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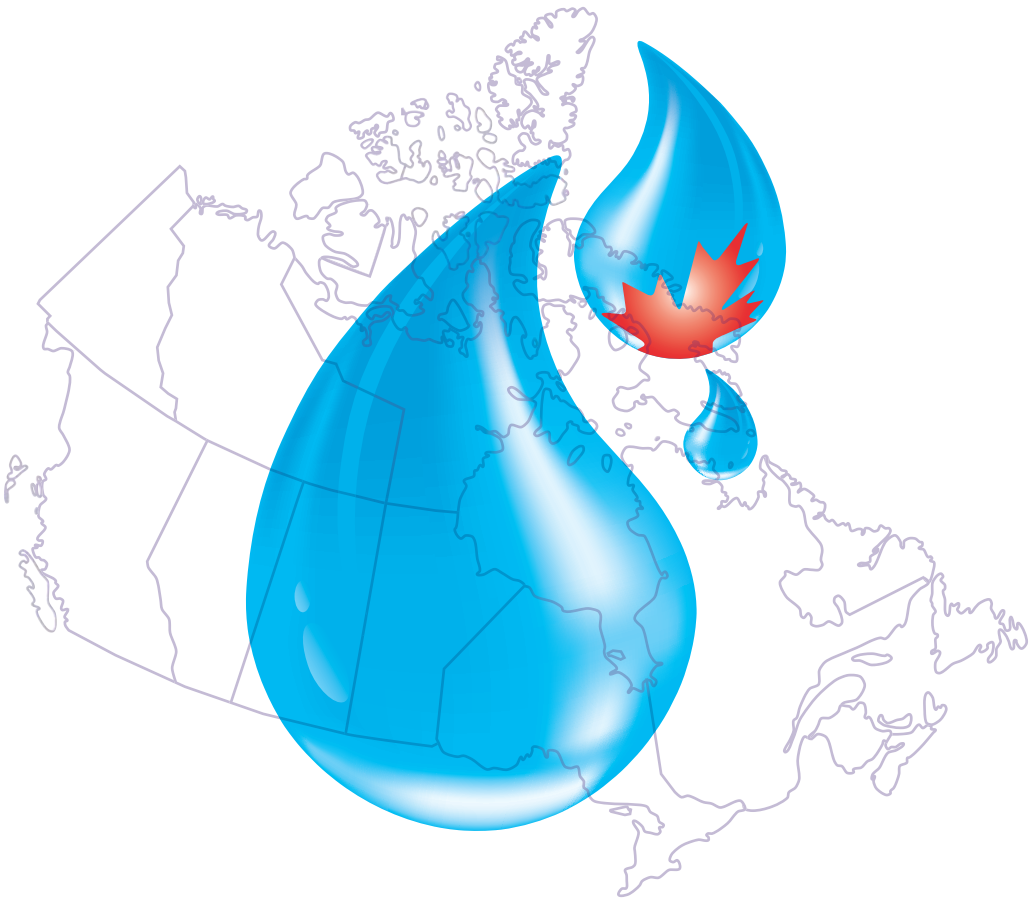
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Benzene



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Publications
Health Canada
Ottawa, Ontario K1A 0K9
Tel.: 613-954-5995
Fax: 613-941-5366
E-mail: info@hc-sc.gc.ca

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Guidelines for Canadian Drinking Water Quality:

Guideline Technical Document

Benzene

Prepared by the
Federal-Provincial-Territorial Committee on Drinking Water
of the
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Any questions or comments on this document may be directed to:

Water, Air and Climate Change 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

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Benzene

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for benzene in drinking water is 0.005 mg/L (5 µg/L).

2.0 Executive summary

Although benzene is naturally occurring at low concentrations, its presence in the environment is mostly related to human activities. Gasoline contains low concentrations of benzene (below 1%), and emissions from vehicles are the main source of benzene in the environment. Benzene can be introduced into water by industrial effluents and atmospheric pollution.

This Guideline Technical Document reviews and assesses all identified health risks associated with benzene in drinking water, incorporating multiple routes of exposure to benzene from drinking water, including ingestion and both inhalation and skin absorption from showering and bathing. It assesses new studies and approaches and takes into consideration the availability of appropriate treatment technology. From this review, the guideline for benzene in drinking water is established at a maximum acceptable concentration (MAC) of 0.005 mg/L (5 µg/L). The guideline for benzene is established based on cancer end-points and is considered protective for all health effects.

2.1 Health effects

Benzene is classified as a human carcinogen. Both animal and human studies report similar toxic effects from exposure to benzene. The most sensitive effects are found in the blood-forming organs, including the bone marrow.

The MAC for benzene in drinking water is established based on the incidence of bone marrow effects and malignant lymphoma in mice, through the calculation of a lifetime unit risk.

2.2 Exposure

For most Canadians, the major source of exposure to benzene is air; this accounts for an estimated 98–99% of total benzene intake for Canadian non-smokers. Like food, drinking water is considered to be only a minor source of exposure to benzene.

Benzene can be found in both surface water and groundwater sources, but it is not generally a concern in surface water, because benzene tends to evaporate into the atmosphere.

Some provinces and territories across Canada have detected benzene in drinking water supplies; however, data collected indicate that the levels are generally below the MAC of 0.005 mg/L.

2.3 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. Benzene can be reliably measured to concentrations as low as 0.4 µg/L, which is below the MAC.

Several municipal-scale treatment processes can remove benzene from drinking water to levels below 0.005 mg/L. At the residential scale, drinking water treatment devices are available that have been certified to reduce the concentrations of volatile organic compounds (VOCs), including benzene, to below 0.005 mg/L, although lower levels may be achieved with the use of these devices.

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.

Benzene is a human carcinogen, which means that exposure to any level in drinking water may increase the risk of cancer. Jurisdictions may establish more stringent limits than the MAC.

Generally, benzene is not a concern for the majority of Canadians who rely on surface water as their source of drinking water, because it volatilizes easily. However, ice cover in the winter may pose a concern, since it will impair benzene volatilization from surface waters. Benzene is not a widespread problem in Canada, affecting only some groundwater supplies, but accidental releases of benzene may occur at any stage of the production, storage, use, and transport of isolated benzene and crude oil and gasoline, including emissions resulting from fuel combustion.

The drinking water guideline is based on lifetime exposure (70 years) to benzene from drinking water. For drinking water supplies that occasionally experience short-term exceedances above the guideline value, 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.

The guideline for a carcinogen is normally established at a level at which the increased cancer risk is “essentially negligible” when a person is exposed at that level in drinking water over a lifetime. In the context of drinking water guidelines, Health Canada has defined this term as a range from one new cancer above background levels per 100 000 people to one new cancer above background levels per 1 million people (i.e., 10^{-5}–10^{-6}). The estimated lifetime cancer risk associated with the ingestion of drinking water containing benzene at 5 µg/L is partly within the range considered generally to be “essentially negligible,” although the upper level of the risk range at the MAC extends beyond that range. Because exposure from drinking water represents

only a small fraction (1–2%) of the total exposure to benzene, this slight exceedance in risk at the MAC is deemed acceptable. The MAC is also achievable and measurable with current treatment technology.

The overall risk associated with exposure to benzene in drinking water is reported as a range (Table 1), since lifetime exposure to benzene has been linked to several types of cancers in animals.

Table 1: Estimated lifetime range of risk of excess cancers associated with various concentrations of benzene in drinking water.

Benzene levels in drinking water (µg/L)	Estimated lifetime range of risk of excess cancers[a] ($\times 10^{-6}$)
1	2.0–4.2
5	10.1–20.8

[a] The estimated lifetime risk of excess cancer is calculated from the risk range associated with ingesting 1 µg/L of benzene in drinking water. This estimated unit risk range is 2.03×10^{-6} to 4.17×10^{-6}, with the lower bound representing malignant lymphoma and the upper bound representing bone marrow tumours in mice (Health Canada, 2005a).

