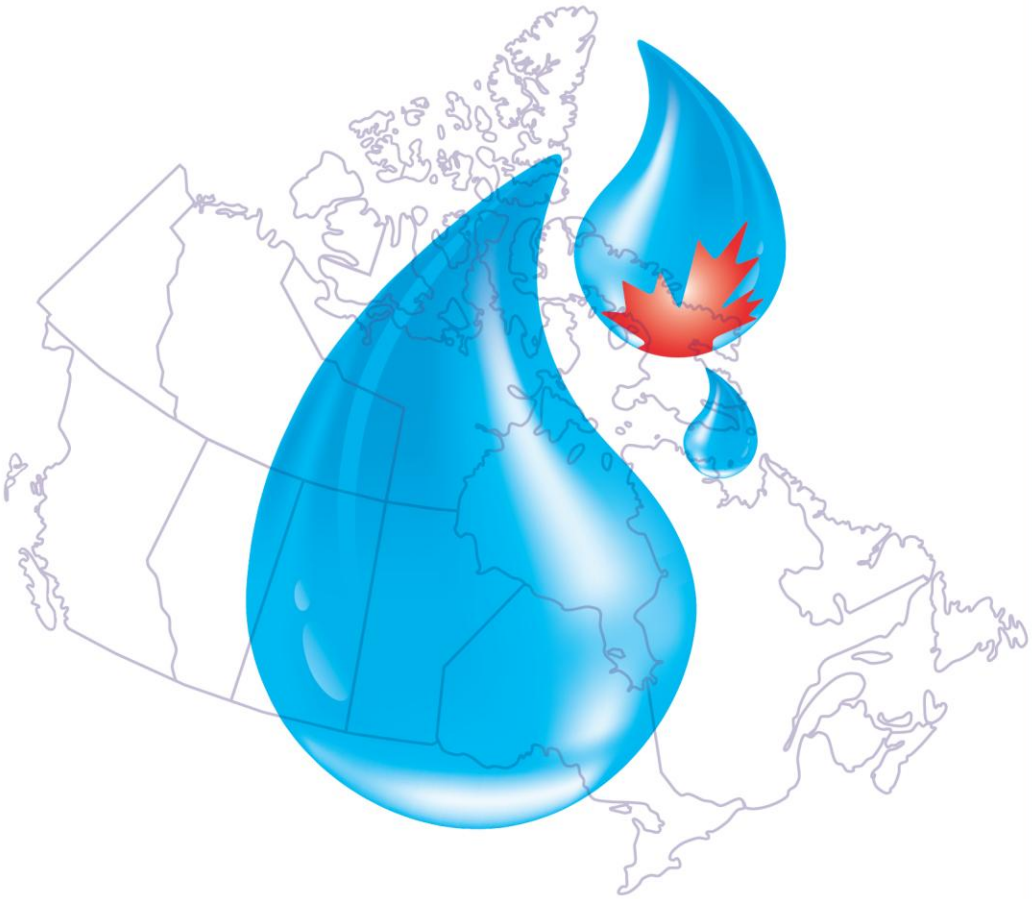
Health Canada Santé Canada

Your health and safety… our priority. *Votre santé et votre sécurité… notre priorité.*

Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Toluene, Ethylbenzene and Xylenes



Canada

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. *We assess the safety of drugs and many consumer products, help improve the safety of food, and provide information to Canadians to help them make healthy decisions. We provide health services to First Nations people and to Inuit communities. We work with the provinces to ensure our health care system serves the needs of Canadians.*

Published by authority of the Minister of Health.

Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Toluene, Ethylbenzene and Xylenes

is available on Internet at the following address:
www.healthcanada.gc.ca

Également disponible en français sous le titre :
Recommandations pour la qualité de l'eau potable au Canada : Document technique – Le toluène, l'éthylbenzène et les xylènes

This publication can be made available on request in a variety of alternative formats.

Pub. Number: 140429
Cat.: H144-20/2015E-PDF
ISBN: 978-1-100-25652-8

Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Toluene, Ethylbenzene and Xylenes

Prepared by the
Federal-Provincial-Territorial Committee on Drinking Water
of the
Federal-Provincial-Territorial Committee on Health and the Environment

Health Canada
Ottawa, Ontario

August, 2014

This document may be cited as follows:

Health Canada (2014). Guidelines for Canadian Drinking Water Quality: Guideline Technical Document — Toluene, Ethylbenzene and Xylenes. Water and Air Quality Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. (Catalogue No H144-20/2015E-PDF).

The document was prepared by the Federal-Provincial-Territorial Committee on Drinking Water of the Federal-Provincial-Territorial Committee on Health and the Environment.

Any questions or comments on this document may be directed to:

Water and Air Quality Bureau
Healthy Environments and Consumer Safety Branch
Health Canada
269 Laurier Avenue West, Address Locator 4903D
Ottawa, Ontario
Canada K1A 0K9

Tel.: 613-948-2566
Fax: 613-952-2574
E-mail: water_eau@hc-sc.gc.ca

Other Guideline Technical Documents for the Guidelines for Canadian Drinking Water Quality can be found on the following web page: www.healthcanada.gc.ca/waterquality

Table of Contents

August 2014

Toluene, Ethylbenzene and Xylenes[1]

Part I. Overview and Application

1.0 Guidelines

Toluene

A maximum acceptable concentration (MAC) of 0.06 mg/L (60 µg/L) is established for toluene in drinking water. An aesthetic objective (AO) of 0.024 mg/L (24 µg/L) is also established for toluene in drinking water.

Ethylbenzene

A MAC of 0.14 mg/L (140 µg/L) is established for ethylbenzene in drinking water. An AO of 0.0016 mg/L (1.6 µg/L) is also established for ethylbenzene in drinking water.

Xylenes

A MAC of 0.09 mg/L (90 µg/L) is established for total xylenes in drinking water. An AO of 0.02 mg/L (20 µg/L) is also established for total xylenes in drinking water.

2.0 Executive summary

Toluene, ethylbenzene and xylenes are primarily synthetic chemicals. These compounds are mainly found in petroleum hydrocarbons, such as gasoline and diesel fuel, or used as industrial solvents or as intermediates in styrene or benzene production. They can enter drinking water through leaching from contaminated sites or from industrial discharges of chemical manufacturing plants, or as a result of a spill during transportation or storage.

Because these chemicals are generally found together, and based on their similar chemical properties and treatment strategies, they have been grouped in one guideline technical document although individual guideline values are derived for each substance. This guideline technical document reviews and assesses all identified health risks associated with toluene, ethylbenzene and xylenes in drinking water, incorporating all relevant routes of exposure from drinking water—namely, ingestion as well as inhalation and skin absorption from showering and bathing.

It assesses new studies and approaches and takes into consideration the availability of appropriate treatment technology in order to establish maximum acceptable concentrations that are protective of human health, measurable and achievable by both municipal and residential scale treatment technologies. Based on this review, the drinking water guidelines are maximum acceptable concentrations of 0.06 mg/L (60 µg/L) for toluene, 0.14 mg/L (140 µg/L) for ethylbenzene, and 0.09 mg/L (90 µg/L) for xylenes.

[1] For the purpose of this document, the term "xylenes" refers to the total of all xylene isomers

2.1 Health effects

2.1.1 Toluene

There is currently insufficient information from both animal and human studies to determine whether toluene is carcinogenic to humans. The health effects of toluene have been studied in humans in various occupational settings. These studies have revealed an array of neurological effects including loss of colour vision, and disturbances in memory, concentration and cognitive function in general upon long-term inhalation of toluene. Studies of oral exposure in animals support adverse neurological effects as the endpoint of concern to derive a guideline for toluene in drinking water.

2.1.2 Ethylbenzene

Ethylbenzene is classified as possibly carcinogenic to humans, based on sufficient evidence of carcinogenicity in experimental animals but inadequate data in humans. Chronic studies in rats and mice suggest that exposure to ethylbenzene may lead to tumour formation at various sites, including kidney (male and female rats), lung (male mice), liver (female mice) and testes (male rats).

As for non-cancer health effects, animal data has identified liver and kidney as primary targets of ethylbenzene. Inhalation and ingestion of ethylbenzene in rats and mice lead to enlarged liver and kidney, increased severity of renal disease and effects on the pituitary gland. Effects on the liver and pituitary gland have been identified as the endpoints of concern to derive a guideline for ethylbenzene. There are little data available on the effects of ethylbenzene in humans, due to the lack of occupational settings in which exposure to ethylbenzene is predominant.

2.1.3 Xylenes

Xylenes are not classifiable with respect to carcinogenicity in humans, based on insufficient information. Data from both animal and human studies show that the primary health effects following exposure to xylenes will depend on the route of exposure: xylenes can affect the central nervous system by all routes of exposure, the respiratory tract following inhalation exposure, and the liver, kidney and body weight following oral exposures. Adverse neurological effects have been identified as the endpoint of concern to derive a guideline for xylenes in drinking water.

2.2 Aesthetic considerations

The presence of toluene, ethylbenzene and xylenes can be detected by their odour when present in water at levels below the MACs. Although there are no adverse effects associated with these levels, they will affect the acceptability of the water by consumers. The aesthetic objectives for these compounds are established at the level of the lowest reported odour thresholds, specifically 0.024 mg/L (24 µg/L) for toluene, 0.0016 mg/L (1.6 µg/L) for ethylbenzene, and 0.02 mg/L (20 µg/L) for xylenes.

2.3 Exposure

The general population is primarily exposed to toluene, ethylbenzene and xylenes from inhalation of ambient air and usage of various products including gasoline and diesel fuels and solvents. To a lesser extent, exposure can also occur from drinking water, contaminated soil, or from food. Toluene, ethylbenzene and xylenes are rarely detected in Canadian drinking water supplies. Canadians may also be exposed to toluene, ethylbenzene and xylenes from drinking water through inhalation and dermal absorption.

2.4 Analysis and treatment

The establishment of a drinking water guideline must take into consideration the ability to both measure the contaminant and remove it from drinking water supplies. Toluene, ethylbenzene and xylenes can be reliably measured in drinking water at the MACs.

At the municipal level, conventional treatment techniques are not effective at removing toluene, ethylbenzene and xylenes. The best available technologies for removing all three compounds from drinking water are packed tower aeration and granular activated carbon. Taking into consideration currently available technologies, municipal treatment plant are expected to be able to consistently achieve concentrations below the MACs and aesthetic objectives.

At the residential scale, there are certified point-of-use treatment devices available that can remove volatile organic chemicals (VOCs) such as toluene, ethylbenzene and xylenes from drinking water to meet the MACs and aesthetic objectives. They rely on adsorption (activated carbon) and reverse osmosis technologies. Filtration systems may be installed at the faucet (point-of-use) or at the location where water enters the home (point-of-entry). Point-of-entry systems are preferred for the reduction of VOCs, because they provide treated water for bathing and laundry as well as for cooking and drinking. This will reduce the potential for VOC exposure through inhalation.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

Generally, toluene, ethylbenzene and xylenes are not a concern for the majority of Canadians who rely on surface water as their source of drinking water, because it volatilizes easily. However, the anaerobic conditions of groundwater increases biodegradation time of toluene, ethylbenzene and xylenes, which are usually detected in groundwater in the vicinity of sites where there have been spills or other potential contamination with these compounds.

The drinking water guidelines are based on lifetime exposure (70 years) to toluene, ethylbenzene and xylenes in drinking water. For drinking water supplies that occasionally experience short-term exceedances above the guideline values, it is suggested that a plan be developed and implemented to address these situations. For more significant, long-term exceedances that cannot be addressed through treatment, it is suggested that alternative sources of water for drinking, showering, and bathing be considered.

3.1 Monitoring

Groundwater sources should be characterized to determine if toluene, ethylbenzene and xylenes are present, especially if the land use history is unknown. Quarterly monitoring for toluene, ethylbenzene and xylenes should be conducted for groundwater sources that are or may have been impacted by hydrocarbon spills or other potential contamination with these compounds. Monitoring of the distribution system is recommended when contamination has occurred in soil where there are plastic pipes.

Authorities may consider reduced monitoring when it has been demonstrated that a previously contaminated site has been successfully remediated. In the event that monitoring data show elevated levels of toluene, ethylbenzene and xylenes, it is suggested that a plan be developed and implemented to address these situations.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Toluene, ethylbenzene and xylenes are volatile, flammable and colourless liquids with a sweet, pungent or gasoline-like odour. Toluene may also be referred to as methylbenzene and was formerly known as toluol. Xylenes are also known as dimethylbenzenes. All three compounds are monoaromatic hydrocarbons and thus derivatives of benzene. Toluene and ethylbenzene differ from benzene by the addition of a single methyl or ethyl group, respectively, whereas xylenes have two methyl group substitutions. The position of the methyl groups on the benzene ring determines the isomer of xylene: *ortho*- (*o*-), *meta*- (*m*-) or *para*- (*p*-) xylene, also known as 1,2-, 1,3- and 1,4-dimethylbenzene (U.S. EPA, 1990). Typical mixtures of xylenes contain approximately 40% *m*-xylene, 24% *o*-xylene and 19% *p*-xylene, as well as 17% ethylbenzene (Hancock, 1982).

Toluene, ethylbenzene and xylenes are moderately soluble in water and have relatively low log *n*-octanol/water partition coefficient (K_{ow}) (Mitra and Roy, 2011). Toluene is the most water soluble of these compounds. All of these compounds have relatively elevated vapour pressures and vapours that are highly flammable and explosive at sufficient concentrations (Vallero, 2004). Specific physicochemical properties for toluene, ethylbenzene, xylenes (which vary in composition and include a variety of impurities, ethylbenzene being the largest) and *o*-, *m*- and *p*-xylene isomers are presented in Table 1.

Table 1. Physical and chemical properties of toluene, ethylbenzene and xylenes

Property	Toluene	Ethylbenzene	Xylenes	*o*-Xylene	*m*-Xylene	*p*-Xylene
Molecular formula	$C_6H_5CH_3$	$C_6H_5CH_2CH_3$	$C_6H_4(CH_3)_2$			
CAS No.	108-88-3	100-41-4	1330-20-7	95-47-6	108-38-5	106-42-3
Molecular weight (g/mol)	92.13[a]	106.17[b]	106.17[c]			
Melting point (°C)	−95.0[a]	−95.0[d]	-47.4	−25.0[c]	−47.4[c]	13–14[c]
Boiling point (°C)	110.6[a]	136.2[d]	137.0–140.0[c]	144.4[c]	139.0[c]	138.4[c]
Log K_{ow}	2.69[e]	3.15[f]	3.12–3.20[g]	2.77[h]	3.20[h]	3.15[h]
Vapour pressure (mmHg)[i]	22.0 (20°C)[j]	7.0 (20°C)[j]	6.0–16.0 (20°C)[h]	6.6 (25°C)[h]	8.3 (25°C)[h]	8.8 (25°C)[h]
Density (g/mL)	0.87 (20°C)[k]	0.87[l]	0.86[h]	0.86[h]	0.88[h]	0.86[h]
Solubility in water (mg/L)	515 (20°C)[j]	152 (20°C)[j]	106 (25°C)[h]	178 (25°C)[h]	161 (25°C)[h]	162 (25°C)[h]
Conversion factors for air (ppm to mg/m^3)	3.77	4.34	4.34			

CAS, Chemical Abstracts Service; K_{ow}, *n*-octanol/water partition coefficient
[a] Budavari et al. (1989); [b] Lide (1994); [c] Budavari et al. (1996); [d] Cannella (2007); [e] U.S. EPA (1995a); [f] U.S. EPA (1995b); [g] U.S. EPA (1995c); [h] ATSDR (1995); [i] 1 mmHg = 133.3 Pa; [j] Verschueren (1983); [k] HSDB (1999); [l] Welch et al. (2005).

Alexander et al. (1982) measured aqueous odour and taste thresholds for various chemicals, including toluene, ethylbenzene and xylenes. The odour threshold values were reported as milligrams of compound per litre of odour-free water at 60°C. The authors stated that

the odour thresholds measured at 60°C should be applicable to ambient temperature, since the temperature effect appeared to be small. The taste threshold values were reported as milligrams of compound per litre of odour-free water at 40°C. For toluene, two odour threshold measurements of 0.024 mg/L were reported; for ethylbenzene, two odour threshold measurements of 0.0016 and 0.0032 mg/L were reported. Also for toluene, two taste threshold measurements of 0.12 and 0.16 mg/L (average value 0.14 mg/L) were reported; for ethylbenzene, two taste threshold measurements of 0.064 and 0.080 mg/L (average value 0.072 mg/L) were reported. For the xylenes, Middleton et al. (1958) stated that taste and odour could be detected at concentrations ranging from 0.3 to 1.0 mg/L; WHO (2003b) reported from VanGemert and Nettenbrijer (1977) and from Verschueren (1983) that the odour threshold for xylene isomers in water ranges from 0.02 to 1.8 mg/L.

Toluene is primarily manufactured by catalytic reforming of petroleum, ethylbenzene by alkylation of benzene, and xylene by the dehydrocyclodimerization and methylation of toluene and benzene (Camford Information Services Inc., 1996, 2003, 2004). Many industrial and technical applications exist for all three compounds. They are primarily used in the synthesis of specific chemical compounds or as industrial solvents. Toluene is a common solvent used in making paints, paint thinners, fingernail polish, lacquers, adhesives and rubber, as well as in some printing and leather tanning procedures (ATSDR, 2000). It is a common gasoline additive (ATSDR, 2000) and is used in the production of various organic compounds, including benzene and toluene diisocyanate (U.S. EPA, 1995d). It is also employed as a carbon source in the synthesis of multiwall carbon nanotubes (Mi et al., 2005). The uses of toluene are estimated as follows: 46% for benzene production, 37% as a gasoline additive, 8% as a solvent, 7% for toluene diisocyanate production and 2% for other purposes (U.S. EPA, 1995d). Ethylbenzene is used almost exclusively as an intermediate in the production of styrene. In 2003, 789 kilotonnes of styrene were manufactured by two Canadian manufacturers (Ontario and Alberta); 811 kilotonnes of styrene were forecasted to be manufactured in 2006 (Camford Services, 2004). It is also present in gasoline (< 15%) and in mixed xylenes (< 25%) (IARC, 2000). Xylenes are frequently used as solvents and in paint thinners, varnishes and cleaning agents (ATSDR, 2007). Similarly to toluene and ethylbenzene, xylenes are fuel additives that comprise approximately 10% of gasoline. Approximately 82% of xylenes produced is *p*-xylene, which is used in the production of terephthalic acid and dimethyl terephthalate, both of which are needed to produce polyethylene terephthalate plastic bottles and polyester clothing. *o*-Xylene and *m*-xylene isomers are used to a lesser extent in the production of phthalic anhydride and isophthalic acid, respectively (Swedish Chemicals Agency, 2010).

In 2009 Canadians used 42.3 billion litres of gasoline; the Ontario market accounts for 39% of motor gasoline sales in Canada, followed by Québec (21%), Alberta (13%), British Columbia (11%), and Atlantic Canada (7%) (NRCan, 2011). Canadian domestic sales of diesel fuel in 2009 were 26.0 billion litres with approximately 49% of the diesel sales occurring in the western provinces and territories, followed by Ontario (25%), Quebec (18%) and Atlantic Canada (8%). (NRCan, 2011). Toluene, ethylbenzene and xylenes (along with benzene) are part of the aromatic fraction in gasoline and diesel fuel. In 2008, the aromatic content for typical Canadian gasoline ranges from 24.8 to 30.3 % volume (Rahumathulla et al. 2010). The average weight % aromatic content in diesel fuel (regular or low sulphur summer or winter diesel) in Canada ranges from 28.76 to 36.8% (Guthrie et al., 2003). With the widespread use of gasoline and diesel fuel in Canada, unintentional releases to the environment from activities associated with production, transportation and storage, as well as during refuelling of vehicles can contaminate nearby soil and water (Mitra and Roy, 2011). Due to their volatile nature, toluene, ethylbenzene and xylenes will readily vaporize from water and soil upon contact with air (Vallero, 2004). Additional

toluene can be released to the atmosphere via several manufacturing processes, including fuel production from crude oil, coke production from coal and as a by-product of styrene production (ATSDR, 2000).

4.1 Environmental fate

Toluene, ethylbenzene and xylenes will tend to partition to air and water due to their relatively high vapour pressure, moderate water solubility and low log K_{ow}. The atmosphere is an important sink for toluene, ethylbenzene and xylenes, as over 98% of the compounds released in the environment will eventually partition to air (ASTER, 1995; IPCS, 1997; OECD, 2002). The primary processes for the removal of toluene, ethylbenzene and xylene from water are volatilization and microbial degradation, the latter being more important with increased water depths (Arthurs et al., 1995). In surface water, toluene, ethylbenzene and xylenes can float near the surface, where they readily volatilize (Mitra and Roy, 2011). Half-lives ranging from 5 hours to 16 days for toluene and from 3.1 hours to 4.1 days for ethylbenzene and xylenes have been reported in conditions ranging from turbulent to static waters (Mackay and Leinonen, 1975; Thomas, 1982; HSDB, 1986, 2010; ATSDR, 2000). Toluene, ethylbenzene and xylenes are readily biodegradable in soil and water under aerobic conditions. Biodegradation half-lives ranging from 2 to 92 days, from 0.1 to 231 days and from 24 to 161 days have been reported for toluene, ethylbenzene and xylenes, respectively (Barker et al., 1986; Wilson et al., 1986; Slooff and Blokzijl, 1988; Mackay et al., 1992; Earl et al., 2003). Biodegradation of these compounds can be slowed significantly when their concentrations are sufficient to cause microbial death or under anaerobic conditions. For example, ethylbenzene degradation can extend to 1155 days under anaerobic conditions (Earl et al., 2003). Slower degradation of toluene, ethylbenzene and xylenes can contribute to transportation of the compounds considerable distances from the original source (Zogorski et al., 2006). Toluene, ethylbenzene and xylenes are not expected to bioconcentrate or biomagnify to a great extent in aquatic organisms (ATSDR, 2010).

5.0 Exposure

For the most part, Canadians are exposed to toluene, ethylbenzene and xylenes through air, predominantly via vapours from various consumer products. Exposure through drinking water and soil can also occur, but usually to a lesser extent, although it can be considerable in areas of contamination. Although some exposure data are available, they are not sufficient to modify the default proportion of 20% of the daily intake allocated to drinking water.

5.1 Water

Toluene, ethylbenzene and xylenes have been detected at low levels in some Canadian drinking water supplies. In a 1979 study of 30 water treatment facilities across Canada, average toluene levels of 2 μg/L were measured in treated drinking water, whereas ethylbenzene and *m*-xylene levels were below the detection limit of 1 μg/L (Otson et al., 1982). In a study in Ontario, toluene and xylenes were detected at levels below 0.5 μg/L in samples collected from drinking water supplies, including groundwater, lake water and river water, in 1975 in proximity to and apart from the Great Lakes (Smillie et al., 1978).

Monitoring of toluene, ethylbenzene and xylenes by provinces and territories show undetectable or low levels of these chemicals in most Canadian drinking water supplies. In various locations representing all of Ontario from 2007 to 2012, toluene was detected above the method detection limit (MDL) (0.5 μg/L) in 62 of 46 472 samples; the highest concentration of toluene measured was 20.0 μg/L (Ontario Ministry of the Environment, 2012). In Manitoba,

toluene, ethylbenzene and *o*-xylene were measured between 2007 and 2012, with the highest concentrations found being 22.0, 5.5 and 30.0 µg/L, respectively (Manitoba Conservation and Water Stewardship, 2012). From 2003 to the present, toluene, ethylbenzene and xylenes were detected in only 1%, 1.5% and 1.1% of total drinking water samples from New Brunswick (over 5000 samples), respectively; the highest detectable concentrations of these chemical components in drinking water were 1.3 µg/L for toluene, 1.4 µg/L for ethylbenzene and 7.5 µg/L for xylenes (New Brunswick Department of Health, 2012). In Quebec, maximum concentrations of toluene, ethylbenzene, *o*-xylene and *m*/*p*-xylene in untreated water after 2002 were 2.0, 0.12, 0.13 and 0.21 µg/L, respectively (Ministère du Développement Durable, de l'Environnement et des Parcs du Québec, 2012). Data from Saskatchewan indicate contamination event levels of toluene above 1 µg/L in 44 of 321 samples of treated drinking water, with a maximum level of 3300 µg/L; maximum levels of ethylbenzene and xylenes were reported to be 550 and 2825 µg/L, respectively, from 1989 to 2012 (Saskatchewan Ministry of Environment, 2012). Over the 2002 to 2012 time period the maximum levels detected for toluene, ethylbenzene and xylenes in Saskatchewan treated drinking water were 22, 16 and 7 µg/L, respectively.

5.2 Food

There is a lack of information regarding the presence and concentrations of toluene, ethylbenzene and xylenes in food in Canada. The U.S. Food and Drug Administration total diet study reported mean levels of toluene below 0.17 part per million (ppm), ethylbenzene below 0.01 ppm and xylenes below 0.02 ppm in approximately 280 food items, including breads and cereal, dairy products, desserts, fruits and vegetables, as well as raw and prepared meats, from 1991 to 2004 (U.S. FDA, 2008). Toluene, ethylbenzene and xylenes can also be present in food as a result of water use during preparation or indirectly from components of commercial packaging.

5.3 Air

Since toluene, ethylbenzene and xylenes strongly partition to the atmosphere, exposure via air can be considerable. Mean concentrations of toluene in ambient air have been shown to range from 1.0 to 30.7 µg/m^3 in various Canadian cities (Dann et al., 1989; Ontario Ministry of Environment and Energy, 2000), whereas mean concentrations of ethylbenzene were shown to range from 0.1 to 17.0 µg/m^3 (Ontario Ministry of Environment and Energy, 2000; Alberta Environment, 2004). Mean concentrations of xylenes in ambient air at Canadian urban and suburban sites ranged from 0.6 to 20.4 µg/m^3 (Dann et al., 1989; Ontario Ministry of Environment and Energy, 2000). Generally, concentrations of these compounds were lower in rural areas. Mean concentrations of 4.9 and 4.3 µg/m^3 have been reported in rural Walpole Island, Ontario, for toluene and xylenes, respectively (Dann et al., 1989).

Important exposures to toluene, ethylbenzene and xylenes can also occur indoors. Studies of households across Canada spanning all four seasons have reported mean concentrations ranging from 2.5 to 84.3 µg/m^3 and from 0.6 to 14.0 µg/m^3 for toluene and ethylbenzene, respectively (Fellin and Otson, 1994; Zhu et al., 2005; Héroux et al., 2008). Mean concentrations of xylene isomers ranged from 0.8 to 8.2 µg/m^3 for *o*-xylene and from 1.8 to 34.2 µg/m^3 for *m*/*p*-xylene (Fellin and Otson, 1994; Zhu et al., 2005; Héroux et al., 2008).

In 2005–2006, as part of a personal exposure monitoring campaign funded under the Border Air Quality Strategy, Health Canada and the University of Windsor collected 24-hour personal, indoor and outdoor exposure samples for 188 polar and non-polar volatile organic compounds (VOCs) (Health Canada, 2010a). In total, 100 study participants in Windsor, Ontario, were followed over two 1-year periods. Sampling took place in 8-week "winter" and "summer" periods of 2005 and 2006, when five consecutive 24-hour VOC sampling measurements were

obtained to represent indoor, outdoor and personal exposure levels (2005 only). Over the 2-year period, median concentrations of toluene in indoor air ranged from 8.3 to 23.5 μg/m^3, and median concentrations in outdoor air ranged from 1.9 to 4.3 μg/m^3. Median concentrations of ethylbenzene in indoor air ranged from 1.1 to 2.9 μg/m^3, and median concentrations in outdoor air ranged from 0.3 to 0.6 μg/m^3. Median concentrations of xylene in indoor air ranged from 1.0 to 8.6 μg/m^3, and median concentrations in outdoor air ranged from 0.3 to 1.6 μg/m^3. Similar trends were reported in a recent study conducted in Regina, Saskatchewan (Health Canada, 2010b).

Data on Canadian concentrations of toluene, ethylbenzene and xylenes in indoor and ambient air are similar to those reported in the United States (ATSDR, 2000, 2007, 2010).

5.4 Soil

Data on concentrations of toluene, ethylbenzene and xylenes in soil in Canada and other countries are scarce. The Ontario Ministry of Environment and Energy reported 98th percentile concentrations of toluene, ethylbenzene and xylenes to be 0.9, 0.4 and 0.8 μg/kg in old urban parkland soils and 0.9, 0.5 and 0.9 μg/kg in rural parkland soils, respectively (OMEE, 1993). Neither of these regions was affected by local point source pollution. Due to the fate of toluene, ethylbenzene and xylenes in the environment, levels of these compounds in soil are generally low, with considerable contamination occurring only in areas near hazardous waste sites or in cases of chemical spills.

5.5 Consumer products

Due to their extensive use as solvents and their presence in fuels, toluene, ethylbenzene and xylenes are frequently found in various consumer products. These products include gasoline and diesel fuel, paints and inks, as well as various cleaners, polishes and adhesives. Storage of such products is a frequent means of exposure to toluene, ethylbenzene and xylenes. For example, vapours from stored materials or from vehicular exhaust can enter indoor environments via adjacent garages (Graham et al., 2004; Dodson et al., 2008). Cigarette smoking can also be a significant source of exposure to toluene, ethylbenzene and xylenes.

5.6 Multi-route exposure through drinking water

A human physiologically based pharmacokinetic (PBPK) model that was developed for toluene, ethylbenzene and xylenes using data from Tardif et al. (1997) was extended to include a dermal component for assessing multiple routes of exposure. The model was developed in order to extrapolate inhalation data from rats, mice and occupationally exposed workers (Korsak et al., 1994; NTP, 1999; Seeber et al., 2004, 2005) to humans exposed to low concentrations of each chemical in drinking water. The model was also used to estimate litre-equivalent (L-eq) contributions from dermal and inhalation exposures when showering and bathing. Using the external doses generated from the human PBPK model (see Section 8.5.4), litre-equivalent contributions from dermal and inhalation exposures during showering or bathing were estimated by running the human PBPK model for a 30-minute bathing scenario. By comparing the internal doses generated from the dermal and inhalation routes of exposure with the internal dose from ingestion in accordance with total body weight, the litre-equivalent contributions for dermal and inhalation exposures were estimated to be 0.2 L-eq and 0.43 L-eq for toluene, 0.21 L-eq and 0.44 L-eq for ethylbenzene, and 0.21 L-eq and 0.43 L-eq for xylenes, respectively. When added to the standard Canadian drinking water consumption rate of 1.5 L/day, the total litre-equivalent daily exposures to toluene, ethylbenzene and xylenes in drinking water were estimated to be 2.13, 2.15 and 2.14 L-eq, respectively. These litre-equivalent daily exposures were used in both the cancer and non-cancer risk assessments in Section 10.

6.0 Analytical methods

The U.S. Environmental Protection Agency (EPA) currently has three approved analytical methods (502.2 revision 2.1, 524.2 revision 4.1 and 524.3 version 1.0) for measuring toluene, ethylbenzene and xylenes (TEX) in drinking water (U.S. EPA, 2011). These methods are general analytical methods for the identification and measurement of purgeable VOCs. The methods use purge and trap procedures, followed by a capillary gas chromatography (GC) column to separate the analytes. After elution from the GC column, the analytes are identified by different detection techniques.

Method 502.2 revision 2.1 employs purge and trap capillary GC in combination with a photoionization detector. Method 524.2 revision 4.1 includes purge and trap of the samples and desorption of the trapped sample components into a capillary GC column interfaced to a mass spectrometer (MS). Both methods reported multiple MDL values, depending on the GC column and/or GC/MS interface used. Method 524.3 version 1.0 is an updated version of method 524.2. The advantages of this method include an optimization of the purge and trap parameters, an option for use of selected ion monitoring and the use of solid acid preservatives.

In addition, two equivalent standard methods, SM 6200B and SM 6200C, can be used for the analysis of toluene, ethylbenzene and xylenes in drinking water. These methods are based on purge and trap capillary GC followed by MS detection and a photoionization detector, respectively (APHA et al., 2012).

The analytical methods can explicitly identify the three xylene isomers if the isomers have sufficiently different retention times in the GC column. If two of the three xylene isomers cannot be resolved (separated) on the capillary column, the isomers are identified as an isomeric pair (U.S. EPA, 1995d). In this report, the term total xylene concentration refers to the total concentration of the three isomers.

The current U.S. EPA practical quantitation levels (PQLs) for toluene, ethylbenzene and total xylenes are set individually at 0.005 mg/L (5 µg/L) (U.S. EPA, 1991b).

6.1 Toluene

Method 502.2 revision 2.1 has an MDL in the range of 0.01–0.02 µg/L, depending on the GC column used. Method 524.2 revision 4.1 has an MDL in the range of 0.08–0.11 µg/L, depending on the GC column and GC/MS interface used (U.S. EPA, 1995d). Method 524.3 version 1.0 reported a detection limit of 0.024 µg/L (U.S. EPA, 2009).

Method SM 6200B has an MDL of 0.047 µg/L, and method SM 6200C has an MDL of 0.023 µg/L. The minimum quantitation levels, defined as the lowest levels that can be quantified accurately, are 0.188 µg/L and 0.092 µg/L for methods SM 6200B and SM 6200C, respectively (APHA et al., 2012).

6.2 Ethylbenzene

Method 502.2 revision 2.1 has an MDL in the range of 0.01–0.04 µg/L, depending on the GC column used. Depending on the GC column and GC/MS interface used, method 524.2 revision 4.1 allows MDL values in the range of 0.03–0.06 µg/L (U.S. EPA, 1995d). Method 524.3 version 1.0 has a detection limit of 0.01 µg/L (U.S. EPA, 2009).

Method SM 6200B has an MDL of 0.032 µg/L, and method SM 6200C has an MDL of 0.028 µg/L. The minimum quantitation levels, defined as the lowest levels that can be quantified

accurately, are 0.128 µg/L and 0.112 µg/L for methods SM 6200B and SM 6200C, respectively (APHA et al., 2012).

6.3 Xylenes

Method 502.2 revision 2.1 has an MDL of 0.02 µg/L for *o*-xylene. The MDLs for both *m*- and *p*-xylene will be either 0.01 or 0.02 µg/L, depending on the GC column used for this method (U.S. EPA, 1995d). Depending on the GC column and GC/MS interface used, method 524.2 revision 4.1 allows MDL values in the range of 0.06–0.11 µg/L for *o*-xylene, 0.03–0.05 µg/L for *m*-xylene and 0.06–0.13 µg/L for *p*-xylene (U.S. EPA, 1995d). Method 524.3 version 1.0 reports a retention time of 11.3 minutes on the chromatographic column for *o*-xylene, and the method has a detection limit of 0.01 µg/L. The method defines *m*-xylene and *p*-xylene as an isomeric pair, with a detection limit of 0.02 µg/L (U.S. EPA, 2009).

Method SM 6200B reported a retention time of 15.27 minutes for *o*-xylene and has an MDL of 0.038 µg/L. The other two isomers have been defined as an isomeric pair, and the method reported an MDL of 0.038 µg/L. The minimum quantitation level for method SM 6200B is 0.152 µg/L. Method SM 6200C has an MDL of 0.024 µg/L for *o*-xylene and 0.021 µg/L for the *m/p*-isomeric pair. Method SM 6200C has minimum quantitation levels of 0.096 µg/L for *o*-xylene and 0.084 µg/L for the *m/p*-isomeric pair (APHA et al., 2012).

Table 2 summarizes the various analytical methods and their respective detection limits for each of the contaminants.

Table 2. Analytical methods for ethylbenzene, toluene and xylenes

Analytical method	MDLs (µg/L)				
	Toluene	**Ethylbenzene**	***o*-Xylene**	***m*-Xylene**	***p*-Xylene**
502.2 rev. 2.1[a]	0.01–0.02	0.01–0.04	0.02	0.01–0.02	0.01–0.02
524.2 rev. 4.1[a]	0.08–0.11	0.03–0.06	0.06–0.11	0.03–0.05	0.06–0.13
524.3 ver. 1.0[a]	0.024	0.01	0.01	0.02 (isomeric pair)	
SM 6200B[b]	0.047	0.032	0.038	0.038 (isomeric pair)	
SM 6200C[b]	0.023	0.028	0.024	0.021 (isomeric pair)	

[a] U.S. EPA, (1995d)

[b] APHA, American Water Works Association and Water Environment Federation (2012)

7.0 Treatment technology and distribution system considerations

7.1 Municipal scale

Conventional water treatment techniques (coagulation, sedimentation, filtration and chlorination) have little or no effect in reducing concentrations of VOCs in drinking water (Love and Eilers, 1982; Love et al., 1983; Lykins and Clark, 1994). Some incidental removal of VOCs may occur as a result of volatilization in open basins and open weirs (AWWA, 1991; Health and Welfare Canada, 1993).

