkins lymphoma were reported, compared to 0.56 expected for the general population ($p = 0.02$), and one subject whose cause of death was reported as heart disease also had leukaemia (Hodgson and Jones, 1985). There was no apparent association between length of service in styrene-exposed jobs and the incidence of lymphatic and haematopoietic cancer. The extent of exposure to styrene and other chemicals is also unknown.

In two earlier studies of workers involved in the manufacture of styrene/polystyrene, there were only single deaths from individual lymphopoietic malignancies in a cohort of 560 workers (83 deaths in all) at a United States plant (Nicholson *et al.*, 1978), and in 1 960 employees (73 deaths in all) at a plant in the Federal Republic of Germany (Frentzel-Beyme *et al.*, 1978).

Some of the highest occupational exposures to styrene occur in jobs that involve the manufacture of glass-reinforced plastics; to date, however, insufficient time may have elapsed for the development of cancers in studies in this relatively new industry. Okun *et al.* (1985) reported that there were no significant excesses of death (176 in total) from any specific cause in workers with either "high" or "minimal" exposure, and no deaths from any malignant neoplasm of the lymphatic or haematopoietic system, in a

cohort of 5 021 workers at two boat-building facilities in the United States; however, the average length of follow-up was only 8.2 years, and the power of the study to detect a two-fold excess risk was only 14% for leukaemia and 15% for lymphoma.

In a more extensive historical cohort study of workers exposed to styrene in the manufacture of glass-reinforced plastics, Coggon *et al.* (1987) examined the mortality of 7 949 men and women (96% traced) employed at 8 British companies. At the 7 companies where follow-up was reasonably complete, the overall mortality (637 deaths) was less than that for the general population of the U.K. Deaths from lymphatic and haematopoietic cancers occurred less frequently than expected (O:E = 6:14.9; there were, in addition, 8 cases who died from other causes or were alive at the end of follow-up), and only 1 death from this family of neoplasms occurred in a subject with high exposure. The authors cautioned that the study had only limited power to detect cancer with a long latency.

Wong (1990) carried out an historical cohort study of 15 908 men and women who had potentially been exposed to styrene in the reinforced plastics industry. There was no significant excess in mortality from any cause (452 deaths). When the cohort was divided into groups according to their estimated exposure to styrene (separate analyses for max TWA > 20 ppm (> 87 mg/m^3) vs < 20 ppm, or average TWA > 12 ppm (> 52 mg/m^3) vs < 12 ppm), the incidence of leukaemia and aleukaemia was higher in the high-exposure group than in the low-exposure group, but the difference between the two groups was not statistically significant, and was based on only 5 deaths in all. Excesses in respiratory cancers were observed in some subsets of the cohort, but in a nested case-control study of 40 respiratory-cancer cases, there was a significant association with smoking, and not with manufacturing-process type or direct exposure to styrene. It should be noted that there was a high loss to follow-up (16.1%), the number of observed deaths from several causes was quite small, the average duration of follow-up was short (7.7 years), and the participants were quite young and were employed for only a short while. The results of a recent update of this study, sponsored by the Styrene Information and Research Center, were not available at the time of completion of this assessment.

In some community-based and nested case-control studies, nonsignificant excesses of various lymphatic and haematopoietic cancers have been associated with exposure to styrene (Flodin *et al.*, 1986; Ott *et al.*, 1989; Siemiatycki, 1991), although these results were all based on very small numbers of cases for any specific type of malignancy (i.e., between 1 and 4).

Cytogenetic studies of workers exposed to styrene and related chemicals have been reviewed by Preston (1990b) and Barale (1991). The available data indicate that exposure to high levels of styrene (approximately 50 to 100 ppm (217 to 433 mg/m^3) and other chemicals in the workplace may be associated with chromosomal alterations

(most often aberrations) in the peripheral lymphocytes of exposed workers. There are also three independent reports that the prevalence of micronuclei is increased in workers exposed to about 10 to 25 ppm styrene (43 to 108 mg/m^3) [Högstedt *et al.*, 1983; Nordenson and Beckman, 1984; Brenner *et al.*, 1991]. A number of other studies have failed to find evidence of cytogenetic effects at these levels. All of the available studies are limited by one or more of the following factors: small worker populations, uncertainty with respect to the relation between current exposure and exposure at the time when the genetic damage may have occurred (this may account for the frequent lack of dose-response), the high and variable background levels of chromosome aberrations (de Jong *et al.*, 1988) and other potentially confounding factors (such as smoking) that may have contributed to observed effects.

