Ethylbenzene

CAS No. 100-41-4

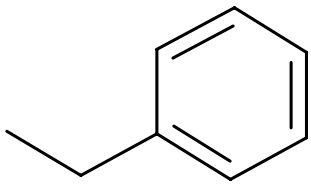

Figure 1: Structure of Ethylbenzene

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) the Minister of Health may gather information, conduct investigations and evaluations, including screening assessments, relevant for the purpose of assessing whether a substance is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Screening health assessments focus initially on conservative assessment of hazard or effect levels for critical endpoints and upper-bounding estimates of exposure, after consideration of all relevant identified information. Decisions based on the nature of the critical effects and margins between conservative effect levels and estimates of exposure take into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. Additional background information on screening health assessments conducted under this program is available at http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/index_e.html.

A State of the Science Report for a screening assessment has been prepared on ethylbenzene (see Figure 1) on the basis that this compound was included in the Domestic Substances List pilot phase for screening as a substance likely to be prioritized on the basis for greatest potential for human exposure.

This draft State of the Science Report for a screening assessment and associated unpublished supporting working documentation were prepared by evaluators within the Existing Substances Division of Health Canada; the content of these documents was reviewed at several meetings of senior Divisional staff. The draft Report was subsequently externally reviewed for

adequacy of data coverage and defensibility of the conclusions. The supporting working documentation is available upon request by e-mail from ExSD@hc-sc.gc.ca

Information identified as of January 2004 was considered for inclusion in this Report. The critical information and considerations upon which this Report is based are summarized below. Additional data identified between this date and the end of the external peer review period (May 2005) were also scoped and determined not to impact upon the conclusions presented here.

Identity, Uses and Sources of Exposure

Ethylbenzene is used in a variety of industrial processes and in the manufacture of many industrial and consumer products. Therefore, there are many potential sources of exposure for the Canadian population.

Ethylbenzene is a volatile organic compound and occurs naturally in petroleum and crude oil (ATSDR, 1999; NLM, 2003). It is produced by various processes from acetophenone, benzene, chlorobenzene, ethylenebenzene, naphthenes and xylene (NLM, 2003). Ethylbenzene can also be extracted from coal and may result from biomass combustion (ATSDR, 1999; NLM, 2003). A survey conducted pursuant to Section 71 of CEPA 1999 indicated that during the year 2000, 1690 kilotonnes of ethylbenzene at a concentration higher than 1% were manufactured in Canada and 18 kilotonnes of ethylbenzene at a concentration higher than 1% were imported into Canada. In addition, several companies reported either importing or manufacturing ethylbenzene at a concentration lower than 1% and in a quantity meeting the reporting threshold of 10 000 kg (Environment Canada, 2001). The survey also reported the use of ethylbenzene as a feedstock for petrochemicals and other organic chemicals, as a solvent in paints and coatings and in other solvent applications (Environment Canada, 2001). Reported uses in other jurisdictions fall into the categories of manufacture, solvents, fuels and coatings (ATSDR, 1999; NLM, 2003). The use of ethylbenzene in insecticides and carpet glues has also been reported (ATSDR, 1999).

Ethylbenzene is released from facilities that manufacture the substance or use it as a solvent or as an intermediate in the production of other chemicals. In 2001, facilities from across Canada reported to the National Pollutant Release Inventory on-site environmental releases totalling approximately 800 tonnes, transfers for disposal totalling 86 tonnes and transfers for recycling totalling 630 tonnes (Environment Canada, 2003). As a component of benzene, toluene, ethylbenzene and xylene (BTEX) emissions, ethylbenzene is also released from glycol dehydrators used to remove water from natural gas. According to the survey conducted pursuant to Section 71 of CEPA 1999, ethylbenzene is used mostly in destructive processes or in non-dispersive uses where release into the environment is unlikely. However, ethylbenzene is also reported for use in consumer products such as paints, solvents and gasoline, from which it may be released. It is also present in adhesives and tobacco smoke (Daisey *et al.*, 1994; ATSDR,

1999). Ethylbenzene has been detected in ambient air, indoor air, drinking water, soil and food; however, the primary route of exposure is expected to be inhalation.

Exposure Assessment, Hazard Characterization and Risk Evaluation

The upper-bounding estimates of exposure to ethylbenzene for the general population of Canada range from 95 µg/kg-bw per day for the 60+ years age group to 287 µg/kg-bw per day for the 0.5–4 years age group (Table 1). Based on the available data, inhalation of indoor air is the primary source of exposure. These estimates are based on data from Canadian surveys of ambient air, indoor air, drinking water and soil (Otson *et al.*, 1982; Dann and Wang, 1989; Fellin *et al.*, 1992; OMEE, 1993). Canadian data on the concentration of ethylbenzene in whitefish muscle (Lockhart *et al.*, 1992) were selected to represent levels in fish and combined with data from the U.S. Food and Drug Administration's Market Basket Survey (U.S. FDA, 2000) as a basis for estimating intake in Canadian foodstuffs. Confidence in the database on exposure to ethylbenzene through environmental media is considered high, as representative surveys are available for all media.

Based on the available information on use patterns of ethylbenzene in Canada, consumer products represent another source of exposure. Smoking may also contribute to overall exposure. To assess the potential increased exposure to ethylbenzene from use of consumer products, estimates of resulting airborne concentrations and daily intake for the Canadian adult population (20–59 years old) were made for exposure from paints (spray paint and latex paint) and gasoline (see Appendix A). These products were selected because they represent important product uses of ethylbenzene and principal consumer products from which exposure to ethylbenzene may occur. The Canadian adult population is expected to be the principal user of these products. Exposure to an aerosol spray paint was considered to be representative of an acute exposure for paint products, whereas exposure to a latex paint was considered to be representative of a chronic exposure, based on the nature of the exposures, event duration and event frequency. Exposure to gasoline was considered most likely to occur while refuelling a vehicle. Based on these screening estimates, inhalation intake from latex paint could contribute substantially to exposure (85 µg/kg-bw per day), while dermal intake is negligible and exposure through gasoline is limited. Smoking may contribute to the overall exposure to ethylbenzene through environmental and mainstream tobacco smoke (see Appendix A); however, the indoor air study used in deriving upper-bounding estimates of exposure did not distinguish between smoking and non-smoking homes. Confidence in the intake estimates of ethylbenzene from consumer products is moderate. The intake estimates were calculated for the most commonly used products with the highest potential for exposure. These estimates are based on modelled exposure scenarios and on use pattern assumptions that may not be valid for all users of the products. Estimated exposures may be higher when averaged over shorter periods of time. Emissions of ethylbenzene from consumer products are expected to contribute significantly to indoor air levels; however, the contributions have not been characterized fully and cannot be quantified at this time.