Granular activated carbon (GAC) and packed tower aeration (PTA) have been identified as the best available technologies (BATs) for TEX removal from drinking water (U.S. EPA, 1998). Small system compliance technologies include GAC, PTA, diffused aeration, multistage bubble aeration, tray aeration and shallow tray aeration (U.S. EPA, 1998).

The selection of an appropriate treatment process for a specific water supply will depend on many factors, including the characteristics of the raw water supply, the concentration of the contaminant and the operational conditions of the specific treatment method. These factors should be taken into consideration to ensure that the treatment process selected is effective for the reduction of TEX in drinking water.

7.1.1 Activated carbon

Activated carbon is used in the water treatment process either as GAC or as powdered activated carbon (PAC). Generally, GAC and PAC are used for different purposes. GAC is used for the control of organic compounds as a barrier to occasional spikes of organics in surface water, taste and odor control as well as disinfection by-products control. In contrast, PAC controls taste and odor compounds and strongly adsorbs low levels of pesticides and herbicides. The adsorption capacity of activated carbon to remove VOCs is affected by a variety of factors, such as competition from other contaminants, preloading with natural organic matter (NOM), temperature and the physicochemical properties of the VOCs and the carbon media (Speth, 1990; AWWA, 1991). The PAC application, most suitable for conventional treatment systems treating surface waters, may remove occasional low concentrations of VOCs such as TEX when it is applied at the treatment plant, allowing sufficient contact time and proper mixing. In conventional treatment plants, the common points of PAC application are at the plant intake, during the rapid mix process and in the filter influent. Sufficient contact time is necessary, and the time required is a function of the characteristics and the concentration of the contaminant to be adsorbed (Najm et al., 1991). In general, PAC adsorption is found to be less efficient than GAC adsorption for VOCs removal largely due to: (1) its use in coagulation/sedimentation basins where the adsorption sites can be blocked due to floc formation; (2) the fact that it will not have the necessary adsorption time to reach its maximum capacity; and (3) the fact that the equilibrium liquid-phase concentration (concentration gradient driving force) goes down during the adsorption process. A conventional water treatment technique in combination with a PAC dose in the range of 8–27 mg/L demonstrated reduction rates of up to 67% for toluene, from 33% to 99% for ethylbenzene and from 60% to > 99% for total xylenes, respectively (U.S. EPA, 1991a).

Higher concentrations of VOCs are typically found in groundwater, and GAC adsorption is the most commonly used treatment process for the removal of VOCs from groundwater (Snoeyink, 1990). In the GAC process, as water passes through the GAC contactor, the contaminants diffuse into the adsorbent granules and accumulate on the inner surface within the pores. The GAC column allows more complete contact between water and the media, greater adsorption efficiency and greater process control than with PAC. Full-scale and pilot-scale data demonstrated that removal efficiency in the range of 75–99% for TEX is achievable using GAC adsorption (Miltner at al., 1987; U.S. EPA, 1990; AWWA, 1991).

The selection of GAC for removing VOCs from drinking water supplies should factor in the following process design considerations: carbon usage rate, empty bed contact time (EBCT), type of adsorbent, pretreatment of the raw water, contactor configuration (e.g., beds in series or parallel operation) and method of GAC regeneration or replacement. During the operation time, and depending on the variety of factors discussed above, organic contaminants will “break through” the carbon bed. Initial breakthrough is defined as the time when the contaminant concentration in the effluent exceeds the treatment objective. In systems with multiple beds, the individual beds can be operated beyond the time of initial breakthrough, provided the blended effluents still meet the treatment objectives. Once the GAC is exhausted, it is removed from the contactor and replaced with fresh or regenerated GAC. For practical reasons, PAC is not recovered and reactivated; thus, its carbon use rate can be high compared with that of GAC

(Chowdhury et al., 2013). The regeneration and/or replacement of exhausted media are important economic considerations in achieving the contaminant removal.

Common operational issues when using GAC adsorption contactors can include biological growth and a concurrent increase in heterotrophic plate counts in the treated water as well as clogging and fouling of the carbon adsorber by chemicals, bacterial precipitants and background organic matter (AWWA, 1991). Operational considerations may also include the need to ensure a proper backwash, maintain the bed depth and bed density after backwashing and control the flow rate. To prevent the bed from clogging, pretreatment of the water before it enters the GAC contactor is often required (Snoeyink, 1990; Speth, 1990; AWWA, 1991; Crittenden et al., 2005).

When designing a GAC system, relevant information and operational parameters are obtained from pilot plant experiments, rapid small-scale columns test (RSSCT) and vendor experience. Mathematical model can also be used to predict process performance and select the optimum process design as an additional or complementary approach to pilot plant and RSSCT experiments.

7.1.1.1 Toluene

Full-scale data demonstrated that two GAC adsorbers operating in series with a hydraulic loading rate of 2.2 gpm/ft^2 (5.4 m/h) and an EBCT of 27 minutes were capable of achieving greater than 99% reduction of a toluene concentration in groundwater. However, the influent concentration of 220 µg/L has been reported as a total BTX (benzene, toluene and xylenes) concentration (AWWA, 1991).

A pilot-scale study indicated that a GAC column operating with a hydraulic loading rate of 2.0 gpm/ft^2 (4.9 m/h) and an EBCT of 1.0 minute was capable of reducing a toluene concentration of 24.55 µg/L in groundwater to 6.1 µg/L, achieving a carbon usage rate of 0.066 lb/1000 gal (0.008 kg/m^3) and a bed life of 1.5 months (Miltner et al., 1987; U.S. EPA, 1990). The results from the pilot-scale study were applied to predict the carbon usage rate of a full-scale GAC contactor. The GAC contactor, designed with a bed depth of 4.05 ft (1.23 m), a hydraulic loading rate of 2.0 gpm/ft^2 (4.9 m/h) and an EBCT of 15 minutes, could reduce an influent concentration of 500 µg/L to 5 µg/L. Under these conditions, a carbon usage rate of 0.33 lb/1000 gal (0.04 kg/m^3) and a bed life of 4.5 months would be required to achieve a 99% reduction of toluene (Miltner at al., 1987).

Operational data from a groundwater remediation site demonstrated that a full-scale GAC system with a bed life of 3.5 months was capable of reducing toluene concentrations ranging from 4.4 to 55.0 mg/L to 5 µg/L. The breakthrough of the carbon bed was defined as the time when the benzene concentration in the effluent exceeded 5 µg/L (369 917 L of treated water) (Giffin and Davis, 1998).

7.1.1.2 Ethylbenzene

Data from a pilot-scale study demonstrated that the influent concentration of ethylbenzene of 4.5 µg/L in groundwater was reduced to 1.1 µg/L using a column with a hydraulic loading rate of 2.0 gpm/ft^2 (4.9 m/h) and an EBCT of 1.0 minute, resulting in a carbon usage rate of 0.071 lb/1000 gal (0.009 kg/m^3) and a bed life of 1.4 months (Miltner et al., 1987; U.S. EPA, 1990). Using the input parameters from this study, Miltner et al. (1987) predicted the carbon usage rate of a full-scale GAC adsorber. The GAC adsorber, designed with a bed depth of 4.05 ft (1.23 m), a liquid loading rate of 2.0 gpm/ft^2 (4.9 m/h) and an EBCT of 15 minutes, could reduce an influent ethylbenzene concentration of 100 µg/L to 10 µg/L (90% reduction). The resulting carbon usage rate would be 0.24 lb/1000 gal (0.03 kg/m^3), and the bed life would be 6.1 months under these conditions (Miltner at al., 1987).

Operational data from a groundwater remediation site demonstrated that a full-scale GAC system with a bed life of 3.5 months was capable of reducing ethylbenzene concentrations in the range of 0.54–3.9 mg/L to below 1 µg/L. The breakthrough of the carbon bed was defined as the time when the benzene concentration in the effluent exceeded 5 µg/L (369 917 L of treated water) (Giffin and Davis, 1998).

7.1.1.3 Xylenes

Full-scale data demonstrated that two GAC adsorbers operating in series with a hydraulic loading rate of 2.2 gpm/ft^2 (5.4 m/h) and an EBCT of 27 minutes were capable of achieving a greater than 99% reduction in the concentration of total xylenes in groundwater. The influent concentration of 220 µg/L was reported as a total BTX concentration (AWWA, 1991).

A pilot-scale study using a GAC column indicated that the influent concentration of *m*-xylene of 5.45 µg/L in groundwater could be reduced to 1.36 µg/L using a hydraulic loading rate of 2.03 gpm/ft^2 (4.9 m/h) and an EBCT of 1.0 minute, resulting in a carbon usage rate of 0.069 lb/1000 gal (0.008 kg/m^3) and a bed life of 1.4 months. Under the same operating conditions, the concentration of *o/p*-xylene of 9.0 µg/L was reduced to 2.25 µg/L, achieving a carbon usage rate of 0.172 lb/1000 gal (0.02 kg/m^3) and a bed life of 0.6 month (Miltner et al., 1987; U.S. EPA, 1990). Based on the pilot-scale results, Miltner et al. (1987) predicted the carbon usage rates of a full-scale GAC adsorber. The GAC contactor, designed with a bed depth of 4.05 ft (1.23 m), a hydraulic loading rate of 2.03 gpm/ft^2 (4.95 m/h) and an EBCT of 15 minutes, could reduce influent concentrations of 1000 µg/L for each of *m*-xylene and *o/p*-xylene to 50 µg/L. Under these conditions, a 95% reduction could be achieved, resulting in a carbon usage rate of 1.9 lb/1000 gal (0.22 kg/m^3) and a bed life of 0.8 month for *m*-xylene and a carbon usage rate of 1.2 lb/1000 gal (0.14 kg/m^3) and a bed life of 1.3 months for *o/p*-xylene (Miltner et al., 1987).

Operational data from a groundwater remediation site demonstrated that a full-scale GAC system with a bed life of 3.5 months was capable of reducing a concentration of total xylenes ranging from 2.7 to 23.0 mg/L to below 3.0 µg/L The breakthrough of the carbon bed was defined as the time when the benzene concentration in the effluent exceeded 5 µg/L (369 917 L of treated water) (Giffin and Davis, 1998).

7.1.2 Air stripping

Air stripping is a well-established technology for removing VOCs from drinking water (Cummins and Westrick, 1990; U.S. EPA, 1991a; Dyksen, 2005; WHO, 2011). A variety of configurations exist with respect to air stripping equipment; however, PTA provides an optimum system for the removal of VOCs from drinking water. Removal efficiencies in the range from 94% to > 99% for TEX in drinking water are considered to be achievable using a PTA column (Hand et al., 1986; U.S. EPA, 1990; AWWA, 1991). PTA application allows for greater air-to-water ratios than with other aeration systems (i.e., diffuser aerator, multiple tray aerator, spray aerator, mechanical aerator). In concurrent PTA, the contaminated water flows downward by gravity over a bed of packing material, while air is introduced into the tower below the packed bed and flows upward, countercurrent to the water flow. As PTA transfers VOCs from water to air, treatment of the stripping tower off-gas to reduce the contaminant concentrations prior to discharge into the atmosphere may be necessary (Crittenden et al., 1988; Adams and Clark, 1991).

Several factors affect the stripping rate of VOCs: air-to-water ratio (A:W), available area of mass transfer, hydraulic loading rate, temperature of the water and air, gas pressure drop, types and size of packing materials and the physical and chemical properties (e.g., liquid-phase mass transfer coefficients) of the contaminant (AWWA, 1991; Crittenden et al., 2005; Dyksen et al.

2005). Diffused aeration, multistage bubble aerators, tray aeration and shallow tray aeration have been identified as alternative air stripping treatment technologies for the reduction of toluene, ethylbenzene and xylenes in drinking water for small systems (U.S. EPA, 1998).

A common operating problem is scaling and fouling of the column. The main causes of fouling are calcium carbonate and/or calcium sulphate scale, iron oxidation, microbial growth and NOM. Methods to prevent fouling of the column include pH suppression of the influent, using scale inhibitors or iron removal prior to the PTA application. Algal growth can also be a problem in locations where light could be introduced into the tower. Post treatment, such as the use of a corrosion inhibitor, may also be required to reduce corrosive properties of the water due to increased dissolved oxygen from the aeration process. Environmental conditions, such as water temperature, may impact the packed tower performance. Although temperatures below freezing can cause operational issues, contact between water and air in PTA will result in a change in the air temperature until it approaches the water temperature. The temperature influences both the Henry's Law constant and the rate of mass transfer coefficient of the contaminant. These parameters affect the size of the equipment and the removal efficiency of the VOCs (Crittenden et al., 2005).

7.1.2.1 Toluene

Full-scale data indicated that a PTA column was capable of reducing an average influent concentration of toluene of 30.9 µg/L in groundwater to an average effluent concentration of 0.94 µg/L. A reduction rate of 96.9% was achieved using an air-to-water ratio of 61, a hydraulic loading rate of 29.8 gpm/ft^2 (72.7 m/h), a tower height of 24.5 ft (7.47 m) and a packed column diameter of 8 ft (2.44 m) (Hand et al., 1986).

A pilot-scale study reported a 98.3% reduction of a toluene concentration in groundwater. An influent concentration of 62.0 µg/L was reduced to 1.1 µg/L using an air-to-water ratio of 25 and a hydraulic loading rate of 30.9 gpm/ft^2 (75.4 m/h) (U.S. EPA, 1990). Another pilot-scale study demonstrated that influent concentrations in the range of 3050–13 400 µg/L were reduced to concentrations in the range of 20.9–168 µg/L (95.5–99.3% reduction). The highest removal rate of 99.3% was reported to be achieved with an influent concentration of 3050 µg/L, an air-to-water ratio of 71 and a hydraulic loading rate of 17.8 gpm/ft^2 (43.4 m/h) (U.S. EPA, 1990).

Studies by Crittenden et al. (1988) and Adams and Clark (1991) estimated that a 99% removal efficiency and a toluene concentration in finished water of 1 µg/L could be achieved. According to Crittenden et al. (1988), typical air stripping design parameters at full scale, for reduction of toluene, include an A:W ratio of 30, an air column height of 39.04 ft (11.9 m) and a packed column diameter of 8.07 ft (2.4 m). Under these conditions, a 99% reduction of toluene could be achieved in water with an influent concentration of 100 µg/L, thus resulting in an effluent concentration of 1 µg/L.

Diffused aeration generally achieves removal efficiencies in the range of 22–89% for toluene and has higher power requirements than PTA systems (U.S. EPA, 1991a). A diffused aeration system was capable of reducing a toluene concentration of 108 µg/L in spiked groundwater to a finished water concentration of 14.0 µg/L. This removal rate of 87% was achieved using an air-to-water ratio of 15 (U.S. EPA, 1990).

7.1.2.2 Ethylbenzene

A full-scale PTA column reduced an influent concentration of ethylbenzene of 5.1 µg/L in groundwater to below 0.3 µg/L. A reduction rate of greater than 94% was achieved using an air-to-water ratio of 61, a hydraulic loading rate of 29.8 gpm/ft^2 (72.7 m/h), a column height of 24.5 ft (7.47 m) and a packed column diameter of 8 ft (2.44 m) (Hand et al., 1986).

Two pilot-scale studies demonstrated that PTA is an effective technology to treat ethylbenzene in drinking water (U.S. EPA, 1990). A pilot-scale column was capable of reducing influent concentrations of ethylbenzene of 202.0 µg/L to 3.9 µg/L and of 59.7 µg/L to below 0.1 µg/L using A:W ratios of 59 and 63, respectively. The column operated with an average hydraulic loading rate of 23 gpm/ft^2 (56.1 m/h). Another pilot PTA system reported greater than 92.0% removal of ethylbenzene from groundwater. An influent concentration of 9.0 µg/L was reduced to below 1.0 µg/L using an air-to-water ratio of 25 and a hydraulic loading rate of 30.9 gpm/ft^2 (75.4 m/h) (U.S. EPA, 1990).

Crittenden et al. (1988) and Adams and Clark (1991) estimated that a 99% removal efficiency and an effluent ethylbenzene concentration of 1 µg/L could be achieved in the treated water. According to Adams and Clark (1991), estimated full-scale plant air stripping design parameters include an air-to-water ratio of 30 and an air stripper length of 36.1 ft (11.0 m).

Diffused aeration generally achieves removal efficiencies in the range of 24–89% for ethylbenzene, and the process has higher power requirements than PTA systems (U.S. EPA, 1991a). A bench-scale diffused aeration system was capable of reducing an ethylbenzene concentration of 113 µg/L in spiked groundwater to 13.6 µg/L. A removal rate of 88% was achieved using an air-to-water ratio of 15 (U.S. EPA, 1990).

7.1.2.3 Xylenes

Full-scale data indicated that a PTA column was capable of reducing an average influent concentration of xylenes of 16.6 µg/L in groundwater to an average effluent concentration of 0.6 µg/L. A removal reduction rate of 96.4% was achieved using an air-to-water ratio of 61, a hydraulic loading rate of 29.8 gpm/ft^2 (72.7 m/h), a tower height of 24.5 ft (7.47 m) and a packed column diameter of 8 ft (2.44 m) (Hand et al., 1986).

A pilot-scale study indicated that a PTA column is an effective technology for reducing the concentration of xylene isomers in drinking water. Influent *m*-xylene concentrations in the range of 1020–1900 µg/L were reduced to concentrations ranging from 18.2 to 121 µg/L, achieving reduction rates between 93.1% and 98.2%. *o/p*-Xylenes concentrations in the range of 1210–1980 µg/L were reduced to concentrations in the range of 62.9–179 µg/L (87.1–94.8% removal). The highest removal rates of 98.2% and 94.8% were achieved for an *m*-xylene influent concentration of 1020 µg/L and for an *o/p*-xylene influent concentration of 1210 µg/L, respectively. The column operated with an air-to-water ratio of 71 and a hydraulic loading rate of 17.8 gpm/ft^2 (43.4 m/h) (U.S. EPA, 1990).

Another pilot study demonstrated that a PTA column using an air-to-water ratio of 25 and a hydraulic loading rate of 30.9 gpm/ft^2 (75.4 m/h) was capable of achieving > 95%, > 83% and > 90% removal for *o*-, *m*- and *p*-xylene, respectively. Reported influent concentrations were 10.0 µg/L, 2.9 µg/L and 6.9 µg/L for *o*-, *m*- and *p*-xylene, respectively (U.S. EPA, 1990).

Studies by Crittenden et al. (1988) and Adams and Clark (1991) estimated that a 99% removal efficiency and an effluent concentration of 1 µg/L of *m*-xylene could be achieved in the treated water. According to Crittenden et al. (1988), estimated full-scale plant air stripping design parameters include an A:W ratio of 37.3, an air column height of 40.5 ft (12.3 m) and a column diameter of 18.34 ft (5.6 m).

Diffused aeration generally achieves removal efficiencies in the range of 18–89% for xylene isomers and has higher power requirements than PTA systems (U.S. EPA, 1991a). A diffused aeration system was capable of achieving reductions of 82%, 84% and 88% in spiked groundwater with influent concentrations of 120 µg/L, 107 µg/L and 103 µg/L for *o*-, *m*- and *p*-xylene, respectively (U.S. EPA, 1990).

7.1.3 Combination of packed tower aeration and granular activated carbon

In air stripping, the VOCs are removed from the water phase to the air phase, potentially creating an air pollution problem. Generally, the use of GAC after air stripping is intended to treat the off-gas from the air stripper and to reduce the release of VOCs into the atmosphere. However, several articles have indicated that combining aeration technologies and liquid-phase GAC into a two-step treatment train is very effective for achieving low finished water concentrations of VOCs (Robeck and Love, 1983; McKinnon and Dyksen, 1984; Stenzel and Gupta, 1985; U.S. EPA, 1991a). Contaminated groundwater with a high concentration of VOCs was treated with PTA followed by GAC. The application of the aeration process and an adsorption technique reduced the VOC concentrations to below detectable levels in the drinking water (McKinnon and Dyksen, 1984).

In a municipal-scale treatment plant combining these processes, air stripping was used for the bulk reduction of VOC concentrations in water, and activated carbon was used in the second step to further reduce residual VOC concentrations below the detection limit of 0.1 µg/L (Robeck and Love, 1983). The air stripping process preceding liquid-phase GAC adsorption can also extend carbon bed life (Hess et al., 1981; Stenzel and Gupta, 1985; U.S. EPA, 1991a). The common operational problems inherent to PTA systems and GAC adsorption contactors are similar and should be considered when these combined technologies are employed. However, no information specific to the effectiveness of the process for reduction of TEX was available in the literature.

7.1.4 Ozonation and advanced oxidation processes

Ozonation and advanced oxidation processes (AOPs) have been reported to be effective for the reduction of TEX concentrations in drinking water, although full-scale data were not available for these treatment techniques (Fronk, 1987; U.S. EPA, 1990; Lykins and Clark, 1994; Topudurti et al., 1998; Bergendahl et al., 2003; Garoma et al., 2008). AOPs generate highly reactive hydroxyl radicals at ambient temperature and atmospheric pressure. Hydroxyl radicals are strong oxidants and react rapidly and non-selectively with organic contaminants. AOPs that are commercially available are ozone with hydrogen peroxide, ozone with ultraviolet (UV), ozone at elevated pH, ultraviolet with hydrogen peroxide, ultraviolet with titanium dioxide and ozone with ultraviolet and titanium dioxide. The primary advantage of AOPs is their capability to completely convert the organic compounds into carbon dioxide and mineral acids (Crittenden et al., 2005), whereas adsorption processes and air stripping techniques transfer the contaminants from one phase to another, and additional treatment may be required (Glaze et al., 1988; U.S. EPA, 1993; Crittenden et al., 2005). Physical and chemical parameters of the water have a major impact on AOPs. Water quality parameters that may impact the effectiveness of the AOPs are alkalinity, pH, NOM, reduced metal ions (iron and manganese) and turbidity (Fronk, 1987; Crittenden et al., 2005). Consequently, in order to reduce excess energy consumption in AOPs and maximize their effectiveness, pretreatment is commonly applied to remove co-occurring contaminants.

The formation of by-products from the oxidation and/or advanced oxidation of VOCs or other inorganic compounds in the source water should be considered when using these processes. AOPs produce reactive peroxy organic radicals, which undergo radical chain reactions and result in a variety of oxygenated by-products. The typical by-products produced by AOPs are aldehydes, ketones and carboxylic compounds. Another potential problem with the use of ozone or AOPs such as ozone in combination with UV or hydrogen peroxide is the formation of bromate in waters containing significant bromide concentrations (Crittenden et al., 2005).

Krasner et al. (1993) and Siddiqui and Amy (1993) reported that the application of ozone with hydrogen peroxide may increase the formation of bromate at pH in the range 8.0-8.5, when compared with ozone application alone. However, it has been observed that bromate formation can be controlled effectively by applying a higher hydrogen peroxide to ozone ratio (Liang et al., 2001). The formation of by-products may require additional treatment following AOPs and/or process optimization to minimize by-product formation.

Photolytic reactions require a significant amount of electrical energy, and the associated costs can be significant. Consequently, comparison of the process efficiency of different photolytic methods is based on electrical usage per amount of compound destroyed (Crittenden et al., 2005).

7.1.4.1 Toluene

Pilot-scale ozonation tests were conducted for the removal of VOCs from drinking water. The experiments used both distilled water and groundwater, each spiked with selected contaminants at concentrations ranging between 50 and 384 µg/L. The influent concentration of toluene was not reported. The study reported that a transferred (absorbed) ozone dose (defined as the applied ozone minus the off-gas concentration) of 10 mg/L achieved 96% reduction of toluene in groundwater (Fronk, 1987). A bench-scale test demonstrated that ozone effectively oxidized toluene in spiked groundwater with a contact time of 13 minutes. The toluene concentrations of 108.0 µg/L and 7.0 µg/L were reduced by 91% and 100% using ozone doses of 10.1 mg/L and 9.4 mg/L, respectively (U.S. EPA, 1990).

A pilot-scale photocatalytic oxidation system was evaluated for the treatment of groundwater contaminated with VOCs, including toluene. The system utilized a 254 nm UV light source combined with the addition of 70.0 mg/L of H_2O_2 and 0.4 mg/L of ozone. The system achieved a reduction rate greater than 93% of the influent toluene concentrations, which ranged from 44 to 85 µg/L. To prevent fouling of the photocatalytic reactor, an ion exchange pretreatment system was used to remove iron and manganese from the groundwater. The authors reported the formation of several oxidation by-products, including aldehydes (formaldehyde: 237 µg/L; acetaldehyde: 50 µg/L) and haloacetic acids (monochloroacetic acid: 14 µg/L; dichloroacetic acid: 15 µg/L) (Topudurti et al., 1998).

Bench-scale AOPs using UV and UV/H_2O_2 have been assessed for the removal of toluene from spiked distilled water. Data demonstrated that UV radiation with an intensity of 85 µW/cm^2 was capable of achieving a 69% reduction of a toluene concentration of 51.7 µg/L. The reduction rate was increased to 100% when 10 mg/L of H_2O_2 has been added to the UV system (U.S. EPA, 1990).

A laboratory study investigated the O_3/UV oxidation process for the degradation of benzene, toluene, ethylbenzene and xylenes (BTEX) in contaminated groundwater under different experimental conditions. UV radiation with an intensity of 2.73 W/L (1.4 kWh/m^3) combined with the addition of an ozone dose of 28 mg/L achieved a greater than 99% reduction of the influent toluene concentration of 83 µg/L in 30 minutes (Garoma et al., 2008).

7.1.4.2 Ethylbenzene

Pilot-scale ozonation tests were conducted for the removal of VOCs from drinking water. The experiments used both distilled water and groundwater, each spiked with selected contaminants. The concentrations of the contaminants ranged between 50 and 384 µg/L, concentrations typically found in groundwater (Fronk, 1987). The influent concentration of ethylbenzene was not reported. The study reported that a transferred (absorbed) ozone dose (defined as the applied ozone minus the off-gas concentration) of 10 mg/L achieved a 95%

reduction of ethylbenzene concentration in groundwater (Fronk, 1987). A bench-scale study demonstrated that ozone effectively oxidized ethylbenzene in spiked groundwater with a contact time of 13 minutes. The study reported a 90% and 100% degradation of the initial ethylbenzene concentrations of 113.0 µg/L and 42.0 µg/L using ozone doses of 10.1 mg/L and 9.4 mg/L, respectively (U.S. EPA, 1990).

7.1.4.3 Xylenes

Pilot-scale ozonation tests were conducted for the removal of VOCs from drinking water. The experiments used both distilled water and groundwater spiked with selected contaminants at concentrations ranging between 50 and 384 µg/L. Although the influent concentrations of xylene isomers were not reported specifically, the tests demonstrated that a transferred (absorbed) ozone dose of 10 mg/L achieved 95%, 97% and 97% reductions of *o*-, *m*- and *p*-xylene in groundwater, respectively (Fronk, 1987). A bench-scale test reported that the ozone effectively oxidized xylene isomers. Spiked groundwater concentrations of 120.0 µg/L for *o*-xylene, 107.0 µg/L for *m*-xylene and 103.0 µg/L for *p*-xylene were reduced to 8.4 µg/L, 7.5 µg/L and 7.2 µg/L, respectively, using an ozone dose of 10.1 mg/L. However, an ozone dose of 9.4 mg/L achieved 100% reduction when the initial concentrations were 60.0 µg/L, 46.0 µg/L and 44.0 µg/L for *o*-, *m*- and *p*-xylene, respectively (U.S. EPA, 1990).

A pilot-scale photocatalytic oxidation system was capable of achieving a reduction rate of greater than 98.0% of total xylene concentrations ranging from 55 to 203 µg/L. The system used a 254 nm UV light source combined with the addition of 70 mg/L of H_2O_2 and 0.4 mg/L of ozone. To prevent fouling of the photocatalytic reactor, an ion- exchange pretreatment system was used to remove iron and manganese from the groundwater. The authors reported the formation of several by-products, including aldehydes (formaldehyde: 237 µg/L; acetaldehyde: 50 µg/L) and haloacetic acids (monochloroacetic acid: 14 µg/L; dichloroacetic acid: 15 µg/L) (Topudurti et al., 1998).

A laboratory study investigated the O_3/UV oxidation process for the degradation of BTEX from contaminated groundwater under different experimental conditions. UV radiation with an intensity of 2.73 W/L (1.4 kWh/m^3) combined with an ozone dose of 28 mg/L achieved a greater than 99% reduction of an influent concentration of total xylenes of 71 µg/L in 30 minutes (Garoma et al., 2008).

7.1.5 Emerging technologies

New technologies have demonstrated the potential for removing VOCs, including TEX, but there is insufficient information available at present to fully evaluate them:

- *Membrane pervaporation*—Although the use of membranes for the pervaporation extraction of VOCs has been applied primarily in wastewater treatment, this technique has also been studied for the removal of VOCs from groundwater (Jian and Pintauro, 1997; Uragami et al., 2001; Peng et al., 2003). Pervaporation is a process in which a liquid stream containing contaminants is placed in contact with one side of a non-porous polymeric membrane while a vacuum or gas purge is applied to the other side. The components in the liquid stream sorb into the membrane, permeate through it and evaporate into the vapour phase (Lipski and Cote, 1990; Peng et al., 2003).
- *Alternative adsorbents*—A study reported that an adsorbent impregnated with platinum and titanium dioxide catalyst reduced an influent concentration of BTEX in the range of 24–201 mg/L, achieving removal efficiencies ranging from 96% to 100% (Crittenden et al., 1997).

Fibreglass-supported activated carbon filters demonstrated improved kinetics of adsorption for BTEX when compared with the adsorption kinetics of the GAC filter (Yue et al., 2001).

- *AOPs using Fenton's reagent*—A pilot-scale system investigated an AOP using Fenton's reagent for the treatment of organic compounds in groundwater. The study demonstrated that initial concentrations of ethylbenzene (500 µg/L), toluene (1700 µg/L), *o*-xylene (140.0 µg/L) and *m*/*p*-xylene (360.0 µg/L) were reduced to non-detectable levels (detection limits not provided) for each contaminant using a molar ratio of hydrogen peroxide to iron of 75 and an average iron concentration of 10 mg/L. The optimum pH was in the range of 3.5–4. It should be noted that a pH adjustment may be needed after this treatment process (Bergendahl et al., 2003).
- *Bioremediation*—A bioremediation technology uses microorganisms under fully controlled conditions to degrade the contaminants to less toxic compounds, such as carbon dioxide, methane, water and inorganic salt (Huck et., 1991; Guerin, 2002; Ohlen et al., 2005; Zein at al., 2006; Farhadian et al., 2008). A field-scale aerobic gravity-flow membrane bioreactor consistently degraded TEX concentrations in groundwater (to below 1 µg/L), achieving removal efficiency of greater than 99.9%. The reactor was operated for 6 months with an influent flow rate of 5 gpm (0.31 L/s). The influent concentrations of 508.24 µg/L for toluene and 235.96 µg/L for ethylbenzene were degraded to 0.11 µg/L and 0.04 µg/L, respectively. A biodegradation of greater than 99.9% was achieved for each xylene isomer. The influent concentrations of *o*-, *m*- and *p*-xylene of 431.61, 638.07 and 716.59 µg/L were reduced to 0.07, 0.14 and 0.1 µg/L, respectively (Zein et al., 2006). Laboratory experiments were conducted with two bioreactor configurations: a submerged fixed film reactor (SFFR) and a fluidized bed reactor (FBR), and both were reported to be effective for the biodegradation of TEX in spiked groundwater. Both bioreactors were aerated throughout the experiments to provide oxygen to the attached aerobic microorganisms on activated carbon support medium. The hydraulic retention time was 32.6 hours for the SFFR and 26.1 hours for the FBR (Guerin, 2002). The initial toluene concentration of 0.19 mg/L was biodegraded in the two reactors, achieving a 99.4% reduction rate. The initial ethylbenzene concentration of 0.015 mg/L was reduced by 97.6% in the SFFR reactor. A 97.6% degradation of ethylbenzene was also achieved with the FBR reactor with an initial concentration of 0.018 mg/L. Each of the reactors achieved a biodegradation of 99% for total influent xylene concentrations ranging from 0.23 to 0.26 mg/L (Guerin, 2002). Laboratory experiments demonstrated that the use of activated carbon as a biomass support in a fluidized bed reactor produces a system in which both adsorption and biodegradation affect the BTEX removal in groundwater. During the start-up period BTEX is removed primarily by adsorption. Once the biofilm is established and steady-state conditions are reached, the removal of BTEX is dominated by biodegradation (Voice et al., 1992).

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. In cases where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device may be an option for decreasing TEX concentrations in drinking water.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been

designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2014):

- Canadian Standards Association International (www.csa-international.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);
- Quality Auditing Institute (www.qai.org); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (2014).

A number of certified residential treatment devices from various manufacturers are available that can remove TEX from drinking water. The certified devices for removal of TEX from drinking water rely on adsorption (activated carbon) and reverse osmosis (RO) technologies.

Filtration systems may be installed at the faucet (point of use) or at the location where water enters the home (point of entry). Point-of-entry systems are preferred for the reduction of VOCs such as TEX, because they provide treated water for bathing and laundry as well as for cooking and drinking. This will reduce the potential for VOC exposure through inhalation.

Where certified point-of-entry treatment devices are not available for purchase, systems can be designed and constructed from certified materials. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the water it produces to verify that the treatment device is effective. Devices can lose their removal capacity through usage and time and need to be maintained and/or replaced. Consumers should verify the expected longevity of the components in their treatment device as per the manufacturer's recommendations.

RO systems should only be installed at the point of use as the water they have treated may be corrosive to internal plumbing components. This system requires larger quantities of influent (incoming) water to obtain the required volume of drinking water, as the systems reject (waste) part of the influent water. A consumer may need to pretreat the influent water to reduce the fouling and extend the service life of the membrane.

7.2.1 Toluene

The certified devices for the removal of toluene from drinking water that rely on an adsorption (activated carbon) technology can be certified either specifically for toluene removal or for the removal of VOCs as a group, using surrogate testing.

For a drinking water treatment device to be certified to NSF/ANSI Standard 53 for the reduction of toluene only, the device must be capable of reducing an average influent concentration of 3.0 mg/L to a maximum effluent concentration of 1.0 mg/L (NSF/ANSI, 2013a). For a drinking water treatment device to be certified to NSF/ANSI Standard 53 by surrogate testing, the device must be capable of reducing an influent toluene concentration of 0.078 mg/L to a maximum product water concentration of 0.001 mg/L (NSF/ANSI, 2013a).

Although no certified residential treatment devices using reverse osmosis are currently available for the reduction of toluene in drinking water, toluene is included in NSF/ANSI Standard 58 (RO). For a drinking water treatment device to be certified to NSF/ANSI Standard 58 by surrogate testing, the device must be capable of reducing toluene from an influent concentration of 0.078 mg/L to a maximum concentration of 0.001 mg/L (NSF/ANSI, 2013b).

7.2.2 Ethylbenzene

The certified devices for the removal of ethylbenzene from drinking water that rely on an adsorption (activated carbon) technology can be certified either specifically for ethylbenzene removal or for the removal of VOCs as a group, using surrogate testing.

For a drinking water treatment device to be certified to NSF/ANSI Standard 53 for the reduction of ethylbenzene only, the device must be capable of reducing an average influent concentration of 2.1 mg/L to a maximum effluent concentration of 0.7 mg/L (NSF/ANSI, 2013a). For a drinking water treatment device to be certified to NSF/ANSI Standard 53 by surrogate testing, the device must be capable of reducing an influent ethylbenzene concentration of 0.088 mg/L to a maximum product water concentration of 0.001 mg/L (NSF/ANSI, 2013a).

Although no certified residential treatment devices using reverse osmosis are currently available for the reduction of ethylbenzene in drinking water, ethylbenzene is included in NSF/ANSI Standard 58 (RO). For a drinking water treatment device to be certified to NSF/ANSI Standard 58 by surrogate testing, the device must be capable of reducing ethylbenzene from an influent concentration of 0.088 mg/L to a maximum concentration of 0.001 mg/L in the treated water (NSF/ANSI, 2013b).

7.2.3 Xylenes

The certified devices for the removal of total xylenes from drinking water that rely on an adsorption (activated carbon) technology can be certified either specifically for total xylene removal or for the removal of VOCs as a group, using surrogate testing.