Part II. Science and Technical Considerations

4.0 Identity, use, and sources in the environment

Benzene, the simplest homologue of the aromatic hydrocarbons, is a planar, cyclic molecule with six carbon atoms arranged in a regular hexagon. The molecular formula for benzene is C_6H_6. It is a volatile, colourless liquid with a characteristic odour; the odour and taste thresholds for benzene are 4.68 ppm* and 0.5–4.5 mg/L, respectively (HSDB, 2005). Benzene has a relatively high vapour pressure (10.1–13.2 kPa at 25°C), a high water solubility (820–2167 mg/L at 25°C), and a low log octanol/water partition coefficient (1.56–2.69) (Mackay et al., 1992).

Benzene is produced commercially from petroleum, natural gas, or coal. From 1988 to 2002, benzene production in Canada rose from 827 to 1142 kt per year; imports dropped from 29 to 2 kt per year, and exports rose from 92 to 210 kt per year (CPI, 2003). In Canada, benzene is produced in Ontario, Alberta, and Quebec. Benzene is used in industry as a volatile solvent and as an intermediate in the production of many chemicals, including ethylbenzene/styrene (used in plastics), cumene, linear alkyl benzene, and maleic anhydride (Jaques, 1990; CPI, 2003). The majority of benzene produced or imported into Canada is used in the production of ethylbenzene/styrene, with benzene usage for this purpose increasing from 582 kt in 1988 to 737 kt in 2002 (CPI, 2003). Benzene is also present in gasoline as an octane enhancer and anti-knock agent; since July 1999, however, levels of benzene in gasoline have been reduced to below 1% by volume.

Benzene is found naturally in the environment in very low concentrations; concentrations in the Atlantic and Pacific oceans have been reported to range between 100 and 200 ppt (Singh and Zimmerman, 1992). Natural sources of benzene include volcanoes, crude oil, forest fires, and plant volatiles (Graedel, 1978; IARC, 1982). Benzene may enter water and soil through petroleum seepage and weathering of exposed coal-containing rock. It can enter groundwater from petroliferous rocks and can enter air from volcanoes, forest fires, and releases of volatile chemicals from plants (Graedel, 1978; Westberg et al., 1981; Whelan et al., 1982; Fishbein, 1984; Slaine and Barker, 1990). Natural sources are believed to be generally low in comparison with anthropogenic sources (Rasmussen and Khalif, 1983; Rudolph et al., 1984). Anthropogenic releases of benzene may occur at any stage of the production, storage, use, and transport of isolated benzene and crude oil and gasoline, including emissions resulting from fuel combustion. Vehicular emissions constitute the main source of benzene in the environment.

The atmosphere and surface waters are the major environmental sinks for benzene owing to its relatively high vapour pressure, moderate water solubility, and low octanol/water partition coefficient. Virtually all (99.9%) of the benzene released into the environment eventually distributes itself into the air (Wallace, 1989a). Volatilization and biodegradation are the major processes involved in the removal of benzene from water. The half-life of benzene in water 1 m

* Conversion factor in air: 1 ppm = 3.19 mg/m^3 at 20°C and 101.3 kPa.

deep is estimated to be 4.8 hours as a result of volatilization (ATSDR, 2007); ice cover in the winter may impair benzene volatilization from surface waters. Reported half-lives of benzene have ranged from 33 to 384 hours for aerobic biodegradation in surface waters; for anaerobic biodegradation in deeper waters or in groundwater, half-lives ranged from 28 days to 720 days (Vaishnav and Babeu, 1987; Howard et al., 1991).

It is estimated that every year in Canada, 34 kt of benzene are released into the atmosphere (Jaques, 1990); major sources include combustion of gasoline and diesel fuels, emissions during benzene production, primary iron and steel production, solvent uses, residential fuel combustion, and gasoline marketing. Benzene is generally introduced into water from industrial effluents and atmospheric pollution.

5.0 Exposure

For non-smoking Canadians, exposure to benzene is primarily from air (98–99%), with a small proportion from drinking water (1–2%). Benzene has been detected in some foods, and some exposure may occur through automobile-related activities. Smokers may be exposed to significantly higher levels of benzene, in the range of 10 times the daily intake of a non-smoker.

5.1 Water

Monitoring results are available for benzene in surface water and groundwater; if benzene is present, its levels are generally less than 1 µg/L.

In Alberta, benzene levels in municipal treated surface water ranged from 0.01 to 4.92 µg/L (mean 0.28 µg/L, 30 samples) for 26 locations from 1998 to mid-2005; levels in more than 96% of samples were less than 1 µg/L. Levels in municipal treated groundwater ranged from 0.01 to 0.23 µg/L (mean 0.097 µg/L, 15 samples) for 11 locations for the same period. These ranges represent 45 detects out of a total of 1500 samples. Approximately 60 samples of raw "feed" water were analysed for benzene, and all samples had levels below the method detection limit (MDL); the reported MDLs ranged from 1.0 µg/L in 1988 to 0.1 µg/L from 1999 to 2005. Ambient benzene levels from six different river/stream sampling sites as part of an ambient monitoring program from 2000 to 2004 ranged from 0.02 to 0.42 µg/L; this range represented six detects out of a total of 860 samples (Alberta Department of Environment, 2005).

In Saskatchewan, levels of benzene in municipal treated surface water ranged from < 0.2 to < 1 µg/L (mean 0.25 µg/L, 30 samples) in nine locations from 1995 to 2005; levels in all samples were less than 1 µg/L. Municipal treated groundwater levels ranged from 0.1 to 1700 µg/L[**] (mean 0.71 µg/L, 34 samples) for 13 locations from 1995 to 2005; levels in more than 91% of samples were less than 1 µg/L. The level of benzene in raw (pretreated) water from two locations using surface water and one location using groundwater was 0.2 µg/L (three samples). Municipal treated water from a mixed surface water and groundwater source for three

[**] This value represents a one-time sample taken near a leaky underground storage tank. Although it is included in the range, it has not been included in the calculation of the mean.

locations over the same period had benzene levels ranging from 0.1 to 1 µg/L (mean 0.46 µg/L, 12 samples); levels in all of the samples were less than 1 µg/L (Saskatchewan Department of Environment and Resource Management, 2005). The reported MDLs ranged from 0.0005 to 1 µg/L, depending on the analytical method used.

Benzene was not detected in raw or municipal treated surface water or groundwater in Newfoundland sampled between 1995 and 2005 (detection limit 1 µg/L) (Newfoundland and Labrador Department of Environment and Conservation, 2005).

In Ontario, the levels of benzene in municipal drinking water systems, using either groundwater or surface water, ranged from below the detection limit (0.05 µg/L) to 0.2 µg/L in 2277 treated water samples between January 2002 and March 2008. The highest benzene level detected in 2762 raw water samples during the same sampling period was 0.35 µg/L (Ontario Ministry of the Environment, 2008).

In Quebec, a total of 2388 samples from municipal treated drinking water were collected between 2001 and 2005 from 191 locations using either groundwater or surface water sources and analysed for benzene. In total, 26 samples taken from 21 locations contained benzene levels ranging from 0.03 to 3.6 µg/L (mean 0.35 µg/L), with only one sample of the 26 having a concentration greater than 1 µg/L. The remaining 2362 samples were reported as being below the limits of detection, with detection limits ranging from 0.03 to 2 µg/L, depending on the accredited laboratory used (Ministère du Développement durable, de l'Environnement et des Parcs du Québec, 2005).

The New Brunswick Analytical Services Laboratory analysed a total of 3903 samples for municipal surface water or groundwater supplies for benzene from January 2001 to May 2008. All samples were reported as non-detects (New Brunswick Department of Environment, 2008).

In Nova Scotia, levels of benzene in 104 municipally treated surface water or groundwater samples from 95 locations from 2001 to 2005 were all below the MDLs, which ranged from 0.5 to 1 µg/L (five samples out of the 104 total samples were reported as non-detects); levels of benzene in 27 raw (pretreated) surface water and groundwater samples were also reported as being below the MDL of 1 µg/L (six samples were reported as non-detects) (Nova Scotia Department of the Environment, 2005).