An assessment by the International Agency for Research on Cancer (IARC, 2000) concluded that ethylbenzene was *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence* in experimental animals and *inadequate evidence* in humans. In a carcinogenicity bioassay, male and female mice and rats were exposed to concentrations up to 750 ppm (0, 326, 1090 or 3260 mg/m^3) ethylbenzene for 103 and 104 weeks, respectively (Chan *et al*., 1998; NTP, 1999). In male mice, there were concentration-related increases in the incidence of both alveolar/bronchiolar adenomas and combined alveolar/bronchiolar adenomas and carcinomas of the lung, which were significant at the highest concentration. In females, there were concentration-related increases in the incidence of both hepatocellular adenomas and combined adenomas and carcinomas, which were significant at the highest concentration. These incidences were within the ranges of historical controls. In rats, significant increases in the incidences of renal tubular adenomas and combined adenomas and carcinomas were observed in males at the highest concentration. Significant increases in incidences of renal adenomas were observed in females at the highest concentration. In both groups, there was also a significant increase in the incidence of focal renal tubular hyperplasia at the highest concentration, which was considered to be a precursor stage of adenoma by the authors of the study.

Ethylbenzene has not been mutagenic or clastogenic in *in vivo* assays, with results of well-conducted studies being negative for chromosome aberrations in rat bone marrow and mouse micronuclei. It has also been negative in well-conducted assays for mutations in bacteria and yeast *in vitro* and in insects, as well as for chromosomal aberrations in mammalian cells. However, there have been a limited number of positive results in well-conducted assays *in vitro* in mammalian cells, including cell transformation and micronuclei in Syrian hamster embryo cells, a cell line noted for its metabolic capacity. In addition, there was an unequivocal positive response at a single elevated dose in the mouse lymphoma assay. With the exception of a positive *in vivo* micronucleus prediction, results predicted using quantitative structure–activity relationships (QSARs) within the domains of the models for a range of genotoxicity endpoints were all negative, including the subset of models for which ethylbenzene was not included in the training set. Therefore, while the weight of evidence for direct interaction of ethylbenzene with DNA is limited, it cannot be precluded.

Overall, the confidence in the database on the toxicity of ethylbenzene is considered to be moderate to high, as a wide range of study types is available (Table 2). However, there is some uncertainty concerning whether the tumours observed in the long-term bioassays could be associated with a genotoxic mode of action, since the genotoxic potential of ethylbenzene is unclear. It was noted that significant increases in tumours were observed only at the higher concentrations and were within the range observed in historical controls.

The lowest identified effect level for inhalation of ethylbenzene in air, the principal route of human exposure, is a lowest-observed-effect concentration (LOEC) of 326 mg/m^3, at which there was an increased severity of nephropathy in female rats exposed for 104 weeks (NTP, 1999). Reductions in liver pentoxyresorufin *O*-dealkylase (PROD) and ethoxyfluorocoumarin-*O*-

dealkylase (EFCOD) and lung ethoxyresorufin *O*-dealkylase (EROD) and PROD activities were observed in male and female mice exposed to 326 mg/m^3 for 5 days (Stott *et al.*, 2003).

Comparison of the lowest inhalation effect level (326 mg/m^3) with the highest concentration in indoor air (539.31 µg/m^3) results in a margin of exposure of 600. In addition, exposures when using consumer products such as paints may reach or exceed concentrations reported to have adverse effects in laboratory animals exposed for similarly short durations. The likely significant contribution of consumer products to total exposure is supported by the large variation between mean and maximum concentrations reported in indoor air (e.g., 50-fold).

In light of the possible carcinogenicity of ethylbenzene in humans, for which a mode of induction involving direct interaction with DNA cannot be precluded, and potentially significant exposures from use of consumer products, the outcome of this evaluation is that it is suspected that the margins between levels causing health effects in experimental animals and exposure may not be adequate to account for the uncertainties in the database. Information addressing the mode of action for tumour induction and potential genotoxicity would permit a more definitive conclusion. In addition, data on measured human exposure from use of products containing ethylbenzene, such as acrylic enamel spray paint and latex paint is desirable.

Table 1: Upper-bounding estimates of daily intake of ethylbenzene by the general population in Canada

Route of exposure	**Estimated intake (µg/kg-bw per day) of ethylbenzene by various age groups**						
	0–6 months[1–3]		**0.5–4 years[4]**	**5–11 years[5]**	**12–19 years[6]**	**20–59 years[7]**	**60+ years[8]**
	Formula fed	**Not formula fed**					
Ambient air[9]	0.6		1.3	1	0.6	0.5	0.4
Indoor air[10]	132		283	221	126	107.8	93.7
Drinking water[11]	1.1	0.4	0.4	0.4	0.2	0.2	0.2
Food and beverages[12]		1.7	2.4	1.8	1.1	1	0.7
Soil[13]	2.0×10^{-4}		3.3×10^{-4}	1.1×10^{-4}	2.6×10^{-5}	2.2×10^{-5}	2.1×10^{-5}
Total intake	134	135	287	224	128	110	95

1 Data for concentrations of ethylbenzene in breast milk were not identified.

2 Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (EHD, 1998).