For a drinking water treatment device to be certified to NSF/ANSI Standard 53 for the reduction of total xylenes, the device must be capable of reducing an average influent concentration of 30.0 mg/L to a maximum effluent concentration of 10.0 mg/L (NSF/ANSI, 2013a). For a drinking water treatment device to be certified to NSF/ANSI Standard 53 by surrogate testing, the device must be capable of reducing an influent concentration of total xylenes of 0.07 mg/L to a maximum product water concentration of 0.001 mg/L (NSF/ANSI, 2013a).

Although no certified residential treatment devices using reverse osmosis are currently available for the reduction of xylenes in drinking water, xylenes are included in NSF/ANSI Standard 58 (RO). For a drinking water treatment device to be certified to NSF/ANSI Standard 58 by surrogate testing, the device must be capable of reducing total xylenes from an influent concentration of 0.07 mg/L to a maximum concentration of 0.001 mg/L (NSF/ANSI, 2013b).

8.0 Kinetics and metabolism

8.1 Absorption

8.1.1 Toluene

Toluene is well absorbed by the lungs and the gastrointestinal tract and to a lesser extent through the skin.

Baelum et al. (1993) reported that gastrointestinal absorption of toluene was complete in human volunteers, as indicated by the presence of toluene in exhaled air and toluene metabolites (hippuric acid and *o*-cresol) in urine following oral administration of toluene at 2 mg/minute via a 3-hour gastric tube. Animal studies, however, have shown that toluene is absorbed less rapidly than in humans by the oral route (Pyykkö et al., 1977; Ameno et al., 1992).

Toluene is rapidly absorbed by the inhalation route in both humans and experimental animals (Benignus et al., 1984; Hobara et al., 1984; Wigaeus Hjelm et al., 1988; Löf et al., 1993). In humans, Carlsson (1982) reported that exposure of exercising male individuals to 79.5 ppm (300 mg/m^3) toluene for 2 hours resulted in an average uptake (percentage of inspired air) of 55%, which dropped to 50% following 2 hours at rest. Similar results were reported by Löf et al. (1990), who exposed 10 male individuals to 79.5 ppm (300 mg/m^3) toluene for 4 hours at rest, resulting in absorption of approximately 50% of the dose. Benoit et al. (1985) reported that the exposure of four individuals (sex not specified) to 50 ppm (188 mg/m^3) toluene for 90 minutes at rest resulted in an average retention of 83%. In humans, toluene appears in blood 10–15 minutes after the onset of exposure, and its concentration in blood is strongly correlated with alveolar concentration. In rats, peak blood and cerebral levels appear in less than 1 hour after the onset of exposure (Tardif et al., 1991; INRS, 2008).

The rate of absorption of toluene through human skin is slow (Dutkiewicz and Tyras, 1968); it has been reported to range from 14 to 23 mg/cm^2 per hour (forearm skin). Brown et al. (1984) calculated that bathing in water containing a toluene concentration of 5–500 µg/L (15 minutes/day) would result in an absorbed dermal dose ranging from 0.2 to 20 µg/kg body weight (bw) per day for a 70 kg adult and from 0.4 to 40 µg/kg bw per day for a 10.5 kg infant. Soaking the skin in a solvent containing 65% toluene for 5 minutes produced a maximum concentration of toluene in blood of 5.4 µmol/L (Aitio et al., 1984). This latter experiment, conducted with two volunteers, revealed individual differences in absorption, which is consistent with the high variability reported by Sato and Nakajima (1978). Monster et al. (1993) measured toluene levels in alveolar air samples of six rotogravure printing workers who washed their hands with toluene for 5 minutes; the next morning, toluene levels in alveolar air ranged between 0.5 and 10 mg/m^3. Morgan et al. (1991) reported that dermal absorption of toluene in aqueous solution (saturated, two-thirds saturated and one-third saturated solutions) and neat toluene in rats was significant, even though only 1% of the body surface was exposed; for example, 24 hours of exposure to neat toluene resulted in a peak blood concentration of 9.5 µg/mL.

8.1.2 Ethylbenzene

Ethylbenzene can be absorbed from the respiratory tract, from the gastrointestinal tract and through the skin.

Data pertaining to the oral absorption of ethylbenzene are from animal studies only. For instance, the recovery of ethylbenzene metabolites in the 24-hour urine of rabbits following exposure to a single oral dose of 593 mg/kg bw was between 72% and 92% of the administered dose, suggesting rapid and effective absorption by this route (El Masry et al., 1956). Consistent with those results, 84% of the radioactivity from a single oral dose of ^{14}C-labelled ethylbenzene at 30 mg/kg bw administered to female rats was recovered within 48 hours (Climie et al., 1983). More recently, Faber et al. (2006) reported that ethylbenzene was detected at 0.49, 3.51 and 18.28 mg/L in maternal blood of rats 1 hour after the last of four daily administrations of ethylbenzene by gavage at equal doses of 0, 8.67, 30 and 114 mg/kg bw, respectively (total doses: 0, 26, 90 and 342 mg/kg bw per day); ethylbenzene was not detected in blood of weanlings from the same dams.

Inhalation studies in humans have shown that ethylbenzene is rapidly absorbed via this route of exposure (Bardodej and Bardodejova, 1970; Gromiec and Piotrowski, 1984; Tardif et al., 1997; Knecht et al., 2000). Volunteers exposed to 23–85 ppm (approximately 100-370 mg/m^3) ethylbenzene for 8 hours were shown to retain 64% of the inspired dose, with only trace amounts of ethylbenzene being detected in expired air at the end of the exposure period (Bardodej and Bardodejova, 1970). A mean retention of 49% was reported by Gromiec and Piotrowski (1984)

when humans were exposed by inhalation to ethylbenzene at 18–200 mg/m^3 (approximately 4–46 ppm). The differences may be attributable to human variability in absorption rates as well as methodological differences. Tardif et al. (1997) reported a steady-state blood-to-alveolar air concentration ratio of approximately 30 within 1 hour of beginning exposure.

Animal studies also show a rapid absorption of ethylbenzene via the inhalation route of exposure. In a study by Chin et al. (1980), exposure of Harlan-Wistar rats for 6 hours to radiolabelled ethylbenzene resulted in a rapid absorption of the dose, with a reported retention of 44%. Radioactivity was detected in intestine, kidney, liver and adipose tissue for up to 42 hours post-exposure. Freundt et al. (1989) reported that blood concentrations of ethylbenzene in rats following 2 hours of inhalation exposure were proportional to its concentration in the atmosphere.

Overall, studies on dermal exposure to ethylbenzene showed rapid absorption of the liquid form and poor absorption of the vapour form (Dutkiewicz and Tyras, 1967; Gromiec and Piotrowski, 1984) and suggested that skin absorption could be a major route of uptake for liquid ethylbenzene or ethylbenzene in water; for instance, the average amounts of ethylbenzene absorbed after volunteers immersed one hand for up to 2 hours in an aqueous ethylbenzene solution at 112 or 156 mg/L were 39.2 and 70.7 mg, respectively. Morgan et al. (1991) reported that in Fischer 344 rats, the peak blood level of ethylbenzene (5.6 µg/mL) was reached within 2 hours of topical application of neat ethylbenzene to approximately 1% of the body surface and slowly declined during the 24-hour observation period. In contrast, the total amount absorbed was reduced when ethylbenzene was administered in aqueous solutions (saturated, two-thirds saturated and one-third saturated solutions).

8.1.3 Xylenes

In humans, xylene isomers are absorbed by the respiratory tract (60–65%), gastrointestinal tract (up to 90%) and skin (2%). However, limited information is available on the absorption of xylenes in humans and experimental animals following ingestion. In addition, xylenes can cross the placental barrier (Ghantous and Danielsson, 1986).

Ogata et al. (1979) reported that the absorption of xylene in human volunteers (oral ingestion of 40 mg/kg bw) was at least 34% for *o*-xylene and 53% for *m*-xylene, based on the recovery of urinary metabolites.

In male and female rats dosed with 0.15 mL of radiolabelled *m*-xylene (0.27 mg/kg bw) by oral gavage, peak blood levels of radioactivity were observed within 20 minutes, indicating rapid absorption (Turkall et al., 1992). Kaneko et al. (1995) reported that blood concentrations of *m*-xylene (peak concentration approximately 2.5 µM) rapidly increased within 5 hours following oral administration of 8.64 mg/kg bw in corn oil to rats.

Dermal absorption of xylene from water is not well known. However, a dermal absorption rate coefficient (K_p) of 0.08 cm/hour has been estimated (U.S. EPA, 1992). Results of experimental studies with humans indicate that the degree of penetration and absorption of *m*-xylene following dermal exposure is not as efficient as that following exposure by the respiratory tract (Engström et al., 1977; Riihimäki and Pfäffli, 1978; Riihimäki, 1979b). Morgan et al. (1991) reported that in Fischer 344 rats, a peak blood level of *m*-xylene (8.8 µg/mL) was reached within 2 hours of topical application of neat *m*-xylene and slowly declined during the 24-hour observation period. The total amount absorbed was reduced, however, when *m*-xylene was administered in aqueous solutions (saturated, two-thirds saturated and one-third saturated solutions).

Simulations of the Kaneko et al. (1991a) PBPK model estimated that increased physical activity increased the blood concentration of *m*-xylene. The concentration of *m*-xylene in the

blood during exposure was lower in women than in men, but was higher in women 10 hours after exposure.

8.2 Distribution

8.2.1 Toluene

The highest concentration of toluene measured in a human (51 years old) who died 30 minutes following accidental ingestion of toluene at 625 mg/kg bw was found in the liver (433.5 μg/g), followed by the pancreas (88.2 μg/g), brain (85.3 μg/g), heart (62.6 μg/g), blood (27.6 μg/g), body fat (12.2 μg/g) and cerebrospinal fluid (11.1 μg/g) (Ameno et al., 1989). Following a presumed inhalation overdose, toluene has been measured in brain (highest concentration), liver, lung and blood in a human (Paterson and Sarvesvaran, 1983). Takeichi et al. (1986) reported similar findings in a 20-year-old male painter who died while working with a toluene-based paint; the highest concentrations were found in the brain, followed by the liver and blood.

In an experiment using rabbit tissue homogenates, tissue distribution of toluene has been reported as follows (from highest to lowest levels): adipose (fat), bone marrow, brain, liver, heart, lung, kidney and muscle (Sato et al., 1974). In dogs, following inhalation exposure, toluene concentrations in the liver and brain were higher than those found in the kidney (Endoh et al., 1989). In rats, however, oral and inhalation exposure to toluene resulted in higher toluene concentrations in the liver compared with the brain (Pyykkö et al., 1977).

Once in the blood, toluene is distributed between red blood cells and serum (1:1 in human; 1:2 in rat), and several studies have shown relationships between blood and tissue levels of toluene, particularly for the brain (Benignus et al., 1984; Harabuchi et al., 1993). In rats orally exposed to toluene at 400 mg/kg bw, the highest blood level occurred 1.5 hours after exposure (Ameno et al., 1992), and toluene distribution in the brain was similar after both inhalation and oral exposure (Ameno et al., 1992). In humans, data suggest that the accumulation of toluene in the brain is more important than that in the liver following inhalation exposure, whereas following oral exposure, toluene appears to have a greater affinity for the liver (ATSDR, 2000).

Animal studies involving the inhalation exposure of pregnant mice report that the distribution of toluene occurs via rapid uptake by lipid tissues (brain and fat); in addition, toluene easily crosses the placental barrier, and fetal concentrations reportedly correspond to approximately 75% of maternal blood levels (Ghantous and Danielsson, 1986). Toluene has also been detected in human breast milk (Pellizzari et al., 1982).

Fisher et al. (1997) used a generic lactation model developed for various VOCs to estimate the amount of toluene an infant would ingest through breast milk if the mother was occupationally exposed to toluene at the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value at the time of the study (50 ppm) throughout a workday. The model, which was not validated and did not include metabolic parameters for toluene, predicted that the intake for a 10 kg infant would be 0.46 mg/day.

8.2.2 Ethylbenzene

There is limited information regarding the distribution of ethylbenzene in humans following oral or dermal exposure. Engström and Bjurström (1978) reported that the distribution of ethylbenzene is rapid in humans after inhalation and that ethylbenzene is distributed throughout the body, including the fat, intestine, kidneys and liver. Inhalation studies in animals support these observations (Elovaara et al., 1982; Engström et al., 1985). Chin et al. (1980) reported that ethylbenzene is efficiently distributed throughout the body in rats following inhalation exposure

to radiolabelled ethylbenzene; the highest amounts of radioactivity in tissues 42 hours following exposure to 230 ppm ethylbenzene for 6 hours were found in the carcass, liver and gastrointestinal tract, with lower amounts detected in the adipose tissue. In addition, ethylbenzene has been observed to cross the placental barrier in humans (WHO, 2003a; INRS, 2008).

The percentages of absorbed doses in hairless mice following dermal application of ^{14}C-labelled ethylbenzene were as follows: 15.5%, carcass; 4.5%, application site; 14.3%, expired breath; and 65.5%, excreta (Susten et al., 1990).

8.2.3 Xylenes

Limited information is available on the distribution of xylenes in humans and experimental animals following ingestion. Xylene isomers are relatively soluble in blood.

Turkall et al. (1992) reported that adipose tissue contained the highest concentration of radioactivity after oral gavage: approximately 0.3% of the initial administered dose/mg tissue was reported for female rats and 0.1% was reported for male rats (the authors did not report the total weight of adipose tissue analysed).

Kumarathasan et al. (1998) determined tissue/blood partition coefficients in several tissues and organs (brain, muscle, kidney, liver and fat) and blood from Sprague-Dawley rats for each xylene isomer in a mixture. For *m*-xylene, the blood/air partition coefficient averaged 62. The highest tissue/blood partition coefficient was for fat (50), followed by kidney (2.1), liver and brain (2) and muscle (1.8). There were no differences between isomers.

Riihimaki and Savolainen (1980) found that 10–20% of a xylene dose was distributed to the adipose tissue. Adipose has the highest concentration of neutral fat and the highest affinity for xylene of all tissues. Astrand et al. (1978) reported that following rapid uptake of xylene vapours, the amount detected in the blood generally amounted to 2–3% of the total xylene dose absorbed; this may be explained by the high lipid solubility of xylenes, resulting in their distribution and storage in various tissues.

The highest concentration of xylene (combined concentration of xylene and its metabolites) following a 4-hour exposure to ^{14}C-labelled *p*-xylene (48 ppm) was found in the kidneys of male rats, followed by the subcutaneous fat (Carlsson, 1981). Bergman (1983) investigated the distribution of ^{14}C-labelled *m*-xylene in mice and found high levels of radioactivity in the body fat, bone marrow, white matter of the brain, spinal cord, spinal nerves, liver and kidney immediately following inhalation exposure. No radioactivity was detected in the body by 48 hours post-exposure.

Fisher et al. (1997) used a generic lactation model developed for various VOCs to estimate the amount of *o*-, *p*- and *m*-xylene an infant would ingest through breast milk if the mother were occupationally exposed to xylenes at the ACGIH Threshold Limit Value at the time of the study (100 ppm) throughout a workday. The model, which was not validated and did not include metabolic parameters for xylenes, predicted that the intake for a 10 kg infant would be 6.59 mg/day.

8.3 Metabolism

A number of animal and human PBPK models have shown that exposure to binary mixtures of aromatic solvents could result in metabolic interactions that modify their rates of metabolism and elimination (Tardif et al., 1991, 1992, 1993, 1997). These metabolic interactions probably result from the mutual competition between solvents for metabolizing enzymes (e.g., cytochrome P450 [CYP] 2E1). As a result, the half-lives of both solvents increase. Such interactions resulting from exposure to a ternary mixture (i.e., toluene, xylene, ethylbenzene) were also shown to occur in animals and humans (Tardif et al., 1997).

8.3.1 Toluene

Approximately 80% of absorbed toluene from inhalation exposure is recovered in urine as hippuric acid, the principal metabolite of toluene (Ogata, 1984; Löf et al., 1993; Tardif et al., 1998). Toluene metabolism, which takes place mainly in the liver, consists of sequential hydroxylation and oxidation by CYP enzymes (CYP2E1, CYP2B6, CYP2C8, CYP1A2 and CYP1A1) to benzoic acid (Phase I reactions), followed by conjugation of benzoic acid (Phase II) with glycine to form hippuric acid. Several studies of urinary metabolites in toluene-exposed humans (Angerer, 1979; Andersen et al., 1983; Dossing et al., 1983; Inoue et al., 1986; Baelum et al., 1987, 1993; Jonai and Sato, 1988; Löf et al., 1990, 1993; Ng et al., 1990; Kawai et al., 1992; Maestri et al., 1997; Angerer et al., 1998) and rats (Bray et al., 1949; Van Doorn et al., 1980; Wang and Nakajima, 1992) have identified hippuric acid as the major urinary metabolite of toluene. A minor CYP-related pathway involves a previous epoxidation of the aromatic ring to form either *o*- or *p*-cresol, which undergoes conjugation reactions to form mainly sulphate and glucuronide derivatives. Glutathione conjugation also occurs, resulting in *S*-benzylglutathione and *S*-benzylmercapturic acid (conjugation to benzyl alcohol) or *S*-*p*-toluyl glutathione and *S*-*p*-toluylmercaptic acid (conjugation to the epoxidated ring). Urinary excretion of these minor metabolites accounts for less than 5% of absorbed toluene (Nakajima et al., 1991, 1992a, 1992b, 1993, 1997; Nakajima and Wang, 1994; Tassaneeyakul et al., 1996). CYP2E1, one of the major CYP isozymes involved in the major toluene pathway (Tassaneeyakul et al., 1996; Nakajima et al., 1997), is reported to be expressed several hours after birth in humans and continues to increase during the first year of life (Vieira et al., 1996). Excretion of non-metabolized toluene in exhaled air can represent from 7% to 20% of absorbed toluene (Carlsson, 1982; Leung and Paustenbach, 1988; Löf et al., 1993).

8.3.2 Ethylbenzene

Ethylbenzene is metabolized mainly through oxidation (hydroxylation) by microsomal enzymes (Phase I), which is followed by conjugation reactions (Phase II) to form a number of metabolites that are excreted in urine. The first step involves the hydroxylation of ethylbenzene to 1-phenylethanol, which is catalyzed by specific isoforms of CYP (CYP2E1/CYP2B6) (Sams et al., 2004). No significant qualitative differences in metabolism between the oral and inhalation routes of exposure were reported in humans or experimental animals.

In humans exposed via inhalation, the major metabolites of ethylbenzene are mandelic acid (approximately 64–71%) and phenylglyoxylic acid (approximately 19–25%) (Bardodej and Bardodejova, 1970; Engström et al., 1984; Tardif et al., 1997; Knecht et al., 2000; Jang et al., 2001). Dutkiewicz and Tyras (1967) reported that following dermal exposure of human volunteers, maximum excretion of mandelic acid via the urine occurred at 3 hours after skin exposure and represented only 4.6% of the absorbed dose; the rate of absorption of an aqueous solution of ethylbenzene was greater than that of liquid (pure) ethylbenzene.

Differences in the biotransformation of ethylbenzene between species have been reported (El Masry et al., 1956; Bakke and Scheline, 1970; Climie et al., 1983; Engström et al., 1984, 1985). The most important difference concerns the major metabolites that differ in nature and percentages between species. In rats exposed by inhalation or orally to ethylbenzene, the major metabolites were identified as benzoic acid, hippuric acid, 1-phenylethanol, mandelic acid and phenylglyoxylic acid (Climie et al., 1983; Engström et al., 1984, 1985). Nakajima and Sato (1979) showed that the *in vitro* metabolic activity of rat liver microsomal enzymes on ethylbenzene is increased by fasting, despite a marked loss of liver weight. The authors also reported that the metabolic rate was significantly higher in fasted males than in fasted females.

8.3.3 Xylenes

The metabolism of the three xylene isomers occurs primarily in the liver and to a lesser extent in the lung and kidneys. The main metabolic pathway that accounts for almost the entire absorbed dose of xylenes (90%) in humans involves hydroxylation of a methyl group, which is catalyzed mainly by an isoform of CYP (CYP2E1), forming methylbenzyl alcohols. This methyl hydroxylation is both a saturable and an inducible metabolic process (Tassaneeyakul et al., 1996). In a subsequent step, the alcohol moieties are oxidized to form methylbenzoic acids, which conjugate with glycine to form methylhippuric acids, the main metabolites that are excreted into the urine (Ogata et al., 1970, 1979; Sedivec and Flek, 1976; Astrand et al., 1978; Senczuk and Orlowski, 1978; Riihimäki et al., 1979; Norström et al., 1989). Further metabolic pathways produced minor urinary metabolites that account for < 10% of the absorbed dose: methylbenzyl alcohols, *o*-toluylglucuronides, xylene mercapturic acids such as *S*-(*o*-methylbenzyl)-*N*-acetylcysteine (Norström et al., 1988) and xylenols.

In animals, the metabolism of xylene is qualitatively similar to that in humans. Quantitative differences, especially in the metabolism of methylbenzoic acids (toluic acids), have been reported (Bakke and Scheline, 1970; Sugihara and Ogata, 1978; Ogata et al., 1979; van Doorn et al., 1980). According to some authors, those differences may be explained in part by differences in the size of the doses given to humans and animals in experimental studies (David et al., 1979; Ogata et al., 1979; van Doorn et al., 1980).

Results from rat studies demonstrate that orally administered xylenes are subject to a first-pass metabolic effect that limits the amount of absorbed parent material reaching the general circulation (Kaneko et al., 1995).

Studies in animals showed that the metabolism of xylene may be influenced by prior exposures (inhalation or oral) to xylene (Elovaara et al., 1989). For instance, pretreatment of rats with *m*-xylene increased the percentage of *m*-methylhippuric acid and thioethers (glutathione conjugates) in the urine. Thioether excretion in 24-hour urine was enhanced about 10-fold after inhalation exposure to xylene and 20-fold after oral administration.

8.4 Excretion

8.4.1 Toluene

Toluene for the most part is eliminated in the urine (Löf et al., 1990, 1993; Turkall et al., 1991; Tardif et al., 1992, 1998), mainly as hippuric acid, in experimental animals and humans. Elimination from the blood is rapid (Sato and Nakajima, 1978; Carlsson, 1982; Löf et al., 1990, 1993), displaying three-phase elimination half-lives of 3, 40 and 738 minutes following a single inhalation exposure in humans (Löf et al., 1993). Elimination of unchanged (non-metabolized) toluene is also detected in the expired air (Carlsson, 1982; Leung and Paustenbach, 1988; Pellizzari et al., 1992; Laparé et al., 1993; Löf et al., 1993; Monster et al., 1993), especially immediately after exposure, and can represent from 7% to 20% of the absorbed dose; elimination via expired air subsequently decreases rapidly thereafter (Benoit et al., 1985).

Unchanged toluene was detected in alveolar air samples of eight human volunteers for up to 4 hours after cessation of exposure (2 mg/minute gastric infusion for 3 hours), and rates of urinary excretion of hippuric acid and *o*-cresol were elevated compared with those for unexposed volunteers (Baelum et al., 1993). Interestingly, co-administration of ethanol (0.32 g/kg bw, corresponding to two alcoholic drinks) with the 2 mg/minute dosage decreased hippuric acid urinary excretion and increased the area under the time versus concentration curve for alveolar toluene, which is consistent with previous studies showing that ethanol inhibits the major toluene metabolic pathway of side-chain oxidation (Dossing et al., 1984; Wallen et al., 1984). Urinary

hippuric acid has generally been used as a biomarker of exposure to toluene; however, it best correlates with acute exposure given its short half-life (Lowry, 1987). Urinary *o*-cresol, which is more specific, is currently used as a biomarker of occupational exposure to toluene (Truchon et al., 1999). Both hippuric acid and *o*-cresol in urine have been found to serve as good markers for exposure by inhalation to toluene concentrations greater than 50 ppm (188.5 mg/m^3) (Ikeda et al., 2008). Blood concentrations of toluene have been reported as the most reliable measure of toluene exposure (Kawai et al., 1993; Brugnone et al., 1995). Toluene blood levels appear to correlate well with air toluene levels below 1–3 ppm (3.8–11.3 mg/m^3) (Kawai et al., 1994; Ikeda et al., 2008), for which hippuric acid as a marker of exposure is no longer useful. Finally, a small fraction of toluene is also excreted in urine and has been proposed as a biomarker for monitoring occupational exposure to toluene (Kawai et al., 2008).

In rats, approximately 22% of a single oral dose of ^{14}C-labelled toluene (185 kBq) was reported to be eliminated in the expired air (Turkall et al., 1991); combined with urinary excretion, Turkall et al. (1991) reported that almost 100% of the single dose of radiolabelled toluene was eliminated within 48 hours after exposure.

8.4.2 Ethylbenzene

Elimination of ethylbenzene and its metabolites in animals after oral exposure has been shown to be similar to that following inhalation exposure (ATSDR, 2010). Female rats that received a single oral dose of 30 mg ^{14}C-labelled ethylbenzene per kilogram body weight excreted 82% of radioactivity in the urine and 1.5% in the feces. The major metabolites were mandelic acid (23%), hippuric acid (34%) and 1-phenylethyl glucuronide (4%). Consistent with the differences observed in the biotransformation pathways, quantitative and qualitative metabolic differences between species and exposure routes were shown to exist in the percentages of metabolites excreted in the urine (Climie et al., 1983).

Rabbits orally exposed to ethylbenzene excreted large amounts of glucuronide conjugates (32%) in the urine (Smith et al., 1954; El Masry et al., 1956) instead of mandelic acid (2%), hippuric acid and phenylglyoxylic acid, which are the major metabolites in rats.

Susten et al. (1990) reported that the absorbed dose of ^{14}C-labelled ethylbenzene collected in expired breath during the first 15 minutes of ethylbenzene application was 9.3% in hairless mice exposed by the percutaneous route.

8.4.3 Xylenes

In humans, approximately 95% of absorbed xylenes following inhalation are biotransformed and excreted as methylhippuric acids, while the remaining 5% are eliminated unchanged in the exhaled breath (Sedivec and Flek, 1976; Astrand et al., 1978; Senczuk and Orlowski, 1978; Ogata et al., 1979; Riihimäki et al., 1979; Pellizzari et al., 1992). A small fraction (< 0.005%) is eliminated unchanged in the urine, and < 2% is eliminated as xylenols (Sedivec and Flek, 1976).

Turkall et al. (1992) reported that excretion of radioactivity by rats following an oral dose of ^{14}C-labelled *m*-xylene showed that urinary excretion occurred mostly during the first 12 hours after administration and approximated 50–59% of the dose. Whereas 96.2% was eliminated in the urine in males and 73.7% in the urine in females over 48 hours, approximately 8% and 22% of the total dose were excreted unchanged in exhaled air by males and females, respectively, during the first 12 hours. Overall, *m*-methylhippuric acid comprised 67–75% of the urinary radioactivity, with xylenol representing 2–18% and unchanged *m*-xylene comprising approximately 1%.

Simulations of the Kaneko et al. (1991a) PBPK model estimated that increased physical activity increased the rate of urinary excretion of the *m*-xylene metabolite *m*-methylhippuric acid.

The rate of urinary excretion of the metabolite was lower in women than in men both during and after exposure.

8.5 Physiologically based pharmacokinetic models

In human health risk assessment for toluene, ethylbenzene and xylenes, PBPK modelling is useful, since no appropriate toxicity data are available for humans ingesting these chemicals in drinking water, many of the animal studies rely on inhalation exposure and metabolite generation over low to high parent compound exposures is non-linear. Several PBPK models have been developed for each of the compounds. The structural basis of these models is the initial Ramsey and Andersen (1984) styrene model, which compartmentalizes organs into liver, fat, richly perfused tissues and slowly perfused tissues.

In addition to the PBPK models for each of the compounds that are described in the following sections, several models have been designed to evaluate exposure to combinations of the compounds or to gasoline-like mixtures. The first model developed for this purpose was used to investigate the interactions between toluene and *m*-xylene; it considered the metabolism of both compounds by CYP2E1 and contained four organ compartments (liver, fat, slowly perfused tissues and richly perfused tissues), as well as equations for pulmonary exposure and excretion (Tardif et al., 1993, 1995). A subsequent model added ethylbenzene to the mixture (Tardif et al., 1997). PBPK models were also developed to consider mixtures of gasoline, which considered the three aforementioned compounds as well as other VOCs (Haddad et al., 1999, 2000, 2001) or toluene, ethylbenzene and *o*-xylene in combination with other VOCs (Dennison et al., 2003).

8.5.1 Toluene

PBPK models describing the kinetics of inhaled toluene have been developed and validated for rats (Tardif et al., 1993, 1995, 1997; DeJongh and Blaauboer, 1996; Haddad et al., 1999, 2000, 2001; Dennison et al., 2003) and scaled to—and validated for—humans (Pierce et al., 1996a; Tardif et al., 1997; Nong et al., 2006).Most models are based on the same four compartments (liver, fat, and richly and slowly perfused tissues), with saturable oxidative metabolism restricted to the liver. Modifications to this approach included the addition of a brain compartment to allow for estimates of toluene levels in the target organ (DeJongh and Blaauboer, 1996) or consideration of extrahepatic metabolism, specifically in the lungs (Pierce et al., 1996a). One model was also adapted to simulate pharmacokinetics in different stages of childhood using child-specific physiological and metabolic parameters (Nong et al., 2006); the same model also incorporated population distributions of various parameters for adults using Monte Carlo simulation.

Two additional generic human PBPK models for VOCs included toluene. Fisher et al. (1997) developed a lactation model, which added a milk compartment to estimate the transfer of toluene and other VOCs from women exposed by inhalation to their nursing infants; however, metabolic parameters for toluene do not seem to be incorporated, and the model was not validated. In a generic model for several non-polar organic non-electrolytes diluted in aqueous solution, dermal absorption of toluene (with three compartments of stratum corneum, viable epidermis and blood) was described (Shatkin and Brown, 1991); however, the model could not be validated for toluene because of large discrepancies between model estimates and empirical data.

8.5.2 Ethylbenzene

Several models have been developed and validated to simulate the kinetics of inhaled ethylbenzene in rats (Tardif et al., 1997; Haddad et al., 1999, 2000, 2001; Dennison et al., 2003),

mice (Nong et al., 2007) and humans (Tardif et al., 1997). In general, all of the models have similar structures—with compartments for liver, fat, and slowly and richly perfused tissues, as well as the modelling of lungs for inhalation and excretion—with saturable oxidative metabolism occurring in the liver. Extrahepatic metabolism was also incorporated into the mouse model, with calculations for metabolic activity also being developed for the lungs and richly and poorly perfused tissues (Nong et al., 2007). Dermal exposure to ethylbenzene has also been simulated and validated in humans using a generic model developed for several non-polar organic non-electrolytes diluted in aqueous solution, which describes only the absorption through stratum corneum and viable epidermis into the blood and not the subsequent distribution to other organs (Shatkin and Brown, 1991).

8.5.3 Xylenes

PBPK models have been designed to describe the inhaled kinetics of *m*-xylene (Tardif et al., 1993, 1995; Haddad et al., 1999, 2000, 2001; Kaneko et al., 2000), *o*-xylene (Dennison et al., 2003) or all three xylene isomers (Adams et al., 2005). These models have been developed and validated for rats (Tardif et al., 1993, 1995; Haddad et al., 1999, 2000, 2001; Kaneko et al., 2000; Dennison et al., 2003) and humans (Kaneko et al., 2000; Adams et al., 2005). Only one model considered compartments other than the liver, fat, richly and slowly perfused tissues, and lung, in which equations for the distribution of *m*-xylene to muscle were included (Kaneko et al., 2000). Most of the models restricted saturable oxidative metabolism to the liver, with additional consideration of lung metabolism in one study (Adams et al., 2005). Although equations were designed to estimate only the rate of metabolism for most models, one model allowed for the estimation of concentrations of the metabolite *m*-methylhippuric acid excreted in urine (Kaneko et al., 2000).

Thrall and Woodstock (2003) also developed a model to simulate exposures to *o*-xylene via the dermal route. The model was based on the Tardif et al. (1993) model, with an extra skin compartment, and was validated in humans and rats.

In a generic lactation model, Fisher et al. (1997) added a milk compartment to estimate the transfer of *o*-, *m*- and *p*-xylene and other VOCs to nursing infants based on maternal inhalation exposures. The relevance of this model is limited, because metabolic parameters for xylenes do not seem to be incorporated, and the model was not validated.

8.5.4 Health Canada model

Health Canada developed a PBPK model based on the Tardif et al. (1997) model to facilitate inhalation to oral, experimental animal to human and high dose to low dose extrapolations for toluene, ethylbenzene and xylenes (Nong, 2014). The same basic compartments as in the Tardif et al. (1997) model (fat, liver, slowly perfused and richly perfused tissues, with exposure and excretion via the lungs) were used in the Health Canada model, but the model was updated to include equations for oral exposure as well as a dermal compartment that could be used in estimates of the contribution of showering and bathing to exposure to toluene, ethylbenzene and xylenes. Dermal uptake is based on a previous PBPK model for VOCs (Thrall et al., 2000, 2002, 2003), with the compounds being absorbed directly to the bloodstream with no first-pass effect. The multiroute model represented metabolism as a saturable oxidative process that occurs in the liver, with no extrahepatic metabolism included. Each compound was modelled separately, with no metabolic interaction between the compounds being considered. Since past work conducted by Nong et al. (2007) indicated that model predictions without extrahepatic metabolism refinements were still within a 2-fold variation from low to high dose exposure, the simulation for each compound separately is still valid. Validation of inhalation exposures in the

model was performed by comparing model simulations for rats and humans with those presented in the previously validated Tardif et al. (1997) model; validation for the mouse was performed by comparing simulations with those presented in Nong et al. (2007). Human dermal exposure was validated against data from Thrall and Woodstock (2002) for toluene, Mattie et al. (1994) for ethylbenzene (determined from benzene in accordance with very similar partition coefficients for skin exposure) and Thrall and Woodstock (2003) for xylenes. The human oral component of the multiroute model was compared with equivalent dose estimates from inhalation exposures as a means to internally validate extrapolation between routes, even though there was a lack of human oral exposure data.

Data from Seeber et al. (2004, 2005), NTP (1999) and Korsak et al. (1994) were used for PBPK modelling of toluene, ethylbenzene and xylenes, respectively. The dose metric that was used for this modelling was average concentrations of the parent compounds, which are considered to be the toxic moieties, in the blood. Blood concentration is used as a proxy for brain concentration, which is considered to be appropriate, since the absorption and elimination curves for blood and brain concentrations of toluene have been previously demonstrated to be almost identical (DeJongh and Blaauboer, 1996; van Asperen et al., 2003; Bushnell et al., 2007).

For toluene, an external dose of 26 ppm (Seeber et al., 2003; 2004), which was identified as a no-observed-adverse-effect level (NOAEL) from a study of humans exposed occupationally, was inputted into a human PBPK model to estimate the lifetime average internal blood concentrations of toluene (in mg/L). The external human oral dose generated by the model corresponds to the level of exposure identified above, assuming daily consumption of 1.5 L of drinking water.

Lifetime internal blood concentrations of ethylbenzene were determined using PBPK models for mouse (using hyperplasia of the pituitary gland and liver cellular alterations as endpoints). For these effects, a NOAEL of 75 ppm from the NTP (1999) study was identified in mice and used to determine the lifetime average internal blood and liver concentrations of ethylbenzene (in mg/L) in the mouse PBPK model. External human oral doses were generated by the model to correspond to a blood and liver concentration of ethylbenzene equivalent to the external mouse NOAEL of 75 ppm, assuming daily consumption of 1.5 L of drinking water.

Ethylbenzene exposure was also shown to cause various tumours in rodents (NTP, 1999). However, only alveolar/bronchiolar tumours found in male mice were determined to be of relevance to humans. External doses were inputted into the mouse PBPK model in order to estimate the lifetime average internal blood concentrations of ethylbenzene (in mg/L). Using the log logistic model as the best fit model from the U.S. EPA's benchmark dose (BMD) software (U.S. EPA, 2010), these internal doses were then analysed to determine the most appropriate point of departure for inputting into the human model. This internal dose was then inputted into the human PBPK model in order to determine the human external dose required to result in blood concentrations similar to those in the mouse, assuming 1.5 L consumption of drinking water per day and 70 years of exposure.

For xylenes, an external dose of 50 ppm *m*-xylene was identified as a NOAEL in exposed rats based on performance on the rotarod test (Korsak et al. 1994). This dose was inputted into a rat PBPK model in order to estimate the lifetime average internal blood concentrations of *m*-xylene (in mg/L). The external human oral dose generated by the model corresponds to the level of exposure identified above, assuming daily consumption of 1.5 L of drinking water.