5.2 Food

Benzene has been detected in a variety of foods. The U.S. Food and Drug Administration sponsored a 5-year study to determine the amount of volatile organics in food from 1996 to 2000. Benzene was found in a variety of foods, including dairy products—cheddar cheese, cream cheese, margarine, butter, sour cream; meats and fish—ground beef, bologna, hamburger, cheeseburger, pork, beef frankfurters, tuna canned in oil, chicken nuggets; desserts and baked goods—chocolate cake icing, sandwich cookie, chocolate chip cookies, graham crackers, sugar cookies, cake doughnuts with icing, apple pie, sweet roll danish, blueberry muffins; nuts and nut products—mixed nuts, peanut butter; fruits and vegetables—bananas, avocados, oranges, strawberries; and eggs. Concentrations of benzene in foods generally ranged from 1 to 190 µg/kg; some examples include the following: ground beef (9–190 µg/kg), bananas

(11–132 µg/kg), carbonated cola (1–138 µg/kg), and coleslaw with dressing (11–102 µg/kg) (Fleming-Jones and Smith, 2003). Benzene detections in the above food types represented only a few detects per sample, indicating that food does not represent a significant source of benzene exposure. Further support is provided by a Canadian review of benzene exposures (Environment Canada and Health and Welfare Canada, 1993).

In another study by the U.S. FDA (2006), the Center for Food Safety and Applied Nutrition conducted an initial limited survey on benzene levels in beverages, with a focus on soft drinks that contain both benzoate salts and ascorbic or erythorbic acid. Over 100 soft drinks and other beverage samples were collected from retail stores in Maryland, Virginia, and Michigan. Two beverage products containing added benzoates and 27 beverage products containing both added benzoates and ascorbic acid had benzene levels above 1 µg/L. Four cranberry beverage products and one orange beverage product with added ascorbic acid and natural levels of benzoic acid (i.e., no added benzoates) also contained benzene above 1 µg/L. In general, however, most of the beverages sampled contained either no detectable benzene or levels below 1 µg/L. Exposure to heat and light can stimulate the formation of benzene in some beverages that contain benzoate salts and ascorbic acid (vitamin C). Benzoate salts are naturally present in some fruits and their juices, or sodium or potassium benzoate may be added to beverages to prevent the growth of bacteria, yeast, and moulds.

5.3 Air

In general, mean benzene concentrations in ambient air were found to be highest at sites influenced by industrial sources and urban sites and lowest at rural and suburban sites (Environment Canada, 2001). Mean benzene concentrations in Canadian ambient air between 1989 and 1998 ranged from 1.8 to 3.6 µg/m^3 for typical urban sites with no industrial source influences; mean benzene levels were found to range from as high as 10.3 µg/m^3 at an urban site in Sault Ste. Marie, Ontario, influenced by emissions from a coke oven/iron and steel mill facility to as low as 0.3 µg/m^3 at a rural remote site in Kejimkujik National Park, Nova Scotia (Environment Canada, 2001). Survey data from the period 1995–1997 showed mean concentrations at the urban/suburban sites ranging from 1.0 to 3.5 µg/m^3, with approximately 78% (31 out of 40) of sites recording mean concentrations of less than 2.5 µg/m^3 (Environment Canada, 2001). Mean concentrations for rural sites reportedly ranged from 0.3 and 0.8 µg/m^3. Sites near roadways or industrial sources had mean benzene concentrations ranging from 4.1 to 13.1 µg/m^3 (Environment Canada, 2001).

Benzene levels in indoor air are generally higher than those in outdoor air. Sources of benzene in indoor air include glues, paints, furniture wax, and some detergents. Zhu et al. (2005) measured indoor and outdoor air levels of benzene for 75 residences in Ottawa, Ontario, during the winter of 2002–2003. Indoor temperatures remained relatively constant (19 ± 2°C), and the majority of participating homes were single family homes located in residential areas using natural gas as the heating source. The average age of the houses was 37 years, with a range from newly constructed to over 100 years old. Roughly 13% (10 homes) of the homes in the study were homes with smokers. Mean indoor air levels of benzene were reported as 2.85 µg/m^3

(range 0.025–20.99 µg/m^3),[***] with a detection frequency of 97%; outdoor air sampling revealed a mean benzene level of 1.19 µg/m^3 (0.025–16.88 µg/m^3), with a detection frequency of 62%.

5.4 Consumer products

The general population may also be exposed to benzene through automobile-related activities and cigarette smoking. An average smoker (smoking 32 cigarettes per day with an average tar content) inhales approximately 1.8 mg of benzene per day, which is about 10 times the daily intake of a non-smoker; environmental tobacco smoke can also result in measurable increases in benzene intake (Wallace, 1989b,1996; Thomas et al., 1993). Duarte-Davidson et al. (2001) compared the daily doses of rural non-smokers, urban non-smokers, urban passive smokers (non-smokers exposed to secondhand smoke), and urban smokers and found very little difference between the rural non-smokers' estimated absorbed dose of 70–75 µg/day and the urban non-smokers' estimated absorbed dose of 89–95 µg/day; the absorbed dose for passive urban smokers was estimated to be 116–122 µg/day, whereas smokers were estimated to be exposed to 516–522 µg/day. On average, non-smokers in urban and rural environments have estimated benzene intakes of 1.15 and 1.5 µg/kg bw per day. Daily doses were determined using time–activity patterns and inhalation and absorption rates, in conjunction with measured benzene air concentrations.

Automobile-related activities can contribute to increased benzene intake through inhalation of gasoline fumes and from tailpipe emissions. Increased benzene exposure has been attributed to driving times, filling gas tanks, and indoor air of homes with attached garages (Wallace, 1989b). A 1990 German study analysed factors predicting human exposures to VOCs and found that cigarette smoking was the most significant determinant of benzene exposure; automobile-related activities, such as refuelling and driving, were found to be the second highest source of benzene exposure (Hoffmann et al., 2000).

5.5 Soil

Benzene contamination of soil generally results from the spilling or leaking of gasoline or other benzene-containing petroleum products from containment vessels, such as underground storage tanks. The primary pathways responsible for benzene loss from soil are volatilization to the atmosphere, runoff to surface water and groundwater, and, to a much lesser extent, biodegradation (Environment Canada and Health and Welfare Canada, 1993). Hydrocarbon-degrading microorganisms are ubiquitous in soil, and both sorbed and vapour-phase benzene are likely biodegraded under aerobic conditions (Rosenberg and Gutnick, 1981; English and Loehr, 1991); biodegradation practically ceases when conditions become anaerobic (Smith, 1990; Aelion and Bradley, 1991; Barbaro et al., 1991). Soil contamination does not lead directly to significant levels of human exposure to benzene, since benzene volatilizes rapidly from soil (IPCS, 1993). Benzene levels in the soil surrounding industrial facilities that produce or use benzene have been reported to range between < 2 and 191 µg/kg (U.S. EPA, 1979; IARC, 1982).

[***] Levels below the detection limit were reported as one-half of the MDL of 0.05 µg/m^3.

5.6 Multi-route exposure through drinking water

Exposure to benzene in drinking water was previously assessed (Health Canada, 1986) using ingestion as the only route of exposure. Owing to benzene's high volatility, exposure by inhalation and dermal absorption during bathing and showering may also serve as important routes of exposure. Lindstrom et al. (1994) carried out a study looking at the exposure to benzene while showering with gasoline-contaminated groundwater in a home in North Carolina. The groundwater had a measured benzene concentration of 292 µg/L. Three 20-minute showers on consecutive days were reported to have resulted in peak shower stall concentrations of 800–1670 µg/m^3, with bathroom concentrations reaching 370–500 µg/m^3 and concentrations in the remainder of the house peaking 0.5–1 hours later at 40–140 µg/m^3. The dose of benzene inhaled during the 20-minute shower ranged from 80 to 100 µg. A dermal dose of 160 µg was also determined using measured breath concentrations. The combined dose of about 250 µg from the 20-minute shower was found to be within the same magnitude of the mean total daily inhalation dose of about 200 µg for all non-smokers in the Total Exposure Assessment Methodology (TEAM) study (assuming 15 µg/m^3 × 14 m^3/day alveolar inspiration) (Wallace, 1987).