3 For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of ethylbenzene in water used to reconstitute formula was based on a study of water taken from water treatment plants across Canada (Otson *et al.*, 1982). Data on concentrations of ethylbenzene in formula were not identified. Approximately 50% of not-formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW, 1990).

4 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (EHD, 1998).

5 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (EHD, 1998).

6 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

7 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

8 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (EHD, 1998).

9 Dann and Wang (1989) monitored ambient air at 11 sites in the Greater Vancouver Regional District. The maximum concentration observed (17.9 µg/m^3) was used to calculate the upper-bounding estimate of exposure. Canadians are assumed to spend 3 hours outdoors each day (EHD, 1998). Data considered in the selection of critical data also included Health Canada (2003), Gagnon (2001), OMEE (2000), Bell *et al.* (1991), Chan *et al.* (1990) and Environment Canada (1989, 1990). Concentrations as high as 1163 µg/m^3 have been observed (PACE, 1989) in the areas surrounding service stations but were not included in the calculation for upper-bounding estimate of exposure due to the transient nature of exposure. Other exposure sources such as smoking and vehicle operation were not included in the upper-bounding estimate of exposure due to the variability in exposure within the general population.

10 Fellin *et al.* (1992) conducted a study in which volatile organic chemicals, including ethylbenzene, were monitored for 3–24 hours in 754 homes across Canada. A maximum concentration of 539.31 µg/m^3 was observed in a family dwelling and has been used to calculate the upper-bounding estimate of exposure. Canadians are assumed to spend 21 hours indoors each day (EHD, 1998). Fellin *et al.* (1992) did not appear to distinguish between smoking and non-smoking homes. Data considered in the selection of critical data also included Health Canada (2003), Otson *et al.* (1994), Bell *et al.* (1991), Chan *et al.* (1990) and CH2M Hill Engineering Ltd. (1989).

[11] A concentration of 10 µg/L was detected in 1 of 35 samples taken from various water treatment plants across Canada between August and December 1979 (Otson *et al.*, 1982). This concentration has been used to calculate the upper-bounding estimate of exposure. Data considered in the selection of critical data also included City of Toronto (1990, 2002), Goss *et al.* (1998), OME (1989), Environment Canada (1988) and Otson (1987).

[12] Lockhart *et al.* (1992) analyzed fish samples from northern Manitoba and the Northwest Territories, observing a maximum concentration of 273 µg/kg in whitefish muscle. This value was used to estimate the "fish" component of the calculation of intake due to the ingestion of food. The other 11 categories represented by the foodstuffs with the highest concentration following analysis in the U.S. Food and Drug Administration's Total Diet Study (U.S. FDA, 2000) were as follows: dairy products: cheese, 12 µg/kg; fats: olive or safflower oil, 23 µg/kg; fruits and fruit products: 34 products, not detected; vegetables: potato chips, 19 µg/kg; cereal products: pumpkin pie, 29 µg/kg; meat and poultry: hamburger, 38 µg/kg; eggs: three different preparations, not detected; foods — primarily sugar: chocolate bar, 13 µg/kg; mixed dishes and soups: eight products, not detected; nuts and seeds: mixed nuts, 21 µg/kg; soft drinks and alcohol: coffee, 17 µg/kg. No detection limit was identified, and a value of zero was used in the calculation of upper-bounding estimate of exposure where applicable. This calculation includes exposure due to beverages other than drinking water. Amounts of foods consumed on a daily basis by each age group are described by Health Canada (EHD, 1998). Data considered in the selection of critical data also included Enviro-Test Laboratories (1991, 1992, 1993).

[13] The highest concentration of ethylbenzene detected (0.51 ng/kg) in 122 soil samples collected from typical urban residential and parkland locations in Ontario was used to calculate the upper-bounding estimate of exposure (OMEE, 1993). No other data were identified.

Table 2: Summary of health effects information for ethylbenzene

Endpoint	Lowest effect levels[1]/Results
Acute toxicity	**Lowest oral LD_{50}** = 3500 mg/kg-bw in rats (Wolf *et al.*, 1956) [Additional studies: Smyth *et al.*, 1962; NTP, 1986] **Lowest dermal LD_{50}** = 15 354 mg/kg-bw in rabbits (Smyth *et al.*, 1962) [Additional studies: Harton and Rawl, 1976] **Lowest inhalation LC_{50}** = 17 200 mg/m^3 in rats (4 hours) (Smyth *et al.*, 1962) [Additional studies: Ivanov, 1962]
Short-term repeated-dose toxicity	**Lowest inhalation LOEC** = 75 ppm (326 mg/m^3): reductions in liver pentoxyresorufin *O*-dealkylase (PROD) and ethoxyfluorocoumarin-*O*-dealkylase (EFCOD) activities in male and female mice exposed to 75 ppm ethylbenzene after a 5-day exposure. For the same exposure period, concentration-related reductions in lung ethoxyresorufin *O*-dealkylase (EROD) and PROD activities were observed in male and female mice exposed to all tested concentrations (i.e., 75 and 750 ppm) of ethylbenzene (Stott *et al.*, 2003). [Additional studies: Andersson *et al.*, 1981; Toftgård and Nilsen, 1982; Romanelli *et al.*, 1986; Mutti *et al.*, 1988; Cragg *et al.*, 1989; Cappaert *et al.*, 1999; Stott *et al.*, 2003 (rats)]
Subchronic toxicity	**Lowest inhalation LOEC** = 100 ppm (434 mg/m^3): increased blood alkaline phosphatase levels in female rats exposed for 6 hours/day, 5 days/week for 13 weeks (NTP, 1992) [Additional studies: Wolf *et al.*, 1956; Elovaara *et al.*, 1985] **Lowest oral LOEL** = 408 mg/kg-bw per day via stomach tube to female Wistar rats 5 days/week for 6 months: increase in absolute liver and kidney weights and cloudy swelling of the parenchymal cells of the liver and the tubular epithelium of the kidney (Wolf *et al.*, 1956)
Chronic toxicity/ carcinogenicity	**Lowest inhalation LOEC** = 75 ppm (326 mg/m^3): increased severity of nephropathy in female rats (104-week study) (NTP, 1999) **Neoplastic endpoints:** F344 rats and B6C3F1 mice were exposed to concentrations of 0, 75, 250 or 750 ppm (0, 326, 1090 or 3260 mg/m^3) for 104 and 103 weeks, respectively. At the highest concentration, there were significantly increased incidences of renal tubule neoplasms (3/50, 5/50, 8/50, 21/50; historical control range 0–4%) and testicular adenomas (36/50, 33/50, 40/50, 44/50; historical control range 54–83%) in male F344 rats and renal tubule neoplasms (0/50, 0/50, 1/50, 8/50; no historical control range provided) in female F344 rats. There were significantly increased incidences of alveolar/bronchiolar neoplasms in male B6C3F1 mice (7/50, 10/50, 15/50, 19/50; historical control range 10–42%) and hepatocellular neoplasms in female B6C3F1 mice (13/50, 12/50, 15/50, 25/50; historical control range 3–54%) (Chan *et al*., 1998; NTP, 1999). [Additional studies: Maltoni *et al.*, 1985, 1997]