The PBPK model as described above was also used to estimate litre-equivalent contributions from dermal and inhalation exposures when showering and bathing (see Section 5.6). These litre-equivalent contributions were estimated by running the human PBPK model for a 30-minute bathing scenario. By comparing the internal doses generated from the dermal and inhalation

routes of exposure with the internal dose from ingestion, the litre-equivalent contributions for dermal and inhalation exposures were estimated to be 0.2 L-eq and 0.43 L-eq for toluene, 0.21 L-eq and 0.44 L-eq for ethylbenzene, and 0.21 L-eq and 0.43 L-eq for xylenes, respectively.

9.0 Health effects

9.1 Effects in humans

9.1.1 Acute toxicity

Accidental ingestion of toluene was shown to cause severe acute toxicity, including oropharyngeal and gastric irritation with vomiting and hematemesis (Von Burg, 1993). Abdominal pain, hemorrhagic gastritis and central nervous system depression were observed following ingestion of approximately 1 L of paint thinner known to contain toluene (Caravati and Bjerk, 1997). Death was reported to occur within 30 minutes of ingestion of approximately 60 mL (625 mg/kg bw) of toluene in one individual (Ameno et al., 1989). Ingestion of xylene was shown to cause severe gastrointestinal distress (Sandmeyer, 1981). No information was available on human ingestion of ethylbenzene.

Exposure via inhalation to a mixture of VOCs that included toluene, ethylbenzene and xylenes for 2.75 hours at concentrations as low as 5 mg/m^3 was associated with irritation of the eyes, nose and throat (Molhave et al., 1986). Additional acute effects of toluene, ethylbenzene and xylene exposure generally target the central nervous system. Accidental exposures to high concentrations of toluene (≥ 10 000 ppm or 37 500 mg/m^3) have resulted in central nervous system excitation followed by progressive impairment of consciousness, seizures and coma (IPCS, 1986). Controlled human studies have identified decreased neurological functions at toluene concentrations between 100 and 150 ppm (~ 377 and 566 mg/m^3) (Andersen et al., 1983; Baelum et al., 1985; Echeverria et al., 1989). A controlled human co-exposure to toluene and xylene suggested that exposure as low as 200 ppm (~ 754 mg/m^3) toluene (for 7 hours with one break) causes prolongation of reaction time, decrease in pulse and decrease in systolic blood pressure (Ogata et al., 1970). It has been demonstrated in studies of controlled human exposure to *m*-xylene over several days that concentrations as low as 90 ppm (~ 339 mg/m^3) had deleterious effects on reaction time, manual coordination, body balance and equilibrium (Savolainen et al., 1979, 1980). However, Olson et al. (1985) noted that 4-hour exposure of males to toluene at 3.25 mmol/m^3, to *p*-xylene at 2.84 mmol/m^3 or to a mixture of both chemicals (toluene at 2.20 mmol/m^3 and xylene at 0.94 mmol/m^3) had no impact on reaction time, short-term memory or choice reaction either immediately upon exposure or 2 and 4 hours after exposure.

Thus, studies indicate that acute exposure to toluene and xylenes is associated with effects on the central nervous system. Exposure to toluene, ethylbenzene and xylene vapours may also irritate mucous membranes, and exposure via ingestion may cause moderate to severe gastrointestinal effects.

9.1.2 Subchronic and chronic toxicity and carcinogenicity

Studies of exposure in humans are primarily limited to the inhalation route and involve co-exposure to other solvents in the occupational setting. Limited evidence has associated chronic exposure to toluene and xylenes with neurological effects, malignancies and other effects. Very little information was available regarding the chronic toxicity of ethylbenzene due to the lack of working environments with predominant ethylbenzene exposure.

9.1.2.1 Neurological effects

The neurological implications of exposure to toluene and xylenes have been examined in individuals exposed occupationally. However, no studies of ethylbenzene exposure were available, and none of the studies pertained to oral exposure.

Several studies have investigated the effects of toluene in individuals working within the printing and rubber industry, where toluene exposure is prevalent. An effect that has been carefully documented is a reduction in colour vision. Colour vision loss was noted in workers in a printing press at a mean toluene concentration of 120 ppm (452 mg/m^3) and in rubber workers that had urinary toluene levels ranging from 60 to 73 µg/L (Zavalic et al., 1998; Cavalleri et al., 2000). In both cases, workers were exposed primarily to toluene and were not exposed to other neurotoxicants. One study at lower toluene levels of approximately 44–48 ppm or 166-181 mg/m^3 (and where toluene accounted for at least 90% of the exposure, however, did not show a significant alteration in colour vision (Nakatsuka et al., 1992). Toluene exposure was also associated with increased amplitudes in visually evoked potential of printing press workers exposed to approximately 40–60 ppm (151-226 mg/m^3)toluene and employed for an average of 20.6 years (Vrca et al., 1995); a follow-up study, however, did not support these findings (Vrca et al., 1997). Additional studies of toluene exposure pertain to more generalized neurological effects, including decreased concentration and reasoning and self-reporting of subjective symptoms. Several studies have shown that workers exposed to toluene had decreased concentration, memory and reasoning, even at concentrations below 100 ppm or 377 mg/m^3 (Foo et al., 1990; Boey et al., 1997; Eller et al., 1999; Neubert et al., 2001; Kang et al., 2005; Nordling Nilson et al., 2010). Other studies of cognitive effects at lower levels report no effect of exposure to toluene at concentrations of up to 50 ppm or 189 mg/m^3 (Zupanic et al., 2002; Seeber et al., 2004, 2005). One study demonstrated a clear concentration–response relationship with regards to memory disturbances (Chouaniere et al., 2002). However, the effect was not significant when cumulative exposure was investigated, thus suggesting that the effect may not persist. Furthermore, occupational exposure to toluene caused increases in reporting of subjective symptoms (Ukai et al., 1993; Tanaka et al., 2003), and one study suggested that chronic exposure to toluene may be related to damage to the central autonomic nervous system, as demonstrated by altered nerve conduction in exposed individuals (Murata et al., 1993; Tanaka et al., 2003).

In a repeated measures study by Seeber et al. (2004), the authors investigated the effects of toluene on cognitive function, as measured by attention (symbol–digit substitution, switching attention, simple reaction), memory (digit span, Syndrom-Kurztest) and psychomotor (steadiness, line tracing, aiming, tapping, pegboard) tests in a subsample of 192 subjects who participated in four examinations over 5 years. Exposures and exposure durations were as follows: high current exposure = 26 ppm (98 mg/m^3) for 106 subjects; low current exposure = 3 ppm (11 mg/m^3) for 86 subjects; long duration = 21 years; and short duration = 6 years. Current exposures were determined by four measures, whereas lifetime-weighted averages were determined using a job exposure matrix. Analyses by repeated measures analysis of variance and stepwise regression adjusting for age, level of education, alcohol consumption and anxiety revealed a significant difference in error time of the steadiness test between exposures and error time in line tracing when exposure level and duration were combined. However, in further analyses, the between-subject effect for exposure level in the steadiness test was not significant, and the results of the line tracing test were not consistent with an exposure-related response. Analyses also showed no differences between exposure groups when they were stratified by duration (short or long). In a later study by Seeber et al. (2005), these results were analyzed using a case-control method in which cases with impaired function were defined as those that were 20% above or below the mean (depending on the measure of effect) of the reference group. The only significant finding

(errors with steadiness with the dominant hand) was only marginally significant when errors and error time in a repeated measures approach were included (Seeber et al., 2005).

Non-specific neurological effects of xylene exposure have been observed in an occupational setting and a controlled human study. When exposure to xylenes accounted for more than 70% of total occupational exposure to chemicals (sum of all isomers, geometric mean concentration 14 ppm or 61 mg/m^3) in rubber, plastic and printing workers, a significant increase in the prevalence of subjective neurological symptoms was noted. Significant symptoms included dizziness, heavy feeling in the head and headache. However, no dose–response trends were observed, and the potential effects of other chemicals were unclear (Uchida et al., 1993). Chronic symptoms of dizziness, easy fatigability, depressed mood and palpitation were also observed when humans were exposed to approximately to a mixture comprising 50% xylenes along with 24% toluene (corresponding to 18 ppm or 78 mg/m^3 xylenes and 10 ppm or 38 mg/m^3 toluene) and traces of other solvents (Wang and Chen, 1993). Savolainen et al. (1985) reported that increases in blood levels of *m*-xylene correlated with decreased balance following controlled human exposure to a fixed *m*-xylene concentration of 200 ppm (868 mg/m^3) or to fluctuating *m*-xylene concentrations in the range 135–400 ppm (586–1,736 mg/m^3) over 6 weeks (4 hours/day, 6 days/week). The persistence of this effect, however, is not known.

Overall, data indicate that toluene and xylenes may be neurotoxic, although more information was available for toluene due to its widespread use in the printing industry. Toluene exposure may be associated with adverse neurological effects, including colour vision loss and decreased cognitive functions. It is unclear whether ethylbenzene is neurotoxic in humans.

9.1.2.2 Renal, hepatic and other tissue effects

No study has investigated the long-term effects of toluene, ethylbenzene or xylene exposure on renal, hepatic and other tissues via the oral route in humans. However, some studies have focused on occupational exposure to the three chemicals, especially toluene. In the case of toluene, limited data from chronic solvent abusers were also available.

Several studies have investigated impacts on liver toxicity in humans as measured by markers of hepatic toxicity in blood. Most studies that have examined toluene-exposed workers in printing, painting and shoe manufacturing plants have reported negative findings at toluene concentrations of up to 324 ppm or 1 221 mg/m^3 (Seiji et al., 1987; Ukai et al., 1993). One study of eight print workers occupationally exposed to low levels of toluene (≤ 200 ppm or 754 mg/m^3) reported mild elevation of serum transaminases including aspartate aminotransferase with concomitant pericentral fatty changes in the liver, as measured by liver biopsy (Guzelian et al., 1988). Studies of chronic solvent abusers exposed primarily to toluene have reported kidney injury, including tubular degeneration and necrosis (Kamijima et al., 1994; Kamijo et al., 1998). However, only very mild effects on kidney function, such as alterations in creatinine clearance, were observed in printers (Stengel et al., 1998). This suggests that renal toxicity is likely to increase in a dose-dependent trend in human populations. Studies have also reported acidosis following inhalation exposure to toluene, although this effect most likely does not lead to permanent kidney damage (ATSDR, 2000). Human studies pertaining to tissues other than liver and kidney were not found.

Occupational exposure to ethylbenzene, for the most part, occurs in combination with exposure to other organic solvents. Thus, it is difficult to determine any ethylbenzene-specific effects in human studies. One study evaluated the health impacts of exposure of workers within an ethylbenzene manufacturing facility over 20 years (Bardodej and Cirek, 1988). Although specific air concentrations were not reported, a mean air concentration of 6.4 mg/m^3 was estimated from the mean urinary mandelic acid concentrations in the workers (Bardodej and

Bardodejova, 1970; ATSDR, 2010). The study did not demonstrate any damage to liver tissue as a result of chronic exposure to ethylbenzene. However, the concentration may have been too low to elicit any health effects.

Only one study has investigated chronic exposure (average of 7 years) to approximately 14 ppm (61 mg/m^3) mixed xylenes, representing over 70% of the total exposure to solvents (Uchida et al., 1993). This study did not reveal any changes in serum chemistry that would suggest abnormal liver or kidney effects. Thus, low-level inhalation of xylenes is unlikely to cause any adverse hepatic or nephritic effects.

Thus, toluene appears to cause adverse effects in the kidney and liver upon inhalation exposures in humans. However, there is insufficient information on ethylbenzene and xylenes to draw conclusions with regards to the adverse effects in various tissues.

9.1.2.3 Cancer

Studies investigating the carcinogenic potential of toluene, ethylbenzene and xylenes are limited to occupational exposures. No studies have investigated carcinogenic outcome following oral exposure in humans.

The carcinogenic potential of toluene in humans has been studied in three cohort studies of workers exposed primarily to toluene. Svensson et al. (1990) showed that a minimum of 3 months of exposure of rotogravure printers employed between 1925 and 1985 increased mortality due to gastrointestinal and stomach cancers (standardized mortality ratio [SMR] 2.1, 95% confidence interval [CI] 1.1–3.5; and SMR 2.7, 95% CI 1.1–5.6; for gastrointestinal and stomach cancers, respectively) and increased morbidity due to respiratory tract cancers (standardized incidence ratio [SIR] 1.8, 95% CI 1.0–2.9). However, gastrointestinal cancer was significant only when a 5-year minimum exposure and a 10-year latency period were considered, and exposure to benzene was also noted for those exposed prior to the 1960s. A study of shoe manufacturer workers employed for at least 1 month between 1940 and 1979–1982 showed an increase in lung cancer that was more significant in men (Walker et al., 1993; Lehman and Hein, 2006). However, workers were also exposed to methyl ethyl ketone, acetone and hexane and may have been in contact with benzene. Moreover, smoking was an important confounding factor in the study. In a study by Anttila et al. (1998), Finnish workers were monitored for biological markers of toluene, xylenes and styrene. No significant findings were observed, and possible exposure to benzene was noted. One case-control study determined that professions with the highest exposure to toluene had an increased risk of rectal cancer, but no other forms of cancer (Gérin et al., 1998). Other epidemiological studies have involved individuals exposed to solvent mixtures that included toluene. These studies did not report significant increases in cancer (Wen et al., 1985; Carpenter et al., 1988; Blair et al., 1998; Lundberg and Milatou-Smith, 1998; Costantini et al., 2008), other than an increase in the incidences of Hodgkin's/non-Hodgkin's lymphoma (Olsson and Brandt, 1980; Miligi et al., 2006) and colon cancer (Dumas et al., 2000; Goldberg et al., 2001). However, individuals in these studies were exposed to various other solvents, and thus it is difficult to determine the impact of toluene alone among these findings. Overall, there is little evidence that toluene is associated with cancer, and the significant results that were found may be confounded by exposure to other chemicals, including benzene.

Only one study examined predominant ethylbenzene exposure in workers within an ethylbenzene manufacturing facility. Although the exposure was very low (estimated to be approximately 6.4 mg/m^3, based on the mean urinary mandelic acid concentrations in the workers), no excess cases of malignancy were recorded in this facility (Bardodej and Cirek, 1988). Thus, there is insufficient information to determine the carcinogenicity of ethylbenzene in humans.

There is no occupational study in which xylene exposure was predominant, and there is very little evidence of xylene-induced carcinogenicity in humans. One study that examined lymphocytic leukemia among solvent-exposed rubber workers indicated a possible association with exposure to xylenes (Arp et al., 1983). Miligi et al. (2006) reported a potential increased risk of non-Hodgkin's lymphoma for medium to high exposures (according to occupation and exposure control metrics) to xylenes (odds ratio [OR] 1.7, 95% CI 1.0–2.6). However, no increased risk was found by Costantini et al. (2008) for chronic lymphatic leukemia as a result of medium/high xylene exposure. Gérin et al. (1998) determined that professions with the highest exposure to xylenes had an increased risk of rectal cancer, but no excess risk was found for any other cancer. A population-based case-control study that examined rectal cancer determined a slightly elevated risk for those exposed to xylenes (Dumas et al., 2000). However, due to exposure to various other solvents, it is difficult to draw any conclusions from these studies.

Due to the limited studies of toluene, ethylbenzene and xylene exposure in humans and the various confounding factors presented in each study, there is insufficient evidence to establish the carcinogenic effects of the three compounds in humans.

9.1.2.4 Other effects

Studies have investigated the effects of toluene, ethylbenzene and xylenes on hearing and cardiovascular/pulmonary health. None of these studies evaluated oral exposure to the chemicals.

Exposure to solvents in general has been associated with hearing loss beyond what can be expected in work environments with elevated noise. Of the three chemicals of interest, data are limited to toluene. Hearing loss was observed among printing workers exposed primarily to toluene (Morata et al., 1997). Workers exposed on average to 97 ppm (366 mg/m^3) toluene had alterations in auditory evoked potentials indicative of hearing impairments (Abbate et al., 1993). Alterations in auditory evoked potentials were further observed in printing press workers exposed to low levels of toluene for an average of 20.3 years (Vrca et al., 1996, 1997). However, investigations in rotogravure printers classified in various groups according to the length and level of exposure found that auditory thresholds were affected by noise, but not by toluene (Schäper et al., 2003). Although it is unclear whether the effects of toluene exposure on hearing in humans are a result of direct ototoxicity or adverse impacts on the brain, data in humans suggest that the effect may be neurological.

Additional studies pertain to adverse cardiovascular, immune and pulmonary effects. Xu et al. (2009) reported significant associations between blood levels of toluene, ethylbenzene, *o*-xylene and *m/p*-xylene (0.248, 0.05, 0.058 and 0.210 ng/mL, respectively) and cardiovascular disease prevalence; associations were especially significant for toluene. Yoon et al. (2010) reported that urinary levels of hippuric acid and methylhippuric acid (metabolites of toluene and xylene, respectively) in elderly people are associated with a reduction in forced expiratory volume, suggesting decreased lung function as well as increased urinary markers of oxidative stress. Billionnet et al. (2011) showed that exposure of individuals to ethylbenzene, *m*/*p*-xylene and *o*-xylene is associated with rhinitis. Studies have not reported significant adverse hematological effects of toluene exposure (Matsushita et al., 1975; Ukai et al., 1993); no data were available for ethylbenzene or xylenes.

Thus, occupational exposure to toluene may be associated with hearing loss. Data are not adequate to establish any relationships for risk of adverse cardiovascular or pulmonary effects.

9.1.3 Reproductive and developmental toxicity

Limited data were available on the reproductive and developmental effects of exposure to toluene, ethylbenzene and xylenes in humans. The studies were limited to occupational exposure.

Overall, there was very little evidence of reproductive and developmental toxicities for all three chemicals.

9.1.3.1 Reproductive effects

Relevant epidemiological studies include investigations of occupational exposure to organic solvents. Studies were limited to the inhalation route of exposure and primarily investigated spontaneous abortions. No studies examined the risk of reproductive toxicities in humans exposed to ethylbenzene via any route of exposure.

Reproductive studies of occupational exposure to toluene have examined risk of spontaneous abortion and fertility. The only study that investigated an almost exclusive exposure to toluene reported increases in rats of spontaneous abortion. A significant spontaneous abortion rate of 12.4% was reported in women working in an audio speaker factory exposed almost exclusively to toluene (mean concentration 88 ppm or 332 mg/m^3), compared with rates of 2.9% and 4.5% in the internal and external control groups, respectively (Ng et al., 1992). An additional study of laboratory workers demonstrated an increased rate of spontaneous abortion in women reporting routine toluene-related work at least 3–5 days/week (OR 4.7, 95% CI 1.4–15.9) (Taskinen et al., 1994). One study of Finnish female shoe workers exposed to high levels of toluene showed an increased risk of spontaneous abortion, although the significance was lost when regression models specific to toluene were applied (Lindbohm et al., 1990). The significant findings may be due to exposure of the shoe workers to additional chemicals, including acetone and hexane. One study reported small, non-significant increases in spontaneous abortion rate upon exposure to toluene in women employed in eight Finnish pharmaceutical companies (Taskinen et al., 1986). Reproductive success was also investigated. Women categorized as highly exposed to toluene according to occupation exhibited a small, non-significant decrease in fertility as measured by time to pregnancy (Sallmén et al., 2008). Although there are few data to support reproductive effects of toluene, exposure may be associated with spontaneous abortions.

Although no studies have investigated the reproductive effects of ethylbenzene, two of the aforementioned studies pertaining to solvent exposure examined the effects of xylenes. Laboratory workers who reported handling xylenes more than three times per week exhibited increased rates of spontaneous abortion (OR 3.1; 95% CI 1.3–7.5) (Taskinen et al., 1994), whereas spontaneous abortion was not affected in another study of occupational exposure (Lindbohm et al., 1990). Like toluene, xylene did not significantly affect fertility in occupationally exposed women (Sallmén et al., 2008).

Although contradictory findings were reported, there is evidence of toluene-induced effects on spontaneous abortion in humans. However, data are insufficient to establish any human reproductive effects associated with exposure to ethylbenzene and xylene.

9.1.3.2 Developmental effects

There are very few epidemiological data on developmental effects associated with exposure to toluene, ethylbenzene and xylenes in humans. Studies of elevated toluene exposure through abuse during pregnancy have reported excess cases of premature birth, reduced birth weight/size, microcephaly and postnatal developmental delays (Arnold et al., 1994; Pearson et al., 1994). However, no association with congenital malformation was found in female laboratory workers reporting frequent exposure to toluene or xylenes (Taskinen et al., 1994). Moreover, a study of neural tube defects in relation to estimated ambient air levels of toluene (0.01–14.3 μg/m^3), ethylbenzene (0.01–2.74 μg/m^3) and xylenes (0.18–8.84 μg/m^3) reported no increased rate of spina bifida or anencephaly (Lupo et al., 2011). Thus, developmental effects of exposure to

toluene, ethylbenzene and xylenes are unlikely, other than at very high exposures, as observed in chronic solvent abusers.

9.2 Effects on experimental animals

9.2.1 Acute toxicity

The acute toxicity of toluene, ethylbenzene and xylenes is relatively low. The oral median lethal dose (LD_{50}) for toluene in rats ranges from 5300 to 7400 mg/kg bw, whereas dermal exposure in rabbits resulted in an LD_{50} of 12 400 mg/kg bw (INRS, 2008). Via inhalation, the 4-hour median lethal concentration (LC_{50}) of toluene is 7500 ppm (2828 mg/m^3) in rats and 5308–7440 ppm (20,011-28,048 mg/m^3) in mice (INRS, 2008). Oral exposure to ethylbenzene in rats resulted in LD_{50} values of approximately 2500 mg/kg bw (Wolf et al., 1956), and 4769 mg/kg bw (Smyth et al., 1962). LD_{50}s for exposure of rats to xylene isomers via the oral route range from 3.6 to 5.8 g/kg bw, whereas the 4-hour LC_{50}s for inhalation exposure are approximately 6500 ppm (28,210 mg/m^3) in rats and 4000–5000 ppm (17,360-18,850 mg/m^3) in mice (IARC, 1989; WHO, 2004).

9.2.2 Short-term exposure

9.2.2.1 Neurological effects

Multiple studies have investigated the neurological effects of exposure to toluene, ethylbenzene and xylenes in experimental animals. Although most of the data pertain to inhalation exposure, neurotoxic effects following oral exposure were also documented.

Toluene exposure in animals was associated with altered behaviour and central nervous system effects, including modifications in neurotransmission. Only one study of oral exposure through drinking water was found. This study reported that toluene concentrations as low as 17 mg/L over 28 days (corresponding to a daily intake of 5 mg/kg bw) increased norepinephrine, dopamine and serotonin levels in the hypothalamus of male CD-1 mice as well as in other regions of the brain (Hsieh et al., 1990). Another study by oral gavage indicated neuronal necrosis in the dentate gyrus and Ammon's horn of the hippocampus in male and female rats at doses as low as 1250 mg/kg bw per day 5 days per week, after a thirteen-week exposure (Huff, 1990; NTP, 1990). Decreases in brain tissue may be related to breakdown of phospholipids (Kyrklund et al., 1987). Additional studies of exposure by inhalation have also noted alterations in levels of neurotransmitters, including norepinephrine, dopamine and serotonin, within rat brain and in prolactin levels in serum at toluene concentrations as low as 40 ppm or 151 mg/m^3 (Ladefoged et al., 1991; Von Euler et al., 1994; Berenguer et al., 2003; Soulage et al., 2004). Studies suggest that these effects can persist considerably after exposure to toluene. For example, an increase in the affinity of dopamine D_2 agonist binding in the rat caudate-putamen was observed 29–40 days following exposure to 80 ppm (302 mg/m^3) toluene over 4 weeks (6 hours/day, 5 days/week) (Hillefors-Berglund et al., 1995). Six months of exposure to toluene concentrations as low as 500 ppm (1885 mg/m^3) for 6 hours/day, 5 days/week, altered levels of norepinephrine, dopamine and serotonin in various regions of rat brain even 4 months post-exposure (Ladefoged et al., 1991). Exposure to toluene by inhalation also altered behaviour in rats at doses as low as 40 ppm (151 mg/m^3) over 104 hours/week (Forkman et al., 1991; Berenguer et al., 2003; Beasley et al., 2010, 2012; Bikashvili et al., 2012), whereas others reported no effects on behaviour (Ladefoged et al., 1991; Von Euler et al., 1994). Significant behavioural changes were related to memory, problem solving, sensitization to toluene-induced narcosis and rearing activity. Other studies suggest that toluene inhalation may be related to neuronal death, as demonstrated by reduced weight of the whole brain and cerebral cortex following a 30-day inhalation of 320 ppm (1206 mg/m^3) toluene in rats and reduced weight of the subcortical limbic area following a 4-week exposure to toluene

in rats at concentrations exceeding 80 ppm or 302 mg/m^3 (Kyrklund et al., 1987; Hillefors-Berglund et al., 1995). One study involving intraperitoneal injection of toluene at 300 mg/kg bw in mice demonstrated reduced memory accompanied by transcriptional down-regulation of memory-related genes (i.e., *Nr1* and *Nr2b*) in the hippocampus.

Only two studies have investigated the neurological effects of exposure to ethylbenzene in animals. Li et al. (2010) reported that exposure of up to 500 mg/kg bw per day by oral gavage over 90 days in rats did not induce neurological abnormalities with regards to motor activity, autonomic functions, sensorimotor responses, reaction, gait or any other related clinical observation. Some neurological effects, including a decrease in landing foot splay in male rats and an increase in motor activity in female rats exposed to 750 mg/kg bw per day over 13 weeks (5 days/week), were observed by Mellert et al. (2007). However, the effects were only observed in males. No effects were observed at the lower exposure doses.

Oral exposure of B6C3F1 mice to xylenes by gavage over 13 weeks caused lethargy, rapid and shallow breathing, unsteadiness, tremors and paresis at the high dose of 2000 mg/kg bw, but only for a period of 15–60 minutes, approximately 5–10 minutes post-exposure (NTP, 1986). However, an inhalation concentration of 80 ppm (347 mg/m^3) for 6 hours/day, 5 days/week, did not affect dopamine D_2 agonist binding in rat caudate-putamen (Hillefors-Berglund et al., 1995). These findings suggest that transient neurological effects may occur shortly after exposure to xylenes. However, studies in rats that measured balance and coordination using the rotarod and other neurobehavioural tests identified some potential longer-term effects of *m*-xylene exposure. Korsak et al. (1992) demonstrated that exposure of 12 Wistar rats to 100 ppm (434 mg/m^3) *m*-xylene over 6 months and exposure to 1000 ppm (4340 mg/m^3) over 3 months significantly decreased rotarod performance and spontaneous activity 24 hours after the final exposure (which would allow most xylene to be eliminated from the animals). In a similar study by the same group, inhalation exposure of 12 male Wistar rats to 0, 50 or 100 ppm (or 0, 217 and 434 mg/m^3) resulted in decreased rotarod performance at 100 ppm and decreased latency in the paw-lick response in the hot plate test at 50 ppm (Korsak et al., 1994). Additional studies done in rats indicated that exposure to *m*-xylene over several weeks affected the ability of the animals to navigate through a maze and caused other neurobehavioural abnormalities (Gralewicz et al., 1995; Gralewicz and Wiaderna, 2001).

Thus, toluene and xylene were associated with altered behaviour, impaired neurotransmission and damage to brain tissue, which may be implicated in persistent neurological dysfunction. It is unclear whether ethylbenzene is associated with adverse neurological effects.

9.2.2.2 Renal, hepatic and other tissue effects

Short-term oral and inhalation exposures to toluene, ethylbenzene and xylenes can affect multiple tissues. The most affected tissues were liver and kidney, although some effects have also been observed in the brain, heart and lung.

Oral and inhalation exposures to toluene are associated with effects in various tissues. Toluene exposure of rats by oral gavage over 13 weeks (5 days/week) and by whole body inhalation over 15 weeks (6.5 hours/day, 5 days/week) increased relative liver and kidney weights in both sexes at doses as low as 625 mg/kg bw and concentrations as low as 1250 ppm or 47125 mg/m^3 (NTP, 1990). In rats exposed by inhalation, increases in relative brain, lung and heart weights were observed in both sexes, and increases in relative testis weight were observed in males, at doses exceeding 2500 ppm (9425 mg/m^3). An increase in relative liver weight was also apparent in toluene-exposed mice of both sexes at doses as low as 312 mg/kg bw (5 days/week, 13 weeks) and concentrations as low as 625 ppm or 2356 mg/m^3 (6.5 hours/day, 5 days/week, 14

weeks) (NTP, 1990). Male mice exposed to more than 1250 mg/kg bw also had increased relative brain and testis weights. Despite liver and kidney weight increases in rats and mice, no significant evidence of histopathological lesions was detected in these tissues. A significant increase in lesions was found only in rats exposed by oral gavage. These rats exhibited an increase in brain necrosis, particularly in the hippocampus, at doses exceeding 1250 and 2500 mg/kg bw in males and females, respectively. Also, an increase in hemorrhaging was observed within the urinary bladder, although rats in this dose group (5000 mg/kg bw) died shortly after exposure (NTP, 1990). Other studies showed that rats exposed to toluene by oral gavage (up to 422 mg/kg bw for up to 193 days) and by intubation (560 mg/kg bw for up to 6 months) displayed no signs of toxicity (Wolf et al., 1956; IPCS, 1986). Thus, toluene exposure was associated with increased weight in some organs, particularly the liver and kidneys, but few signs of histopathological lesions were present, other than in the brain.

It was reported by Mellert et al. (2007) that ethylbenzene administration in male and female rats by oral gavage (up to 750 mg/kg bw per day for 4 and 13 weeks) induced histopathological and serum chemistry changes. At the 13-week exposure mark, serum chemistry changes included increased alanine aminotransferase, total bilirubin, cholesterol, potassium, calcium and magnesium levels at doses exceeding 250 mg/kg bw and histopathological changes including increased liver and kidney weights at doses as low as 75 mg/kg bw. Increased incidences of hepatocyte centrilobular hypertrophy and hyaline droplet nephropathy were observed after 4 and 13 weeks of exposure. However, these increases were not statistically significant.. Another study of oral exposure in rats over 90 days demonstrated enlarged liver and kidney, which were significant at doses exceeding 250 mg/kg bw per day, but only in male rats (Li et al., 2010). Ethylbenzene exposure via inhalation for 13 weeks (6 hours/day, 5 days/week) also resulted in increased liver and kidney weights in male F344/N rats exposed by inhalation at concentrations of 500–750 ppm or 2170-3255 mg/m^3 (NTP, 1992). Alkaline phosphatase, a marker of liver dysfunction, was elevated in male and female rats throughout exposure at doses as low as 100 ppm (434 mg/m^3). Increased liver weight was also observed in male and female B6C3F1 mice at doses exceeding 750 ppm (3255 mg/m^3). However, ethylbenzene did not induce any histopathological changes in any tissues in rats and mice in this study.

Enlarged liver and kidney were also observed in rats that were administered mixed xylenes by oral gavage for 90 consecutive days at doses as low as 750 mg/kg bw per day (Condie et al., 1988). Minimal chronic nephropathy in females was also observed (Condie et al., 1988). Nephrotic effects were not observed in male rats dosed with *m*-xylene at 0.5 or 2.0 g/kg bw by oral gavage for 5 days/week for 4 weeks (Borriston Laboratories Inc., 1983). Studies of xylene exposure (*m*- and *p*-xylene) by oral gavage in rats revealed no abnormal histopathological findings in any tissue or organ at doses as high as 800 mg/kg bw for 90 days (Wolf, 1988a, 1988b). However, survival incidence was decreased, and one study showed evidence of mottled lungs and a failure of lungs to collapse at doses as low as 200 mg/kg bw per day (90-day exposure) (Wolf, 1988a).

Thus, exposure to toluene, ethylbenzene and xylenes is primarily associated with hepatic and renal effects, including increased liver and kidney weights, nephropathy and hepatic hypertrophy. There is also evidence of toluene-mediated effects on the brain.

9.2.2.3 Other effects

(a) Ototoxicity

Ototoxicity was consistently observed for all three chemicals. Although most data were relevant to the inhalation exposure route, one study reported hearing loss following an oral exposure of rats to each of toluene, ethylbenzene and *o*-, *m*- and *p*-xylene individually at 8.47

mmol/kg bw per day (Gagnaire and Langlais, 2005). The study demonstrated ototoxicity, as shown by losses in outer hair cells of the organ of Corti. Ethylbenzene induced severe ototoxicity, as shown by an almost complete loss of three rows of outer hair cells in the medium and apical parts of the cochlea. Moderate ototoxicity was reported for toluene and *p*-xylene, but not for the other xylene isomers. Exposure to ethylbenzene and to two mixed xylenes by inhalation (6 hours/day, 6 days/week, for 13 weeks) induced hearing loss, as determined by brainstem auditory evoked responses and moderate to severe loss of outer hair cells of the organ of Corti at concentrations ranging from 200 to 800 ppm (or 868 to 3472 mg/m^3) for ethylbenzene and from 250 to 2000 ppm (or 1085 to 8680 mg/m^3) for mixed xylenes (Gagnaire et al., 2007). Other studies of toluene and ethylbenzene inhalation exposure in experimental animals have demonstrated ototoxicity, but only at relatively high doses of at least 1000 ppm or (3770 mg/m^3) and 400 ppm or (1736 mg/m^3) for toluene and ethylbenzene, respectively (Johnson and Canlon, 1994; Campo et al., 1997; Lataye and Campo, 1997; Cappaert et al., 1999, 2000). In contrast to humans, experimental animal data regarding ototoxicity suggest that direct damage to the auditory system may be the cause of ototoxicity. The exact role of neurological effects on ototoxicity is unknown.

(b) Immunotoxicity

Several studies have suggested that toluene is immunosuppressive. One study of mice exposed via drinking water showed a decrease in thymus weight, splenocyte lymphoproliferation in response to alloantigens, antibody plaque-forming cell responses and interleukin-2 production, but only at a high dose of 405 mg/L (Hsieh et al., 1989). These findings were supported in another study by the same group using the same doses (Hsieh et al., 1991). An additional study in which the highest dose was 325 mg/L showed no obvious immunotoxic effects (Hsieh et al., 1991).

Exposure of rats to up to 500 ppm (2170 mg/m^3) ethylbenzene over 28 days was not immunotoxic, as demonstrated by the lack of plaque-forming cell response to sheep red blood cells (Li et al., 2010). The only evidence of xylene immunotoxicity was a decrease in thymus and spleen weights in rats exposed to *p*-xylene at 2000 mg/kg bw per day (Condie et al., 1988).

9.2.3 Long-term exposure and carcinogenicity

Long-term animal studies have been carried out for toluene, ethylbenzene and xylenes. Overall, these studies did not support toluene and xylenes as tumour-inducing chemicals via the oral, inhalation or dermal route. However, evidence was found of ethylbenzene-induced tumorigenesis, as well as nephropathy and renal hyperplasia.

The potential carcinogenicity of toluene has been investigated for oral and inhalation exposures. In the oral exposure study, toluene in olive oil at 500 or 800 mg/kg bw was administered by stomach tube (4–5 days/week for 104 weeks) to male and female Sprague-Dawley rats. Following the 104-week exposure, the rats were allowed to die of natural causes. This study suggested an increase in head cancers and leukemia and lymphoma in both sexes and mammary cancers in females (Maltoni et al., 1997). However, dose-related effects were not apparent, and study details were not adequately reported to draw any firm conclusions on carcinogenicity. Tumour incidence was not observed for toluene following a 2-year inhalation study in mice and rats at concentrations of up to 1200 ppm or 4524 mg/m^3 (administered 6.5 hours/day, 5 days/week) (NTP, 1990; Huff, 2003). Although a few cases of nasal, kidney and forestomach neoplasms were reported in the female rats, these were determined to be not related to toluene exposure. Almost all rats, including controls, exhibited nephropathy, but the severity was slightly increased in rats of both sexes exposed to 1200 ppm. Thus, there is little evidence of

toluene-induced carcinogenicity in experimental animals. However, chronic exposure may be associated with an increased severity of nephropathy.