In well-documented studies in the United States and in Finland (Härkönen and Holmberg, 1982; Lemasters *et al.*, 1985), there was no association between exposure to styrene and menstrual disorders, in contrast to the results of earlier Russian studies, which were inadequately reported (Brown, 1991). An increased prevalence of abnormal sperm was reported in workers exposed to styrene (Jelnes, 1988), although these results were based on a small number of subjects, an inadequate number of samples per worker, and questionable controls (i.e., from an infertility clinic). There was no significant association of paternal exposure to styrene and reproductive outcome in a case-control study of men exposed to solvents in the workplace (Taskinen *et al.*, 1989), but the numbers of styrene-exposed cases were small. A slightly increased risk of spontaneous abortion was reported in Canadian women employed in the processing of polystyrene, but this observation was based on small numbers of cases whose exposures were poorly characterized (McDonald *et al.*, 1988). Initial indications that exposure to styrene was associated with CNS defects and spontaneous abortion in Finnish workers (Holmberg, 1977; Hemminki *et al.*, 1980) have not been confirmed in either follow-up or independent studies (Holmberg, 1979; Härkönen and Holmberg, 1982; Holmberg *et al.*, 1982; Härkönen *et al.*, 1984; Hemminki *et al.*, 1984; Lindbohm *et al.*, 1985; Holmberg *et al.*, 1986).

A number of reports indicate that exposure to styrene in the workplace is associated with effects on the liver, kidney, blood system, and lung (reviewed in U.S. EPA, 1988). There is no clear evidence from these studies, however, that styrene has adverse effects on these organs; the effects reported are generally mild and are often not consistent among studies, and possible confounders have not generally been taken into account.

2.5.3 Ecotoxicology

The information that was identified on the toxicity of styrene to aquatic organisms was restricted to acute studies for a number of trophic levels from bacteria and algae through to fish. All studies were conducted under open and static conditions, and the results were expressed in terms of nominal or initial concentrations. Because of its

high volatility, styrene disappears rapidly from open systems and, therefore, the concentrations at which effects occurred would have been considerably less than those reported. Studies on the effects of chronic exposure to styrene on aquatic organisms, amphibians and terrestrial wildlife have not been identified.

The lowest concentration of styrene reported to cause an adverse effect in microorganisms was 5.4 mg/L (a 5-min EC_{50} for reduction of light emitted) for the bacterium *Photobacterium phosphoreum* (Qureshi *et al.*, 1982). Levels at which adverse effects were observed in algae, bacteria and protozoan species exposed to styrene in solution ranged between 67 and > 256 mg/L (Bringmann and Kühn, 1978, 1980; Bringmann *et al.*, 1980).

Acute 24-h LC_{50} values identified for rainbow trout (*Oncorhynchus mykiss*), and the marine sheepshead minnow (*Cyprinodon variegatus*), were 2.5 mg/L (Qureshi *et al.*, 1982) and 9.1 mg/L (Heitmuller *et al.*, 1981), respectively. Acute 24-96-h LC_{50} values for five other species of fish ranged from 25 mg/L for the goldfish (*Carassius auratus*) [Jensen, 1978] to 74.83 mg/L for the guppy (*Poecilia reticulata*) [Pickering and Henderson, 1966].

The lowest no-observed-effect-concentration (NOEC) identified for mortality in aquatic invertebrates was < 6.8 mg/L for daphnids (LeBlanc, 1980); the 48-h LC_{50} was reported to be 23 mg/L. In a study with the amphipod (*Pontoporeia affinis*), exposure to concentrations of styrene of between 35 and 45 mg/L caused an immediate cessation of swimming that lasted several days (Lindström and Lindström, 1980).

Only one study concerning the phytotoxicity of styrene to a terrestrial plant has been identified. Linnainmaa *et al.* (1978) reported that chromosomal abnormalities were observed in root tip cells of onion (*Allium cepa*), following exposure to 450 mg/L styrene or styrene oxide in distilled water.

3.0 Assessment of "Toxic" under CEPA

3.1 CEPA 11(*a*): Environment

Styrene is produced and used in large quantities in Canada, which results in its release to the environment, primarily the atmosphere. Once in the environment, styrene does not persist in air, water or soil. Measurable concentrations are found in ambient air in Canada and in some industrial and municipal effluents. Much of the data that were identified on the concentrations of styrene in other media, including surface water and biota, are limited primarily to those generated in the late 1970s and early 1980s.

Estimation of exposure based on these older data suggests that styrene in food and water may have contributed significantly to the overall intake of aquatic-based wildlife, such as mink, to the substance at that time. Because of the lack of recent data on concentrations in these media, their current contribution to overall exposure cannot be evaluated. It was, however, possible to estimate the intake of styrene from air. The lowest lowest-observed-effect-level (LOEL) for meaningful effects in laboratory animals was 60 ppm (260 mg/m^3) air, in a study by Kishi *et al.* (1992a, 1992b), in which female rats were exposed to styrene through inhalation during pregnancy. In offspring, body weight was significantly reduced and reflex responses were abnormal. Based on a net factor of 100 (10 to account for interspecies differences and to extrapolate from the laboratory to the field, and 10 to extrapolate a NOEL from a LOEL), the effects threshold for wild mammals was estimated to be 2.6 mg/m^3. The highest concentration measured at Walpole Island (3.2 µg/m^3), a rural site located near an industrial region, is over 800 times less than this threshold.