Endpoint	Lowest effect levels[1]/Results
Genotoxicity and related endpoints: *in vivo*	**Chromosomal aberrations** *Negative:* Rat bone marrow cells [note that substance tested was a xylene mixture with 18.3% ethylbenzene] (Donner *et al.*, 1980) **Micronuclei test** *Negative:* Mouse peripheral lymphocytes (NTP, 1992), mouse bone marrow (Mohtashamipur *et al.*, 1985), mouse peripheral erythrocytes (NTP, 1999) **Non-mammalian sex-linked recessive lethal assay** *Negative: Drosophila* (Donner *et al.*, 1980)
Genotoxicity and related endpoints: *in vitro*	**Cell transformation assay** *Positive:* Syrian hamster embryo (Kerckaert *et al.*, 1996) *Negative:* Syrian hamster embryo (Heidelberger *et al.*, 1983) **Chromosomal aberrations** *Negative:* Chinese hamster ovary (NTP, 1992); Chinese hamster ovary, with and without activation (NTP, 1999) **Gene conversion** *Negative: Pseudomonas putida* (Leddy *et al.*, 1995) **Micronuclei test** *Positive:* Syrian hamster embryo cell (Gibson *et al.*, 1997) **Mutagenicity** *Positive:* Mouse lymphoma cells, without activation (McGregor *et al.*, 1988; NTP, 1992, 1999) *Negative: Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 with and without activation (NTP, 1992, 1999); *Escherichia coli* WP2, Wp2uvrA and *Saccharomyces cerevisiae* JD1 (Dean *et al.*, 1985) **Sister chromatid exchange** *Positive:* Human lymphocytes, with activation (Norppa and Vainio, 1983) *Negative:* Chinese hamster ovary cells (NTP, 1992); Chinese hamster ovary, with and without activation (NTP, 1999)
Developmental/ reproductive toxicity	**Lowest inhalation LOAEC** = 100 ppm (435 mg/m^3): extra ribs (rat), reduced litter size (rabbit) (Hardin *et al.*, 1981) [Additional studies: Ungvary and Tatrai, 1985; Saillenfait *et al.*, 2003]

[1] LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LOAEC = lowest-observed-adverse-effect concentration; LOEC = lowest-observed-effect concentration; LOEL = lowest-observed-effect level.

APPENDIX A: Estimates of Exposure to Ethylbenzene from Consumer Products by Adult Canadians[1]

Consumer product type	Assumptions	Estimated concentrations and daily intakes
Acrylic enamel aerosol spray paint[2]	**Inhalation**[3] - based on a reported maximum concentration of 40% in a coating product (Environment Canada, 2001), a concentration of 40% in an acrylic enamel aerosol spray paint is assumed in the determination of an upper-bounding estimate of intake - assuming the amount of product used is 460 g per event, a 0.17-hour duration of exposure, a room volume of 20 m^3, a breathing rate of 1.3 m^3/hour for an average adult engaged in light-level activity and a frequency of use of 1 day per year (Versar Inc., 1986) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHD, 1998) Air concentration = $\frac{(\%\text{ in product})(\text{amount of product})}{(\text{room volume})}$ Air concentration = $\frac{(0.40)(460\,000\text{ mg})}{(20\text{ m}^3)}$ Dose = $\frac{(\%\text{ in product})(\text{amount of product})(\text{event duration})(\text{breathing rate})}{(\text{body weight})(\text{room volume})}$ Dose = $\frac{(0.40)(460\,000\text{ mg})(0.17\text{ h})(1.3\text{ m}^3/\text{h})(1/365\text{days})(1000\ \mu\text{g/mg})}{(70.9\text{ kg-bw})(20\text{ m}^3)}$	Air concentration = 9200 mg/m^3 Estimated daily intake = 78.6 µg/kg-bw per day
	Dermal[4] - assuming an estimated permeation coefficient (K_p) of 9.55×10^{-5} cm/h (U.S. EPA, 1992), a paint density of 0.9 g/cm^3 (Versar Inc., 1986), a surface area of the hands of 910 cm^2 (EHD, 1998) and significant coverage of 50% of the hands while painting Dose = $\frac{(K_p)(\text{event duration})(\%\text{ in product})(\text{product density})(\text{surface area exposed})}{(\text{body weight})}$ Dose = $\frac{(9.55 \times 10^{-5}\text{ cm/h})(0.17\text{ h})(0.40)(0.9\text{ g/cm}^3)(455\text{ cm}^2)(1/365\text{ days})(10^6\ \mu\text{g/g})}{(70.9\text{ kg-bw})}$	Estimated daily intake = 0.10 µg/kg-bw per day