The carcinogenicity of ethylbenzene has been reported in experimental animals through both the inhalation and oral exposure routes. In the inhalation carcinogenicity bioassays, groups of 50 male and female B6C3F1 mice and F344/N rats were exposed to 0, 75, 250 or 750 ppm (0, 326, 1090 or 3260 mg/m^3) ethylbenzene vapour for 103 and 104 weeks, respectively (Chan et al., 1998; NTP, 1999). A significant, concentration-related increase in the incidence of both alveolar/bronchiolar adenomas and combined alveolar/bronchiolar adenomas and carcinomas of the lung as well as a significant increase in the incidence of alveolar epithelium metaplasia were observed in male mice in the 750 ppm group. Female mice exhibited concentration-related increases in the incidence of both hepatocellular adenomas and combined adenomas and carcinomas, which were significant at the 750 ppm dose compared with concurrent controls, but remained within the historical control ranges. The incidence of eosinophilic foci in the liver was significantly greater in the female mice at 750 ppm, and the eosinophilic foci were considered a precursor to hepatocellular neoplasia. Male rats exhibited a concentration-dependent increase in the incidence of combined renal tubular adenomas and carcinomas, which was significant at 750 ppm. Significant increases in the incidence of renal tubular adenomas in female rats and testicular adenomas in male rats were also observed in the 750 ppm dose group. In rats of both sexes, there was a significant increase in the incidence of focal renal tubular hyperplasia at 750 ppm; this was considered to be a precursor stage of adenoma development by the authors of the study. Dose-dependent increases in the severity of chronic progressive nephropathy were observed in female rats at all exposure levels and in male rats at the highest concentration (Chan et al., 1998; NTP, 1999).

One study reported non-dose-related increases in total malignant tumours and head cancers over controls in male and female Sprague-Dawley rats exposed to ethylbenzene mixed in extra virgin olive oil and administered by stomach tube at 500 and 800 mg/kg bw per day over 104 weeks (Maltoni et al., 1997). However, it is not possible to draw firm conclusions from this study due to the lack of dose–response relationships and inadequate reporting of study details.

Additional studies have investigated long-term effects specific to xylenes. No increased tumour incidence was observed in male and female Fischer 344 rats exposed to mixed xylenes (60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene and 17% ethylbenzene) at 0–500 mg/kg bw per day or in male and female B6C3F1 mice exposed to mixed xylenes at 0–1000 mg/kg bw per day by oral gavage in corn oil for 103 weeks (5 days/week) (NTP, 1986). Although some cases of testis tumours were reported in the highest exposure group in rats, these effects were considered not to be treatment related. Both male and female mice exposed to the 1000 mg/kg bw per day dose exhibited hyperactivity 5–30 minutes post-exposure as of week 4. Non-dose-related increases in mammary cancers were observed in female rats exposed to xylenes at 500 mg/kg bw per day, and head cancer, lymphomas and leukemias were observed in male and female rats exposed to 500 and 800 mg/kg bw per day over 104 weeks (Maltoni et al., 1997). However, as stated previously, the lack of information provided in this study does not allow for adequate interpretation of the data.

Thus, long-term studies of toluene and xylene toxicity suggest that these chemicals are not likely to induce tumours or other adverse health effects upon chronic exposure. No acceptable study of oral ethylbenzene exposure was available. However, ethylbenzene inhalation was associated with an increased tumour incidence. Long-term exposure to ethylbenzene was also associated with nephropathy and renal hyperplasia.

9.2.4 Genotoxicity

Overall, studies of toluene, ethylbenzene and xylenes using cultured cells and experimental animals provided very little evidence of genotoxic activity.

9.2.4.1 In vitro *findings*

Overall evidence did not support toluene, ethylbenzene or xylenes as genotoxic agents. Toluene tested negative in the *Salmonella typhimurium* reverse mutation assay with and without metabolic activation (Nestman et al., 1980; Bos et al., 1981; Connor et al., 1985; Nakamura et al., 1987; NTP, 1990; Huff, 2003). Moreover, toluene did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells (NTP, 1990) or in human lymphocytes (Gerner-Smidt and Friedrich, 1978), even at concentrations that inhibited cellular growth in human lymphocytes (Richer et al., 1993). Ethylbenzene tested negative in the *S. typhimurium* reverse mutation assay (Florin et al., 1980; Nestman et al., 1980; Dean et al., 1985; Zeiger et al., 1992), in the *Escherichia coli* reverse mutation assay (Dean et al., 1985), in the *Saccharomyces cerevisiae* gene conversion assay and in the mouse lymphoma forward mutation assay (Wollny, 2000; Seidel et al., 2006), both with and without metabolic activation in each assay. One study reported the presence of single, but not double, deoxyribonucleic acid (DNA) strand breaks (Chen et al., 2008).

Ethylbenzene does not induce chromosomal damage in rat liver epithelial cells or in Chinese hamster ovary cells (Dean et al., 1985), although micronuclei were reported in Syrian hamster embryo cells (Gibson et al., 1997). Sister chromatid exchange was generally not observed, although one study reported marginal increases of sister chromatid exchanges in human lymphocytes at a cytotoxic dose of ethylbenzene (Norppa and Vainio, 1983).

Xylene mixtures and individual xylene isomers (o-, *m*- and *p*-xylene) tested negative in the *S. typhimurium* reverse mutation assay (Florin et al., 1980; Bos et al., 1981; Haworth et al., 1983; Connor et al., 1985; Shimizu et al., 1985) and in the *E. coli* reverse mutation assay (Shimizu et al., 1985; DeMarini et al., 1991), both with and without metabolic activation in each assay. Ethylbenzene did not induce sister chromatid exchanges or chromosomal aberrations in human lymphocytes (Gerner-Smidt and Friedrich, 1978; Richer et al., 1993) or in Chinese hamster ovary cells (Anderson et al., 1990). DNA strand breaks were observed in human lymphocytes, although it was established that they were associated with cytotoxicity (Morozzi et al., 1999). Thus, data do not suggest that toluene, ethylbenzene or xylenes are genotoxic *in vitro*.

9.2.4.2 In vivo *findings*

No tangible evidence of toluene, ethylbenzene or xylene genotoxicity was found in experimental animals. Intraperitoneal injection of all three solvents (e.g., toluene, ethylbenzene and individual isomers of xylene [*o*-, *m*- and *p*-xylene]) into mice at doses that ranged from 0.12 to 0.75 mL/kg bw (up to 70% LD_{50}) administered twice did not induce micronuclei in polychromatic bone marrow erythrocytes for any of the solvents except for toluene, for which micronuclei could be detected at concentrations as low as 0.25 mL/kg bw (Mohtashamipur et al., 1985). However, a toluene inhalation exposure of up to 500 ppm (1885 mg/m^3) for 6 hours/day over 8 weeks did not induce DNA strand breaks in peripheral blood cells, bone marrow or liver of mice (Plappert et al., 1994). Oral exposure to mixed isomers of xylene of up to 1000 mg/kg bw in mice induced neither chromosomal aberrations nor micronuclei in reticulocytes (ATSDR, 2007). Despite evidence of carcinogenicity in experimental animals, the few studies of ethylbenzene genotoxicity report negative findings. Intraperitoneal exposure to ethylbenzene at doses up to 650 mg/kg bw in both mice and rats revealed no evidence of genotoxic outcomes (Litton Bionetics,

1978; Washington et al., 1983; Mohtashamipur et al., 1985). Thus, toluene, ethylbenzene and xylenes are not likely to be genotoxic.

9.2.5 Reproductive and developmental toxicity

9.2.5.1 Reproductive effects

Convincing evidence of adverse reproductive effects was not found for toluene, ethylbenzene or xylenes. The one study that investigated the reproductive effects of oral toluene exposure revealed no effects on litter viability in mice exposed to a high dose of 2350 mg/kg bw on gestation days 7 through 14 (Smith, 1983). Other studies pertain to the inhalation route of exposure. Decreased sperm counts and weights of the epididymides were reported in male rats exposed to 2000 ppm (7540 mg/m^3) for 90 days (6 hours/day) (Ono et al., 1996), whereas female rats exposed to 3000 ppm (11,310 mg/m^3) for 7 days produced abundant vacuoles, lytic areas and mitochondrial degeneration in the antral follicles of the ovaries (Tap et al., 1996). However, no treatment-related histopathological lesions were observed in mouse and rat testes and ovaries, even after a 2-year exposure to 1200 ppm (4524 mg/m^3) toluene (NTP, 1990). Ungváry (1985) showed that continuous exposure of pregnant rabbits to 267 ppm (1007 mg/m^3) toluene during gestation days 7–20 caused decreased maternal weight gain and abortions. Exposure of rats to doses of up to 3000 ppm toluene revealed no adverse effects on implantation, number or viability of fetuses or sex distribution upon caesarean section on gestation day 20 (Roberts et al., 2007). However, reduced maternal body weight was observed at 1500 ppm. Both two-generation studies for toluene revealed no adverse reproductive effects. Mating, fertility and pregnancy indices in offspring of pregnant rats exposed to up to 1200 ppm (6 hours/day between gestation days 9 and 21) were unaffected (Thiel and Chahoud, 1997). Moreover, impaired reproductive performance was not observed in rats exposed intermittently up to 2000 ppm (6 hours/day for up to 95 days) in comparison to controls (API, 1985).

Only one study examined the direct effects of ethylbenzene exposure in experimental animals via the oral route. Oral administration of 500 mg/kg bw and above in rats resulted in decreased peripheral hormone levels during the diestrous stage (Ungváry, 1986). One two-generation study examined reproductive capability following ethylbenzene inhalation (Faber et al., 2006). Rats were exposed to up to 500 ppm throughout premating (at least 70 days in both sexes), throughout gestation (up to gestation day 20) and on lactation days 5–21 (with oral exposure that would result in the same blood concentration on lactation days 1–4). The study revealed no effect on reproductive parameters, including mating and fertility, gestation time, size and viability of litters and sex distribution. The only significant effect was a reduction in estrous cycle length in F_0 (parent) females (Faber et al., 2006). Inhalation exposure to up to 1000 ppm ethylbenzene in Wistar rats for 3 weeks did not affect female fertility (Hardin et al., 1981). An ethylbenzene inhalation exposure in mice and rats ranging from 99 to 975 ppm over 13 weeks caused a decrease in epididymal weight in mice, though no other reproductive effects on sperm or menstrual cycle were observed in mice or rats (NTP, 1992). Thus, there is little evidence of ethylbenzene-induced reproductive effects in experimental animals.

Little information was available for reproductive effects of exposure to xylenes. None was relevant to oral exposure. Testicular alterations were not observed at exposure concentrations as high as 1000 ppm or 4340 mg/m^3 (Nylén et al., 1989; Korsak et al., 1994). Thus, xylenes are unlikely to cause adverse reproductive effects.

The information that was available on toluene, ethylbenzene and xylenes does not support adverse reproductive effects of exposure, even at the high doses administered in these studies.

9.2.5.2 Developmental effects

Limited evidence of developmental toxicity was associated with exposure to toluene, ethylbenzene and xylenes.

In a series of experiments in rats, it was determined that oral gavage of toluene at 520 or 650 mg/kg bw caused a reduction in fetal, liver and kidney weights (Gospe et al., 1994, 1996; Gospe and Zhou, 2000). Reductions in heart weight and skeletal ossification were also observed at the higher dose (Gospe et al., 1996; Gospe and Zhou, 2000). Effects on organ weights occurred on gestation day 19 and persisted until postnatal day 10. Although organ weights did not differ from those of controls by postnatal day 21, histological analyses of the brain revealed decreased neuronal packing and alterations in the patterns of staining with bromodeoxyuridine, indicating toluene-induced alterations in neurogenesis and neuronal migration (Gospe and Zhou, 2000). Exposure of rats by inhalation also resulted in reduced fetal weight at toluene concentrations of 1000 mg/m^3 (8 hours/day on gestation days 1–21) (IPCS, 1986) and as low as 250 ppm or 943 mg/m^3 (6 hours/day on gestation days 6–15) (Roberts et al., 2007). An additional study reported a reduction in sperm count and weight of epididymides in rats exposed to 2000 ppm (7540 mg/m^3), 6 hours/day, for 90 days, despite there being no effect on reproductive performance (Ono et al., 1996). A two-generation reproduction study reported no adverse effects in rats exposed to 2000 ppm toluene (6 hours/day) for up to 95 days (API, 1985).

Studies of oral exposure to ethylbenzene were not located. In rats, an increased number of fetuses with extra ribs was observed at inhalation concentrations as low as 100 ppm (434 mg/m^3) ethylbenzene (Hardin et al., 1981). Exposure of pregnant rats to ethylbenzene concentrations exceeding 1000 ppm (4340 mg/m^3) on gestation days 6–20 caused decreased fetal weight (Saillenfait et al., 2003, 2006, 2007), whereas 2000 ppm (8680 mg/m^3) ethylbenzene caused increased incidences of skeletal variations in offspring (Saillenfait et al., 2003). However, no significant findings pertaining to pup survival and weight, neurological functioning or developmental landmarks were found in the F_1 and F_2 generations of mice exposed to up to 500 ppm or 2170 mg/m^3 (for 6 hours/day) for 70 consecutive days (Faber et al., 2006, 2007). Thus, developmental effects may be possible, but only at elevated doses.

Two studies reported adverse developmental effects of xylenes in animals via oral exposure. A high exposure of 2060 mg/kg bw per day on gestation days 6–15 was associated with decreased body weight and an increase in malformations (primarily cleft palate) (Marks et al., 1982). However, no evidence of teratogenic effects was observed in mice exposed to *m*-xylene at 2000 mg/kg bw per day on gestation days 8–12 (Seidenberg et al., 1986). Inhalation exposure to xylenes has been associated with neurological deficits in offspring at doses as low as 200 ppm or 868 mg/m^3 (Hass and Jakobsen, 1993; Hass et al., 1997). Developmental effects, including skeletal abnormalities and decreased fetal weight, have occurred in rats. Taking into consideration the various limitations of the rat studies, these effects were determined to occur only at concentrations above 350 ppm or 1519 mg/m^3 (ATSDR, 2007).

Thus, it is possible that developmental effects may occur as a result of exposure to toluene, ethylbenzene and xylenes. However, the exact role of maternal toxicity in these endpoints is not fully understood.

9.3 Mode of action

Due to their similar chemical properties, toluene, ethylbenzene and xylenes are distributed to lipid-rich tissues, where they exert toxic outcomes through various modes of action.

The lipophilic properties of these solvents are primarily responsible for their acute symptoms of exposure. The narcotic and anesthetic effects of toluene, ethylbenzene and xylenes that occur upon acute exposure may be related to the rapid intercalation of these solvents within

the lipid bilayer of nerve membranes, leading to biochemical modifications of membrane-bound proteins and subsequent altered synaptic transmission. One study reported decreases in acetylcholinesterases, total adenosine triphosphate (ATP) and Mg^{2+}-ATPase activities in erythrocytes and synaptosomes of rats exposed to 2000 ppm (7540 mg/m^3) toluene for 2 hours (Korpela and Tahti, 1988). Altered synaptic functioning is further supported by global gene expression analysis of various brain regions in the rat following inhalation of toluene over 6 hours (Hester et al., 2011). The analysis revealed pathways associated with altered synaptic plasticity. Similar observations were made for ethylbenzene and xylenes. Ethylbenzene and xylenes decreased activities of Na^+/K^+-ATPase and Mg^{2+}-ATPase in cultured astrocytes from the cerebella of neonatal Sprague-Dawley rats (Vaalavirta and Tahti, 1995). Effects on the activities of these membrane-bound proteins were more substantive for ethylbenzene and xylenes than for toluene. Overall, these data suggest that toluene, ethylbenzene and xylenes can perturb membrane-bound proteins, leading to adverse central nervous system effects.

Disturbances in brain function may be further related to effects on neurotransmitters, such as persistent alterations in enzymes that regulate their synthesis, degradation and binding. Exposure to toluene by inhalation in experimental animals has resulted in increases in neurotransmitters, including glutamate, taurine, dopamine, norepinephrine, serotonin and acetylcholine, in various brain regions (Rea et al., 1984; Aikawa et al., 1997). Receptor binding of glutamate and γ-aminobutyric acid generally increased in various brain regions following toluene exposure at concentrations exceeding 50 ppm or 189 mg/m^3 (Bjornaes and Naalsund, 1988). One study noted that toluene-induced inhibition of *N*-methyl d-aspartate receptor binding may play a role in the incoordination and memory impairment that occur following toluene exposure (Lo et al., 2009). Xylenes were shown to increase dopamine and catecholamine levels in various brain regions of rats exposed to 2000 ppm (8680 mg/m^3), whereas the same concentration of ethylbenzene decreased catecholamine levels (Andersson et al., 1981). An exposure to 750 ppm (3255 mg/m^3) ethylbenzene caused a reduction of stratial and tubero-infundibular dopamine in rabbits, whereas exposure to toluene and xylenes had no effect (Mutti et al., 1988). Altered neurotransmitter concentrations resulting from solvent exposure appear to be a transient, reversible effect. Nonetheless, chronic exposure may be associated with persistent alterations in behaviour, depressed mood and loss of memory.

Longer-term neurological effects may be related to cytotoxicity and damage to the central nervous system. Central nervous system cytotoxicity may result from phospholipid degradation, as noted especially for toluene. Toluene exposure has been shown to decrease phospholipid concentrations in the cerebral cortex of rats, leading to a loss of grey matter upon continuous exposure to 320 ppm (1206 mg/m^3) toluene over 30 days (Kyrklund et al., 1987). Exposure to 1500 ppm (5655 mg/m^3) in rats over 6 months (6 hours/day, 5 days/week) with 4 months of recovery decreased the number of neurons within the regio inferior of the hippocampus (Korbo et al., 1996). Such effects are supported in humans by diagnostic magnetic resonance imaging of chronic solvent abusers (Borne et al., 2005). Chronic abuse of toluene resulted in irreversible damage, including central nervous system atrophy, demyelination and minimal gliosis. Although adverse neurological effects have been documented for ethylbenzene and xylenes, their exact role in tissue damage within the central nervous system is unknown.

The mode of action of toluene, ethylbenzene and xylenes in inducing ototoxicity appears to be attributed to the death of cochlear hair cells in experimental animals (Gagnaire et al., 2001; Gagnaire and Langlais, 2005). This effect appears to be mediated by the presence of a single short side-chain on the benzene ring in aromatic solvents (Gagnaire and Langlais, 2005). However, there is evidence in humans that a neurological component may be involved.

Studies in animals investigating the metabolic interactions between toluene and other chemicals and ototoxicity indicate that toluene-induced hearing loss is caused by toluene itself, not its metabolites (Wallen et al., 1984; Römer et al., 1986; Pryor, 1991; Imbriani and Ghittori, 1997; Campo et al., 1998). Other neurological effects, including central nervous system depression and narcosis, are also believed to involve toluene itself and not its metabolites (ATSDR, 2000).

In the case of xylenes, for neurological effects such as changes in levels of various neurotransmitters and lipid composition observed following exposures to xylene of acute and intermediate durations (Savolainen and Seppalainen, 1979; Andersson et al., 1981; Honma et al., 1983), it is unclear whether the effects are due to xylene itself or to its metabolic intermediates, such as arene oxides or methylbenzaldehyde (Savolainen and Pfäffli, 1980). Methylbenzaldehyde (the product of the action of alcohol dehydrogenase on methylbenzyl alcohol) has been detected in animals; however, its presence has not been confirmed in humans (ATSDR, 2007).

There is strong evidence that tissue damage observed within the central nervous system, liver, kidney and other tissues affected by toluene, ethylbenzene and xylenes would be mediated by oxidative stress. For toluene, substantive evidence of oxidative stress, including increased generation of reactive oxygen species and markers of oxidative damage, has been observed in the brain (Mattia, 1993; Burmistrov et al., 2001; El-Nabi Kamel and Shehata, 2008), liver (Tokunaga et al., 2003) and kidney (Mattia, 1993; Tokunaga et al., 2003) of experimental animals following inhalation exposure to and intraperitoneal injection of toluene. Moreover, the synaptosomes of rats exposed *in utero* had an increased level of oxidative stress upon reexposure to toluene *in vitro*, thus indicating long-lasting changes in oxidative status that can affect offspring upon maternal exposure (Edelfors et al., 2002). Markers of oxidative stress have been reported in the brains of rats following inhalation exposure to ethylbenzene concentrations exceeding 433.5 mg/m^3 (Wang et al., 2010). This is supported by urinary markers of oxidative stress correlated with ethylbenzene exposure in spray painters (Chang et al., 2011). Although analyses for xylenes were in other tissues, they appeared to cause less oxidative stress, as demonstrated by indicators of oxidative damage in kidney but not in liver (Kum et al., 2007a, 2007b) and the lack of correlation between exposure and excretion of urinary markers (Chang et al., 2011). Such tissue damage may be attributed to induction of apoptosis, inflammation and cellular proliferation, leading to toxicities in affected organs.

Exposure to ethylbenzene has been shown to induce kidney and Leydig cell tumours in rats and lung and liver tumours in mice. Genotoxicity screening studies for ethylbenzene indicate that it is non-genotoxic *in vivo* and predominantly non-genotoxic *in vitro* (VCCEP, 2007), and thus other modes of action have been proposed for its propensity towards tumour induction. Ethylbenzene is not likely carcinogenic at doses below a toxic threshold. More information on ethylbenzene's modes of action involved in tumour induction in rodents is presented below.

There is evidence to support the mode of action of kidney tumours in rats resulting from an increased incidence of chronic progressive nephropathy by the primary ethylbenzene metabolite, 1-phenylethanol (VCCEP, 2007). The mode of action may also include a possible weak accentuation of chronic progressive nephropathy by involvement of α2u-globulin in male rats. Because of critical qualitative and, to a certain extent, quantitative species differences, this mode of action is not expected to be relevant in humans. Therefore, rat kidney tumours are not a suitable basis for risk assessment. A study by Hard et al. (2012) thoroughly reevaluated studies of chronic progressive nephropathy in rats. The authors determined there was definitive evidence that advanced stages of chronic progressive nephropathy represent a risk for development of a low incidence of basophilic renal tubule adenomas and their precursor form of hyperplasia in both male and female F344 rats. This work adds to the weight of evidence that chemical exacerbation

of chronic progressive nephropathy represents a secondary mode of action for tumour development that is unlikely to have relevance for species extrapolation in risk assessment because there is no counterpart of rat chronic progressive nephropathy (biologically and histopathologically) in humans.

The postulated mode of action for liver tumours in female rats is a phenobarbital-like induction, which was also considered not relevant to humans. Leydig cell tumours were likely induced by alterations of serum testosterone, although such tumours are common in aged rats. Because of many well-documented qualitative and quantitative differences between rats and humans, the Leydig cell tumours observed are not expected to be relevant to human health risk assessment (VCCEP, 2007).

Lung tumours occurring upon inhalation are likely formed as a result of regenerative cellular proliferation following metabolism and exposure to cytotoxic metabolites. The proposed mode of action for ethylbenzene-induced lung tumours is as follows: (1) absorption of ethylbenzene; (2) distribution of ethylbenzene to lung; (3) metabolism of ethylbenzene to active metabolite; (4) detoxification/elimination of active metabolite; (5) possible oxidative stress secondary to high-dose glutathione depletion and/or high-dose-mediated CYP450 ethylbenzene metabolism; (6) arylation of macromolecules, leading to cytotoxicity when detoxification and repair capacities are exceeded; and (7) promotion/progression of lung tumours. The potential role for oxidative metabolites in the mode of action of ethylbenzene-induced lung tumours suggests that these tumours observed in mice are relevant to humans. This mode of action does suggest that there is a threshold below which tumours are not expected to be observed. It should be noted that there are qualitative differences between mouse and human pulmonary metabolism that may lead to increased sensitivity in mice (VCCEP, 2007) and that lung tumours were within the National Toxicology Program historical control range (NTP, 1999). However, considering the mode of action analysis as described above and that other cancer endpoints (liver, Leydig and kidney) have been concluded as being non-relevant to humans, lung tumours were determined to be the most relevant cancer endpoint for humans.

10.0 Classification and assessment

The assessments of toluene, ethylbenzene and xylenes are combined into one supporting document, as co-exposure to these compounds (along with benzene) is likely during a contamination event in drinking water. Although all three compounds show some overlap in health effects (i.e., neurological impairment), they were not assessed as a mixture, given that the modes of action involved in the most sensitive health effects are different for each compound. It is unclear whether current PBPK models are adequate for characterizing interactions from oral exposure to mixtures of toluene, ethylbenzene and xylenes (as well as benzene) (ATSDR, 2004).

The results of PBPK model simulations and experimental exposures to mixtures of toluene, ethylbenzene and xylenes (with benzene) in rats and humans indicate that inhalation exposure to mixtures containing each component at a concentration of approximately 20 ppm is unlikely to result in biologically significant increased blood levels of these chemicals compared with exposure to each component individually (Tardif et al., 1997; Haddad et al., 1999, 2000, 2001). For these reasons, toluene, ethylbenzene and xylenes were modelled separately, with no metabolic interactions considered, and three separate maximum acceptable concentrations (MACs) are established.

10.1 Toluene

Toluene is an extensively used solvent found in paints, paint thinners, lacquers and adhesives. It is also found in gasoline and used as an intermediate in chemical synthesis. The health effects of toluene have been studied in humans in several occupational environments in which toluene use is predominant, including printing, painting, the rubber industry and shoe manufacturing. These studies have revealed an array of neurological effects, including loss of colour vision and disturbances in memory, concentration and cognitive function in general, upon long-term inhalation of toluene. Studies of oral exposure in animals support adverse neurological effects as a critical endpoint of toluene toxicity, as shown by altered behaviour, changes in neurotransmitter levels and brain necrosis. The International Agency for Research on Cancer (IARC, 1999) has determined that toluene is not classifiable as to its carcinogenicity to humans (Group 3). Consequently, Health Canada has focused on neurological endpoints in determining the risk associated with toluene exposure via drinking water.

Due to the number of epidemiological studies available and to the availability of human PBPK models to estimate oral doses, the risk assessment of toluene was based on human data. No chronic oral studies in animals pertaining to neurological effects were identified. Neurological endpoints were determined to be the most significant adverse effect, as they were consistently observed in occupationally exposed humans as well as in experimental animals exposed via oral and inhalation administration. Several occupational studies were identified that had adequate exposure information and examined chronic neurological effects. These included studies of auditory and visual adverse effects (Nakatsuka et al., 1992; Abbate et al., 1993; Vrca et al., 1995; Zavalic et al., 1998; Cavalleri et al., 2000) as well as other neurobehavioural and neurophysiological alterations (Foo et al., 1990; Murata et al., 1993; Boey et al., 1997; Eller et al., 1999; Neubert et al., 2001; Seeber et al., 2004, 2005).

Two studies that examined the same population of exposed individuals within 14 rotary printing plants stood out in particular (Seeber et al., 2004, 2005). These studies covered all of the aforementioned neurological endpoints, including vibration thresholds, colour discrimination, auditory thresholds, attention (symbol–digit substitution, switching attention and simple reaction), memory (digit span forward and backward, immediate and delayed reproduction of pictures) and psychomotor functions (steadiness, line tracing, aiming, tapping, pegboard). Moreover, the neurological effects were investigated in terms of length of exposure, with an average of 21 years as a lifetime-weighted average and an average of 6 years as a current exposure level. The shorter-term data were more relevant in the selection of a point of departure, as toluene levels were measured four times over the period of 5 years directly in the breathing environment of workers over full days, whereas long-term data were estimated using a job exposure matrix. In addition to adequate exposure monitoring, the Seeber et al. (2004, 2005) studies had a large sample size, a reference group from the same population as the exposed group, and appropriate controls for age, education and alcohol intake. None of the endpoints investigated within these studies was indicative of an adverse effect following exposure to toluene. As such, a NOAEL of 26 ppm or 98 mg/m^3 (as an average of highly exposed individuals) was retained as the point of departure. It should be noted that all effects investigated in other epidemiological studies were observed at concentrations that exceeded 26 ppm. Although the true NOAEL for neurological endpoints may be higher than 26 ppm, we considered 26 ppm as the most appropriate point of departure based on available studies.

In order to determine an oral dose from an inhalation study, PBPK modelling was employed to estimate an internal toluene blood concentration of 0.0075 mg/L following inhalation exposure. This internal dose was then inputted into the human PBPK model in order to determine the external oral dose required to result in a similar blood concentration, assuming consumption

of 1.5 L of drinking water per day. The resulting human external dose from drinking water was determined to be 0.097 mg/kg bw per day. Since 21 years of exposure to a lifetime-weighted average concentration of 45 ppm or 170 mg/m^3 did not reveal any effects on any of the neurological endpoints assessed by Seeber et al. (2004, 2005), the addition of an uncertainty factor for the use of a short-term study was deemed unnecessary. Moreover, studies of toluene included chronic studies in two species, developmental toxicity studies in two species as well as a two-generation reproductive toxicity study. As such, the database of information was determined to be adequate, and thus no additional uncertainty factor was added with regards to database adequacy. However, an uncertainty factor was added to account for intraspecies variability. Taking this into consideration, the tolerable daily intake (TDI) was calculated as follows:

$$\text{TDI} = \frac{0.097 \text{ mg/kg bw per day}}{10}$$

$$= 0.0097 \text{ mg/kg bw per day}$$

where:

- 0.097 mg/kg bw per day is the external oral dose required to give a blood concentration that is equivalent to the NOAEL of 26 ppm (Seeber et al., 2004, 2005); and
- 10 is the uncertainty factor to account for intraspecies variability.

The TDI was employed to calculate the MAC, as follows:

$$\text{MAC} = \frac{0.0097 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{2.13 \text{ L-eq/day}}$$

$$= 0.064 \text{ mg/L}$$

$$\approx 0.06 \text{ mg/L}$$

where:

- 0.0097 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure, and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 2.13 L-eq is the daily volume of water consumed by an adult, accounting for multiple routes of exposure (see Section 5.6).

10.2 Ethylbenzene

Ethylbenzene is primarily used as an intermediate in the production of styrene, but also occurs in gasoline and as a component of mixed xylenes. The health effects of ethylbenzene have been studied in experimental animals, with similar outcomes occurring in all species. However,

effects in humans are relatively unknown, due to the lack of occupational settings in which exposure to ethylbenzene is predominant. Animal data have identified liver and kidney as the primary targets of ethylbenzene. Inhalation and ingestion of ethylbenzene in rats and mice lead to enlarged liver and kidney and increased severity of nephropathy. Chronic studies of exposure to ethylbenzene by inhalation and ingestion suggest that exposure may lead to tumour formation at various sites. Mechanistically, it is suggested that ethylbenzene-induced carcinogenesis may result from excessive tissue damage and proliferation in the absence of genotoxicity. Due to sufficient evidence of carcinogenicity in experimental animals but inadequate data in humans, ethylbenzene was classified as possibly carcinogenic to humans (Group 2b) by the International Agency for Research on Cancer (IARC, 2000). Health Canada has considered both cancer and non-cancer endpoints in deriving a health-based value (HBV) for ethylbenzene.

10.2.1 Cancer risk assessment

There is significant evidence of ethylbenzene-induced carcinogenesis in experimental animals. Inhalation of ethylbenzene is carcinogenic in animals, producing tumours in the kidney (male and female rats), lung (male mice), liver (female mice) and Leydig cells (male rats). In rats, renal cancers through exacerbation of chronic progressive nephropathy, Leydig cell tumours through the perturbation of serum testosterone levels and liver tumours through phenobarbital-like induction are all considered to be not relevant to humans (see Section 9.3). The potential role for oxidative metabolites in the mode of action of ethylbenzene-induced lung tumours in mice, however, suggests that these tumours may be relevant to humans. The mode of action for lung tumours suggests that there is a threshold below which tumours are not expected to be observed. As a result, Health Canada deemed it appropriate to determine an HBV for lung tumours using a tolerable daily intake approach.

The NTP (1999) study was determined to be the most appropriate animal study for the derivation of an HBV for lung tumour development from ethylbenzene exposure. A mouse PBPK model was employed in order to adjust for an oral dose that is relevant to humans. The cumulative lifetime internal blood concentration of ethylbenzene (in milligrams of parent compound per litre of blood) generated by the mouse PBPK model was determined to be the most appropriate dose metric to represent the concentration of ethylbenzene in the lung. This dose metric is supported by the proposed mode of action for lung tumours, which suggests that ethylbenzene metabolism occurs in the lung, generating toxic metabolites leading to potential oxidative stress and the possible promotion of lung tumours (see Section 9.3). As ethylbenzene generates several oxidative stress–inducing metabolites, the parent compound level in blood was selected in order to establish the most conservative estimate of oxidative stress in lung. PBPK modelling allows for the use of an inhalation study instead of an ingestion study and accounts for metabolic differences between animals and humans as well as metabolic differences between high and low exposure levels. Although it is likely that the additional lung tumours in this experimental model are due to the inhalation route of exposure, ethylbenzene is also expected to exert its toxicity systemically. The use of blood concentrations provides a more conservative estimate of cancer risk than the internal dose in the lung compartment and is more appropriate for the derivation of a drinking water guideline. Consequently, blood concentrations have been used as the dose metric in the cancer risk assessment. The external doses associated with lung tumours in mice from the NTP (1999) study were inputted into the mouse PBPK model in order to estimate the cumulative lifetime internal blood concentrations of ethylbenzene (in mg/L blood). Using the log logistic model (as the best fit model) from the U.S. EPA's BMD software (U.S. EPA, 2010), these internal doses were then analysed to determine the most appropriate point of departure for inputting into the human model; the animal point of departure was determined to be the lower

95% confidence limit of the BMD corresponding to a 10% increase in lung tumours ($BMDL_{10}$) of 1.43 mg of ethylbenzene per litre of blood. This internal dose was then inputted into the human PBPK model in order to determine the human external dose required to give a blood concentration similar to that in the mouse, assuming 1.5 L consumption of drinking water per day and 70 years of exposure. The resulting external human oral dose was determined to be 10.17 mg/kg bw per day. Using this human external dose, the TDI for ethylbenzene can be determined as follows:

$$\text{TDI} = \frac{\text{10.17 mg/kg bw per day}}{25}$$

$$= \text{0.41 mg/kg bw per day}$$

where:

- 10.17 mg/kg bw per day is the $BMDL_{10}$ for lung tumours in mice observed in the NTP (1999) study; and
- 25 is the uncertainty factor accounting for intraspecies variability (10) and interspecies variability (2.5) (see below).

The interspecies uncertainty factor can be divided in two components: a toxicokinetic (delivered dose) component (×4) and a toxicodynamic (differential tissue sensitivity) component (×2.5) (IPCS, 2005). PBPK modelling accounts for differences in the toxicokinetics between animals and humans; as a result, the toxicokinetic component of the interspecies uncertainty factor (×4) can be removed from the TDI calculation. As the toxicodynamic variation (relating to tissue sensitivity) between animals and humans for ethylbenzene is not well known, the toxicodynamic portion of the interspecies uncertainty factor was retained for determining the TDI.

The TDI was employed to calculate an HBV, as follows:

$$\text{HBV} = \frac{\text{0.41 mg/kg bw per day} \times \text{70 kg} \times 0.2}{\text{2.15 L-eq/day}}$$

$$= \text{2.67 mg/L}$$

$$\approx \text{3 mg/L}$$

where:

- 0.41 mg/kg bw per day is the TDI as derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure, and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 2.15 L-eq/day is the daily volume of water consumed by an adult, accounting for multiple routes of exposure (see Section 5.6).

10.2.2 Non-cancer risk assessment

Due to the abundance of animal studies and the lack of epidemiological studies, animal data were considered in the non-cancer risk assessment of ethylbenzene. Oral and inhalation studies, including one study spanning two years of exposure by inhalation in mice, were shown to target the liver and kidneys of exposed rodents, as demonstrated by increased weights of these organs. Chronic exposures to ethylbenzene produced lesions in mouse liver, lung, thyroid and pituitary gland and in rat kidney, prostate gland, bone marrow and liver. Ethylbenzene is not considered to be teratogenic, is not a reproductive toxicant, is not selectively toxic to the developing nervous system and is not harmful to the immune system. Based on an evaluation of all the non-cancer data in mice and rats, a NOAEL of 75 ppm or 326 mg/m^3 was identified from the NTP (1999) study for hyperplasia of the pituitary gland and liver cellular alterations in mice. To adjust for an oral dose that is relevant to humans, PBPK modelling was employed to estimate internal blood and liver concentrations in the mouse of 0.324 and 0.08 mg/L, respectively. The liver level is chosen to calculate the HBV, since it is lower than the blood concentration associated with the NOAEL. This internal dose was then inputted into the human PBPK model in order to determine the human external dose required to give a blood concentration similar to that in the rat, assuming 1.5 L consumption of drinking water per day. The resulting human external dose corresponding to a liver concentration of 0.08 mg/L is 0.54 mg/kg bw per day. This value was used to derive the TDI:

$$\text{TDI} = \frac{0.54 \text{ mg/kg bw per day}}{25}$$

$$= 0.022 \text{ mg/kg bw per day}$$

where:

- 0.54 mg/kg bw per day is the human external oral dose required to give a blood concentration equivalent to the NOAEL of 75 ppm based on hyperplasia of the pituitary gland and liver cellular alterations in mice (NTP 1999); and
- 25 is the uncertainty factor to account for intraspecies variability (×10) and interspecies variability (×2.5) (see Section 10.2.1).