The toxicological data identified for aquatic biota were limited to acute studies for various trophic levels. In each case, the study protocols did not adequately address the volatility of styrene and, therefore, the actual concentrations that caused effects were much lower than reported.

The data that were identified on the extent of exposure of most biota to styrene, and on the effects that may result, were insufficient to conclude whether styrene is 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

Although styrene is volatile at tropospheric temperatures and absorbs infrared radiation in wavelengths ranging from 7 to 13 µm (a range associated with trace gas warming of the troposphere), this substance is removed from the atmosphere by

photooxidation (half-life ≤ 9 hours), resulting in low steady-state concentrations in the atmosphere (Canadian urban air average = 0.59 μg/m^3). As such, styrene is not expected to contribute to global warming or depletion of stratospheric ozone.

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

3.3 CEPA 11(*c*): Human Life or Health

3.3.1 General Population Exposures

Estimated daily intakes of styrene from various media, for different age groups of the Canadian general population, are presented in Table 2. Indoor air contributes a substantial fraction of exposure for non-smokers in the general population (estimated daily intake for various age classes ranges from 0.07 to 0.10 μg/kg bw/day). The estimated daily intake of styrene from ambient air ranges from 0.004 to 0.17 μg/kg bw/day for various age classes. Intakes of styrene from drinking water and from soil are estimated to be negligible, ranging from < 0.001 to 0.03 μg/kg bw/day and from < 0.000003 to < 0.00005 μg/kg bw/day, respectively. Food may also make a substantial contribution to the intake of styrene by the general population, although the available data on styrene levels in the Canadian food supply are limited by analytical sensitivity. Based on the limits of detection in a 1992 survey, in which styrene was not detected in samples of 34 food groups purchased in Windsor, Ontario (ETL, 1992), the estimated intakes of styrene via food range from < 0.11 to < 0.58 μg/kg bw/day for various age classes. These estimated intakes in food are obviously uncertain, but are within the range of estimates based on other data, as noted in the footnotes to Table 2.

Based on the above estimates, the total estimated daily intakes for the non-smoking general population range from < 0.20 to < 0.79 μg/kg bw/day overall. Estimated intakes are maximum values, since the intakes from food and soil are upper limits for potential exposure from these media. On the other hand, the mean concentrations in indoor air reported from limited Canadian and extensive United States surveys of homes in urban areas are severalfold higher than those used here.

The estimated daily intake of styrene from cigarettes ranges from 2.86 to 3.51 μg/kg bw/day for adults and teens, respectively, based on data on amounts of styrene in mainstream cigarette smoke in a United States report (U.S. Department of Health and Human Services, 1989).

Table 2
Estimated Daily Intake (µg/kg bw) of Styrene by Canadians for Various Media

	Estimated Intake (µg/kg bw/day)				
Medium	0-6 mo[a]	7 mo-4 yr[b]	5-11 yr[c]	12-19 yr[d]	20-70 yr[e]
Air Ambient[f]	0.004-0.11	0.006-0.15	0.007-0.17	0.006-0.14	0.005-0.13
Indoor[g]	0.07	0.09	0.10	0.09	0.08
Drinking Water[h]	< 0.005-0.03	< 0.003-0.02	< 0.002-0.008	< 0.001-0.006	< 0.001-0.005
Soil[i]	< 0.00005	< 0.00004	< 0.00001	< 0.000004	< 0.000003
Food[j]	< 0.58	< 0.53	< 0.30	< 0.15	< 0.11
Total Intake (not including cigarettes)	< 0.66-< 0.79	< 0.63-< 0.79	< 0.41-< 0.58	< 0.25-< 0.39	< 0.20-< 0.33
Intake by cigarette smokers[k]	–	–	–	3.51	2.86