Consumer product type	Assumptions	Estimated concentrations and daily intakes
Latex wall paint[5]	**Inhalation**[6] - using the Wall Paint Exposure Model (version 3.2; U.S. EPA, 2001) and its default values, unless otherwise stated - model assumes 38 exposure events in a 75-year lifetime - assuming an adult do-it-yourself painter in the painted area where only the walls are painted - based on a reported maximum concentration of 40% in a coating product (Environment Canada, 2001), a concentration of 40% in a latex wall paint is assumed in the determination of an upper-bounding estimate of intake - assuming a body weight of 70.9 kg for an average Canadian adult (EHD, 1998) - the model calculates the highest instantaneous concentration to which an individual is exposed (C_p) and the estimated lifetime average daily dose	Air concentration (C_p) = 250 mg/m^3 Estimated lifetime average daily dose = 85 µg/kg-bw per day
	Dermal[7] - assuming an estimated permeation coefficient (K_p) of 9.55×10^{-5} cm/h (U.S. EPA, 1992) - assuming a paint density of 1.22 g/cm^3 (Versar Inc, 1986), a surface area of the hands of 910 cm^2 (EHD, 1998) and significant coverage of 50% of the hands while painting - assuming 38 exposure events in a 75-year lifetime with an average of 5.135 hours per event (WPEM, version 3.2; U.S. EPA, 2001) - assuming a body weight of 70.9 kg for an average Canadian adult (EHD, 1998) $\text{Dose} = \frac{(\%\text{ in product})(\text{product density})(K_p)(\text{event frequency})(\text{event duration})(\text{exposure area})}{(\text{body weight})(\text{averaging time})}$ $\text{Dose} = \frac{(0.40)(1.22\ g/cm^3)(9.55 \times 10^{-5}\ cm/h)(38\ \text{events})(5.135\ h/\text{event})(455\ cm^2)(10^6\ \mu g/g)}{(70.9\ \text{kg-bw})(75\ \text{yr})(365\ \text{days/yr})}$	Estimated daily intake = 2.13 µg/kg-bw per day
Gasoline[8]	**Inhalation while pumping gas**[9] - based on a maximum concentration of 1862 $\mu g/m^3$ measured in samples taken while pumping gas (PACE, 1987) - assuming an event frequency of one gas fill-up per week, a duration of exposure of 15 minutes and a breathing rate of 1.3 m^3/hour for an average adult engaged in light-level activity (Versar Inc., 1986; PACE, 1987) - a body weight of 70.9 kg is assumed for an average Canadian adult (EHC, 1998) $\text{Dose} = \frac{(\text{event duration})(\text{event frequency})(\text{concentration})(\text{breathing rate})}{(\text{body weight})}$ $\text{Dose} = \frac{(15\ \text{min})(1\ h/60\ \text{min})(1\ \text{event/week})(1\ \text{week}/7\ d)(1862\ \mu g/m^3)(1.3\ m^3/h)}{70.9\ \text{kg-bw}}$	Maximum concentration = 1.862 mg/m^3 Estimated daily intake = 1.22 µg/kg-bw per day
Cigarettes[10]	**Inhalation from tobacco smoke**[11] - based on a maximum concentration of 19.3 $\mu g/m^3$ measured over a 4-hour period after 24- to 27-minute sessions of smoking in an environmental chamber with a volume of 225 mL - measurements were taken after the third cigarette was removed; therefore,	Maximum concentration = 0.0193 mg/m^3

Consumer product type	Assumptions	Estimated concentrations and daily intakes
	an event frequency of 3 cigarettes per day was assumed - body weights of 59.4 kg, 70.9 kg and 72.0 kg are assumed for average Canadians 12–19 years old, 20–59 years old and 60 years old and more, respectively (EHD, 1998) $\text{Dose} = \frac{(\text{concentration})(\text{chamber volume})(\text{event frequency})}{(\text{body weight})}$ 12–19 years old: $\text{Dose} = \frac{(19.3\ \text{mg/m}^3)(2.25 \times 10^{-4}\ \text{m}^3)(3\ \text{events/day})}{59.4\ \text{kg-bw}}$ 20–59 years old: $\text{Dose} = \frac{(19.3\ \text{mg/m}^3)(2.25 \times 10^{-4}\ \text{m}^3)(3\ \text{events/day})}{70.9\ \text{kg-bw}}$ 60+ years old: $\text{Dose} = \frac{(19.3\ \text{mg/m}^3)(2.25 \times 10^{-4}\ \text{m}^3)(3\ \text{events/day})}{72.0\ \text{kg-bw}}$	Estimated daily intake = 2.19×10^{-4} µg/kg-bw per day Estimated daily intake = 1.84×10^{-4} µg/kg-bw per day Estimated daily intake = 1.81×10^{-4} µg/kg-bw per day

[1] Since these products are used primarily by adults (20–59 years old), estimated exposures have been derived for this age group only, with the exception of cigarettes, for which exposure for three age groups (12–19, 20–59 and 60+ years old) was considered.

[2] Exposure to an aerosol spray paint was considered representative of an acute exposure for paint products based on use pattern parameters (compare with latex paint, footnote 5).

[3] For this scenario, it was assumed that exposure occurred only during the time the product was in use and that the total amount of ethylbenzene released during each event was present in the room air throughout the period of use (i.e., evaporation was assumed to be instantaneous). Thus, the user of the product was assumed to be exposed to the peak ethylbenzene concentration throughout the exposure period. It was also assumed that the ethylbenzene vapours were confined to the room where the product was used throughout the exposure period (i.e., household air exchange rate was assumed to be negligible throughout the exposure period). Also assumed is 100% absorption across the lungs.

[4] Dermal exposure may occur during use of aerosol spray paints. A skin permeation coefficient (K_p) for ethylbenzene from water of 0.517 cm/h has been estimated according to the equation $\log K_p = -2.72 + 0.71 \log K_{ow} - 0.0061$ MW, where K_{ow} is the octanol/water partition coefficient and MW is the molecular weight (U.S. EPA, 1992). Since ethylbenzene is assumed to comprise 40% of the paint product, a K_p for the neat substance is considered more appropriate. The relationship $K_{p(neat)} = K_{p(water)} \times$ (water solubility / density of neat substance) has been determined (U.S. EPA, 1992). Therefore, $K_{p(neat)}$ was calculated to be 9.55×10^{-5} cm/h. For this scenario, an acute exposure dose was calculated. It was assumed that exposure occurred only during the time the product was in use and that there was 100% absorption through the skin.