To assess the overall exposure to benzene in drinking water, the relative contribution of each exposure route is assessed through a multi-route exposure assessment approach (Krishnan, 2004). Contributions developed through this approach are expressed in litre-equivalents (L-eq) per day. Both the dermal and inhalation routes of exposure for a volatile organic chemical are considered significant if they contribute to at least 10% of the drinking water consumption level (Krishnan, 2004).

5.6.1 Dermal exposure

To determine whether dermal exposure represents a significant route of exposure for benzene, tier 1 of the multi-route exposure assessment determines whether or not this route of exposure contributes a minimum of 10% of the drinking water consumption level (i.e., 10% of 1.5 L = 0.15 L). For a tier 1 goal of 0.15 L-eq, the skin permeability coefficient (K_p) for benzene should be higher than 0.028 cm/h. Since the K_p for benzene of 0.14 cm/h (Nakai et al., 1997) is greater than 0.028 cm/h, exposure to benzene via dermal absorption from bathing or showering is considered significant. Tier 2 of the assessment is then used to calculate the litre-equivalent value, using the following equation (Krishnan, 2004):

$$\text{Dermal L-eq} = K_p \times t \times F_{abs} \times A \times C_f$$

$$\begin{aligned}\text{Dermal L-eq} &= 0.14\ \text{cm/h} \times 0.5\ \text{h} \times 0.6 \times 18\,000\ \text{cm}^2 \times 0.001\ \text{L/cm}^3 \\ &= 0.76\ \text{L-eq} \\ &\approx 0.8\ \text{L-eq}\end{aligned}$$

where:

- K_p is the skin permeability coefficient of 0.14 cm/h (Nakai et al., 1997)
- t is the duration of the shower or bath, assumed to be 0.5 h

- F_{abs} is the fraction of dose absorbed, assumed to be 0.6 (Lindstrom et al., 1994)
- A is the area of skin exposed, assumed to be 18 000 cm^2 for adults
- C_f is the conversion factor from cm^3 to litres.

5.6.2 Inhalation exposure

A two-tier assessment was also used to evaluate the inhalation route of exposure. Similar to the approach used for dermal exposure, tier 1 of the assessment determines whether the inhalation of benzene during bathing or showering is likely to contribute at least 10% of the drinking water consumption level. For a tier 1 goal of 0.15 L-eq, the air to water benzene concentration ($F_{air:water}$) value should be greater than 0.000 89. Using the estimated Henry's law constant (K_{aw}) obtained from the U.S. EPA's EPI Suite program (U.S. EPA, 2000), the $F_{air:water}$ value for benzene was determined using the following equation by Krishnan (2004):

$$F_{air:water} = \frac{0.61 \times K_{aw}}{1 + (80.25 \times K_{aw})}$$

$$F_{air:water} = \frac{0.61 \times 0.22}{1 + (80.25 \times 0.22)}$$

$$= 0.0072$$

where:

- K_{aw} is the unitless Henry's law constant of 0.22 at 25°C (U.S. EPA, 2000)
- 0.61 is 61% transfer efficiency (McKone and Knezovich, 1991)
- 80.25 is the ratio of the volume of air in an average bathroom (6420 L) to the average volume of water (80 L) used during the showering/bathing event (Krishnan, 2004).

Since the $F_{air:water}$ value is greater than 0.000 89, exposure to benzene via inhalation from bathing or showering is considered to be significant. Tier 2 of the assessment calculates what the litre-equivalents should be as a function of using the following formula (Krishnan, 2004):

$$\text{Inhalation L-eq} = F_{air:water} \times Q_{alv} \times t \times F_{abs}$$

$$\text{Inhalation L-eq} = 0.0072 \times 675 \text{ L/h} \times 0.5 \text{ h} \times 0.5$$
$$= 1.22 \text{ L-eq/day}$$
$$\approx 1.2 \text{ L-eq/day}$$

where:

- $F_{air:water}$ is the ratio (partitioning) of air to water benzene concentrations

- Q_{alv} is the adult alveolar ventilation rate, assumed to be 675 L/h
- t is the exposure duration, assumed to be 0.5 h
- F_{abs} is the fraction absorbed, assumed to be 0.5 (Perbellini et al., 1988; Pekari et al., 1992; ATSDR, 2007).

It should be noted that this multi-route exposure assessment is a conservative approach used to estimate the contribution that both the dermal and inhalation routes of exposure make towards total exposure. Using physiologically based pharmacokinetic (PBPK) modelling to estimate the litre-equivalent contributions to the total daily dose from the dermal and inhalation pathways does not take into account exposure to benzene metabolites. Therefore, the approach does not place any "toxicological" weight on a particular route of exposure due to metabolite production.

Using the above approach, the litre-equivalent exposure was calculated as 0.8 L-eq for the dermal route and 1.2 L-eq for the inhalation route. Adding these values to the standard Canadian drinking water consumption rate of 1.5 L/day results in a total litre-equivalent daily exposure of 3.5 L-eq.

In a Canadian review of benzene exposures (Environment Canada and Health and Welfare Canada, 1993), it was concluded that food and drinking water each contributed a total daily benzene intake of only 0.02 µg/kg bw; the total daily intake of benzene from airborne exposures was reported to be 2.4 µg/kg bw per day (3.3 µg/kg bw per day if exposed to cigarette smoke). It can therefore be concluded that airborne exposure accounts for an estimated 98–99% of total benzene intake for Canadian non-smokers.

6.0 Analytical methods

The United States Environmental Protection Agency (U.S. EPA) has approved two analytical methods, based on purge and trap gas chromatography, for the analysis of benzene in drinking water (U.S. EPA, 2002a). EPA Method 502.2 Revision 2.1, which employs purge and trap capillary gas chromatography with photoionization detectors and electrolytic conductivity detectors in series, has an MDL of 0.01 µg/L. EPA Method 524.2 Revision 4.1, which uses purge and trap capillary gas chromatography with mass spectrometry detection, has an MDL range of 0.03–0.04 µg/L. A detection limit range is cited, as multiple detection limits are possible as a result of variability in reagents, instrumentation, and/or laboratory analyst performance (U.S. EPA, 1995).

The current U.S. EPA practical quantitation limit (PQL) for benzene is set at 5 µg/L. This limit was previously considered the lowest level that could be reliably achieved within specified limits of accuracy and precision (U.S. EPA, 1985a). More recently, the U.S. EPA has identified benzene as a possible candidate for a PQL revision. Analysis of laboratory survey data indicated that a high percentage of laboratories were capable of measuring benzene concentrations in water at lower levels using common analytical methods (EPA Method 524.2) (U.S. EPA, 2003a). As a result, the U.S. EPA (2002b) has estimated a lower possible PQL of 0.4 µg/L.

Two equivalent standard methods, SM 6200B and SM 6200C, are based on purge and trap capillary gas chromatography followed by mass spectrometry detectors or photoionization detectors and electrolytic conductivity detectors in series, respectively. SM 6200B has an MDL of 0.036 µg/L, and SM 6200C has an MDL of 0.017 µg/L. The minimum quantitation levels, defined as the lowest level that can be quantified accurately, are 0.144 µg/L and 0.068 µg/L for methods SM 6200B and SM 6200C, respectively (APHA et al., 2005).