a. Assumed to weigh 7 kg, breathe 2 m^3 of air per day, drink 0.75 L of water per day and ingest 35 mg soil per day (EHD, 1992).
b. Assumed to weigh 13 kg, breathe 5 m^3 of air per day, drink 0.8 L of water per day and ingest 50 mg soil per day (EHD, 1992).
c. Assumed to weigh 27 kg, breathe 12 m^3 of air per day, drink 0.9 L of water per day and ingest 35 mg soil per day (EHD, 1992).
d. Assumed to weigh 57 kg, breathe 21 m^3 of air per day, drink 1.3 L of water per day and ingest 20 mg soil per day (EHD, 1992).
e. Assumed to weigh 70 kg, breathe 23 m^3 of air per day, drink 1.5 L of water per day and ingest 20 mg soil per day (EHD, 1992).
f. Based on range of mean concentrations of styrene reported in 24-h samples of ambient air from 18 Canadian sites in 5 provinces (0.09 to 2.35 µg/m^3) [Dann, 1990], assuming 4 of 24 hours are spent outdoors daily (EHD, 1992).
g. Based on mean concentration of styrene (0.28 µg/m^3) reported in a national pilot study of indoor air of 757 homes across Canada (Concord Environmental, 1992), assuming 20 of 24 hours are spent indoors daily (EHD, 1992). The average concentration determined in this study is similar to or slightly lower than those from most other more limited Canadian and from extensive U.S. studies.
h. Based on range of mean concentrations of styrene (< 0.050-0.250 µg/L) in treated water from 80 drinking water supplies in Ontario's 1990 Drinking Water Surveillance Program (Lachmaniuk, 1991). Findings were similar in a survey from Alberta, in which styrene was detected at only trace levels in one of 1 081 samples from 220 locations (Halina, 1992).
i. Based on analysis of a limited number of samples of urban soils removed from point sources, in Port Credit and Oakville/Burlington, Ontario, in which the soils analyzed contained less than 10 µg/kg (Golder Associates, 1987).
j. Based on a 1992 survey in Windsor, Ontario, in which styrene was not detected in retail samples of 34 food groups (each a composite of individual food items, combined in proportion to their consumption by the Canadian general population) [ETL, 1992]. Limits of detection were 0.005 and 0.001 µg/g for solid and liquid foods, respectively; estimates were made by assuming that the food groups contained styrene at less than the limit of detection. These estimated intakes are within the range of those based on monitoring of raw agricultural commodities in the U.S. (MRI, 1992), assuming that the styrene levels in specific food items in this survey were representative of their food groups as a whole (0.026 to 0.132 µg/kg bw/day), of foods packaged in styrene-based polymers and copolymers in the U.K. (average and maximum of 1 µg/day and 4 µg/day, respectively [0.014 to 0.057 µg/kg bw/day for a 70 kg person]) [MAFF, 1983], and on modelling of migration of styrene monomer from styrene-based polymers and copolymers in the U.S. (9.1 µg/day [or 0.15 µg/kg bw/day for a 60 kg adult]) [Ad Hoc Styrene Migration Task Group, 1992].
k. Based on the styrene content in the mainstream cigarette smoke (10 µg/cigarette) from a U.S. report (U.S. Department of Health and Human Services, 1989). Approximately 20 cigarettes per day are smoked by Canadians aged 15 years or older as of 1990 (Kaiserman, 1992).

3.3.2 *Effects*

Based on available data, carcinogenicity and heritable mutations are potentially the most sensitive end-points for assessment of "toxic" for styrene under CEPA. The weight of evidence for the carcinogenicity and potential to induce heritable mutations of styrene has been assessed, therefore, on the basis of the classification schemes developed for this purpose (EHD, 1992).

The results of chronic studies in rodents exposed to styrene provide only limited evidence that styrene is carcinogenic. Borderline increases in the combined incidence of leukaemias and lymphosarcomas have been observed in female Sprague-Dawley rats following inhalation (Jersey *et al.*, 1978), although it is currently considered inappropriate to combine these tumour types (McConnell, 1986). An increase in malignant mammary tumours occurred in female Sprague-Dawley rats exposed to styrene by inhalation; however, it was not dose-related and its relevance to exposure to styrene could not be assessed, owing to inadequate documentation of non-neoplastic effects in this study (Conti *et al.*, 1988). There have also been two reports of marginal increases in lung tumours in male $B6C3F_1$ mice exposed to styrene orally (NCI, 1979) and in both sexes of O_{20} mice with combined *in utero* and oral exposure (Ponomarkov and Tomatis, 1978).

There is consistent evidence (observed in two studies), therefore, only for small increases in lung tumours in mice associated with exposure to styrene. It should be noted, however, that there are limitations in all of the studies conducted to date that complicate the assessment of the weight of evidence of carcinogenicity. For example, in the NCI (1979) bioassay in $B6C3F_1$ mice, there was an apparent deficit in the incidence of lung tumours in the small concurrent control group, in which no lung tumours were observed, and the increase in the high-dose group was within the range observed for these tumours in historical controls. The study in O_{20} mice by Ponomarkov and Tomatis (1978) is also limited in that only a single-dose level was administered and lung tumours also occurred at relatively high frequencies in controls. Increases in the incidences of other types of tumours have not been consistently observed and have been marginal, even at relatively high exposures.