[5] Exposure to a latex wall paint was considered representative of a chronic exposure for paint products based on use pattern parameters (compare with spray paint, footnote 2).

[6] The Wall Paint Exposure Model was developed by the U.S. Environmental Protection Agency to estimate an individual's inhalation exposure to a chemical in a latex wall paint, during and after the time when a building is painted. It is a sophisticated model that may give a more realistic output than simple equations for inhalation

exposure. The model's use of a certain number of exposure events over a lifetime makes it appropriate for estimating chronic exposure to a substance.

[7] Dermal exposure may occur during use of wall paints. A skin permeation coefficient (K_p) for ethylbenzene from water of 0.517 cm/h has been estimated according to the equation $\log K_p = -2.72 + 0.71 \log K_{ow} - 0.0061$ MW, where K_{ow} is the octanol/water partition coefficient and MW is the molecular weight (U.S. EPA, 1992). Since ethylbenzene is assumed to comprise 40% of the paint product, a K_p for the neat substance is considered more appropriate. The relationship $K_{p(neat)} = K_{p(water)} \times$ (water solubility / density of neat substance) has been determined (U.S. EPA, 1992). Therefore $K_{p(neat)}$ was calculated to be 9.55×10^{-5} cm/h. For this scenario, a lifetime chronic exposure dose was calculated. It was assumed that there was 100% absorption through the skin.

[8] Ethylbenzene occurs naturally in gasoline and may also be used as a fuel additive. Estimated exposures have been derived for the average Canadian adult (20–59 years old).

[9] The study by PACE (1987) involved taking air samples from pump operators at full-serve stations and kiosk operators at self-serve stations. For this scenario, the maximum concentration used was measured for pump operators at full-serve stations. Samples from kiosk operators at self-serve stations were also taken in the study; however, they are not involved with filling the gas tank and are not considered representative of the average Canadian adult. The duration of exposure was assumed to be the same as the short-term sample times from the study. It is noted that the sample time may represent three to five gas fill-ups for a pump operator; therefore, the duration of exposure used in the scenario may overestimate the actual potential dose for an average adult.

[10] Daisey *et al.* (1994) measured volatile organic compounds over a 4-hour period after 24- to 27-minute sessions of smoking in an environmental chamber. The average concentrations of ethylbenzene in environmental tobacco smoke ranged from 11.5 to 19.3 $\mu g/m^3$ (detection limit not stated). The estimated daily intake was not included in the total intake estimate, as active exposure (i.e., smoking) to ethylbenzene from cigarettes may not be representative of the general Canadian population.

[11] Doses were calculated for three relevant age groups. Exposure resulting from cigarette smoking was not included in the calculation of total intake, as cigarette smoke may have contributed to measured indoor air levels.

References

Andersson, K., K. Fuxe, O.G. Nilsen, R. Toftgård, P. Eneroth and J.Å. Gustafsson. 1981. Production of discrete changes in dopamine and noradrenaline levels and turnover in various parts of the rat brain following exposure to xylene, *ortho*-, *meta*-, and *para*-xylene, and ethylbenzene. Toxicol. Appl. Pharmacol. 60: 535–548 [cited in IPCS, 1996; IARC, 2000].

ATSDR (Agency for Toxic Substances and Disease Registry). 1999. Toxicological profile for ethylbenzene (update). U.S. Department of Health and Human Services, Atlanta, Georgia.

Bell, R.W., R.E. Chapman, B.D. Kruschel, M.J. Spencer, K.V. Smith and M.A. Lusis. 1991. The 1990 Toronto Personal Exposure Pilot (PEP) Study. Air Resources Branch, Ontario Ministry of the Environment, Toronto, Ontario.

Cappaert, N.L.M., S.F.L. Klis, H. Muijner, J.C.M.J. De Groot, B.M. Kulig and G.F. Smoorenburg. 1999. The ototoxic effects of ethylbenzene in rats. Hearing Res. 137(1–2): 91–102.

CH2M Hill Engineering Ltd. 1989. CMHC Kitchener townhouse study of soil gas ventilation as a remedial measure for methane entry into basements. Waterloo, Ontario.

Chan, C.C., L. Vainer and J.W. Martin. 1990. Determination of organic contaminants in residential indoor air using an adsorption–thermal desorption technique. J. Air Waste Manage. Assoc. 40: 62–67.

Chan, P.C., J.K. Hasemani, J. Mahleri and C. Aranyi. 1998. Tumor induction in F344/N rats and B6C3F1 mice following inhalation exposure to ethylbenzene. Toxicol. Lett. 99(1): 23–32.

City of Toronto. 1990. The quality of drinking water in Toronto. A review of tap water, bottled water and water treated by a point-of-use device. Department of Public Health, City of Toronto, Toronto, Ontario.

City of Toronto. 2002. Water quality quarterly report January–March 2002. Water and Wastewater Services, City of Toronto, Toronto, Ontario.

Cragg, S.T., E.A. Clarke, I.W. Daly, R.R. Miller, J.B. Terrill and R.E. Ouellette. 1989. Subchronic inhalation toxicity of ethylbenzene in mice, rats, and rabbits. Fundam. Appl. Toxicol. 13(3): 399–408.

Daisey, J.M., A.T. Hodgson, W.J. Fisk, M.J. Mendell and J.T. Brinke. 1994. Volatile organic compounds in twelve California office buildings: classes, concentrations and sources. Atmos. Environ. 28(22): 3557–3562.

Dann, T. and D. Wang. 1989. Volatile organic compounds in the Greater Vancouver Regional District. Pollution Measurement Division, Conservation and Protection, Environment Canada.