7.0 Treatment technology

7.1 Municipal scale

Municipal drinking water treatment plants that rely on conventional treatment techniques (coagulation, sedimentation, filtration, and chlorination) have generally been found to be ineffective in reducing concentrations of VOCs in drinking water (Love et al., 1983; Robeck and Love, 1983). Coagulation and filtration treatment techniques were reported to achieve benzene reductions ranging from 0 to 29%; however, the observed reductions may be partially attributed to incidental volatilization during the treatment process (Clark et al., 1988; Najm et al., 1991; U.S. EPA, 1991a; Lykins and Clark, 1994).

Two common treatment technologies reported to be effective for the reduction of benzene in drinking water are granular activated carbon (GAC) adsorption and air stripping (Love et al., 1983; U.S. EPA, 1985a, 1991a, 1991b; AWWA, 1991; Lykins and Clark, 1994). These treatment methods are capable of achieving effluent concentrations of benzene below 1 µg/L. To a lesser degree, oxidation and reverse osmosis membrane filtration may also be effective for the removal of benzene from drinking water (Whittaker and Szaplonczay, 1985; Fronk, 1987; Lykins and Clark, 1994).

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 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 benzene in drinking water.

7.1.1 Activated carbon adsorption

GAC adsorption is widely used to reduce the concentration of VOCs in drinking water, and a removal efficiency of 99% (U.S. EPA, 1985a, 2003b; Lykins and Clark, 1994) to achieve effluent concentrations below 1 µg/L is considered feasible for benzene under reasonable operating conditions (Koffskey and Brodtmann, 1983; Lykins et al., 1984; AWWA, 1991; Dyksen et al., 1995).

The adsorption capacity of activated carbon to remove VOCs is affected by a variety of factors, such as concentration, pH, competition from other contaminants, preloading with natural

organic matter (NOM), contact time, and the physical/chemical properties of the VOC and carbon (Speth, 1990). GAC filtration effectiveness is also a function of the empty bed contact time (EBCT), flow rate, and filter run time.

Full-scale studies of fixed-bed GAC adsorbers and GAC sand replacement filters have demonstrated that both methods are capable of reducing influent benzene concentrations of 10 µg/L to below 0.1 µg/L in the finished water. Operating conditions of the GAC filter adsorber included a bed volume of 23.8 m^3, a flow rate of 1.5 ML/day, and an EBCT of 23.7 minutes. No breakthrough of benzene was observed during the 180-day study period (Koffskey and Brodtmann, 1983). Other full-scale data demonstrated that three GAC adsorbers operating in parallel with a flow rate of 5 ML/day, an EBCT of 21 minutes, and a bed life of 12 months were capable of reducing benzene concentrations of 20 µg/L to 0.2 µg/L (AWWA, 1991).

Model predictions using equilibrium data (Weber and Pirbazari, 1982; Speth and Miltner, 1990) have been used to predict full-scale GAC performance for the reduction of benzene in drinking water (Clark et al., 1990; Lykins and Clark, 1994). The estimated carbon use rate to reduce an influent benzene concentration of 100 µg/L to an effluent concentration of 5 µg/L is 0.013 kg/m^3 using an EBCT of 15 minutes and a bed life of 389 days (Lykins and Clark, 1994). As demonstrated with the full-scale data reported above, effluent benzene concentrations of 1 µg/L or lower should be achievable within reasonable operating conditions and costs.

The use of powdered activated carbon (PAC) adsorption has shown limited success as a treatment for the removal of benzene in drinking water. Pilot-scale studies demonstrated that a combined jet flocculation/PAC system was capable of reducing benzene concentrations from 100 to 5 µg/L using 60 mg/L of PAC, 100 mg/L of silica clay, and a contact time ranging between 2 and 8 minutes (Sobrinho et al., 1997).

7.1.2 Air stripping

Air stripping is commonly used to reduce the concentration of VOCs in drinking water (Cummins and Westrick, 1990; U.S. EPA, 1991a; WHO, 2004; Dyksen, 2005). Although various air stripping equipment configurations exist, packed tower aeration (PTA) is recognized as the most effective method for the reduction of benzene in drinking water. Removal efficiencies of 99% (U.S. EPA, 1985a, 2003b) to obtain effluent concentrations of 1 µg/L are considered to be achievable using PTA (Crittenden et al., 1988; U.S. EPA, 1990; Adams and Clark, 1991).

Design considerations for PTA include the temperature of the air and water, physical and chemical characteristics of the contaminant, air-to-water ratio, contact time, and available area for mass transfer (Adams and Clark, 1991; U.S. EPA, 1991a; Crittenden et al., 2005; Dyksen, 2005). PTA provides an optimum system for the removal of VOCs from water, as it allows for greater air-to-water ratios than with traditional diffused aeration systems. As PTA transfers VOCs from water to air, treatment of the stripping tower off-gas to reduce the contaminant concentrations prior to discharge may be necessary (Crittenden et al., 1988; Adams and Clark, 1991).

Data from a full-scale drinking water treatment plant demonstrated that countercurrent-flow PTA can reduce average influent levels of benzene of 30 µg/L to 1.5 µg/L in finished water

using an air-to-water ratio of 75, an air stripper length of 5.50 m, and a packed column diameter of 1.52 m (Allan, 1988). Other full-scale data demonstrated that PTA using an air-to-water ratio of 100, an air stripper length of 10.05 m, and a packed column diameter of 3.05 m was capable of reducing influent benzene concentrations of 200 µg/L to less than 2 µg/L (AWWA, 1991). Pilot testing data have demonstrated that modification of the air-to-water ratio, air stripper length, or packing material can increase the removal efficiencies to achieve effluent concentrations below 1 µg/L (U.S. EPA, 1990).

Typical and model-generated PTA designs for the removal of commonly occurring VOCs have been reported by several authors (Crittenden et al., 1988; Adams and Clark, 1991; Clark and Adams, 1991). Typical full-scale plant design (> 8 ML/day) parameters for the reduction of benzene from drinking water include an air-to-water ratio of 32.7, an air stripper length of 11.05 m, and a packed column diameter of 2.55 m. Under these conditions, a 99% reduction of benzene in drinking water from an influent concentration of 100 µg/L to an effluent concentration of 1 µg/L may be achievable (Crittenden et al., 1988). Modelling conducted by Adams and Clark (1991) to determine the cost-effective design criteria for PTA contactors estimated that an air-to-water ratio of 40 and a packing depth of 12.95 m may also be capable of achieving a 99% reduction of benzene to effluent concentrations of 1 µg/L.

Pilot plant studies examining the most effective operating conditions of PTA for the reduction of VOCs in groundwater demonstrated removal efficiencies for benzene ranging from 77% to over 99% and in some cases achieved effluent concentrations below 1 µg/L (Stallings et al., 1985; U.S. EPA, 1985b, 1990; Ball and Edwards, 1992).

Alternative air stripping treatment technologies that have been identified as potential methods for the reduction of benzene in drinking water include diffused aeration, multistage bubble aerators, tray aeration, and shallow tray aeration. These technologies may be particularly useful for small systems where the installation of GAC or PTA treatment is not feasible (U.S. EPA, 1998a).

Cost evaluations conducted by Adams and Clark (1991) indicate that in most cases the use of PTA for the reduction of benzene in drinking water is more cost-effective than GAC, even when vapour-phase GAC treatment of the stripping tower off-gas is required (Adams and Clark, 1991). The analysis included evaluation of system sizes ranging from 1 to 100 ML/day.

Combining PTA and GAC into a two-step treatment train has been suggested as the most effective method for achieving low effluent levels of VOCs. In a municipal-scale treatment plant combining these processes, air stripping is used for the bulk reduction of VOCs in the water, and activated carbon is used in the second step to further reduce the residual VOC concentrations (McKinnon and Dyksen, 1984; Stenzel and Gupta, 1985; U.S. EPA, 1991a). In addition, the use of air stripping preceding GAC can significantly extend carbon bed life. However, no performance data were available for demonstrating benzene removal efficiencies using this combined treatment method.

7.1.3 Oxidation

Oxidation and advanced oxidation processes (AOPs) have been reported to be effective for the reduction of benzene in drinking water, although full-scale data were not obtained for these treatment methods.