In epidemiological studies conducted to date, mortality from lymphatic and haematopoietic cancers has been significantly increased in some studies of workers from several industries with mixed exposures to styrene and other chemicals (i.e., those manufacturing styrene-butadiene rubber, styrene/polystyrene, and fibrous glass products). In the most sensitive study conducted to date, there were small but significant excesses of mortality from several lymphopoietic malignancies in styrene-butadiene copolymer industry production workers (Matanoski *et al.*, 1990). In a follow-up nested case-control study in which exposure to styrene and butadiene was ascertained, multivariate analysis indicated that there was excess leukaemia risk

related to butadiene, whereas the increase for styrene was not significant. There was little evidence of excess risk of other lymphopoietic cancers (Matanoski *et al.*, 1989; Santos-Burgoa *et al.*, 1992). Small increases in mortality from lymphatic and haematopoietic cancers have also been reported in studies of workers from a number of other cohorts (McMichael *et al.*, 1976; Meinhardt *et al.*, 1982; Hodgson and Jones, 1985; Bond *et al.*, 1992), although most of these reports have been based on very small numbers of deaths. In some case-control studies, nonsignificant excesses of various lymphatic and haematopoietic cancers have been associated with exposure to styrene (Flodin *et al.*, 1986; Ott *et al.*, 1989; Siemiatycki, 1991), although these observations were all based on very small numbers of cases (i.e., between 1 and 4) for any specific type of malignancy.

The results of several earlier epidemiological studies that did not reveal a significant excess of these neoplasms in workers exposed to styrene (Nicholson *et al.*, 1978; Frentzel-Beyme *et al.*, 1978; Okun *et al.*, 1985) do not contribute to the weight of evidence, as they were seriously limited by one or more of very small numbers of subjects/deaths, inadequate reporting or the passage of insufficient time since exposure to styrene. Even in more powerful studies of workers with relatively high exposures (Coggon *et al.*, 1987; Wong, 1990), in which significant excesses of mortality from these neoplasms have not been identified, insufficient time may have elapsed for their development. In the cohort studied by Wong (1990), however, the mortality from leukaemia and aleukaemia was increased, although not significantly, in groups of workers with relatively high exposure to styrene, but not in those with lower exposure. This observation, in the largest cohort from an industry where exposures would have been relatively high, is suggestive of a dose-response relationship in the association between exposure to styrene and deaths from these malignancies. The results of a recent update of this study were not available at the time of completion of this assessment.

In most cases in these studies, mortality due to these cancers has not been related to either the duration or intensity of exposure (Hodgson and Jones, 1985; Coggon *et al.*, 1987; Matanoski *et al.*, 1990; Bond *et al.*, 1992). With the exception of some recent studies in the fibrous glass industry, however, exposures have generally been poorly characterized, and historical exposures, particularly in the styrene/polystyrene and styrene-butadiene industries, are unknown.

It could be argued that the lack of consistency in the subtypes of lymphatic and haematopoietic cancers that are increased does not support a causative role for styrene in their development; however, because these neoplasms all arise from cells that are derived from a common multipotential progenitor cell in the bone marrow, it is possible that a carcinogenic agent that affected this tissue could give rise to more than one type of lymphatic and/or haematopoietic cancer.

Interpretation of all of the available epidemiological studies is complicated by the fact that, in each case, there were concomitant exposures to a number of other substances, although styrene was the principal common agent to which workers were exposed in the variety of industries studied (styrene-butadiene rubber, styrene/polystyrene, and fibrous glass products). In particular, the frequent concomitant exposure to benzene (a leukaemogen) is problematic, and Matanoski *et al.* (1989; Santos-Burgoa *et al.*, 1992) reported that an observed increase in leukaemia was significantly associated with exposure to butadiene, but not with styrene. Largely as a consequence of these concurrent exposures, and in combination with the weakness of the associations and the uncertainties concerning the lack of specificity and of a dose-response relationship, the evidence that exposure to styrene has caused the observed increases in mortality from lymphatic and haematopoietic cancers in these populations of workers is considered to be limited.

The weight of evidence indicates that styrene is genotoxic in animals following metabolic activation. Thus, the results of short-term tests (Section 2.5.1) indicate that, following metabolic activation, styrene is an *in vitro* clastogen capable of inducing chromosomal aberrations and micronuclei in mammalian test systems. The observed ability of styrene to bind to DNA and to induce SCE and DNA single-strand breaks supports the conclusion that styrene is genotoxic *in vitro*. In *in vivo* tests, styrene has induced SCE and chromosomal aberrations in mice following inhalation, and was clastogenic following intraperitoneal injection to mice and rats.