Dean, B.J., T.M. Brooks, G. Hodson-Walker and D.H. Hutson. 1985. Genetic toxicology testing of 41 industrial chemicals. Mutat. Res. 153: 57–77 [cited in IPCS, 1996].

Donner, M., J. Maki-Paakkanen, H. Norppa, M. Sorsa and H. Vainio. 1980. Genetic toxicology of xylenes. Mutat. Res. 74: 171–172 [cited in IPCS, 1996].

Dynamac Corporation. 1986. Information review ethylbenzene. Rockville, Maryland (IR-478).

EHD (Environmental Health Directorate). 1998. Exposure factors for assessing total daily intake of Priority Substances by the general population of Canada. Draft internal report. Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario.

Elovaara, E., K. Engstrom, J. Nickels, A. Aitio and H. Vainio. 1985. Biochemical and morphological effects of long-term inhalation exposure of rats to ethylbenzene. Xenobiotica 15: 299–308 [cited in IPCS, 1996].

Environment Canada. 1988. Atlantic Region Federal–Provincial Toxic Chemical Survey of Municipal Drinking Water Sources 1985–1988.

Environment Canada. 1989. Detroit Incinerator Monitoring Program Data Report No. 3.

Environment Canada. 1990. Detroit Incinerator Monitoring Program Data Report No. 4.

Environment Canada. 2001. *Canadian Environmental Protection Act, 1999*. Notice with respect to certain substances on the Domestic Substances List (DSL). Canada Gazette, Part I, 135(46): 4194–4211. http://canadagazette.gc.ca/partI/2001/20011117/pdf/g1-13546.pdf.

Environment Canada. 2003. National Pollutant Release Inventory. Searched December 5, 2003 for 2001 data (http://www.ec.gc.ca/pdb/querysite/query_e.cfm).

Enviro-Test Laboratories. 1991. Cayley Background Study: Analysis of food products for target organic and inorganic parameters. Series: 91-E1208. Prepared under contract to Hazardous Waste Section, Environmental Health Directorate, Health and Welfare Canada, Ottawa, Ontario.

Enviro-Test Laboratories. 1992. Windsor Area Background Study: Analysis of food products for target organic and inorganic parameters. Prepared under contract to Hazardous Waste Section, Environmental Health Directorate, Health and Welfare Canada, Ottawa, Ontario.

Enviro-Test Laboratories. 1993. Ville-Mercier Background Study: Analysis of food products for target organic and inorganic parameters. Prepared under contract to Hazardous Waste Section, Environmental Health Directorate, Health and Welfare Canada, Ottawa, Ontario.

Fellin, P., S.E. Barnett and Q.A. Tran. 1992. Results of a national pilot survey of airborne volatile organic compounds in Canadian residences. Prepared by Concord Environmental for Health and Welfare Canada.

Gagnon, C. 2001. Rapport annuel de la qualité de l'air 2000. Communauté urbaine de Montréal, Service de l'environnement, Assainissement de l'air et de l'eau.

Gibson, D.P., R. Brauninger, H.S. Shaffu, G.A. Kerckaert, R.A. LeBoeuf, R.J. Isfort and M.J. Aardema. 1997. Induction of micronuclei in Syrian hamster embryo cell: comparison to results in SHE cell transformation assay for National Toxicology Program test chemicals. Mutat. Res. 392(1–2): 61–70.

Goss, M.J., D.A.J. Barry and D.L. Rudolph. 1998. Contamination in Ontario farmstead domestic wells and its association with agriculture: 1. Results from drinking water wells. J. Contam. Hydrol. 32(3–4): 267–293.

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health 7(Suppl. 4): 66–75 [cited in IPCS, 1996].

Harton, E.E. and R.R. Rawl. 1976. Toxicological and skin corrosion testing of selected hazardous chemicals. Prepared for the Office of Hazardous Materials Operation, U.S. Department of Transportation, Washington, D.C. (NTIS Report No. PB264-975) [cited in Dynamac Corporation, 1986].

Health Canada. 2003. Personal communication from J. Zhu, Chemistry Research Division.

Heidelberger, C., A.C. Freeman, R.J. Pientra, A. Sivak, A.S. Bertram, B.C. Casto, V.C. Dunkel, M.W. Francis, T. Kakunaga, J.B. Little and J.M. Schechtman. 1983. Cell transformation by chemical agents: a review and analysis of the literature: a report of U.S. Environmental Protection Agency GENETOX program. Mutat. Res. 114: 283–385.

IARC (International Agency for Research on Cancer). 2000. Some industrial chemicals. IARC Monogr. Eval. Carcinogen. Risks Hum., 77: 227–241.

IPCS (International Programme on Chemical Safety). 1996. Environmental Health Criteria 186: Ethylbenzene. World Health Organization, Geneva (http://www.inchem.org/documents/ehc/ehc/ehc186.htm).

Ivanov, S.V. 1962. Toxicity of ethylbenzene. Tr. Voronezh. Gos. Med. Inst. 47: 80 [cited via International Uniform Chemical Information Database (IUCLID) in Dynamac Corporation (1986)].

Kerckaert, G.A., R. Brauninger, R.A. LeBoeuf and R.J. Isfort. 1996. Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. Environ. Health Perspect. 104(Suppl. 5): 1075–1084.

Leddy, M.B., D.W. Phipps and H.F. Ridgway. 1995. Catabolite-mediated mutations in alternate toluene degradative pathways in *Pseudomonas putida*. J. Bacteriol. 177(16): 4713–4720.

Lockhart, W.L., R. Wagemann, B. Tracey, D. Sutherland and D.J. Thomas. 1992. Presence and implications of chemical contaminants in the freshwaters of the Canadian Arctic. Sci. Total Environ. 122(1–2): 165–245.

Maltoni, C., B. Conti, G. Cotti and F. Belpoggi. 1985. Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology; current results and ongoing research. Am. J. Ind. Med. 7: 415–446 [cited in IPCS, 1996].