Pilot-scale treatment tests demonstrated that ozone doses of 6 mg/L achieved an 81% degradation of benzene in distilled water from approximately 50 µg/L to effluent concentrations of 10 µg/L. Ozone doses of 12 mg/L achieved a 94% reduction of benzene in both distilled water and groundwater matrices over a wide range of pH (Fronk, 1987). Additional pilot studies observed greater than 75% degradation of benzene with an ozone dose between 0.8 and 1.5 mg/L (Kang et al., 1997).

The rate of degradation of benzene in natural water is also dependent on the reaction of ozone with NOM, which produces hydroxyl radicals. The reaction rate between hydroxyl radicals and benzene is higher than the reaction rate between benzene and ozone; therefore, the ratio of the concentration of hydroxyl radical to the concentration of ozone is considered to be an important factor in the effectiveness of ozonation for the reduction of benzene in drinking water (Crittenden et al., 2005). Lower effluent concentrations may be achievable depending on the influent concentrations of benzene and NOM in the source water and by varying the ozone dose, contact time, and pH of the water.

A pilot-scale photocatalytic oxidation system was successful at reducing influent benzene concentrations from 123 µg/L to below 0.5 µg/L in the finished water. The oxidation system utilized ultraviolet (UV) light with a titanium dioxide semiconductor combined with the addition of 70 mg/L of hydrogen peroxide 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 (Topudurti et al., 1998). Similar pilot studies found that greater than 99% removal of benzene could be achieved using a UV/titanium dioxide oxidation process (Al-Bastaki, 2003).

The formation of by-products during the application of ozonation or AOPs for the treatment of benzene in drinking water should be considered in the process selection, optimization, and post-treatment monitoring. By-product formation will depend on several factors, including the source water quality, the type and dose of the oxidant, and the reaction contact time. Smaller, oxygenated compounds such as phenolics, aldehydes, ketones, and carboxylic acids have been suggested as potential by-products of the ozonation of benzene (Fronk, 1987). In addition, by-products such as bromate and nitrite may form as a result of the oxidation of inorganic material present in the source water.

7.1.4 Membrane filtration

Reverse osmosis has shown some promise for its potential to remove VOCs from drinking water (Clark et al., 1988). Pilot plant investigations demonstrated that selected reverse osmosis membranes were capable of reducing 94% of benzene in water; however, the influent concentrations were 1000 µg/L, and the applicability of this treatment to achieve lower effluent concentrations was not investigated (Whittaker and Szaplonczay, 1985). Other studies, however,

have found less than 20% removal of benzene using cellulose, polyamide, and thin film composite membranes (Lykins et al., 1988). The ability of reverse osmosis to remove other synthetic organic chemicals has been found to be dependent on a variety of system components, including type of membrane, flux, recovery, chemical solubility, charge, and molecular weight (Taylor et al., 2000).

7.1.5 Emerging treatment technologies

New drinking water treatment technologies for benzene are being developed but are still primarily in the experimental stage and/or do not have published information on the effectiveness of pilot- or large-scale application. Some of the emerging technologies include the following:

- *Other AOPs*: Laboratory studies examining the effectiveness of various AOP methods demonstrated the complete degradation of benzene using a UV-assisted photo-Fenton process and titanium dioxide-mediated photocatalysis (Ollis et al., 1991; Tiburtius et al., 2005).
- *Alternative adsorbents*: Synthetic carbonaceous resins and fibreglass-supported activated carbon filters have been shown to have a higher adsorbent capacity for benzene, toluene, ethylbenzene, and xylenes (BTEX) in water relative to activated carbon (Yue et al., 2001; Shih et al., 2005). In addition, the use of an adsorbent impregnated with a platinum and titanium dioxide catalyst demonstrated high removal efficiencies over a prolonged adsorbent bed life (Crittenden et al., 1997). The use of organoclays to enhance carbon filtration has also been shown to be successful (Alther, 2002).
- *Bioreactors*: Bioreactors using various materials to support microbial growth have been effective for the biodegradation of benzene in water (De Nardi et al., 2002; Sedran et al., 2003).
- *Electron beam radiation*: The use of a low-energy electron beam to generate electrons and hydroxyl radicals that oxidize benzene in water has demonstrated moderate effectiveness for the reduction of benzene in water (Lubicki et al., 1997).
- *Membrane pervaporation*: Although the use of membranes for the pervaporation extraction of benzene has been applied primarily in wastewater treatment, this technique has more recently been studied for the removal of benzene from groundwater (Jian and Pintauro, 1997; Uragami et al., 2001; Peng et al., 2003).

7.2 Residential scale

Municipal treatment of drinking water is designed to reduce contaminants to levels at or below their guideline values. As a result, the use of residential-scale treatment devices on municipally treated water is generally not necessary, but is primarily based on individual choice. 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 reducing benzene concentrations in drinking water.

A number of residential treatment devices from various manufacturers are available that can remove benzene from drinking water to concentrations below 1 µg/L. 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 VOCs such as benzene, because they provide treated water for bathing and laundry as well as for cooking and drinking. Certified point-of-use treatment devices as well as a limited selection of point-of-entry devices are currently available for the reduction of VOCs, including benzene. In the case 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 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.

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, 2003):

- 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);
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

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

Treatment devices to remove benzene from untreated water (such as a private well) can be certified either specifically for benzene removal or for the removal of VOCs as a group. However, only treatment devices certified for the removal of VOCs as a group can verify that a final benzene concentration of less than 0.001 mg/L is achieved. For a drinking water treatment device to be certified to NSF/ANSI Standard 53 (Drinking Water Treatment Units—Health Effects) for the removal of VOCs, the device must be capable of reducing the concentration of benzene by greater than 99% from an influent (challenge) concentration of 0.081 mg/L to a maximum final (effluent) concentration of less than 0.001 mg/L (NSF/ANSI, 2006). Treatment devices that are certified to remove VOCs under NSF/ANSI Standard 53 are generally based on activated carbon adsorption technology. Reverse osmosis systems certified to NSF/ANSI

Standard 58 (Reverse Osmosis Drinking Water Treatment Systems) may also be certified for the reduction of VOCs to achieve a final concentration of less than 0.001 mg/L (NSF/ANSI, 2005). This standard is applicable only for point-of-use reverse osmosis systems.

8.0 Kinetics and metabolism

Oral exposure to benzene at low concentrations in animals has been shown to result in complete absorption. Sabourin et al. (1987) administered radiolabelled (^{14}C) benzene orally (through corn oil gavage and intraperitoneally) to Sprague-Dawley and F344/N rats and B6C3F1 mice and analysed urine and faeces at 4, 8, 16, 24, 32, and 48 hours after dosing for radiolabelled benzene (and/or benzene metabolites). The percentages of the dose excreted by each route were similar following gavage or intraperitoneal injection. The absorption of benzene in F344/N rats, Sprague-Dawley rats, and B6C3F1 mice was determined by comparing excretion routes following administration (by gavage or intraperitoneal injection) of benzene at 0.5 or 150 mg/kg bw; it was found that the absorption of benzene was essentially 100% for all three test species.

Results from the Sabourin et al. (1987) study are supported by a study on rats, mice, and hamsters by Mathews et al. (1998). Animals treated by oral gavage (in corn oil) with a range of benzene doses that overlapped those in the Sabourin et al. (1987) study displayed complete absorption from the gastrointestinal tract (in all three species); however, excretion routes were influenced by dose. For example, at a high dose of 100 mg/kg bw, a significant portion of benzene was eliminated by exhalation (from 22% in mice to 50% in rats). Both studies reported a greater proportion of metabolites excreted in urine at the low doses, with a shift to greater amounts of unmetabolized benzene excreted in exhaled air at the high doses. These results suggest that saturation of metabolism occurs at doses greater than approximately 100 mg/kg bw. At oral doses that could be found in drinking water, however, animal results suggest a linear increase in total metabolite production with exposure level.