The TDI was employed to calculate an HBV, as follows:

$$\text{HBV} = \frac{0.022 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{2.15 \text{ L-eq/day}}$$

$$= 0.141 \text{ mg/L}$$

$$\approx 0.14 \text{ mg/L}$$

where:

- 0.022 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;

- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure, and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 2.15 L-eq/day is the daily volume of water consumed by an adult, accounting for multiple routes of exposure (see Section 5.6).

10.2.3 Comparison of cancer and non-cancer risk assessments

In Section 10.2.1, using a TDI (threshold) approach, an HBV for ethylbenzene that is protective of lung tumours was determined to be 3 mg/L. In Section 10.2.2, also using a TDI approach, an HBV of 0.14 mg/L was determined to be protective of hyperplasia of the pituitary gland and liver cellular alterations. As the non-cancer risk assessment resulted in a more conservative HBV for ethylbenzene, the MAC of 0.14 mg/L is deemed to be protective of both cancer and non-cancer health effects.

10.3 Xylenes

Xylenes (*o*-, *m*- and *p*-isomers) are used as industrial solvents, synthetic intermediates and solvents in paints, coatings, adhesive removers and paint thinners; they are also a naturally occurring component of petroleum. There is insufficient information from both animal and epidemiological studies to determine whether xylenes are carcinogenic in humans; both IARC and the U.S. EPA consider xylenes as not classifiable with respect to human carcinogenicity. The primary health effects following exposure to xylenes are effects on the central nervous system by all routes of exposure, effects on the respiratory tract following inhalation exposure and hepatic, renal and body weight effects following higher oral exposures. The scientific literature indicates that the isomers of xylene have displayed similar toxicokinetic properties and toxicological effects, with no single isomer consistently exhibiting any greater potency for a given health endpoint. Thus, studies of both mixtures and individual isomers were considered for risk assessment. Due to the lack of evidence of tumour formation and the non-genotoxic mode of action of xylenes, the MAC for xylenes is derived using non-cancer endpoints.

Few studies were available for a risk characterization of xylenes, and most of these lacked adequate dose–response characterization or demonstrated no adverse effects upon exposure. No suitable oral exposure studies were identified in animals or humans. Among the endpoints investigated, neurobehavioural alterations were the most consistently observed. One study in particular examined the performance of male rats on the rotarod test, as a measure of motor coordination disturbances (indicative of adverse neuromuscular effects), after a 3-month inhalation exposure to 50 and 100 ppm (or 217 and 434 mg/m^3) *m*-xylene (Korsak et al., 1994). The tests were performed 24 hours after the last exposure, thus allowing complete excretion of *m*-xylene from the animals. This study was selected as the most appropriate, given that it is a well-controlled animal study that employed multiple doses with no co-exposure to other chemicals. Furthermore, the established lowest-observed-adverse-effect concentration (LOAEL) of 100 ppm was further supported by a 6-month study in rats demonstrating decreased performance on the rotarod test at the same concentration (Korsak et al., 1992). The Korsak et al. (1992) study was not considered in the derivation of the point of departure, since only one dose was studied.

Since the central nervous system is a major target of xylenes in various exposure scenarios, the inhalation route of exposure was considered to be appropriate for deriving a MAC. The increase in failures on the rotarod test showed a clear dose–response relationship in the studied animals. Information considered necessary for proper BMD analysis was not available.

However, clearly significant effects were observed at the 100 ppm concentration. As such, the 50 ppm dose was retained as the point of departure.

In order to adjust for an oral dose that is relevant to humans, PBPK modelling was employed to estimate internal blood concentrations of 0.1380 mg/L for the 50 ppm concentration in the rat exposed for 3 months. This internal dose was then inputted into the human PBPK model in order to determine the human external doses required to give blood concentrations similar to those in the rat, assuming 1.5 L consumption of drinking water. The resulting human external doses corresponding to blood *m*-xylene concentrations of 0.14 and 0.40 mg/L were determined to be 1.00 and 2.91 mg/kg bw per day, respectively.

Uncertainty factors considered in deriving the TDI include interspecies and intraspecies variability as well as the use of a subchronic study instead of a chronic study. Because the effects on the rotarod test observed in this study were consistent 6 months after exposure, the uncertainty factor for use of a subchronic study was reduced. The TDI was calculated as follows:

$$\text{TDI} = \frac{1.00 \text{ mg/kg bw per day}}{75}$$

$$= 0.013 \text{ mg/kg bw per day}$$

where:

- 1.00 mg/kg bw per day is the human external oral dose required to give a blood concentration equivalent to a NOAEL of 50 ppm in the rat; and
- 75 is the uncertainty factor to account for intraspecies variability (10), interspecies variability (2.5) (see Section 10.2.1) and the use of a subchronic study instead of a chronic study (3).

The TDI was employed to calculate the MAC, as follows:

$$\text{MAC} = \frac{0.013 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{2.14 \text{ L-eq/day}}$$

$$= 0.085 \text{ mg/L}$$

$$\approx 0.09 \text{ mg/L}$$

where:

- 0.013 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure, and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 2.14 L-eq/day is the daily volume of water consumed by an adult, accounting for multiple routes of exposure (see Section 5.6).

10.4 International considerations

This section presents the various drinking water guidelines and standards from other international organizations. Variation in these limits can be attributed simply to the year of assessment, or to differing policies and approaches including the choice of key study, as well as the use of different consumption rates, body weights, and allocation factors.

10.4.1 Toluene

The U.S. EPA has established a maximum contaminant level (MCL) for toluene in drinking water of 1.0 mg/L (1000 µg/L) based on a NOAEL of 312 mg/kg bw/day (adjusted to 223 mg/kg bw/day to adjust from five to seven exposure days per week) for increased kidney and liver weight observed in a 13-week oral gavage study in rats (NTP, 1989). An uncertainty of 1000 is applied (100 for interspecies and intraspecies variation and 10 for database insufficiencies and contradictions in the immunotoxicity data). An allocation factor for drinking water of 20% was employed in deriving the final guideline value.

The WHO (2004) established a drinking water guideline for toluene of 0.7 mg/L (700 µg/L). This guideline is based on a LOAEL of 312 mg/kg bw per day for marginal hepatotoxic effects observed in a 13-week gavage study in mice (NTP, 1990), correcting for 5 days/week dosing and using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for the use of a short-term study and the use of a LOAEL instead of a NOAEL). An allocation factor for drinking water of 10% was employed in deriving the final guideline value.

The California EPA (OEHHA, 1999) developed a non-mandatory public health goal (PHG) of 0.15 mg/L (150 µg/L) for toluene in drinking water based on a subchronic study (Hsieh et al., 1989) in which toluene was administered to mice via drinking water. Significantly increased liver weights (hepatomegaly) and decreased thymus weights were observed at a treatment level of 105 mg/kg bw per day, but not at 22 mg/kg bw per day. From this study, a NOAEL of 22 mg/kg bw per day was identified. Due to the volatility of toluene, a relative source contribution of 40% and an adult drinking water consumption rate of 4 L/day were assumed. A factor of 1000 (10-fold for interspecies variation, 10-fold for human variability and 10-fold to account for the use of a subchronic study for determining a lifetime value) was used to account for uncertainty in the PHG calculation.

10.4.2 Ethylbenzene

The U.S. EPA has established an MCL for ethylbenzene in drinking water of 0.7 mg/L (700 µg/L), based on a NOAEL of 136 mg/kg bw per day for histopathological changes in liver and kidney observed in a limited 6-month study in rats (Wolf et al., 1956), correcting for 5 days/week dosing and using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for the use of a short-term study). An allocation factor for drinking water of 20% was employed in deriving the final guideline value.

The WHO (2003a) drinking water guideline for ethylbenzene of 0.3 mg/L (300 µg/L) is based on a NOAEL of 136 mg/kg bw/day for hepatotoxicity and nephrotoxicity observed in a limited 6-month study in rats (Wolf et al., 1956), correcting for 5 days/week dosing and using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for database deficiencies and the use of a short-term study). An allocation factor for drinking water of 10% was employed in deriving the final guideline value.

The California EPA (OEHHA, 1997a) established a non-mandatory PHG of 0.3 mg/L (300 µg/L) for ethylbenzene in drinking water based on non-carcinogenic effects observed in experimental animals. The NTP (1996) study, a preliminary draft of NTP (1999) study available at the time of assessment, provided evidence of hepatotoxicity in mice exposed to 250 ppm

ethylbenzene in air for 2 years. A NOAEL for hepatotoxicity was determined to be 75 ppm from the NTP (1999) study, corresponding to a daily dose of 49 mg/kg bw. For the calculation of the PHG, factors accounting for uncertainty in interspecies extrapolation, potentially sensitive human subpopulations and the potential for a severe effect (cancer) were incorporated, for a cumulative uncertainty factor of 1000.

10.4.3 Xylenes

The U.S. EPA (1987) established a maximum contaminant level (MCL) for total xylenes in drinking water of 10.0 mg/L based on a NOAEL of 250 mg/kg-day for reduced body weight and decreased survival in male rats from a 2-year gavage study (NTP, 1986). The NOAEL was adjusted for dosing 5 days/week to 179 mg/kg bw/day and an uncertainty factor of 100 (for intra- and inter-species variation) was applied to arrive at an oral RfD of 2 mg/kg bw/day. A relative source contribution (RSC) of 20% was applied in deriving the final MCL.

The WHO (2003b) drinking water guideline for xylenes of 0.5 mg/L (500 µg/L) is based on a NOAEL of 250 mg/kg bw per day for decreased body weight in a 103-week gavage study in rats (NTP, 1986), correcting for 5 days/week dosing and using an uncertainty factor of 1000 (100 for interspecies and intraspecies variation and 10 for the limited toxicological endpoints). An allocation factor for drinking water of 10% was employed in deriving the final guideline value.

The California EPA (OEHHA, 1997b) developed a non-mandatory PHG of 1.8 mg/L for individual xylene isomers or the sum of xylene isomers in drinking water based on neurotoxic effects in chronic exposures to xylene in humans as reported in Uchida et al. (1993). The LOAEL from this study of 7.5 mg/kg bw per day was divided by a factor of 30 (3 for extrapolation from a LOAEL to a NOAEL and 10 for potential variations in sensitivity among humans), then further divided by 2 to account for extra exposure by the inhalation route from the household water supply and corrected for an assumed relative source contribution from drinking water of 40%.

11.0 Rationale

Toluene, ethylbenzene and xylenes are volatile, flammable and colourless liquids used primarily in the synthesis of specific chemical compounds or as industrial solvents. All three compounds occur naturally in small quantities in crude oil and are further added to gasoline and other fuels. Entry into drinking water sources can occur from leaching of fuel at various sites, including refineries and fuel filling stations, as well as from spills during the transportation and storage of fuels. Given the volatility of toluene, ethylbenzene and xylenes, the contribution from inhalation and dermal exposure during bathing and showering was also estimated using a multiroute exposure approach. As part of its ongoing guideline review process, Health Canada will continue to monitor new research and recommend any change to the guidelines that is deemed necessary.

11.1 Toluene

Toluene is considered to be not classifiable with regard to carcinogenicity due to insufficient animal and human carcinogenicity data. The health effects of toluene in occupationally exposed workers include an array of neurological effects, such as loss of colour vision as well as disturbances in memory, concentration and cognitive function. Oral exposure in animals has resulted in altered behaviour, changes in neurotransmitter levels and brain necrosis, which support adverse neurological effects as a critical endpoint of toluene toxicity.

The MAC for toluene in drinking water has been determined to be 0.06 mg/L (60 µg/L), based on several neurological endpoints reported in human occupational studies.

The lowest reported odour threshold for toluene is 0.024 mg/L (24 µg/L); this is close to the MAC, indicating that toluene may not be detected by smell at the MAC.

11.2 Ethylbenzene

Ethylbenzene is considered to be possibly carcinogenic to humans based on sufficient evidence of carcinogenicity in experimental animals but inadequate data in humans. The health effects of ethylbenzene in humans are relatively unknown, due to the lack of occupational settings with predominant exposure to ethylbenzene. Studies of rats and mice exposed to ethylbenzene via inhalation and ingestion have identified liver and kidney as primary targets for ethylbenzene. Inhalation and ingestion of ethylbenzene in rats and mice lead to enlarged liver and kidney, effects on the pituitary gland, as well as increased severity of nephropathy. Chronic exposure of animals by inhalation and ingestion also suggests tumour formation at various sites, including the liver, kidney and lung. As a result, both cancer and non-cancer endpoints were considered in deriving the MAC.

A MAC of 0.14 mg/L (140 µg/L) for ethylbenzene in drinking water has been determined based on kidney effects and body weight reduction in rats and on liver and pituitary gland effects in mice; this MAC is protective of both cancer and non-cancer endpoints.

The lowest reported odour threshold for ethylbenzene is 0.0016 mg/L (1.6 µg/L); this is much lower than the MAC, indicating that drinking water containing ethylbenzene will become unpalatable at a concentration much lower than that which may cause adverse health impacts.

11.3 Xylenes

The primary health effects associated with exposure to xylenes in animals are effects on the central nervous system by all routes of exposure, effects on the respiratory tract following inhalation exposure and hepatic, renal and body weight effects following higher oral exposures. Occupational exposure studies have also reported neurological effects in workers.

A MAC of 0.09 mg/L (90 µg/L) for xylenes in drinking water has been determined based on neuromuscular effects in rats.

The lowest reported odour threshold for xylenes is 0.02 mg/L (20 µg/L); this is close to the MAC, indicating that xylenes may not be detected by smell at the MAC.

11.4 Analytical and treatment considerations

The MACs and aesthetic objectives for toluene, ethylbenzene and xylenes can be measured by available analytical methods and are achievable by municipal and residential treatment technologies. A number of residential treatment devices are available to remove toluene, ethylbenzene and xylenes from drinking water.

12.0 References

Abbate, C., Giorgianni, C., Munao, F. and Brecciaroli, R. (1993). Neurotoxicity induced by exposure to toluene: an electrophysiologic study. Int. Arch. Occup. Environ. Health, 64: 389–392.

Adams, J.C., Dills, R.L., Morgan, M.S., Kalman, D.A. and Pierce, C.H. (2005). A physiologically based toxicokinetic model of inhalation exposure to xylenes in Caucasian men. Regul. Toxicol. Pharmacol., 43(2): 203–214.

Adams, J.Q. and Clark, R.M. (1991). Evaluating the costs of packed-tower aeration and GAC for controlling selected organics. J. Am. Water Works Assoc., 83(1): 49–57.

Aikawa, H., Yoshida, T. and Shigeta, S. (1997). Changes in the amounts of neurotransmitters released from the striatum and spontaneous motor activity in rats exposed to high doses of toluene. Environ. Health Prev. Med., 1: 171–177.

Aitio, A., Pekari, K. and Jarvisalo, J. (1984). Skin absorption as a source of error in biological monitoring. Scand. J. Work Environ. Health, 10: 317–320.

Alberta Environment (2004). Assessment report on ethylbenzene for developing ambient air quality objectives. Prepared by Cantox Environmental Inc. in conjunction with RDWI West Inc. Science and Standards Branch, Alberta Environment, Edmonton, Alberta. Available at: http://environment.gov.ab.ca/info/library/6662.pdf

Alexander, H.C., McCarty, W.M., Bartlett, E.A. and Syverud, A.N. (1982). Aqueous odor and taste threshold values for industrial chemicals. J. Am. Water Works Assoc., 74: 595–599.

Ameno, K., Fuke, C., Ameno, S., Kiriu, T., Sogo, K. and Ijiri, I. (1989). A fatal case of oral ingestion of toluene. Forensic Sci. Int., 41: 255–260.

Ameno, K., Kiriu, T., Fuke, C., Ameno, S., Shinohara, T. and Ijiri, I. (1992). Regional brain distribution of toluene in rats and in a human autopsy. Arch. Toxicol., 66: 153–156.

Andersen, I., Lundqvist, G.R. and Molhave, L. (1983). Human response to controlled levels of toluene in six-hour exposures. Scand. J. Work Environ. Health, 9: 405–418.

Anderson, B.E., Zeiger, E., Shelby, M.D., Resnick, M.A., Gulati, D.K., Ivett, J.L. and Loveday, K.S. (1990). Chromosome aberration and sister chromatid exchange test results with 42 chemicals. Environ. Mol. Mutagen., 16: 55–137.

Andersson, K., Fuxe, K. and Nilsen, O.G. (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.

Angerer, J. (1979). Occupational chronic exposure to organic solvents. VII. Metabolism of toluene in man. Int. Arch. Occup. Environ. Health, 43: 63–67.

Angerer, J., Schildbach, M. and Kramer, A. (1998). *S*-*p*-Toluylmercapturic acid in the urine of workers exposed to toluene: a new biomarker for toluene exposure. Arch. Toxicol., 72: 119–123.

Anttila, A., Pukkala, E., Riala, R., Sallmén, M. and Hemminki, K. (1998). Cancer incidence among Finnish workers exposed to aromatic hydrocarbons. Int. Arch. Occup. Environ. Health, 71: 187–193.

APHA, AWWA and WEF (2012). Standard methods for the examination of water and wastewater, 21st edition. American Public Health Association, American Water Works Association and Water Environment Federation, Washington, DC.

API (1985). Two-generation reproduction/fertility study on a petroleum-derived hydrocarbon (toluene). American Petroleum Institute, Washington, DC.

Arnold, G.L., Kirby, R.S., Langendoerfer, S. and Wilkins-Haug, L. (1994). Toluene embryopathy: clinical delineation and developmental follow-up. Pediatrics, 93: 216–220.

Arp, E.W., Jr., Wolf, P.H. and Checkoway, H. (1983). Lymphocytic leukemia and exposures to benzene and other solvents in the rubber industry. J. Occup. Med., 25: 598–602.

Arthurs, P., Stiver, W.H. and Zytner, R.G. (1995). Passive volatilization of gasoline from soil. J. Soil Contam., 4: 123–135.

ASTER (1995). Assessment Tools for the Evaluation of Risk database. National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Washington, DC. Available at: www.epa.gov/med/Prods_Pubs/aster.htm

Astrand, I., Engström, J. and Ovrum, P. (1978). Exposure to xylene and ethylbenzene: I. Uptake, distribution and elimination in man. Scand. J. Work Environ. Health, 4: 185–194.

ATSDR (1995). Toxicological profile for xylene (update). Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia.

ATSDR (2000). Toxicological profile for toluene. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia. Available at: www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=161&tid=29

ATSDR (2004). Benzene, toluene, ethylbenzene, and xylenes (BTEX) final interaction profile. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia.

ATSDR (2007). Toxicological profile for xylene. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia. Available at: www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=296&tid=53

ATSDR (2010). Toxicological profile for ethylbenzene. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, G Georgia. Available at: www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=383&tid=66

AWWA (1991). Organics Contaminant Control Committee report: existing VOC treatment installations; design, operation and cost. Water Quality Division, American Water Works Association, Denver, Colorado (Report No. 0033986).

Baelum, J., Anderson, I. and Lundqvist, G.R. (1985). Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. Scand. J. Work Environ. Health, 11: 271–280.

Baelum, J., Dossing, M., Hansen, S.H., Lundgvist, G.R. and Andersen, N.T. (1987). Toluene metabolism during exposure to varying concentrations combined with exercise. Int. Arch. Occup. Environ. Health, 59: 281–294.

Baelum, J., Molhave, L., Hansen, S.H. and Dossing, M. (1993). Hepatic metabolism of toluene after gastrointestinal uptake in humans. Scand. J. Work Environ. Health, 19: 55–62.

Bakke, O.M. and Scheline, R.R. (1970). Hydroxylation of aromatic hydrocarbons in the rat. Toxicol. Appl. Pharmacol., 16: 691–700.

Bardodej, Z. and Bardodejova, E. (1970). Biotransformation of ethyl benzene, styrene, and α-methylstyrene in man. Am. Ind. Hyg. Assoc. J., 31: 206–209.

Bardodej, Z. and Cirek, A. (1988). Long-term study on workers occupationally exposed to ethylbenzene. J. Hyg. Epidemiol. Microbiol. Immunol., 32: 1–5.

Barker, J.F., Tessmann, J.S., Plotz, P.E. and Reinhard, M. (1986). Organic geochemistry of a sanitary landfill leachate plume. J. Contam. Hydrol., 1: 171–189.

Beasley, T.E., Evansky, P.A., Gilbert, M.E. and Bushnell, P.J. (2010). Behavioral effects of subchronic inhalation of toluene in adult rats. Neurotoxicol. Teratol., 32: 611–619.

Beasley, T.E., Evansky, P.A. and Bushnell, P.J. (2012). Behavioral effects of sub-acute inhalation of toluene in adult rats. Neurotoxicol. Teratol., 34: 83–89.

Benignus, V.A., Muller, K.E., Graham, J.A. and Barton, C.N. (1984). Toluene levels in blood and brain of rats as a function of toluene level in inspired air. Environ. Res., 33: 39–46.

Benoit, F.M., Davidson, W.R. and Lovett, A.M. (1985). Breath analysis by API/MS—human exposure to volatile organic solvents. Int. Arch. Occup. Environ. Health, 55: 113–120.

Berenguer, P., Soulage, C., Perrin, D., Pequignot, J.M. and Abraini, J.H. (2003). Behavioral and neurochemical effects induced by subchronic exposure to 40 ppm toluene in rats. Pharmacol. Biochem. Behav., 74: 997–1003.

Bergendahl, J., Hubbard S. and Grasso, D. (2003). Pilot scale Fenton's oxidation of organic contamination in groundwater using autochthonous iron. J. Hazard. Mater., B99: 43–56.

Bergman, K. (1983). Application and results of whole-body autoradiography in distribution studies of organic solvents. CRC Crit. Rev. Toxicol., 12(1), 59–118.

Bikashvili, T.Z., Chilachava, L.R., Gelazonia, L.K., Japaridze, N.J., Zhvania, M.G., Lordkipanidze, T.G. and Okuneva, V.G. (2012). Effect of chronic inhalation of toluene on behavior of rats of various age groups in multi-branched maze. Bull. Exp. Biol. Med., 152: 587–589.

Billionnet, C., Gay, E., Kirchner, S., Leynaert, B. and Annesi-Maesano, I. (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings. Environ. Res., 111: 425–434.

Bjornaes, S. and Naalsund, L.U. (1988). Biochemical changes in different brain areas after toluene inhalation. Toxicology, 49: 367–374.

Blair, A., Hartge, P., Stewart, P.A., McAdams, M. and Lubin, J. (1998). Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. Occup. Environ. Med., 55: 161–171.

Boey, K.W., Foo, S.C. and Jeyaratnam, J. (1997). Effects of occupational exposure to toluene: a neuropsychological study on workers in Singapore. Ann. Acad. Med. Singapore, 26: 184–187.

Borne, J., Riascos, R., Cuellar, H., Vargas, D. and Rojas, R. (2005). Neuroimaging in drug and substance abuse. Part II: Opioids and solvents. Top. Magn. Reson. Imaging, 16: 239–245.

Borriston Laboratories Inc. (1983). Four-week oral nephrotoxicity screening in male F-344 rats phases I and II pathology report. FYI submission AX-1283-0280. Submitted by the American Petroleum Institute to the U.S. Environmental Protection Agency, Washington, DC.

Bos, R.P., Brouns, R.M.E. and Van Doorn, R. (1981). Non-mutagenicity of toluene, *o*-, *m*- and *p*-xylene, *o*-methylbenzylalcohol and *o*-methylbenzylsulfate in the Ames assay. Mutat. Res., 88: 273–279.

Bray, H.G., Humphris, B.G. and Thorpe, W.V. (1949). Metabolism of derivatives of toluene. 3. *o*-, *m*- and *p*-xylenes. Biochem. J., 45: 241–244.

Brown, H.S., Bishop, D.R. and Rowan, C.A. (1984). The role of skin absorption as a route of exposure for volatile organic compounds (VOCs) in drinking water. Am. J. Public Health, 74(5): 479–484.

Brugnone, F., Gobbi, M., Ayyad, K., Giuliari, C., Cerpelloni, M. and Perbellini, L. (1995). Blood toluene as a biological index of environmental toluene exposure in the "normal" population and in occupationally exposed workers immediately after exposure and 16 hours later. Int. J. Occup. Environ. Health, 66: 421–425.

Budavari, S., O'Neil, M.J., Smith, A., Heckelman, P.E. and Kinneary, J.F. (eds.) (1996). The Merck index. Merck & Co., Inc., Rahway, New Jersey.

Burmistrov, S.O., Arutyunyan, A.V., Stepanov, M.G., Oparina, T.I. and Prokopenko, V.M. (2001). Effect of chronic inhalation of toluene and dioxane on activity of free radical processes in rat ovaries and brain. Bull. Exp. Biol. Med., 132: 832–836.

Bushnell, P.J., Oshiro, W.M., Samsam, T.E. and Klinger, R. (2007). The role of physical activity and feeding schedule on the kinetics of inhaled and oral toluene in rats. J. Toxicol. Environ. Health A, 70(21): 1806–1814.

Camford Information Services Inc. (1996). Xylenes (xylols, *m*-xylene, *o*-xylene, *p*-xylene, mixed xylenes). Don Mills, Ontario.

Camford Information Services Inc. (2003). Toluene (toluol, methylbenzene, phenylmethane). Don Mills, Ontario.

Camford Information Services Inc. (2004). Ethylbenzene (phenylethane). Don Mills, Ontario.

Campo, P., Lataye, R., Cossec, B. and Placidi, V. (1997). Toluene-induced hearing loss: a mid-frequency location of the cochlear lesions. Neurotoxicol. Teratol., 19: 129–140.

Campo, P., Lataye, R., Cossec, B., Villette, V., Roure, M. and Barthelemy, C. (1998). Combined effects of simultaneous exposure to toluene and ethanol on auditory function in rats. Neurotoxicol. Teratol., 20(3): 321–332.

Cannella, W.J. (2007). Xylenes and ethylbenzene. In: Kirk-Othmer encyclopedia of chemical technology, 5th edition.

Cappaert, N.L.M., Klis, S.F.L., Muijser, H., De Groot, J.C.M.J., Kulig, B.M. and Smoorenburg, G.F. (1999). The ototoxic effects of ethyl benzene in rats. Hear. Res., 137: 91–102.

Cappaert, N.L.M., Klis, S.F.L., Baretta, A.B., Muijser, H. and Smoorenburg, G.F. (2000). Ethyl benzene–induced ototoxicity in rats: a dose-dependent mid-frequency hearing loss. J. Assoc. Res. Otolaryngol., 1: 292–299.

Caravati, E.M. and Bjerk, P.J. (1997). Acute toluene ingestion toxicity. Ann. Emerg. Med., 30: 838–839.

Carlsson, A. (1981). Distribution and elimination of ^{14}C-xylene in rat. Scand. J. Work Environ. Health, 7: 51–55.

Carlsson, A. (1982). Exposure to toluene. Uptake, distribution and elimination in man. Scand. J. Work Environ. Health, 8: 43–55.

Carpenter, A.V., Flanders, W.D., Frome, E.L., Tankersley, W.G. and Fry, S.A. (1988). Chemical exposures and central nervous system cancers: a case-control study among workers at two nuclear facilities. Am. J. Ind. Med., 13: 351–362.

Cavalleri, A., Gobba, F., Nicali, E. and Fiocchi, V. (2000). Dose-related color vision impairment in toluene-exposed workers. Arch. Environ. Health, 55: 399–404.

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

Chang, F.K., Mao, I.F., Chen, M.L. and Cheng, S.F. (2011). Urinary 8-hydroxydeoxyguanosine as a biomarker of oxidative DNA damage in workers exposed to ethylbenzene. Ann. Occup. Hyg., 55: 519–525.

Chen, C.S., Hseu, Y.C., Liang, S.H., Kuo, J.Y. and Chen, S.C. (2008). Assessment of genotoxicity of methyl-*tert*-butyl ether, benzene, toluene, ethylbenzene, and xylene to human lymphocytes using comet assay. J. Hazard. Mater., 153: 351–356.

Chin, B.H., McKelvey, J.A., Tyler, T.R., Calisti, L.J., Kozbelt, S.J. and Sullivan, L.J. (1980). Absorption, distribution, and excretion of ethylbenzene, ethylcyclohexane, and methylethylbenzene isomers in rats. Bull. Environ. Contam. Toxicol., 24: 477–483.

Chouaniere, D., Wild, P., Fontana, J.M., Hery, M., Fournier, M., Baudin, V., Subra, I., Rousselle, D., Toamain, J.P., Saurin, S. and Ardiot, M.R. (2002). Neurobehavioral disturbances arising from occupational toluene exposure. Am. J. Ind. Med., 41(2): 77–88.

Chowdhury, Z., Summers, S., Westerhoff, G., Leto, B., Nowack, K. and Corwin, C. (2013). Activated carbon. Solution for improving water quality. American Water Works Association, Denver, Colorado.

Climie, I.J.G., Hutson, D.H. and Stoydin, G. (1983). The metabolism of ethylbenzene hydroperoxide in the rat. Xenobiotica, 13: 611–618.

Condie, L.W., Hill, J.R. and Borzelleca, J.F. (1988). Oral toxicology studies with xylene isomers and mixed xylenes. Drug Chem. Toxicol., 11: 329–354.

Connor, T.H., Theiss, J.C. and Hanna, H.A. (1985). Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol. Lett., 25: 33–40.

Costantini, A.S., Benvenuti, A., Vineis, P., Kriebel, D., Tumino, R., Ramazzotti, V., Rodella, S., Stagnaro, E., Crosignani, P., Amadori, D., Mirabelli, D., Sommani, L., Belletti, I., Troschel, L., Romeo, L., Miceli, G., Tozzi, G.A., Mendico, I., Maltoni, S.A. and Miligi, L. (2008). Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: evidence from the Italian multicenter case-control study. Am. J. Ind. Med., 51: 803–811.

Crittenden, J.C., Cortright, R.D., Rick, B., Tang, S. and Perram, D. (1988). Using GAC to remove VOCs from air-stripper off-gas. J. Am. Water Works Assoc., 80(5): 73–84.

Crittenden, J.C., Suri, R.P.S., Perram, D.L. and Hand, D.W. (1997). Decontamination of water using adsorption and photocatalysis. Water Res., 31(3): 411–418.

Crittenden, J.C., Trussell, R.R., Hand, D.W., Howe, K.J. and Tchobanoglous, G. (2005). Water treatment: principles and design, 2nd edition. John Wiley & Sons, Hoboken, New Jersey.

Cummins, M.D. and Westrick, J.J. (1990). Treatment technologies and costs for removing volatile organic compounds from water: aeration. In: Significance and treatment of volatile organic compounds in water supplies. Ram, N.M., Christman, R.F. and Cantor, K.P. (eds.). Lewis Publishers, Chelsea, Michigan.

Dann, T., Wang, D. and Etlinger, A. (1989). Volatile organic compounds in Canadian ambient air: a new emphasis. Pollution Measurement Division, Conservation and Protection, Environment Canada (PMD 89-26).

David, A., Flek, J., Frantik, E., Gut, I. and Sedivec, V. (1979). Influence of phenobarbital on xylene metabolism in man and rats. Int. Arch. Occup. Environ. Health, 44: 117–125.

Dean, B.J., Brooks, T.M., Hodson-Walker, G. and Hutson, D.H. (1985). Genetic toxicology testing of 41 industrial chemicals. Mutat. Res., 153: 57–77.

DeJongh, J. and Blaauboer, B.J. (1996). Simulation of toluene kinetics in the rat by a physiologically based pharmacokinetic model with application of biotransformation parameters derived independently *in vitro* and *in vivo*. Fundam. Appl. Toxicol., 32(2): 260–268.

DeMarini, D.M., Lawrence, B.K., Brooks, H.G. and Houk, V.S. (1991). Compatibility of organic solvents with the Microscreen prophage-induction assay: solvent–mutagen interactions. Mutat. Res., 263: 107–113.

Dennison, J.E., Andersen, M.E. and Yang, R.S.H. (2003). Characterization of the pharmacokinetics of gasoline using PBPK modeling with a complex mixtures chemical lumping approach. Inhal. Toxicol., 15: 961–986.

Dodson, R.E., Levy, J.I., Spengler, J.D., Shine, J.P. and Bennett, D.H. (2008). Influence of basements, garages, and common hallways on indoor residential volatile organic compound concentrations. Atmos. Environ., 42: 1569–1581.

Dossing, M., Aelum, J.B., Hansen, S.H., Lundqvist, G.R. and Andersen, N.T. (1983). Urinary hippuric acid and orthocresol excretion in man during experimental exposure to toluene. Br. J. Ind. Med., 40: 470–473.

Dossing, M., Baelum, J., Hansen, S.H. and Lundqvist, G.R. (1984). Effect of ethanol, cimetidine and propranolol on toluene metabolism in man. Int. Arch. Occup. Environ. Health, 54: 309–315.

Dumas, S., Parent, M.E., Siemiatycki, J. and Brisson, J. (2000). Rectal cancer and occupational risk factors: a hypothesis-generating, exposure-based case-control study. Int. J. Cancer, 87: 874–879.

Dutkiewicz, T. and Tyras, H. (1967). A study of the skin absorption of ethylbenzene in man. Br. J. Ind. Med., 24: 330–332.

Dutkiewicz, T. and Tyras, H. (1968). Skin absorption of toluene, styrene and xylene by man. Br. J. Ind. Med., 25: 243.

Dyksen, J.E. (2005). Aeration and air stripping. In: Water treatment plant design, 4th edition. Baruth, E. (ed.). American Society of Civil Engineers and American Water Works Association (McGraw-Hill).

Dyksen, J.E. (2005). Chapter 5. Aeration and air stripping. In: Water treatment plant design, 4th edition. American Water Works Association, Denver, CO, pp 5.1-5.23.

Earl, N., Cartwright, C.D., Horrocks, S.J., Worboys, M., Swift, S., Kirton, J.A., Askan, A.U., Kelleher, H. and Nancarrow, D.J. (2003). Review of the fate and transport of selected contaminants in the soil environment. Environment Agency, Bristol, United Kingdom (Draft Technical Report P5-079/TR1). Available at: http://a0768b4a8a31e106d8b0-50dc802554eb38a24458b98ff72d550b.r19.cf3.rackcdn.com/scho0904biee-e-e.pdf

Echeverria, D., Fine, L., Langolf, G., Schork, A. and Sampaio, C. (1989). Acute neurobehavioural effects of toluene. Br. J. Ind. Med., 46: 483–495.

Edelfors, S., Hass, U. and Hougaard, K.S. (2002). Changes in markers of oxidative stress and membrane properties in synaptosomes from rats exposed prenatally to toluene. Pharmacol. Toxicol., 90: 26–31.

Eller, N., Netterstrøm, B. and Laursen, P. (1999). Risk of chronic effects on the central nervous system at low toluene exposure. Occup. Med., 49: 389–395.

El Masry, A.M., Smith, J.N. and Williams, R.T. (1956). The metabolism of alkylbenzenes: *n*-propylbenzene and *n*-butylbenzene with further observations on ethylbenzene. Biochem. J., 64: 50–56.

El-Nabi Kamel, M.A. and Shehata, M. (2008). Effect of toluene exposure on the antioxidant status and apoptotic pathway in organs of the rat. Br. J. Biomed. Sci., 65: 75–79.

Elovaara, E., Engström, K. and Vainio, H. (1982). Unaltered metabolism of *m*-xylene in the presence of ethylbenzene. In: Cytochrome P-450, biochemistry, biophysics and environmental implications. Hietanen, E., Laitinen, M. and Hanninen, O. (eds.). Elsevier Biomedical Press, Amsterdam, the Netherlands, pp. 765–768.

Elovaara, E., Engström, K., Häyri, L., Hase, T. and Aitio, A. (1989). Metabolism of antipyrine and *m*-xylene in rats after prolonged pretreatment with xylene alone or xylene with ethanol, phenobarbital, or 3-methylcholanthrene. Xenobiotica, 19(9): 945–960.