The weight of evidence in cytogenetic studies of workers exposed to styrene and other compounds (Section 2.5.2) indicates that exposure to high levels (i.e., approximately 50 to 100 ppm [217 to 433 mg/m^3]) may be associated with chromosomal abnormalities (most often aberrations) in the peripheral lymphocytes of exposed workers. There is also some limited indication that exposures to concentrations in the range of 10 to 25 ppm (43 to 108 mg/m^3) are able to induce chromosomal effects [micronuclei]. (It should be noted, however, that there are inconsistencies in the results of the available studies, probably attributable to such limitations as small population size, uncertainty with respect to current and historical exposures, the high and variable background levels of chromosomal aberrations or inadequate control for potential clastogenic effects of smoking and exposure to other chemicals.)

There is, therefore, only limited evidence of the carcinogenicity of styrene to both animals and humans; however, there are limitations of all of the epidemiological studies and carcinogenesis bioassays in animal species conducted to date, which may have contributed to a lack of sensitivity of these investigations to detect increases in tumour incidence. Moreover, the weight of the available evidence from *in vitro* and *in vivo* investigations in experimental animals indicates that styrene is genotoxic following metabolic activation. On the other hand, limited available data indicate that humans may be less sensitive to the carcinogenic and genotoxic effects of styrene than

experimental animals, owing to interspecies differences in metabolism and detoxification of the putatively toxic metabolite. On the basis of *in vitro* studies of tissue from 5 human subjects, it appears that humans form less styrene-7,8-oxide, and hydrolyze it more quickly than rats and mice, the species in which the carcinogenesis and genotoxicity assays have been conducted (Mendrala *et al.*, 1993). Styrene-7,8-oxide has been detected, however, at low levels in the blood of humans exposed to styrene (Wigaeus *et al.*, 1983; Löf *et al.*, 1986a, 1986b), and there is some (albeit weak and inconsistent) evidence of the carcinogenicity and clastogenicity of styrene in occupationally exposed populations. On this basis, styrene has been classified in Group III ("possibly carcinogenic to humans") of the classification scheme for carcinogenicity developed for the determination of "toxic" under CEPA (EHD, 1992).

On the basis of the data summarized above, there is sufficient evidence of the genotoxicity of styrene to somatic cells in animal species; evidence in humans is suggestive. There is also evidence from studies in animals that germ cells are exposed *in vivo*, based on the observed styrene-induced effects on testicular histopathology and biochemistry and on sperm count in rodents exposed by the oral route (Section 2.5.1). An increased frequency of sperm head shape abnormalities in workers exposed to styrene at a reinforced plastics factory in an inadequately designed study (Jelnes, 1988) suggests that this may also be the case in humans. On this basis, styrene has also been classified in Group III ("possible human germ cell mutagens") of the classification scheme developed for mutagenicity in germ cells under CEPA (EHD, 1992).

For compounds classified in Group III of the classification schemes for carcinogenicity and heritable mutations developed for assessment of "toxic" under paragraph 11(*c*) of CEPA (EHD, 1992), in most cases, a tolerable daily intake (TDI) is derived on the basis of a no- or lowest-observed-(adverse)-effect-level (NO(A)EL or LO(A)EL) in humans or animal species (by the most relevant route of exposure) divided by an uncertainty factor.

Owing to limitations of the available data on concentrations in the general environment, the principal route of exposure to styrene for the general population in Canada is not clear (Section 3.3.1). Ambient and indoor air are estimated to contribute a substantial portion of the total daily intake of styrene for all age classes, but the limited available information suggests that intake via food may also contribute a substantial amount of the total exposure, although intake in food has been overestimated in this assessment due to the need to rely on detection limits for calculation of intakes from this medium. (Styrene was not detected in foodstuffs in Canada in the survey (ETL, 1992) on which estimated intake from food is based.) Therefore, TDIs have been developed for both oral and inhalation exposures, for comparison to the estimated intakes derived in Section 3.3.1.

Although workers are exposed to styrene primarily by inhalation, the available data on non-neoplastic effects (principally neurological) in human populations are considered to be inadequate to serve as the basis for the development of a TDI, due to such factors as the lack of precise exposure data, the small numbers of subjects in many studies and simultaneous exposures to other chemicals. The available clinical studies of neurological effects are also considered inadequate to serve as the basis for development of a TDI, because they are limited to short-term investigations of neurological and behavioural effects in very small numbers of subjects. It should be noted, however, that a TDI derived on the basis of neurotoxic effects in cross-sectional epidemiological studies and clinical studies in human volunteers would not vary greatly from that derived below on the basis of studies in animal species.