No relevant animal studies are available that allow a comparison of absorption between gavage and drinking water administration. In theory, ingesting drinking water or food containing benzene may result in some loss from the stomach through volatilization, whereas administration by gavage using an oil vehicle may limit benzene volatilization. It is also possible that a greater proportion of benzene from large bolus doses would escape absorption and pass through into the faeces, while smaller doses would be better absorbed. Since essentially complete absorption has been observed even at high gavage doses in animals, in the absence of human data, it is postulated that complete absorption of benzene by ingestion can be expected in humans as well.

Absorption of benzene through inhalation, like absorption following ingestion, depends on the dose. As seen in oral exposure studies, a larger proportion of benzene is retained at lower exposures versus higher exposures. Humans experimentally exposed to low to moderate levels of benzene (1.7–32 ppm) absorbed on average 50% of the benzene inhaled. Pekari et al. (1992) exposed three males to both 1.7 and 10 ppm benzene for 4 hours, during which six samples of exhaled air and blood were taken from each subject. After exposure, phenol was measured in exhaled air, blood, and urine. The average absorption was found to be 52% ± 7.3% at 1.7 ppm and 48% ± 4.3% at 10 ppm.

Nomiyama and Nomiyama (1974) exposed three females and three males to benzene levels ranging from 52 to 62 ppm for 4-hour periods. At 1-hour intervals during exposure, exhaled air was sampled. The average absorption at the 1-hour exposure period was found to be approximately 60% for women and 45% for men. After 2 hours of exposure, absorption was approximately 43% for women and 35% for men. The average absorption over the 3- to 4-hour time periods was reported at 30.2%. In general, absorption was higher for both sexes during early exposure, approaching a steady state only after 3 hours.

Studies measuring exhaled air from occupational and environmental exposures further support a 50% absorption of benzene following inhalation exposure. In an occupational study by Perbellini et al. (1988), exhaled air from subjects who had low background exposure to benzene (median 19 ng/L in air, or 0.019 ng/m^3) showed an average absorption of 55%. Another study by Wallace et al. (1993) found 70% absorption of benzene from measurements of exhaled air for non-smokers. In most studies of this sort, exhaled air samples are collected in the post-exposure period, with the concentration of benzene in exhaled air falling rapidly following removal from exposure; therefore, post-exposure samples would be expected to predict a lower absorption. In general, however, experimental, occupational, and environmental exposure studies suggest that an absorption fraction of 50% is a good estimate.

Human and animal studies have shown that benzene is readily absorbed through the skin from both the liquid and vapour phases (Franz, 1975; Maibach and Anjo, 1981; Franz, 1984; Susten et al., 1985). Absorption of benzene through the skin, however, depends on several factors, including skin permeability, which increases with increasing temperature (Nakai et al., 1997). Susten et al. (1985) estimated the amount of benzene absorbed through the skin of tire industry workers by conducting a series of *in vivo* studies in hairless mice. Percutaneous absorption, following single dermal applications of [^{14}C]benzene contained in rubber solvent at a concentration of 0.5% (v/v) benzene, was calculated directly from the sums of radioactivity found in excreta, expired breath, and the carcass. Data from the study suggested that benzene absorption via the skin could contribute from 20% to 40% of the total benzene dose of these workers.

Although animal studies show that exposure to oral doses to which humans are likely exposed suggest a linear increase in total metabolite production with exposure level, the dose-related production of benzene metabolites in humans is not well understood, particularly at low levels of exposure. Kim et al. (2006) investigated unmetabolized benzene in urine and all major urinary metabolites (phenol, E,E-muconic acid, hydroquinone, and catechol), as well as the minor metabolite, S-phenylmercapturic acid, in 250 benzene-exposed workers and 139 control workers in Tianjin, China. Metabolite concentrations in urine were found to be consistently elevated when the median air benzene levels were at or above the following: 0.2 ppm for E,E-muconic acid and S-phenylmercapturic acid, 0.5 ppm for phenol and hydroquinone, and 2 ppm for catechol. The dose-related production of E,E-muconic acid, phenol, hydroquinone, catechol, and total metabolites reportedly declined by 2.5- to 26-fold as the median air benzene levels increased from 0.027 to 15.4 ppm. Reductions in metabolite production were found to be most pronounced for catechol and phenol at levels below 1 ppm, indicating that metabolism favoured

the production of the toxic metabolites, hydroquinone and E,E-muconic acid, at low exposures. Another study by Rappaport et al. (2005) investigated the production of benzene oxide and 1,4-benzoquinone in 160 Chinese workers exposed to benzene at levels ranging from 0.074 to 328 ppm. Both benzene oxide and 1,4-benzoquinone levels plateaued at approximately 500 ppm benzene, suggesting that cytochrome P4502E1 (CYP2E1) (which is responsible for oxidizing benzene to benzene oxide, the first step in benzene metabolism) became saturated at this point. These results indicate that benzene metabolism may be much more effective at low levels of benzene and that exposure to levels of benzene above 50 ppm may have a diminished impact on the human health risk of leukaemia, since benzene metabolism becomes substantially saturated at this level. On the other hand, these results suggest that exposure to levels of benzene below 50 ppm may produce the maximum amount of metabolites per unit of benzene exposure.

Scientific evidence suggests that metabolism plays an important role in benzene toxicity (Snyder and Hedli, 1996). As an example, competitive inhibition of metabolism by toluene (at levels much higher than found in drinking water) decreases benzene toxicity. Valentine et al. (1996) reported that transgenic mice lacking CYP2E1 expression had lower benzene metabolism, cytotoxicity, or genotoxicity compared with wild-type mice; there is no indication, however, that the route of exposure has an effect on the metabolites formed (IPCS, 1993). Two major pathways are proposed as being responsible for benzene toxicity. The first involves the metabolites phenol, catechol, and hydroquinone, and the second pathway involves open ring forms of benzene. Benzene is primarily metabolized in the liver by CYP2E1 (Johansson and Ingelman-Sundberg, 1988) to form benzene oxide, which spontaneously rearranges to phenol. Catechol is formed by the oxidation of phenol, or it can be formed by the conversion of benzene oxide to benzene-1,2-dihydrodiol in the liver by epoxide hydrolase, with subsequent conversion to catechol by dehydrogenases. It is believed that catechol formation from phenol oxidation may be significant only during high-dose exposures. Hydroquinone is formed from the oxidation of phenol by mixed-function oxidases.

It is suggested that benzene-induced haematotoxicity, such as aplastic anaemia, pancytopenia, thrombocytopenia, granulocytopenia, lymphocytopenia, and carcinogenesis, involves the metabolism of phenolic metabolites of benzene, in particular the metabolism of hydroquinone to benzoquinone, semiquinones, and free radicals (Smith, 1996; Snyder and Hedli, 1996; Smith and Fanning, 1997). Blood transports phenolic metabolites (phenol, hydroquinone, catechol, and 1,2,4-trihydroxybenzene) to bone marrow, where they can be converted to reactive species by peroxidases and other enzymes. The redox reactions that accompany these reactions generate oxygen free radicals, lipid peroxidation products, and other free radicals (Subrahmanyam et al., 1991). Bone marrow contains approximately 3% dry weight of myeloperoxidase in addition to other peroxidases, such as eosinophil peroxidase and prostaglandin synthetase (Smith, 1996). The primary biological function of a peroxidase enzyme is to oxidize hydrogen donors at the expense of peroxide or molecular oxygen. Snyder and Kalf (1994) found that NADPH-dependent quinone oxidoreductase, an enzyme that efficiently reduces (detoxifies) quinones, is found in low concentrations (relative to other tissues) in bone marrow, which may explain in part why the bone marrow is a target tissue for benzene toxicity. Glutathione conjugates of hydroquinone and

1,2,4-benzenetriol readily auto-oxidize to quinone species, which may react with cellular macromolecules directly or generate free radical species (Snyder and Hedli, 1996). In a review by Witz et al. (1996), it was reported that some researchers have hypothesized that metabolites of benzene where the aromatic ring has been broken may also significantly contribute to benzene haematotoxicity. *Trans,trans*-muconaldehyde co-administration with hydroquinone, for example, is very potent in damaging bone marrow cells.