Maltoni, C., A. Ciliberti, G. Lefemine and M. Soffritti. 1997. Results of a long-term experimental study on the carcinogenicity of vinyl acetate monomer in mice. Ann. N. Y. Acad. Sci. 26(837): 209–238.

McGregor, D.B., A. Brown, P. Cattanach, I. Edwards, D. McBride, C. Riach and W.J. Caspary. 1988. Responses of the L5178Y tk^{+}/tk^{-} mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ. Mol. Mutagen. 12: 85–154 [cited in IPCS, 1996].

Mohtashamipur, E., K. Norpoth, U. Woelke and P. Huber. 1985. Effects of ethylbenzene, toluene, and xylene on the induction of micronuclei in bone marrow polychromatic erythrocytes of mice. Arch. Toxicol. 58(2): 106–109.

Mutti, A., M. Falzoi, A. Romanelli, M.C. Bocchi, C. Ferroni and I. Franchini. 1988. Brain dopamine as a target for solvent toxicity: effects of some monocyclic aromatic hydrocarbons. Toxicology 49: 77–82.

NHW (Department of National Health and Welfare). 1990. Present patterns and trends in infant feeding in Canada. Ottawa, Ontario. 9 pp. (Catalogue No. H39-199/1990E) [cited in EHD, 1998].

NLM (National Library of Medicine). 2003. Ethylbenzene. Hazardous Substances Data Bank (HSDB) Number 84. Last update: March 5, 2003. Database searched on December 5, 2003 (http://toxnet.nlm.nih.gov/).

Norppa, H. and H. Vainio. 1983. Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. Mutat. Res. 116: 379–387 [cited in IPCS, 1996].

NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of xylenes (mixed) (60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene, and 17% ethylbenzene) (CAS No. 1330-20-7) in F344/N rats and B6C3F1 mice (gavage studies). National Institutes of Health, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina (Technical Report Series No. 327; NIH Publication. No. 87-2583).

NTP (National Toxicology Program). 1992. Toxicity studies of ethylbenzene in F344/N rats and B6C3F1 mice (inhalation studies). National Institutes of Health, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina (NIH Publication No. 92-3129).

NTP (National Toxicology Program). 1999. Toxicology and carcinogenesis studies of ethylbenzene (CAS No. 100-41-4) in F344/N rats and B6C3F1 mice (inhalation study). National Institutes of Health, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina (Technical Report Series No. 466; NIH Publication No. 99-3956).

OME (Ontario Ministry of the Environment). 1989. Drinking Water Surveillance Program. Overview annual report 1987. Toronto, Ontario.

OMEE (Ontario Ministry of Environment and Energy). 1993. Ontario typical range of chemical parameters in soil, vegetation, moss bags and snow. Toronto, Ontario.

OMEE (Ontario Ministry of Environment and Energy). 2000. Air quality in Ontario, 2000 report. Environmental Monitoring and Reporting Branch, Ontario Ministry of Environment and Energy, Toronto, Ontario.

Otson, R. 1987. Purgeable organics in Great Lakes raw and treated water. Int. J. Environ. Anal. Chem. 31(1): 41–53.

Otson, R., D.T. Williams and P.D. Bothwell. 1982. Volatile organic compounds in water at thirty Canadian potable water treatment facilities. J. Assoc. Off. Anal. Chem. 65(6): 1370–1374.

Otson, R., P. Fellin and Q. Tran. 1994. VOCs in representative Canadian residences. Atmos. Environ. 28(22): 3563–3569.

PACE (Petroleum Association for Conservation of the Canadian Environment). 1987. A study of exposure to motor gasoline hydrocarbon vapours at service stations. Phase II — Summer study (PACE Report No. 87-5).

PACE (Petroleum Association for Conservation of the Canadian Environment). 1989. A study of exposure to motor gasoline hydrocarbon vapours at service stations. Phase III — Winter study (PACE Report No. 89-3).

Romanelli, A., M. Falzoi, A. Mutti, E. Bergamaschi and I. Franchini. 1986. Effects of some monocyclic aromatic solvents and their metabolites on brain dopamine in rabbits. J. Appl. Toxicol. 6(6): 431–438.

Saillenfait, A.M., F. Gallisot, G. Morel and P. Bonnet. 2003. Developmental toxicities of ethylbenzene, *ortho*-, *meta*-, *para*-xylene and technical xylene in rats following inhalation exposure. Food Chem. Toxicol. 41(3): 415–429.

Smyth, H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani and J.A. Streigel. 1962. Range finding toxicity data: List IV. Am. Ind. Hyg. J. 23: 95–97.

Stott, W.T., K.A. Johnson, R. Bahnemann, S.J. Day and R.J. McGuirk. 2003. Evaluation of potential modes of action of inhaled ethylbenzene in rats and mice. Toxicol. Sci. 71(1): 53–66.

Toftgård, R. and O.G. Nilsen. 1982. Effects of xylene and xylene isomers on cytochrome P-450 and *in vitro* enzymatic activities in rat liver, kidney and lung. Toxicology 23: 197–212.

Ungvary, G. and E. Tatrai. 1985. On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. Arch. Toxicol. 8(Suppl.): 425–430 [cited in IPCS, 1996].

U.S. EPA (United States Environmental Protection Agency). 1992. Dermal exposure assessment: Principles and applications. Washington, D.C.

U.S. EPA (United States Environmental Protection Agency). 2001. Wall Paint Exposure Model (WPEM). Version 3.2, March 2001. Model developed by GEOMET Technologies, Inc. for the U.S. EPA Office of Pollution Prevention & Toxics and National Paint and Coatings Association (http://www.epa.gov/opptintr/exposure/docs/wpem.htm).

U.S. FDA (United States Food and Drug Administration). 2000. Total Diet Study. Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (http://vm.cfsan.fda.gov).

Versar Inc. 1986. Standard scenarios for estimating exposure to chemical substances during use of consumer products. Vol. I. Consumer use of household paints. Prepared for U.S. Environmental Protection Agency.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387–398 [cited in IPCS, 1996].