Endoh, K., Kaneko, T. and Sato, A. (1989). A physiologically based pharmacokinetic model to describe the transfer of organic solvents in the human body. Simulation of kinetic behavior of trichloroethylene using a spreadsheet program. Jpn. J. Ind. Health, 31: 335–341.

Engström, J. and Bjurström, R. (1978). Exposure to xylene and ethylbenzene. II. Concentration in subcutaneous adipose tissue. Scand. J. Work Environ. Health, 4: 195–203.

Engström, K., Husman, K. and Riihimäki, V. (1977). Percutaneous absorption of *m*-xylene in man. Int. Arch. Occup. Environ. Health, 39: 181–189.

Engström, K., Riihimäki, V. and Laine, A. (1984). Urinary disposition of ethylbenzene and *m*-xylene in man following separate and combined exposure. Int. Arch. Occup. Environ. Health, 54: 355–363.

Engström, K., Elovaara, E. and Aitio, A. (1985). Metabolism of ethylbenzene in the rat during long-term intermittent inhalation exposure. Xenobiotica, 15: 281–286.

Faber, W.D., Roberts, L.S.G., Stump, D.G., Tardif, R., Krishnan, K., Tort, M., Dimond, S., Dutton, D., Moran, E. and Lawrence, W. (2006). Two generation reproduction study of ethylbenzene by inhalation in Crl-CD rats. Birth Defects Res. B Dev. Reprod. Toxicol., 77: 10–21.

Faber, W.D., Roberts, L.S.G., Stump, D.G., Beck, M., Kirkpatrick, D., Regan, K.S., Tort, M., Moran, E. and Banton, M. (2007). Inhalation developmental neurotoxicity study of ethylbenzene in Crl-CD rats. Birth Defects Res. B Dev. Reprod. Toxicol., 80: 34–48.

Farhadian, M., Duchez, D., Vachelard, C. and Larroche, C. (2008). Monoaromatics removal from polluted water through bioreactors—A review. Water Res., 42: 1325–1341.

Fellin, P. and Otson, R. (1994). Assessment of the influence of climatic factors on concentration levels of volatile organic compounds (VOCs) in Canadian homes. Atmos. Environ., 28: 3581–3586.

Fisher, J., Mahle, D., Bankston, L., Green, R. and Gearhart, J. (1997). Lactational transfer of volatile chemicals in breast milk. Am. Ind. Hyg. Assoc. J., 58(6): 425–431.

Florin, I., Rutberg, L., Curvall, M. and Enzell, C.R. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology, 15: 219–232.

Foo, S.C., Jeyaratnam, J. and Koh, D. (1990). Chronic neurobehavioural effects of toluene. Br. J. Ind. Med., 47: 480–484.

Forkman, B.A., Ljungberg, T., Johnson, A.C., Nylén, P., Ståhle, L., Höglund, G. and Ungerstedt, U. (1991). Long-term effects of toluene inhalation on rat behavior. Neurotoxicol. Teratol., 13: 475–481.

Freundt, K.J., Römer, K.G. and Federsel, R.J. (1989). Decrease of inhaled toluene, ethyl benzene, *m*-xylene, or mesitylene in rat blood after combined exposure to ethyl acetate. Bull. Environ. Contam. Toxicol., 42(4): 495–498.

Fronk, C.A. (1987). Destruction of volatile organic contaminants in drinking water by ozone treatment. Ozone Sci. Eng., 9: 265–288.

Gagnaire, F. and Langlais, C. (2005). Relative ototoxicity of 21 aromatic solvents. Arch. Toxicol., 79: 346–354.

Gagnaire, F., Marignac, B., Langlais, C. and Bonnet, P. (2001). Ototoxicity in rats exposed to *ortho*-, *meta*- and *para*-xylene vapours for 13 weeks. Pharmacol. Toxicol., 89: 6–14.

Gagnaire, F., Langlais, C., Grossmann, S. and Wild, P. (2007). Ototoxicity in rats exposed to ethylbenzene and to two technical xylene vapours for 13 weeks. Arch. Toxicol., 81: 127–143.

Garoma, T., Gurol, M., Osibodu, O. and Thotakura, L. (2008). Treatment of groundwater contaminated with single components by an ozone/UV process. Chemosphere, 73: 825–831.

Gérin, M., Siemiatycki, J., Désy, M. and Krewski, D. (1998). Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: results of a case-control study in Montreal. Am. J. Ind. Med., 34: 144–156.

Gerner-Smidt, P. and Friedrich, U. (1978). The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. Mutat. Res., 58: 313–316.

Ghantous, H. and Danielsson, B.R.G. (1986). Placental transfer and distribution of toluene, xylene and benzene and their metabolites during gestation in mice. Biol. Res. Pregnancy Perinatol., 7: 98–105.

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

Giffin, S. and Davis, A. (1998). Prediction of carbon BTEX adsorption capacity using field monitoring. J. Environ. Eng., 124(10): 921–931.

Glaze, W.H. and Kang, J.-W. (1988). Advanced oxidation processes for treating groundwater contaminated with TCE and PCE: laboratory studies. J. Am. Water Works Assoc., 80(5): 57–63.

Goldberg, M.S., Parent, M.E., Siemiatycki, J., Desy, M., Nadon, L., Richardson, L., Lakhani, R., Latreille, B. and Valois, M.F. (2001). A case-control study of the relationship between the risk of colon cancer in men and exposures to occupational agents. Am. J. Ind. Med., 39: 531–546.

Gospe, S.M., Jr. and Zhou, S.S. (2000). Prenatal exposure to toluene results in abnormal neurogenesis and migration in rat somatosensory cortex. Pediatr. Res., 47: 362–368.

Gospe, S.M., Jr., Saeed, D.B., Zhou, S.S. and Zeman, F.J. (1994). The effects of high-dose toluene on embryonic development in the rat. Pediatr. Res., 36: 811–815.

Gospe, S.M., Jr., Zhou, S.S., Saeed, D.B. and Zeman, F.J. (1996). Development of a rat model of toluene-abuse embryopathy. Pediatr. Res., 40: 82–87.

Graham, L.A., Noseworthy, L., Fugler, D., O'Leary, K., Karman, D. and Grande, C. (2004). Contribution of vehicle emissions from an attached garage to residential indoor air pollution levels. J. Air Waste Manage. Assoc., 54: 563–584.

Gralewicz, S. and Wiaderna, D. (2001). Behavioral effects following subacute inhalation exposure to *m*-xylene or trimethylbenzene in the rat—a comparative study. Neurotoxicology, 22: 79–89.

Gralewicz, S., Wiaderna, D. and Tomas, T. (1995). Development of spontaneous, age-related nonconvulsive seizure electrocortical activity and radial-maze learning after exposure to *m*-xylene in rats. Int. J. Occup. Med. Environ. Health, 8: 347–360.

Gromiec, J.P. and Piotrowski, J.K. (1984). Urinary mandelic-acid as an exposure test for ethylbenzene. Int. Arch. Occup. Environ. Health, 55(1): 61–72.

Guerin, F.T. (2002). A pilot study for the selection of a bioreactor for the remediation of groundwater from a coal tar contamination site. J. Hazard. Mater., B89: 241–252.

Guthrie, J., Fowler, P., and Sabourin, R. (2003). Gasoline and diesel fuel survey, D1 and oxygenates in gasoline, cetane index, cetane number, aromatics and PAHs in diesel. Technical Report, Oil, Gas and Energy Branch, Environment Canada, Gatineau, Quebec.

Guzelian, P., Mills, S. and Fallon, H.J. (1988). Liver structure and function in print workers exposed to toluene. J. Occup. Med., 30: 791–796.

Haddad, S., Tardif, R., Charest-Tardif, G. and Krishnan, K. (1999). Physiological modeling of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons. Toxicol. Appl. Pharmacol., 161(3): 249–257.

Haddad, S., Charest-Tardif, G., Tardif, R. and Krishnan, K. (2000). Validation of a physiological modeling framework for simulating the toxicokinetics of chemicals in mixtures. Toxicol. Appl. Pharmacol., 167(3): 199–209.

Haddad, S., Béliveau, M., Tardif, R. and Krishnan, K. (2001). A PBPK modeling-based approach to account for interactions in the health risk assessment of chemical mixtures. Toxicol. Sci., 63: 125–131.

Hancock, E.G. (1982). Toluene, the xylenes and their industrial derivatives. Elsevier Scientific Publishing Company, New York, New York.

Hand, D.W., Crittenden, J.C., Gehin, J.L. and Lykins, B.W., Jr. (1986). Design and evaluation of an air-stripping tower for removing VOCs from groundwater. J. Am. Water Works Assoc., 78(9): 87–97.

Harabuchi, I., Kishi, R., Ikeda, T., Kiyosawa, H. and Miyake, H. (1993). Circadian variations of acute toxicity and blood and brain concentrations of inhaled toluene in rats. Br. J. Ind. Med., 50: 280–286.

Hard, G.C., Betz, L.J. and Seely, J.C. (2012). Association of advanced chronic progressive nephropathy (CPN) with renal tubule tumors and precursor hyperplasia in control F344 rats from two-year carcinogenicity studies. Toxicol. Pathol., 40(3): 473–481.

Hardin, B.D., Bond, G.P. and Sikov, M.R. (1981). Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health, 7: 66–75.

Hass, U. and Jakobsen, B.M. (1993). Prenatal toxicity of xylene inhalation in the rat: a teratogenicity and postnatal study. Pharmacol. Toxicol., 73: 20–23.

Hass, U., Lund, S. and Simonsen, L. (1997). Long-lasting neurobehavioral effects of prenatal exposure to xylene in rats. Neurotoxicology, 18: 547–552.

Haworth, S., Lawlor, T. and Mortelmans, K. (1983). *Salmonella* mutagenicity test results for 250 chemicals. Environ. Mutagen., 5: 3–142.

Health and Welfare Canada (1993). Chapter 4. In: Water treatment principles and applications. A manual for the production of drinking water. Canadian Water Works Association, Ottawa, Ontario.

Health Canada (2010a). Windsor Exposure Assessment Study (2005–2006): data summary for volatile organic compound sampling. Water, Air and Climate Change Bureau, Healthy Environments and Consumer Safety Branch.

Health Canada (2010b). Regina Indoor Air Quality Study 2007: VOC sampling data summary. Water, Air and Climate Change Bureau, Healthy Environments and Consumer Safety Branch.

Héroux, M.-E., Gauvin, D., Gilbert, N.L., Guay, M., Dupuis, G., Legris, M. and Lévesque, B. (2008). Housing characteristics and indoor concentrations of selected volatile organic compounds (VOCs) in Quebec City, Canada. Indoor Built Environ., 17: 128–137.

Hess, A.F., Busch, P.L., Barnes, M.J. and Dyksen, J.E. (1981). GAC treatment designs and cost for controlling volatile organic compounds in ground water. Malcolm Pirnie, Inc., Paramus, New Jersey. Paper presented at the National American Chemical Society Meeting, Atlanta, Georgia, March 30–April 3, 1981.

Hester, S.D., Johnstone, A.F.M., Boyes, W.K., Bushnell, P.J. and Shafer, T.J. (2011). Acute toluene exposure alters expression of genes in the central nervous system associated with synaptic structure and function. Neurotoxicol. Teratol., 33: 521–529.

Hillefors-Berglund, M., Liu, Y. and Von Euler, G. (1995). Persistent, specific and dose-dependent effects of toluene exposure on dopamine D2 agonist binding in the rat caudate-putamen. Toxicology, 100: 185–194.

Hobara, T., Kobayashi, H. and Higashihara, E. (1984). Experimental study on the pulmonary absorption and excretion of toluene. Int. Arch. Occup. Environ. Health, 53: 337–344.

Honma, T., Sudo, A., Miyagawa, M., Sato, M. and Hasegawa, H. (1983). Significant changes in the amounts of neurotransmitter and related substances in rat brain induced by subacute exposure to low levels of toluene and xylene. Ind. Health, 21: 143–151.

HSDB (1986). Ethylbenzene. Hazardous Substances Data Bank, National Library of Medicine, Bethesda, Maryland.

HSDB (1999). Hazardous Substances Data Bank, National Library of Medicine, Bethesda, Maryland.

HSDB (2010). 3-Xylene. Hazardous Substances Data Bank, National Library of Medicine, Bethesda, Maryland.

Hsieh, G.C., Sharma, R.P. and Parker, R.D.R. (1989). Immunotoxicological evaluation of toluene exposure via drinking water in mice. Environ. Res., 49: 93–103.

Hsieh, G.C., Sharma, R.P., Parker, R.D.R. and Coulombe, R.A., Jr. (1990). Evaluation of toluene exposure via drinking water on levels of regional brain biogenic monoamines and their metabolites in CD-1 mice. Ecotoxicol. Environ. Saf., 20: 175–184.

Hsieh, G.C., Sharma, R.P. and Parker, R.D.R. (1991). Hypothalamic–pituitary–adrenocortical axis activity and immune function after oral exposure to benzene and toluene. Immunopharmacology, 21: 23–31.

Huck, P.M., Fedorak, P.M. and Anderson, W.B. (1991). Formation and removal of assimilable organic carbon during biological treatment. J. Am. Water Works Assoc., 83(12):69-80.

Huff, J. (1990). Toxicology and carcinogenesis studies of toluene (Cas No. 108-88-3) in F344/N rats and B6C3F1 mice (inhalation studies). U.S. Department of Health and Human Services. National Institute of Health.

Huff, J. (2003). Absence of carcinogenic activity in Fischer rats and B6C3F1 mice following 103-week inhalation exposures to toluene. Int. J. Occup. Environ. Health, 9: 138–146.

IARC (1989). Toluene. Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting. International Agency for Research on Cancer. IARC Monogr. Eval. Carcinog. Risks Hum., 47: 79-156.

IARC (1999). Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. International Agency for Research on Cancer. IARC Monogr. Eval. Carcinog. Risks Hum., 71: 829-864.

IARC (2000). Ethylbenzene. Some industrial chemicals. International Agency for Research on Cancer. IARC Monogr. Eval. Carcinog. Risks Hum, 77: 125-156.

Ikeda, M., Ukai, H., Kawai, T., Inoue, O., Maejima, Y., Fukui, Y., Ohashi, F., Okamoto, S., Takada, S. and Sakurai, H. (2008). Changes in correlation coefficients of exposure markers as a function of intensity of occupational exposure to toluene. Toxicol. Lett., 179(3): 148–154.

Imbriani, M. and Ghittori, S. (1997). Effects of ethanol on toluene metabolism in man. G. Ital. Med. Lav., 19(4): 177–181.

Inoue, O., Seiji, K., Watanabe, T., Kasahara, M., Nakatsuka, H., Yin, S., Li, G., Cai, S., Jin, C. and Ikeda, M. (1986). Possible ethnic difference in toluene metabolism: a comparative study among Chinese, Turkish and Japanese solvent workers. Toxicol. Lett., 34: 167–174.

INRS (2008). Toluene: fiche toxicologique. Institut national de la recherche scientifique, Quebec City, Quebec, pp. 1–10.

IPCS (1986). Toluene. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (Environmental Health Criteria 52).

IPCS (1997). Xylenes. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (Environmental Health Criteria 190).

IPCS (2005). Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (Harmonization Project Document No. 2; www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf).

Jang, J.Y., Droz, P.O. and Kim, S. (2001). Biological monitoring of workers exposed to ethylbenzene and co-exposed to xylene. Int. Arch. Occup. Environ. Health, 74: 31–37.

Jian, K. and Pintauro, P.N. (1997). Asymmetric PVDF hollow-fiber membranes for organic/water pervaporation. J. Memb. Sci., 135(1): 41–53.

Johnson, A.-C. and Canlon, B. (1994). Progressive hair cell loss induced by toluene exposure. Hear. Res., 75: 201–208.

Jonai, H. and Sato, M. (1988). Exposure indices for painters exposed to toluene and xylene at low concentrations. Ind. Health, 26: 197–202.

Kamijima, M., Nakazawa, Y., Yamakawa, M., Shibata, E., Hisanaga, N., Ono, Y., Toida, M. and Takeuchi, Y. (1994). Metabolic acidosis and renal tubular injury due to pure toluene inhalation. Arch. Environ. Health, 49: 410–413.

Kamijo, Y., Soma, K., Hasegawa, I. and Ohwada, T. (1998). Fatal bilateral adrenal hemorrhage following acute toluene poisoning: a case report. J. Toxicol. Clin. Toxicol., 36: 365–368.

Kaneko, T., Endoh, K. and Sato, A. (1991a). Biological monitoring of exposure to organic solvent vapors. I. A physiological simulation model of *m*-xylene pharmacokinetics in man. Yamanashi Med. J., 6(3): 127–135.

Kaneko, T., Wang, P.Y., Tsukada, H. and Sato, A. (1995). *m*-Xylene toxicokinetics in phenobarbital-treated rats: comparison among inhalation exposure, oral administration, and intraperitoneal administration. Toxicol. Appl. Pharmacol., 131: 13–20.

Kaneko, T., Horiuchi, J. and Sato, A. (2000). Development of a physiologically based pharmacokinetic model of organic solvent in rats. Pharmacol. Res., 42(5): 465–470.

Kang, S.K., Rohlman, D.S., Lee, M.Y., Lee, H.S., Chung, S.Y. and Anger, W.K. (2005). Neurobehavioral performance in workers exposed to toluene. Environ. Toxicol. Pharmacol., 19: 645–650.

Kawai, T., Yasugi, T., Mizunuma, K., Horiguchi, S., Iguchi, H., Uchida, Y., Iwami, O. and Ikeda, M. (1992). Comparative evaluation of urinalysis and blood analysis as means of detecting exposure to organic solvents at low concentrations. Int. Arch. Occup. Environ. Health, 64: 223–234.

Kawai, T., Yasugi, T., Mizunuma, K., Horiguchi, S. and Ikeda, M. (1993). Comparative evaluation of blood and urine analysis as a tool for biological monitoring of *n*-hexane and toluene. Int. Arch. Occup. Environ. Health, 65(Suppl. 1): S123–S126.

Kawai, T., Mizunuma, K., Yasugi, T., Horiguchi, S. and Ikeda, M. (1994). Toluene in blood as a marker of choice for low-level exposure to toluene. Int. Arch. Occup. Environ. Health, 66(5): 309–315.

Kawai, T., Ukai, H., Inoue, O., Maejima, Y., Fukui, Y., Ohashi, F., Okamoto, S., Takada, S., Sakurai, H. and Ikeda, M. (2008). Evaluation of biomarkers of occupational exposure to toluene at low levels. J. Int. Arch. Occup. Environ. Health, 81(3): 253–262.

Knecht, U., Reske, A. and Woitowitz, H. (2000). Biological monitoring of standardized exposure to ethylbenzene: evaluation of a biological tolerance (BAT) value. Arch. Toxicol., 73: 632–640.

Korbo, L., Ladefoged, O., Lam, H.R., Ostergaard, G., West, M.J. and Arlien-Soborg, P. (1996). Neuronal loss in hippocampus in rats exposed to toluene. Neurotoxicology, 17: 359–366.

Korpela, M. and Tahti, H. (1988). The effect of *in vitro* and *in vivo* toluene exposure on rat erythrocyte and synaptosome membrane integral enzymes. Pharmacol. Toxicol., 63: 30–32.

Korsak, Z., Sokal, J.A. and Gorny, R. (1992). Toxic effects of combined exposure to toluene and *m*-xylene in animals. III. Subchronic inhalation study. Pol. J. Occup. Med. Environ. Health, 5: 27–33.

Korsak, Z., Wisniewska-Knypl, J. and Swiercz, R. (1994). Toxic effects of subchronic combined exposure to *n*-butyl alcohol and *m*-xylene in rats. Int. J. Occup. Med. Environ. Health, 7: 155–166.

Krasner, S., Glaze, W., Weinberg, H., Daniel, P., and Najm, I. (1993). Formation and control of bromate during ozonation of water containing bromide. J. Am. Water Works Assoc. 85 (1): 73-81.

Krishnan, K. and Carrier, R. (2013). The use of exposure source allocation factor in the risk assessment of drinking-water contaminants. J. Toxicol. Environ. Health B Crit. Rev. 16 (1): 39-51.

Kum, C., Kiral, F., Sekkin, S., Seyrek, K. and Boyacioglu, M. (2007a). Effects of xylene and formaldehyde inhalations on oxidative stress in adult and developing rats livers. Exp. Anim., 56: 35–42.

Kum, C., Sekkin, S., Kiral, F. and Akar, F. (2007b). Effects of xylene and formaldehyde inhalations on renal oxidative stress and some serum biochemical parameters in rats. Toxicol. Ind. Health, 23: 115–120.

Kumarathasan, P., Oyson, R. and Chu, I. (1998). Application of an automated HS-GC method in partition coefficient determination for xylenes and ethylbenzene in rat tissues. Chemosphere, 37(1): 159–178.

Kyrklund, T., Kjellstrand, P. and Haglid, K. (1987). Brain lipid changes in rats exposed to xylene and toluene. Toxicology, 45: 123–133.

Ladefoged, O., Strange, P., Moller, A., Lam, H.R., Ostergaard, G., Larsen, J.J. and Arlien-Soborg, P. (1991). Irreversible effects in rats of toluene (inhalation) exposure for six months. Pharmacol. Toxicol., 68: 384–390.

Laparé, S., Tardif, R. and Brodeur, J. (1993). Effect of various exposure scenarios on the biological monitoring of organic solvents in alveolar air: I. Toluene and *m*-xylene. Int. Arch. Occup. Environ. Health, 64(8): 569–580.

Lataye, R. and Campo, P. (1997). Combined effects of a simultaneous exposure to noise and toluene on hearing function. Neurotoxicol. Teratol., 19: 373–382.

Lehman, E.J. and Hein, M.J. (2006). Mortality of workers employed in shoe manufacturing: an update. Am. J. Ind. Med., 49: 535–546.

Leo, A. (1983). Log P and parameter database Issue No. 24. Prepared by the Medchem Project, Pomona college, Claremont, California.

Leung, H.W. and Paustenbach, D.J. (1988). Application of pharmacokinetics to derive biological exposure indexes from threshold limit values. Am. Ind. Hyg. Assoc. J., 49: 445–450.

Li, A.A., Maurissen, J.P.J., Barnett, J.F., Foss, J., Freshwater, L., Garman, R.H., Peachee, V.L., Hong, S.J., Stump, D.G. and Bus, J.S. (2010). Oral gavage subchronic neurotoxicity and inhalation subchronic immunotoxicity studies of ethylbenzene in the rat. Neurotoxicology, 31: 247–258.

Liang, S., Yates, R., Davis, D., Pastor, S., Palencia, L., and Bruno, J-M. (2001). Treatability of MTBE-contaminated groundwater by ozone and peroxone. J. Am. Water Works Assoc. 93 (6):110-120

Lide, D.R. (ed.) (1994). CRC handbook of chemistry and physics, 75th edition. CRC Press Inc., Boca Raton, Florida.

Lindbohm, M.L., Taskinen, H., Sallmen, M. and Hemminki, K. (1990). Spontaneous abortions among women exposed to organic solvents. Am. J. Ind. Med., 17: 449–463.

Lipski, C. and Cote, P. (1990). Use of pervaporation for removal of organic contaminants from water. J. Chem. Eng. Jpn., 34(8): 1069–1073.

Litton Bionetics (1978). Teratology study in rats. Toluene. Final report. LBI Project No. 20698-4. American Petroleum Institute, Washington, DC.

Lo, P.-S., Wu, C.-Y., Sue, H.-Z. and Chen, H.-H. (2009). Acute neurobehavioral effects of toluene: involvement of dopamine and NMDA receptors. Toxicology, 265: 34–40.

Löf, A., Wallen, M. and Wigaeus Hjelm, E. (1990). Influence of paracetamol and acetylsalicylic acid on the toxicokinetics of toluene. Pharmacol. Toxicol., 66(2): 138–141.

Löf, A., Wigaeus Hjelm, E., Colmsjö, A., Lundmark, B.O., Norström, A. and Sato, A. (1993). Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to $^{2}H_{8}$-toluene. Br. J. Ind. Med., 50: 55–59.

Love, O.T. and Eilers, R.G. (1982). Treatment of drinking water containing trichloroethylene and related industrial solvents. J. Am. Water Works Assoc., 74(8): 413–425.

Love, O.T., Miltner, R.J., Eilers, R.G. and Fronk-Leist, C.A. (1983). Treatment of volatile organic compounds in drinking water. Municipal Environmental Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, Ohio.

Lowry, L.K. (1987). Review of biological monitoring tests for toluene. In: Biological monitoring of exposure to chemicals. Ho, M.H. and Dillon, H.K. (eds.). John Wiley & Sons, New York, New York, pp. 99–109.

Lundberg, I. and Milatou-Smith, R. (1998). Mortality and cancer incidence among Swedish paint industry workers with long-term exposure to organic solvents. Scand. J. Work Environ. Health, 24: 270–275.

Lupo, P.J., Symanski, E., Kim Waller, D., Chan, W., Langlois, P.H., Canfield, M.A. and Mitchell, L.E. (2011). Maternal exposure to ambient levels of benzene and neural tube defects among offspring: Texas, 1999–2004. Environ. Health Perspect., 119: 397–402.

Lykins, B.W., Jr. and Clark, R.M. (1994). US drinking water regulations: treatment technologies and cost. Drinking Water Research Division, U.S. Environmental Protection Agency, Cincinnati, Ohio (EPA-600/J-94/3810).

Mackay, D. and Leinonen, P.J. (1975). Rate of evaporation of low solubility contaminants from water bodies to atmosphere. Environ. Sci. Technol., 9: 1178–1180.

Mackay, D., Shiu, W.Y. and Ma, K.C. (1992). Illustrated handbook of physical-chemical properties and environmental fate for organic chemicals. Lewis Publishers, Boca Raton, Florida.

Maestri, L., Ghittori, S. and Imbriani, M. (1997). Determination of specific mercapturic acids as an index of exposure to environmental benzene, toluene, and styrene. Ind. Health, 35: 489–501.

Maltoni, C., Ciliberti, A., Pinto, C., Soffritti, M., Belpoggi, F. and Menarini, L. (1997). Results of long-term experimental carcinogenicity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. Ann. N. Y. Acad. Sci., 837: 15–52.

Manitoba Conservation and Water Stewardship (2012). Personal communication with Housseini Coalibaly.

Marks, T.A., Ledoux, T.A. and Moore, J.A. (1982). Teratogenicity of a commercial xylene mixture in the mouse. J. Toxicol. Environ. Health, 9: 97–106.

Matsushita, T., Arimatsu, Y. and Ueda, A. (1975). Hematological and neuromuscular response of workers exposed to low concentration of toluene vapor. Ind. Health, 13: 115–121.

Mattia, C.J. (1993). Toluene-induced oxidative stress in several brain regions and other organs. Mol. Chem. Neuropathol., 18: 313–328.

Mattie, D.R., Bates, G.D., Jr., Jepson, G.W., Fisher, J.W. and McDougal, J.N. (1994). Determination of skin:air partition coefficients for volatile chemicals: experimental method and applications. Fundam. Appl. Toxicol., 22: 51–57.

McKinnon, R.J. and Dyksen, J.E. (1984). Removing organics from groundwater through aeration plus GAC. J. Am. Water Works Assoc., 76: 42–47.

Mellert, W., Deckardt, K., Kaufmann, W. and van Ravenzwaay, B. (2007). Ethylbenzene: 4- and 13-week rat oral toxicity. Arch. Toxicol., 81: 361–370.

Mi, Y., Liu, Y., Yuan, D., Zhang, J. and Xiao, Y. (2005). Synthesis of carbon nanotubes via toluene-thermal reduction process at moderate temperature. J. Mater. Sci., 40: 3635–3638.

Middleton, F.M., Rosen, A.A. and Burttschell, R.H. (1958). Taste and odour research tools for water utilities. J. Am. Water Works Assoc., 50: 21.

Miligi, L., Costantini, A.S., Benvenuti, A., Kriebel, D., Bolejack, V., Tumino, R., Ramazzotti, V., Rodella, S., Stagnaro, E., Crosignani, P., Amadori, D., Mirabelli, D., Sommani, L., Belletti, I., Troschel, L., Romeo, L., Miceli, G., Tozzi, G.A., Mendico, I. and Vineis, P. (2006). Occupational exposure to solvents and the risk of lymphomas. Epidemiology, 17: 552–561.

Miltner, R., Speth, T., Endocott, D. and Reionhold, J. (1987). Final internal report on carbon use rate data. Organic Control Branch, Drinking Water Research Division, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH.

Ministère du Développement Durable, de l'Environnement et des Parcs du Québec (2012). Personal communication with Anouka Bolduc.

Mitra, S. and Roy, P. (2011). BTEX: a serious ground-water contaminant. Res. J. Environ. Sci., 5: 394–398.

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

Molhave, L., Bach, B. and Pedersen, O.F. (1986). Human reactions to low concentrations of volatile organic compounds. Environ. Int., 12: 167–175.

Monster, A.C., Kězić, S., van de Gevel, I. and de Wolff, F.A. (1993). Evaluation of biological monitoring parameters for occupational exposure to toluene. Int. Arch. Occup. Environ. Health, 65(Suppl. 1): 159–162.

Morata, T.C., Fiorini, A.C., Fischer, F.M., Colacioppo, S., Wallingford, K.M., Krieg, E.F., Dunn, D.E., Gozzoli, L., Padrão, M.A. and Cesar, C.L.G. (1997). Toluene-induced hearing loss among rotogravure printing workers. Scand. J. Work Environ. Health, 23: 289–298.

Morgan, D.L., Cooper, S.W., Carlock, D.L., Sykora, J.J., Sutton, B., Mattie, D.R. and McDougal, J.N. (1991). Dermal absorption of neat and aqueous volatile organic chemicals in the Fischer 344 rat. Environ. Res., 55: 51–63.

Morozzi, G., De Bartolomeo, A., Fabiani, R., Rosignoli, P. and Lepore, L. (1999). Induction of DNA-damage and apoptosis by volatile organic compounds and by benzene metabolites. Ig. Mod., 112: 1503–1513.

Murata, K., Araki, S., Yokoyama, K., Tanigawa, T., Yamashita, K., Okajima, F., Sakai, T., Matsunaga, C. and Suwa, K. (1993). Cardiac autonomic dysfunction in rotogravure printers exposed to toluene in relation to peripheral nerve conduction. Ind. Health, 31: 79–90.

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

Najm, N.I., Snoeyink, V.L., Lykins, B.W., Jr. and Adams, J.Q. (1991). Using powdered activated carbon: a critical review. J. Am. Water Works Assoc., 83(1): 65–75.

Nakajima, T. and Sato, A. (1979). Enhanced activity of liver drug-metabolizing enzymes for aromatic and chlorinated hydrocarbons following food deprivation. Toxicol. Appl. Pharmacol., 50: 549–556.

Nakajima, T. and Wang, R.-S. (1994). Induction of cytochrome P450 by toluene. Int. J. Biochem., 26: 1333–1340.

Nakajima, T., Wang, R.-S., Elovaara, E., Park, S.S., Gelboin, H.V., Hietanen, E. and Vainio, H. (1991). Monoclonal antibody-directed characterization of cytochrome P-450 isozymes responsible for toluene metabolism in rat liver. Biochem. Pharmacol., 41(3): 395–404.

Nakajima, T., Wang, R.-S., Elovaara, E., Park, S.S., Gelboin, H.V. and Vainio, H. (1992a). A comparative study on the contribution of cytochrome P450 isozymes to metabolism of benzene, toluene and trichloroethylene in rat liver. Biochem. Pharmacol., 43: 251–257.

Nakajima, T., Wang, R.-S., Katakura, Y., Kishi, R., Elovaara, E., Park, S.S., Gelboin, H.V. and Vainio, H. (1992b). Sex-, age- and pregnancy-induced changes in the metabolism of toluene and trichloroethylene in rat liver in relation to the regulation of cytochrome P45011E1 and P45011C11 content. J. Pharmacol. Exp. Ther., 261(3): 869–874.

Nakajima, T., Wang, R.-S., Elovaara, E., Park, S., Gelboin, H. and Vainio, H. (1993). Cytochrome P450-related differences between rats and mice in the metabolism of benzene, toluene and trichloroethylene in liver microsomes. Biochem. Pharmacol., 45(5): 1079–1085.

Nakajima, T., Wang R.-S., Elovaara, E., Gonzalez, F.J., Gelboin, H.V., Raunio, H., Pelkonen, O., Vainio, H. and Aoyama, T. (1997). Toluene metabolism by cDNA-expressed human hepatic cytochrome P-450. Biochem. Pharmacol., 53(3): 271–277.

Nakamura, S., Oda, Y., Shimada, T., Oki, I. and Sugimoto, K. (1987). SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1535/pSK1002: examination with 151 chemicals. Mutat. Res., 192: 239–246.

Nakatsuka, H., Watanabe, T., Takeuchi, Y., Hisanaga, N., Shibata, E., Suzuki, H., Huang, M.Y., Chen, Z., Qu, Q.S. and Ikeda, M. (1992). Absence of blue-yellow color vision loss among workers exposed to toluene or tetrachloroethylene, mostly at levels below occupational exposure limits. Int. Arch. Occup. Environ. Health, 64: 113–117.

Nestman, E.R., Lee, E.G.H. and Matula, T.I. (1980). Mutagenicity of constituents identified in pulp and paper mill effluents using the *Salmonella*/mammalian-microsome assay. Mutat. Res., 79: 203–212.

Neubert, D., Gericke, C., Hanke, B., Beckmann, G., Baltes, M.M., Kühl, K.P., Bochert, G. and Hartmann, J. (2001). Multicenter field trial on possible health effects of toluene. II. Cross-sectional evaluation of acute low-level exposure. Toxicology, 168: 159–183.

New Brunswick Department of Health (2012). Personal communication with Kevin Gould.

Ng, T.P., Ong, S.G., Lama, W.K., Jones, M.G., Cheung, C.K. and Ong, C.N. (1990). Urinary levels of proteins and metabolites in workers exposed to toluene. Int. Arch. Occup. Environ. Health, 62: 43–46.

Nong, A. (2014). Physiologically-based pharmacokinetic modeling of individual components of toluene, ethylbenzene, and xylene exposure in drinking water. Computational Toxicology Laboratory, Exposure and Biomonitoring Division, Environmental Health Science Research Bureau, Health Canada.

Nong, A., McCarver, D.G., Hines, R.N. and Krishnan, K. (2006). Modeling interchild differences in pharmacokinetics on the basis of subject-specific data on physiology and hepatic CYP2E1 levels: a case study with toluene. Toxicol. Appl. Pharmacol., 214(1): 78–87.

Nong, A., Charest-Tardif, G., Tardif, R., Lewis, D.F.V., Sweeney, L.M., Gargas, M.L. and Krishnan, K. (2007). Physiologically based modeling of the inhalation pharmacokinetics of ethylbenzene in B6C3F1 mice. J. Toxicol. Environ. Health A, 70(21): 1838–1848.

Nordling Nilson, L., Karlson, B., Nise, G., Malmberg, B. and Ørbaek, P. (2010). Delayed manifestations of CNS effects in formerly exposed printers—A 20-year follow-up. Neurotoxicol. Teratol., 32: 620–626.

Norppa, H. and Vainio, H. (1983). Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. Mutat. Res., 116: 379–387.

Norström, A., Andersson, B., Levin, J.O., Näslund, P., Wallèn, M. and Löf, A. (1989). Biological monitoring of *o*-xylene after experimental exposure in man: determination of urinary excretion products. Chemosphere, 18: 1513–1523.

Norström, A., Andersson, B., Aringer, L., Levin, J.O., Löf, A., Näslund, P. and Wallèn, M. (1988). Determination of specific mercapturic acids in human urine after experimental exposure to toluene or *o*-xylene. IARC Sci. Publ., 89: 232–234.

NRCan (2011). National Resources Canada. Canadian crude oil, natural gas and petroleum products: Review of 2009 and outlook to 2030. Available at: www.nrcan.gc.ca/sites/www.nrcan.gc.ca.energy/files/pdf/eneene/sources/crubru/revrev/pdf/revrev-09-eng.pdf

NSF/ANSI (2013a). Standard 53: Drinking water treatments units—Health effects. NSF International and American National Standards Institute, Ann Arbor, Michigan.

NSF/ANSI (2013b). Standard 58: Reverse osmosis drinking water treatment systems. NSF International and American National Standards Institute, Ann Arbor, Michigan.