The available data, although limited, indicate that neurological development is among the most sensitive of end-points to the effects of styrene exposure. Kishi *et al.* (1992a) reported that the offspring of Wistar rats exposed to 60 and 293 ppm (260 and 1 270 mg/m^3) styrene for 6 h/day during days 7 to 21 of gestation had significantly lower body weights at day 1 of age at both concentrations. In addition, the levels of serotonin and 5-hydroxytryptamine (5-HT) were reduced in the cerebrum of the pups at both concentrations, although this reduction was not statistically significant at 60 ppm. Neither dose significantly affected maternal body weight. These researchers also conducted behavioural tests on the pups, and reported (the results were only available in an abstract at the time of completion of this assessment) that exposure to 60 ppm (260 mg/m^3) styrene during gestation delayed the development of righting reflex and auditory startle reflex, while exposure to 293 ppm (1 270 mg/m^3) induced alterations in a wider range of behavioural measures (Kishi *et al.*, 1992b). Another group of Japanese researchers also reported that the timing of developmental milestones (pinna detachment, incisor eruption) was delayed, and exploratory and avoidance behaviour altered, in rat pups exposed post-natally (7 h/day, 6 days/week, from birth to 48 days of age) to 25 ppm (108 mg/m^3) and 50 ppm (217 mg/m^3) styrene, respectively (Shigeta *et al.*, 1989). [These authors observed, however, that pup body weight was reduced on the first day of exposure, suggesting that the neonates may not have been at a comparable stage of development at the start of the experiment.]

Similar neurotoxic effects have been observed in rodents following subchronic exposure to higher levels of styrene (i.e., approximately 300 ppm [1 299 mg/m^3]), including alterations in the cellular composition of the brain (Rosengren and Haglid, 1989) and in brain chemistry (Savolainen and Pfaffli, 1977), and decrements in performance in visual discrimination tests (Kulig, 1988). In addition, the numerous reports of neurophysiological and neurobehavioural effects in volunteers and workers exposed to styrene (Section 2.5.2) suggest that studies of neurological end-points in animals exposed to styrene are an appropriate model for assessing potential risks to humans. A range of other non-genotoxic effects has been observed in rodents following subchronic exposure to approximately 300 ppm (1 299 mg/m^3) styrene,

including glutathione depletion in the liver and lung (Vainio *et al.*, 1979), histopathological alterations in the bronchiolar epithelium (Morisset *et al.*, 1979) and effects on the haematopoietic system (Seidel *et al.*, 1990).

Thus, the lowest reported levels inducing meaningful effects fall within a similar range; indeed, there is no clearly superior critical study, and TDIs derived on the basis of the lowest effect levels from several studies reported above would be similar. For this assessment, the study by Kishi *et al.* (1992a, 1992b) has been selected for the derivation of a TDI, since it leads to the most conservative value and since observed effects included both body weight changes and manifestations of neurotoxicity (including biochemical and behavioural effects). Thus, the lowest LOEL for neurotoxic (and other) effects in animals following inhalation of styrene in an adequately conducted study is 60 ppm (260 mg/m^3) in Wistar rats exposed to the compound *in utero* (Kishi *et al.*, 1992a, 1992b). The TDI for inhalation exposure is therefore derived as follows:

$$\text{TDI} = \frac{260 \text{ mg/m}^3 \times 0.11 \text{ m3/day} \times 6/24}{0.35 \text{ kg} \times 500}$$

$$= 0.041 \text{ mg/kg bw/day}$$

$$= 41 \text{ µg/kg bw/day}$$

where:

- 260 mg/m^3 is the LOEL for effects on body weight, the results of behavioural testing, and neurotransmitter levels (the latter not statistically significant) in the cerebrum of rat pups exposed to styrene on days 7 to 21 of gestation in the study by Kishi *et al.* (1992a, 1992b), which leads to development of the most conservative TDI;
- 0.11 m^3/day is the assumed volume of air inhaled daily by rats (EHD, 1992);
- 0.35 kg is the assumed body weight of a rat (EHD, 1992);
- 6/24 is the conversion of 6 h/day to continuous exposure; and
- 500 is the uncertainty factor (× 5 for use of a LOEL (the effects observed at this concentration were not clearly adverse); × 10 for interspecies variation, × 10 for intraspecies variation). An additional factor for limited evidence of carcinogenicity was not incorporated since the observed effects in the critical study are not related to carcinogenesis and occur at concentrations considerably less than those that induce small increases in tumour incidence. Limited available data also indicate that humans form less of the putative toxic metabolite, styrene-7,8-oxide, and hydrolyze it more quickly than experimental animals; however, available data were

insufficient to take these differences into account in the development of the uncertainty factor, and the relevance of this metabolite to developmental and neurotoxic effects is not clear.