NTP (1986). Toxicology and carcinogenesis studies of xylenes (mixed) (60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene, and 17% ethylbenzene) (CAS No. 133020-7) in F344/N rats and B6C3F1 mice (gavage studies). National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC (National Toxicology Program Technical Report Series No. 327; NIH Publication No. 87-2583).

NTP (1990). Toxicology and carcinogenesis studies of toluene (CAS No. 108-88-3) in F344/N rats and B6C3F1 mice (inhalation studies). National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina (National Toxicology Program Technical Report Series No. 371).

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

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

Nylén, P., Ebendal, T., Eriksdotter-Nilsson, M., Hansson, T., Henschen, A., Johnson, A.C., Kronevi, T., Kvist, U., Sjostrand, N.O., Hoglund, G. and Olson, L. (1989). Testicular atrophy and loss of nerve growth factor-immunoreactive germ cell line in rats exposed to *n*-hexane and a protective effect of simultaneous exposure to toluene or xylene. Arch. Toxicol., 63: 296–307.

OEHHA (1997a). Public health goal for ethylbenzene in drinking water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California (OEHHA.1-27). Available at: http://oehha.ca.gov/water/phg/pdf/etbx2_c.pdf

OEHHA (1997b). Public health goal for xylene in drinking water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California (OEHHA.1-26). Available at: http://oehha.ca.gov/water/phg/pdf/xylen_c.pdf

OEHHA (1999). Public health goal for toluene in drinking water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California (OEHHA.1-37). Available at: http://oehha.ca.gov/water/phg/pdf/tolu_f.pdf

Ogata, M. (1984). Estimation of solvent concentrations in ambient air from urinary metabolite levels of workers exposed to solvents. Ind. Health, 22: 319–324.

Ogata, M., Tomokuni, K. and Takatsuka, Y. (1970). Urinary excretion of hippuric acid and *m*- or *p*-methylhippuric acid in the urine of persons exposed to vapours of toluene and *m*- or *p*-xylene as a test of exposure. Br. J. Ind. Med., 27: 43–50.

Ogata, M., Yamasaki, Y., Meguro, T., Sugihara, R. and Shimada, Y. (1979). Quantitation of urinary *o*-xylene metabolites in rats and human beings by high-performance liquid chromatography. Ind. Health, 17: 123–125.

Ohlen, K., Chang, Y., Hegemann, W., Yin, C. and Lee, S. (2005). Enhanced degradation of chlorinated ethylenes in groundwater from a paint contaminated site by two-stage fluidized-bed reactor. Chemosphere, 58: 373–377.

Olson, B.A., Gamberale, F. and Iregren, A. (1985). Coexposure to toluene and *p*-xylene in man: central nervous functions. Br. J. Ind. Med., 42: 117–122.

Olsson, H. and Brandt, L. (1980). Occupational exposure to organic solvents and Hodgkin's disease in man. A case-referent study. Scand. J. Work Environ. Health, 6: 302–305.

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

Ontario Ministry of Environment and Energy (2000). Air quality in Ontario, 2000 report., Toronto, Ontario.

Ono, A., Sekita, K., Ogawa, Y., Hirose, A., Suzuki, S., Saito, M., Naito, K., Kaneko, T., Furuya, T., Kawashima, K., Yasuhara, K., Matsumoto, K., Tanaka, S., Inoue, T. and Kurokawa, Y. (1996). Reproductive and developmental toxicity studies of toluene II. Effects of inhalation exposure on fertility in rats. J. Environ. Pathol. Toxicol. Oncol., 15: 9–20.

Ontario Ministry of the Environment (2012). Personal communication with Satish Deshpande.

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

Paterson, S.C. and Sarvesvaran, R. (1983). Plastic bag death: a toluene fatality. Med. Sci. Law, 23: 64–66.

Pearson, M.A., Hoyme, H.E., Seaver, L.H. and Rimsza, M.E. (1994). Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. Pediatrics, 93: 211–215.

Pellizzari, E.D., Hartwell, T.D., Harris, B.S., 3rd, Waddell, R.D., Whitaker, D.A. and Erickson, M.D. (1982). Purgeable organic compounds in mother's milk. Bull. Environ. Contam. Toxicol., 28: 322–328.

Pellizzari, E.D., Wallace, L.A. and Gordon, S.M. (1992). Elimination kinetics of volatile organics in humans using breath measurements. J. Expo. Anal. Environ. Epidemiol., 2: 341–355.

Peng, M., Vane, L.M. and Liu, S.X. (2003). Recent advances in VOCs removal from water by pervaporation. J. Hazard. Mater., 98(1): 69–90.

Pierce, C.H., Dills, R.L., Morgan, M.S., Nothstein, G.L., Shen, D.D. and Kalman, D.A. (1996a). Interindividual differences in $^{2}H_{8}$-toluene toxicokinetics assessed by semi-empirical physiologically based model. Toxicol. Appl. Pharmacol., 139(1): 49–61.

Plappert, U., Barthel, E. and Seidel, H.J. (1994). Reduction of benzene toxicity by toluene. Environ. Mol. Mutagen., 24: 283–292.

Pryor, G.T. (1991). A toluene-induced motor syndrome in rats resembling that seen in some human solvent abusers. Neurotoxicol. Teratol., 13: 387–400.

Pyykkö, K., Tähti, H. and Vapaatalo, H. (1977). Toluene concentrations in various tissues of rats after inhalation and oral administration. Arch. Toxicol., 38: 169–176.

Rahumathulla, R., Cober, N. and Boyce, J. (2010). Benzene in Canadian gasoline: Effect of the *Benzene in Gasoline Regulations*. 2008 Annual Report. Environment Canada Cat. No. En11-5/2008E-PDF. Available at: http://www.ec.gc.ca/Publications/DB03415D-9754-4D44-835C-86255D9E76A3%5CBenzeneInCanadianGasoline2008.pdf

Ramsey, J.C. and Andersen, M.E. (1984). A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicol. Appl. Pharmacol., 73: 159–175.

Rea, T.M., Nash, J.F. and Zabik, J.E. (1984). Effects of toluene inhalation on brain biogenic amines in the rat. Toxicology, 31: 143–150.

Richer, C.L., Chakrabarti, L., Senecal-Quevillon, M., Duhr, L.A., Zhang, X.X. and Tardif, T. (1993). Cytogenetic effects of low-level exposure to toluene, xylene, and their mixture on human blood lymphocytes. Int. Arch. Occup. Environ. Health, 64: 581–585.

Riihimäki, V. (1979). Percutaneous absorption of *m*-xylene from a mixture of *m*-xylene and isobutyl alcohol in man. Scand. J. Work Environ. Health, 5: 143–150.

Riihimäki, V. and Pfäffli, P. (1978). Percutaneous absorption of solvent vapors in man. Scand. J. Work Environ. Health, 4: 73–85.

Riihimäki, V. and Savolainen, K. (1980). Human exposure to *m*-xylene. Kinetics and acute effects on the central nervous system. Ann. Occup. Hyg., 23: 411–422.

Riihimäki, V., Pfäffli, P., Savolainen, K. and Pekari, K. (1979). Kinetics of *m*-xylene in man: general features of absorption, distribution, biotransformation and excretion in repetitive inhalation exposure. Scand. J. Work Environ. Health, 5: 217–231.

Robeck, G.G. and Love, O.T., Jr. (1983). Removal of volatile organic contaminants from groundwater. Municipal Environmental Research Laboratory, Drinking Water Research Division, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, Ohio (EPA-600/D-83-011).

Roberts, L.G., Nicolich, M.J. and Schreiner, C.A. (2007). Developmental and reproductive toxicity evaluation of toluene vapor in the rat. II. Developmental toxicity. Reprod. Toxicol., 23: 521–531.

Römer, K., Federsel, R. and Freundt, K. (1986). Rise of inhaled toluene, ethyl benzene, *m*-xylene, or mesitylene in rat blood after treatment with ethanol. Bull. Environ. Contam. Toxicol., 37: 874–876.

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

Saillenfait, A.M., Gallissot, F., Sabaté, J.P., Bourges-Abella, N., Cadot, R., Morel, G. and Lambert, A.M. (2006). Developmental toxicity of combined ethylbenzene and methylethylketone administered by inhalation to rats. Food Chem. Toxicol., 44: 1287–1298.

Saillenfait, A.-M, Gallissot, F., Sabaté, J.P., Bourges-Abella, N. and Muller, S. (2007). Developmental toxic effects of ethylbenzene or toluene alone and in combination with butyl acetate in rats after inhalation exposure. J. Appl. Toxicol., 27: 32–42.

Sallmén, M., Neto, M. and Mayan, O.N. (2008). Reduced fertility among shoe manufacturing workers. Occup. Environ. Med., 65: 518–524.

Sams, C., Loizou, G.D., Cocker, J. and Lennard, M.S. (2004). Metabolism of ethylbenzene by human liver microsomes and recombinant human cytochrome P450s (CYP). Toxicol. Lett., 147(3): 253–260.

Sandmeyer, E. (1981). Aromatic hydrocarbons. In: Patty's industrial hygiene and toxicology, Vol. 2B, G.D. Clayton and F.E. Clayton, Eds. pp. 3291–3300.

Saskatchewan Ministry of Environment (2012). Personal communication with Sam Ferris.

Sato, A. and Nakajima, T. (1978). Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichlorethylene and toluene. Br. J. Ind. Med., 35: 43–49.

Sato A., Nakajima T., Fujiwara Y. and Hirosawa, K. (1974). Pharmacokinetics of benzene and toluene. Int. Arch. Arbeitsmed., 33: 169–182.

Savolainen, K. and Pfäffli, P. (1980). Dose-dependent neurochemical changes during short-term inhalation exposure to *m*-xylene. Arch. Toxicol., 45: 117–122.

Savolainen, K. and Seppalainen, A.M. (1979). Biochemical and physiological effects of organic solvents on rat axon membranes isolated by a new technique. Neurotoxicology, 1: 467–477.

Savolainen, K., Riihimäki, V. and Linnoila, M. (1979). Effects of short-term xylene exposure on psychophysiological functions in man. Int. Arch. Occup. Environ. Health, 44: 201–211.

Savolainen, K., Riihimäki, V., Seppalainen, A.M. and Linnoila, M. (1980). Effects of short-term *m*-xylene exposure and physical exercise on the central nervous system. Int. Arch. Occup. Environ. Health, 45: 105–121.

Savolainen, K., Riihimäki, V., Luukkonen, R. and Muona, O. (1985). Changes in the sense of balance correlate with concentrations of *m*-xylene in venous blood. Br. J. Ind. Med., 42: 765–769.

SCC (2014). Directory of accredited product and service certification bodies. Standards Council of Canada, Ottawa, Ontario. Available at: www.scc.ca/en/programs-services/product-certification/directory-of-accredited-clients

Schäper, M., Demes, P., Zupanic, M., Blaszkewicz, M. and Seeber, A. (2003). Occupational toluene exposure and auditory function: results from a follow-up study. Ann. Occup. Hyg., 47: 493–502.

Sedivec, V. and Flek, J. (1976). Exposure test for xylenes. Int. Arch. Occup. Environ. Health, 37: 219–232.

Seeber, A., Schäper, M., Zupanic, M., Blaszkewicz, M., Demes, P., Kiesswetter, E. and van Thriel, C. (2004). Toluene exposure below 50 ppm and cognitive function: a follow-up study with four repeated measurements in rotogravure printing plants. Int. Arch. Occup. Environ. Health, 77: 1–9.

Seeber, A., Demes, P., Kiesswetter, E., Schäper, M., van Thriel, C. and Zupanic, M. (2005). Changes of neurobehavioral and sensory functions due to toluene exposure below 50 ppm? Environ. Toxicol. Pharmacol., 19: 635–643.

Seidel, S.D., Schisler, M.R. and Kleinert, K.M. (2006). Evaluation of ethylbenzene in the mouse lymphoma (L5178TK+/−) forward mutation assay. Toxicology & Environmental Research and Consulting, The Dow Chemical Company (Study ID: 051157).

Seidenberg, J.M., Anderson, D.G. and Becker, R.A. (1986). Validation of an *in vivo* developmental toxicity screen in the mouse. Teratog. Carcinog. Mutag., 6: 361–374.

Seiji, K., Inoue, O., Nakatsuka, H., Kasahara, M., Watanabe, T., Lee, B.K., Lee, S.H., Lee, K.M., Cho, K.S. and Ikeda, M. (1987). No biologically significant changes in liver function after occupational exposure to toluene at over-OEL levels. Ind. Health, 25: 163–168.

Senczuk, W. and Orlowski, J. (1978). Absorption of *m*-xylene vapours through the respiratory tract and excretion. Br. J. Ind. Med., 35: 50–55.

Shatkin, J.A. and Brown, H.S. (1991). Pharmacokinetics of the dermal route of exposure to volatile organic chemicals in water: a computer simulation model. Environ. Res., 56(1): 90–108.

Shimizu, H., Suzuki, Y. and Takemura, N. (1985). The results of microbial mutation test for forty-three industrial chemicals. Jpn. J. Ind. Health, 27: 400–419.

Siddiqui, M., and Amy, G. (1993). Factors affecting the DBP formation during ozone-bromide reaction. J. Am. Water Works Assoc. 85 (1): 63-72

Slooff, W. and Blokzijl, P.J. (eds.) (1988). Integrated criteria document toluene. RIVM Research for Man and Environment, National Institute for Public Health and the Environmental, Bilthoven, the Netherlands (Report No. 758473010).

Smillie, R.D., Sakuma, T. and Duholke, W.K. (1978). Low molecular weight aromatic hydrocarbons in drinking water. J. Environ. Sci. Health A Environ. Sci. Eng., A13: 187–197.

Smith, J.M., Smithies, R.H. and Williams, R.T. (1954). The metabolism of alkylbenzenes. Stereochemical aspects of the biological hydroxylation of ethylbenzene to methylphenylcarbinol, Biochem J., 6(2): 320–324.

Smith, K.N. (1983). Determination of the reproductive effects in mice of nine selected chemicals. Bioassay Systems Corporation (NIOSH Contract No. 219-81-6011; BSC Project No. 10867).

Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C. and Striegel, J.A. (1962). Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J., 23: 95–107.

Snoeyink, V.L. (1990). Chapter 13. Adsorption of organic compounds. In: Water quality and treatment. 4th edition. American Water Works Association, Denver, Colorado.

Soulage, C., Perrin, D., Berenguer, P. and Pequignot, J.M. (2004). Sub-chronic exposure to toluene at 40 ppm alters the monoamine biosynthesis rate in discrete brain areas. Toxicology, 196: 21–30.

Speth, T.F. and Miltner, R.J. (1990). Technical note: adsorption capacity of GAC for synthetic organics. J. Am. Water Works Assoc., 82(2): 72–75.

Stengel, B., Cénée, S., Limasset, J.C., Diebold, F., Michard, D., Druet, P. and Hémon, D. (1998). Immunologic and renal markers among photogravure printers exposed to toluene. Scand. J. Work Environ. Health, 24: 276–284.

Stenzel, M.H. and Gupta, S.G. (1985). Treatment of contaminated groundwater using granular activated carbon and air stripping. J. Air Pollut. Control Assoc., 35: 1304–1309.

Sugihara, R. and Ogata, M. (1978). Quantitation of urinary *m*- and *p*-methylhippuric acids as indices of *m*- and *p*-xylene exposure. Int. Arch. Occup. Environ. Health, 41: 281–286.

Susten, A.S., Niemeier, R.W. and Simon, S.D. (1990). *In vivo* percutaneous absorption studies of volatile organic solvents in hairless mice. II. Toluene, ethylbenzene and aniline. J. Appl. Toxicol., 10(3): 217–225.

Svensson, B.G., Nise, G., Englander, V., Attewell, R., Skerfving, S. and Moller, T. (1990). Deaths and tumours among rotogravure printers exposed to toluene. Br. J. Ind. Med., 47: 372–379.

Swedish Chemicals Agency (2010). Xylene (isomer). Swedish Chemicals Agency (KemI), Sundbyberg, Sweden. Available at: http://apps.kemi.se/flodessok/floden/kemamne_eng/xylen_eng.htm

Takeichi, S., Yamada, T. and Shikata, I. (1986). Acute toluene poisoning during painting. Forensic Sci. Int., 32: 109–115.

Tanaka, K., Maeda, T., Kobayashi, T., Tanaka, M. and Fukushima, T. (2003). A survey of urinary hippuric acid and subjective symptoms among occupational low toluene exposed workers. Fukushima J. Med. Sci., 49: 129–139.

Tap, Ö., Solmaz, S., Polat, S., Mete, U.Ö., Özbilgin, M.K. and Kaya, M. (1996). The effect of toluene on the rat ovary: an ultrastructural study. J. Submicrosc. Cytol. Pathol., 28: 553–558.

Tardif, R., Lapare, S., Plaa, G.L. and Brodeur, J. (1991). Effect of simultaneous exposure to toluene and xylene on their respective biological exposure indices in humans. Int. Arch. Occup. Environ. Health, 63: 279–284.

Tardif, R., Plaa, G.L. and Brodeur, J. (1992). Influence of various mixtures of inhaled toluene and xylene on the biological monitoring of exposure to these solvents in rats. Can. J. Physiol. Pharmacol., 70: 385–395.

Tardif, R., Laparé, S., Krishnan, K. and Brodeur, J. (1993). Physiologically-based modeling of the toxicokinetic interaction between toluene and *m*-xylene in the rat. Toxicol. Appl. Pharmacol., 120: 266–273.

Tardif, R., Lapar, S., Charest-Tardif, G., Brodeur, J. and Krishnan, K. (1995). Physiologically-based pharmacokinetic modeling of a mixture of toluene and xylene in humans. Risk Anal., 15(3): 335–342.

Tardif, R., Charest-Tardif, G., Brodeur, J. and Krishnan, K. (1997). Physiologically based pharmacokinetic modeling of a ternary mixture of alkyl benzenes in rats and humans. Toxicol. Appl. Pharmacol., 144: 120–134.

Tardif, R., Truchon, G. and Brodeur, J. (1998). Comparison of hippuric acid and *o*-cresol in urine and unchanged toluene in alveolar air for the biological monitoring of exposure to toluene in human volunteers. Appl. Occup. Environ. Hyg., 13: 127–132.

Taskinen, H., Lindbohm, M.L. and Hemminki, K. (1986). Spontaneous abortions among women working in the pharmaceutical industry. Br. J. Ind. Med., 43: 199–205.

Taskinen, H., Kyyronen, P., Hemminki, K., Hoikkala, M., Lajunen, K. and Lindbohm, M.L. (1994). Laboratory work and pregnancy outcome. J. Occup. Med., 36: 311–319.

Tassaneeyakul, W., Birkett, D.J., Edwards, J.W., Veronese, M.E., Tassaneeyakul, W., Tukey, R.H. and Miners, J.O. (1996). Human cytochrome P450 isoform specificity in the regioselective metabolism of toluene and *o*-, *m*-, and *p*-xylene. J. Pharmacol. Exp. Ther., 276: 101–108.

Thiel, R. and Chahoud, I. (1997). Postnatal development and behaviour of Wistar rats after prenatal toluene exposure. Arch. Toxicol., 71: 258–265.

Thomas, R.G. (1982). Volatilization from water. In: Lyman, W., Reehl, W.F. and Rosenblatt, D.H. (eds.). Handbook of chemical property estimation methods: environmental behavior of organic compounds. McGraw-Hill, New York, New York.

Thrall, K.D. and Woodstock, A.D. (2002). Evaluation of the dermal absorption of aqueous toluene in F344 rats using real-time breath analysis and physiologically based pharmacokinetic modeling. J. Toxicol. Environ. Health A, 65(24): 2087–2100.

Thrall, K.D. and Woodstock, A.D. (2003). Evaluation of the dermal bioavailability of aqueous xylene in F344 rats and human volunteers. J. Toxicol. Environ. Health A, 66: 1267–1281.

Thrall, K.D., Poet, T.S., Corley, R.A., Tanojo, H., Edwards, J.A., Weitz, K.K., Hui, X., Maibach, H.I. and Wester, R.C. (2000). A real-time in-vivo method for studying the percutaneous absorption of volatile chemicals. Int. J. Occup. Environ. Health, 6(2): 96–103.

Thrall, K.D., Gies, R.A., Muniz, J., Woodstock, A.D. and Higgins, G. (2002). Route-of-entry and brain tissue partition coefficients for common Superfund contaminants. J. Toxicol. Environ. Health A, 65(24): 2075–2086.

Tokunaga, I., Gotohda, T., Ishigami, A., Kitamura, O. and Kubo, S. (2003). Toluene inhalation induced 8-hydroxy-2′-deoxyguanosine formation as the peroxidative degeneration in rat organs. Leg. Med., 5: 34–41.

Topudurti, K., Wojciechowski, M., Anagnostopoulos, S. and Eilers, R. (1998). Field evaluation of a photocatalytic oxidation technology. Water Sci. Technol., 38(7): 117–125.

Truchon, G., Tardif, R. and Brodeur, J. (1999). *o*-Cresol: a good indicator of exposure to low levels of toluene. Appl. Occup. Environ. Hyg., 14(10): 677–681.

Turkall, R.M., Skowronski, G.A. and Abdel-Rahman, M.S. (1991). Differences in kinetics of pure and soil-adsorbed toluene in orally exposed male rats. Arch. Environ. Contam. Toxicol., 20: 155–160.

Turkall, R.M., Skowronski, G.A., Kadry, A.R. and Abdel-Rahman, M.S. (1992). Sex differences in the bioavailability of soil-adsorbed *meta*-xylene in orally exposed rats. Toxicol. Lett., 63: 57–67.

Uchida, Y., Nakatsuka, H., Ukai, H., Watanabe, T., Liu, Y.T., Huang, M.Y., Wang, Y.L., Zhu, F.Z., Yin, H. and Ikeda, M. (1993). Symptoms and signs in workers exposed predominantly to xylenes. Int. Arch. Occup. Environ. Health, 64: 597–605.

Ukai, H., Watanabe, T., Nakatsuka, H., Satoh, T., Liu, S.J., Qiao, X., Yin, H., Jin, C., Li, G.L. and Ikeda, M. (1993). Dose-dependent increase in subjective symptoms among toluene-exposed workers. Environ. Res., 60: 274–289.

Ungváry, G. (1985). The possible contribution of industrial chemicals (organic solvents) to the incidence of congenital defects caused by teratogenic drugs and consumer goods—an experimental study. Prog. Clin. Biol. Res., 163 B, 295–300.

Ungváry, G. (1986). Solvent effects on reproduction: experimental toxicity. Prog. Clin. Biol. Res., 220: 169–177.

Uragami, T., Yamada, H. and Miyata, T. (2001). Removal of dilute volatile organic compounds in water through graft copolymer membranes consisting of poly (alkylmethacrylate) and poly (dimethylsiloxane) by pervaporation and their membrane morphology. J. Memb. Sci., 187(1): 255–269.

U.S. EPA (1982). Aquatic fate process data for organic priority pollutants. U.S. Environmental Protection Agency, Washington, DC.

U.S. EPA (1987). Drinking water criteria document on xylenes. Final draft. Office of Drinking Water, U.S. Environmental Protection Agency, Washington, DC (ECAO-CIN-416).

U.S. EPA (1990). Technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Criteria Standards Division, Office of Drinking Water, U.S. Environmental Protection Agency, Washington, DC (PB91-143438).

U.S. EPA (1991a). Technologies for upgrading existing or designing new drinking water treatment facilities. Center for Environmental Research Information, Office of Drinking Water, U.S. Environmental Protection Agency, Cincinnati, Ohio.

U.S. EPA (1991b). National Primary Drinking Water Regulations; synthetic organic chemicals and inorganic chemicals; final rule. Fed. Regist., 56(20): 3526.

U.S. EPA (1992). Dermal exposure assessment: principles and applications. Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC (EPA/600/8-91/011B).

U.S. EPA (1995a). National primary drinking water regulations: Toluene. Environmental Protection Agency, Office of Water (EPA 811-F-95-004 p-T).

U.S. EPA (1995b). National primary drinking water regulations: Ethylbenzene. Environmental Protection Agency, Office of Water (EPA 811-F-95-004 m-T).

U.S. EPA (1995c). National primary drinking water regulations: Xylenes (total). Environmental Protection Agency, Office of Water (EPA 811-F-95-004 m-T).

U.S. EPA (1995d). Methods for determinations of organic compounds in drinking water. Supplement III. Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC (EPA 600-R-95-131).

U.S. EPA (1998). Small system compliance technology list for the non-microbial contaminants regulated before 1996. Office of Water, U.S. Environmental Protection Agency, Washington, DC (EPA 815-R-98-002).

U.S. EPA (2005a). Toxicological review of toluene. In support of summary information on the Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, DC (EPA/635/R-05/004). Available at: www.epa.gov/iris/toxreviews/0118tr.pdf

U.S. EPA (2005b). Toluene (CASRN 108-88-3). Integrated Risk Information System, U.S. Environmental Protection Agency, Washington, DC. Available at: www.epa.gov/iris/subst/0118.htm

U.S. EPA (2009). Method 524.3 Version 1.0. Measurement of purgeable organic compounds in water by capillary column gas chromatography/mass spectrometry. Technical Support Center, Office of Groundwater and Drinking Water, U.S. Environmental Protection Agency, Cincinnati, Ohio (EPA 815-B-09-009).

U.S. EPA (2010). Benchmark dose software (BMDS) version 2.1.1. U.S. Environmental Protection Agency, Washington, DC. Available at: www.epa.gov/ncea/bmds/about.html

U.S. EPA (2011). Analytical method approved for drinking water compliance monitoring of organic contaminants. U.S. Environmental Protection Agency, Washington, DC. Available at: http://water.epa.gov/scitech/drinkingwater/labcert/upload/methods_organic.pdf

U.S. FDA (2008). Total Diet Study, market baskets 1991-3 through 2003-4. U.S. Food and Drug Administration. Available at: www.fda.gov/downloads/Food/FoodScienceResearch/TotalDietStudy/UCM184303.pdf

Vaalavirta, L. and Tahti, H. (1995). Astrocyte membrane Na^+,K^+-ATPase and Mg^{2+}-ATPase as targets of organic solvent impact. Life Sci., 57: 2223–2230.

Vallero, D.A. (2004). Environmental contaminants: assessment and control. Elsevier Inc., London, United Kingdom.

Van Asperen, J., Rijcken, W.R. and Lammers, J.H. (2003). Application of physiologically based toxicokinetic modelling to study the impact of the exposure scenario on the toxicokinetics and the behavioural effects of toluene in rats. Toxicol. Lett., 138(1–2): 51–62.

Van Doorn, R., Bos, R.P., Brouns, R.M., Leijdekkers, C.M. and Henderson, P.T. (1980). Effect of toluene and xylenes on liver glutathione and their urinary excretion as mercapturic acids in the rat. Arch. Toxicol., 43(4): 293–304.

VanGemert, L.J. and Nettenbrijer, A.H. (1977). Compilation of odour threshold values in air and water. Zeist, Netherlands, National Institute for for Water Supply/Central Institute for Nutrition and Food Research TNO.

VCCEP (2006). Tier 1 pilot submission for ethylbenzene (CAS No. 100-41-4). Voluntary Children's Chemical Evaluation Program, U.S. Environmental Protection Agency, Washington, DC. Available at: www.tera.org/Peer/VCCEP/Ethylbenzene/VCCEP%20EB%20main%20FINAL%20121206.pdf

Verschueren, K. (1983). Handbook of environmental data on organic chemicals. Van Nostrand Reinhold Co., New York, New York.

Vieira, I., Sonnier, M. and Cresteil, T. (1996). Developmental expression of CYP2E1 in the human liver: hypermethylation control of gene expression during the neonatal period. Eur. J. Biochem., 238: 476–483.

Voice, T.C., Pak, D., Zhzo, X. and Hickey. R.F. (1992). Biological activated carbon in fluidized bed reactors for the treatment of groundwater contaminated with volatile aromatic hydrocarbons. Water Research, 26(10): 1389-1401.

Von Burg, R. (1993). Toluene. J. Appl. Toxicol., 13: 441–446.

Von Euler, G., Ogren, S.O., Eneroth, P., Fuxe, K. and Gustafsson, J.A. (1994). Persistent effects of 80 ppm toluene on dopamine-regulated locomotor activity and prolactin secretion in the male rat. Neurotoxicology, 15: 621–624.

Vrca, A., Božičević, D., Karačić, V., Fuchs, R., Prpić-Majić, D. and Malinar, M. (1995). Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. Arch. Toxicol., 69: 337–340.

Vrca, A., Karačić, V., Božičević, D., Božikov, V. and Malinar, M. (1996). Brainstem auditory evoked potentials in individuals exposed to long-term low concentrations of toluene. Am. J. Ind. Med., 30: 62–66.

Vrca, A., Božičević, D., Božikov, V., Fuchs, R. and Malinar, M. (1997). Brain stem evoked potentials and visual evoked potentials in relation to the length of occupational exposure to low levels of toluene. Acta Med. Croatica, 51: 215–219.

Walker, J.T., Bloom, T.F., Stern, F.B., Okun, A.H., Fingerhut, M.A. and Halperin, W.E. (1993). Mortality of workers employed in shoe manufacturing. Scand. J. Work Environ. Health, 19: 89–95.

Wallen, M., Naslund, P.H. and Nordqvist, M.B. (1984). The effects of ethanol on the kinetics of toluene in man. Toxicol. Appl. Pharmacol., 76: 414–419.

Wang, J.D. and Chen, J.D. (1993). Acute and chronic neurological symptoms among paint workers exposed to mixtures of organic solvents. Environ. Res., 61: 107–116.

Wang, R.S. and Nakajima, T. (1992). Effects of ethanol and phenobarbital treatments on the pharmacokinetics of toluene in rats. Br. J. Ind. Med., 49: 104–112.

Wang, Y.R., Yang, D.Y., Zhang, M., Wang, Q., Liu, J., Yang, X.Y. and Jiang, S.Q. (2010). [Effects of ethylbenzene on oxidative damage, ultrastructure and expressions of apoptosis-related genes in rat brain tissues.] Chin. J. Ind. Hyg. Occup. Dis., 28: 810–814 (in Chinese).

Washington, W.J., Murthy, R.C. and Doye, A. (1983). Induction of morphologically abnormal sperm in rats exposed to *o*-xylene. Arch. Androl., 11: 233–237.

Welch, V.A., Fallon, K.J. and Gelbke, H.-P. (2005). Ethylbenzene. In: Ullmann's encyclopedia of industrial chemistry. VCH Verlag GmbH & Co., Weinheim, Germany.

Wen, C.P., Tsai, S.P. and Weiss, N.S. (1985). Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. J. Natl. Cancer Inst., 74: 11–18.

WHO (2003a). Ethylbenzene in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization, Geneva, Switzerland, 10 pp. (WHO/SDE/WSH/03.04/26). Available at: www.who.int/water_sanitation_health/dwq/chemicals/ethylbenzene.pdf

WHO (2003b). Xylenes in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization, Geneva, Switzerland, 10 pp. (WHO/SDE/WSH/03.04/25). Available at: www.who.int/water_sanitation_health/dwq/chemicals/xylenes.pdf

WHO (2004). Toluene in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization, Geneva, Switzerland, 17 pp. (WHO/SDE/WSH/03.04/116). Available at: www.who.int/water_sanitation_health/dwq/chemicals/toluene.pdf

WHO (2011). Guidelines for drinking-water quality, 4th edition. World Health Organization, Geneva, Switzerland. Available at: http://whqlibdoc.who.int/publications/2011/9789241548151_eng.pdf

Wigaeus Hjelm, E., Naslund, P.H. and Wallen, M. (1988). Influence of cigarette smoking on the toxicokinetics of toluene in humans. J. Toxicol. Environ. Health, 25: 155–163.

Wilson, J.T., Miller, G.D., Ghiorse, W.C. and Leach, F.R. (1986). Relationship between the ATP content of subsurface material and the rate of biodegradation of alkylbenzenes and chlorobenzene. J. Contam. Hydrol., 1: 163–170.

Wolf, G.W. (1988a). Subchronic toxicity study in rats with *m*-xylene. Report by Hazleton Laboratories America, Inc. Sponsored by Dynamac Corporation, Rockville, Maryland (Project No. 2399-108). As cited in: ATSDR (2007).

Wolf, G.W. (1988b). Subchronic toxicity study in rats with *p*-xylene. Report by Hazleton Laboratories America, Inc. Sponsored by Dynamac Corporation, Rockville, Maryland (Project No. 2399-110). As cited in: ATSDR (2007).

Wolf, M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L. and Oyes, F. (1956). Toxicological studies of certain alkylated benzenes and benzene; experiments on laboratory animals. AMA Arch. Ind. Health, 14: 387–398.

Wollny, H. (2000). Cell mutation assay at the thymidine kinase locus (TK+/−) in mouse lymphoma L5178Y cells (soft agar method) with ethylbenzene. RCC Cytotest Cell Research GmbH (RCC-CCR Project No. 635300).

Xu, X., Freeman, N.C., Dailey, A.B., Ilacqua, V.A., Kearney, G.D. and Talbott, E.O. (2009). Association between exposure to alkylbenzenes and cardiovascular disease among National Health and Nutrition Examination Survey (NHANES) participants. Int. J. Occup. Environ. Health, 15: 385–391.

Yoon, H.I., Hong, Y.C., Cho, S.H., Kim, H., Kim, Y.H., Sohn, J.R., Kwon, M., Park, S.H., Cho, M.H. and Cheong, H.K. (2010). Exposure to volatile organic compounds and loss of pulmonary function in the elderly. Eur. Respir. J., 36: 1270–1276.

Yue, Z., Mangun, C., Economy, J., Kemme, P., Cropek, D. and Maloney, S. (2001). Removal of chemical contaminants from water to below USEPA MCL using fiber glass supported activated carbon filters. Environ. Sci. Technol., 35(13): 2844–2848.

Zavalic, M., Mandic, Z., Turk, R., Bogadi-Sare, A., Plavec, D., Gomzi, M. and Skender, L.J. (1998). Assessment of colour vision impairment in male workers exposed to toluene generally above occupational exposure limits. Occup. Med., 48: 175–180.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T. and Mortelmans, K. (1992). *Salmonella* mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen., 19: 2–141.

Zein, M., Suidam, M. and Venosa, A. (2006). Bioremediation of groundwater contaminated with gasoline hydrocarbons with oxygen using a membrane-based reactor. Environ. Sci. Technol., 40: 1997–2003.

Zhu, J., Newhook, R., Marro, L. and Chan, C.C. (2005). Selected volatile organic compounds in residential air in the city of Ottawa, Canada. Environ. Sci. Technol., 39: 3964–3971.

Zogorski, J.S., Carter, J.M., Ivahnenko, T., Lapham, W.W., Moran, M.J., Rowe, B.L., Squillace, P.J. and Toccalino, P.L. (2006). The quality of our nation's waters: volatile organic compounds in the nation's ground water and drinking-water supply wells. U.S. Geological Survey, U.S. Department of the Interior, Reston, VA (Circular 1292).

Zupanic, M., Demes, P. and Seeber, A. (2002). Psychomotor performance and subjective symptoms at low level toluene exposure. Occup. Environ. Med., 59: 263–268.

Appendix A: List of acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
ANSI	American National Standards Institute
AOP	advanced oxidation process
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
BMD	benchmark dose
$BMDL_{10}$	lower 95% confidence limit of the benchmark dose corresponding to a 10% response
BTEX	benzene, toluene, ethylbenzene and xylenes
BTX	benzene, toluene and xylenes
CAS	Chemical Abstracts Service
CI	confidence interval
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EBCT	empty bed contact time
EPA	Environmental Protection Agency (U.S.)
FBR	fluidized bed reactor
GAC	granular activated carbon
GC	gas chromatography
gpm	gallons per minute
HBV	health-based value
IARC	International Agency for Research on Cancer
K_{ow}	*n*-octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
L-eq	litre-equivalent
LOAEL	lowest-observed-adverse-effect level
MAC	maximum acceptable concentration
MCL	maximum contaminant level (U.S.)
MDL	method detection limit
MS	mass spectrometer
NOAEL	no-observed-adverse-effect level
NOM	natural organic matter
NSF	NSF International
OR	odds ratio
PAC	powdered activated carbon
PBPK	physiologically based pharmacokinetic
PHG	public health goal (U.S.)
ppm	parts per million
PQL	practical quantification level
PTA	packed tower aeration
SCC	Standards Council of Canada
SFFR	submerged fixed film reactor
SIR	standardized incidence ratio
SMR	standardized mortality ratio
TDI	tolerable daily intake

TEX	toluene, ethylbenzene and xylenes
UV	ultraviolet
VOC	volatile organic compound
WHO	World Health Organization