The most suitable study on which to base a TDI for the oral route of exposure is that conducted by Beliles *et al.* (1985), in which exposure of Sprague-Dawley rats to styrene in drinking water at 250 mg/L, but not 125 mg/L, over three generations, was embryo/foetotoxic. (Based on levels of styrene in the water, the mean doses estimated by the authors in a parallel chronic study, in which the exposure regimen was similar, were 21 and 12 mg/kg bw/day, respectively, in females.) The specific effects observed (reduced gestational survival, pup survival, or pup body weight) differed across generations, but in all instances were observed at the higher dose only. (A variety of other effects, including enzyme induction, histological changes in the liver or testes, and neurochemical or behavioural alterations, have been observed in animals following subchronic exposure to styrene, but at considerably higher doses, i.e., between 200 and 500 mg/kg bw/day [Section 2.5.1]). In addition to yielding the lowest LOAEL among the available studies, the study by Beliles *et al.* (1985) is also the one in which the exposure regimen is most relevant to humans, in that it included transplacental and lactational exposures. (Transfer of styrene across the placenta has been shown to occur in experiments with animals [Section 2.4], and the compound has been detected in the breast milk of women in the United States [Section 2.3.2].)

The lowest NOAEL for non-neoplastic effects in animals following oral exposure in an adequately conducted study is 12 mg/kg bw/day for reproductive effects in a three-generation study in Sprague-Dawley rats (Beliles *et al.*, 1985). The TDI for oral exposure is, therefore, derived as follows:

$$\text{TDI} = \frac{12 \text{ mg/kg bw/day}}{100}$$

$$= 0.12 \text{ mg/kg bw/day}$$

$$= 120 \text{ µg/kg bw/day}$$

where:

- 12 mg/kg bw/day is the NOAEL for reproductive effects (decreased gestational survival, pup survival, pup weight at the next highest dose) in rats exposed to styrene in drinking water in the three-generation study by Beliles *et al.* (1985); and
- 100 is the uncertainty factor (× 10 for interspecies variation, × 10 for intraspecies variation). An additional factor for limited evidence of carcinogenicity was not incorporated since the observed effects in the critical study are not related to carcinogenesis and occur at concentrations considerably less than those which induce small increases in tumour incidence. Limited available data also indicate that humans form less of the putative toxic metabolite, styrene-7,8-oxide, and hydrolyze

it more quickly than experimental animals; however, available data were insufficient to take these differences into account in the development of the uncertainty factor and the relevance of this metabolite to effects on reproduction is not clear.

The estimated total average daily intake of styrene for various age groups in the Canadian general population ranges from < 0.20 to < 0.79 µg/kg bw/day overall. These estimates are from > 50- to > 200-fold less than the TDI derived above, based on inhalation studies in experimental animals exposed *in utero*, and from > 150- to > 600-fold less than the TDI derived from studies in which animals were exposed to styrene over 3 generations by the oral route. In addition, it should be noted that, due to the need to rely on detection limits for calculation of intakes from food, intake from this medium has been overestimated.

On the basis of the available data, it has been concluded that concentrations of styrene present in the Canadian environment do not constitute a danger in Canada to human life or health.

3.4 Conclusion

It has been concluded that the available information is insufficient to determine whether styrene is entering the environment in quantities or under conditions that may be harmful to the environment. It has, however, been concluded that styrene is not entering the environment in quantities or under conditions 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

It is recommended that additional data be obtained on:

(i) the quantities of styrene released to the environment from the production, use and disposal of styrene and styrene-containing materials in Canada (high priority);

(ii) current concentrations of styrene in terrestrial plants, snow, surface water and aquatic organisms, particularly near industrial sources (high priority);

(iii) interspecies variations in the metabolism of styrene, particularly for humans (medium priority);

(iv) the carcinogenicity of styrene in an adequately conducted carcinogenesis bioassay. Long-term inhalation bioassays with rats and mice are currently being conducted under the sponsorship of the Styrene Information and Research Center (Science and Technology Task Group of the Styrene Information and Research Center, 1991). When available, the results of these studies should be evaluated with respect to their implications for designation of "toxic", but in view of other priorities for assessment under CEPA;

(v) the results of the large historical cohort study conducted by Wong (1990), which is currently being updated to extend the latency period by another 10 to 15 years, and of an ongoing study initiated in 1988 by the International Agency for Research on Cancer (IARC), which involves a cohort of approximately 35 000 employees in this industry. When available, the results of these studies should be evaluated with respect to their implications for designation of "toxic", but in view of other priorities for assessment under CEPA;

(vi) immunological effects of styrene in long-term studies in animal species (medium priority);

(vii) acute and chronic toxicity of dissolved styrene in aquatic organisms (using procedures appropriate for volatile substances), and of atmospheric styrene in terrestrial plants (high priority); and

(viii) the chronic effects of styrene on birds, preferably through a reproductive/ developmental study, as this would probably be the most sensitive end-point (medium priority).

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