9.0 Health effects

9.1 Effects in humans

9.1.1 Acute toxicity

Acute exposure to high levels of benzene affects the central nervous system, causing dizziness, nausea, vomiting, headache, and drowsiness. Exposure to levels between 50 and 150 ppm by inhalation over 5 hours can reportedly result in headaches, lethargy, and weakness, although exposure to 25 ppm for 8 hours produced no acute clinical effects (IPCS, 1993; Paustenbach et al., 1993). Inhaling benzene at 20 000 ppm for 5–10 minutes, at 7500 ppm for 30 minutes, or at 1500 ppm for 60 minutes may cause death or severe toxicity in humans (Holliday and Englehardt, 1984; IPCS, 1993). Individuals who have died from sniffing glue containing benzene reportedly had blood concentrations from 1 to 65 mg/L, with death resulting from pulmonary haemorrhaging and inflammation, renal congestion, cerebral oedema, or a combination of these (IPCS, 1993). ATSDR (2007) estimates a lethal oral dose of benzene in humans to be about 125 ppm.

9.1.2 Subchronic and chronic toxicity

Subchronic and chronic exposure to benzene leads to numerous adverse effects, including damage to bone marrow, changes in circulating blood cells, immunological effects, and cancer (see Section 9.1.5). The most commonly reported non-cancer effects from chronic exposure to inhaled benzene include blood disorders, such as aplastic anaemia, pancytopenia, thrombocytopenia, granulocytopenia, and lymphocytopenia. The effects of benzene exposure on several blood cell lineages suggest that benzene and/or its metabolites target the bone marrow or early progenitor cells (IPCS, 1993; ATSDR, 2007).

A study by Lan et al. (2004) of 250 shoe workers in China exposed to benzene found a highly significant dose-dependent decrease in colony formation of progenitor cells with increasing benzene exposure. With a greater proportional decrease in progenitor cell colony formation than the proportional decrease in the levels of differentiated white blood cells and granulocytes, Lan et al. (2004) suggested that early progenitor cells are more sensitive to the haematotoxic effects of benzene than mature blood cells. This is in agreement with other earlier findings in both humans and animals (Smith et al., 2000; Abernathy et al., 2004).

In a group of 44 healthy Chinese workers, Rothman et al. (1996a, 1996b) reported that early biomarkers of exposure to relatively low levels of benzene included significantly depressed numbers of total red blood cells, white blood cells, absolute lymphocyte count, platelets, and haematocrit. The workers were exposed to benzene in the workplace (median 8-hour time-weighted average [TWA] of 31 ppm; minimal exposure to other solvents) for an average of 6.3 years. Age- and gender-matched workers with no history of occupational exposure to benzene served as controls. The authors reported significantly depressed absolute red blood cells and platelets among the 22 workers whose mean 5-day benzene exposure levels did not exceed 31 ppm (median 8-hour TWA of 13.6 ppm); of these, a subgroup of 11 workers with a median 8-hour TWA of 7.6 ppm also showed a significantly decreased absolute lymphocyte count.

9.1.3 Genetic toxicity

Benzene is reported to be clastogenic in humans, with effects including aneuploidy, ploidy, micronuclei, chromosomal deletions, translocations, and rearrangements (IARC, 1982; ATSDR, 2007). Most cytogenetic studies have looked at the blood lymphocytes of exposed workers and report increased structural (chromatid and/or chromosome breaks) and/or numerical chromosomal aberrations in mitogen-stimulated peripheral lymphocytes (ATSDR, 2007). Benzene exposure in humans has also been shown to result in the types of chromosomal aberrations that are common with certain leukaemias, such as acute myelogenous leukaemia and myelodysplastic syndromes (Smith and Zhang, 1998). Aberrations include specific gains or losses in chromosomes, translocations, deletions, and inversions, most commonly associated with chromosome 5, 7, 8, 9, 21, or 22.

Lymphocytes in Chinese workers occupationally exposed to benzene have been shown to contain higher frequencies of specific chromosomal alterations such as chromosome 9 hyperdiploidy, translocations between chromosomes 8 and 21, and aneusomies of chromosomes 8 and 21 (Zhang et al., 1996; Smith and Zhang, 1998). Significant increases in the rates of monosomy for chromosomes 5 and 7 ($p < 0.001$ and $p < 0.0001$, respectively) and increases in the frequencies of trisomy and tetrasomy of chromosomes 1, 5, and 7 have also been reported (Zhang et al., 1998). Many of these chromosomal alterations have also been observed *in vitro* in human cells treated with benzene metabolites. Zhang et al. (1994) and Stillman et al. (1997) found dose-related increases of aneuploidy of chromosomes 5 and 7 in human haematopoietic cells treated with hydroquinone or 1,2,4-trihydroxybenzene. Zhang et al. (1994) reported trisomy and tetrasomy of chromosomes 7 and 9 in a human cell line treated with hydroquinone or 1,2,4-benzenetriol. Exposure of human lymphocytes to hydroquinone resulted in hyperdiploidy in chromosome 9 (Eastmond et al., 1994).

9.1.4 Developmental and reproductive toxicity

Studies are limited regarding the effects of maternal exposure to benzene. Abnormal menstruation and excessive blood loss during childbirth have been reported in women occupationally exposed to benzene (OEHHA, 1997). These reports, however, are limited, since the

comparison groups were exposed to different environments that were not described, the methods were poorly described, and co-exposure to other solvents associated with employment in rubber and/or leather factories likely occurred. More definitive studies with accurate assessment of benzene-specific exposure are needed.

9.1.5 Carcinogenicity

There are numerous studies that report increased cancer rates from occupational exposure to benzene (Bond et al., 1986; Wong, 1987; Hayes et al., 1996; Schnatter et al., 1996; Rushton and Romaniuk, 1997). Reviews of benzene carcinogenicity due to occupational exposure have been published by IARC (1982), IPCS (1993), and ATSDR (2007).

The Ohio Pliofilm (rubber hydrochloride) cohort represents a good published set of data for assessing human cancer risks from exposure to benzene, since it has the fewest reported co-exposures to other possible carcinogenic substances in the workplace that could impact a risk analysis for benzene, and the Pliofilm workers were exposed to a wider range of estimated benzene concentrations than were workers in other cohort studies (U.S. EPA, 1998b). Rinsky et al. (1981) was the first to extensively study the Pliofilm cohort, which included 748 male workers in three facilities in Ohio who were exposed to benzene during employment between 1940 and 1949 and were followed until the end of 1981. Benzene exposure levels were estimated to range from 100 ppm in 1941 to 10 ppm (8-hour TWA) in 1949. A statistically significant increase in mortality due to malignancies of the lymphatic and haematopoietic tissue (standardized mortality ratio [SMR] = 330; $p < 0.01$) was reported, with seven of the deaths due to leukaemia (SMR = 560; $p < 0.001$). Workers exposed for longer than 5 years had an SMR due to leukaemia of 2100. Rinsky et al. (1987) subsequently updated and expanded the Ohio cohort study to include individuals who had worked at least 1 day between 1940 and 1965, with person-years at risk starting in 1950. The updated cohort was composed of 1165 white males followed through 1981, which included an additional 6.5 years of follow-up from the earlier study, as well as individual estimates of personal exposure. Duration of employment and personal exposure estimates during that time of employment were used to generate risk estimates based on grouped data. Once again, a strong positive trend in leukaemia mortality was seen with increasing exposure to benzene; a statistically significant increase was observed for all lymphatic and haematopoietic cancers (15 deaths) compared with that expected in the general population (SMR = 227, 95% confidence interval [CI] = 127–376). For total leukaemia deaths (nine deaths), the SMR was 337 (95% CI = 159–641). An increased risk of multiple myeloma (four deaths) was also reported (SMR = 398, 95% CI = 110–1047). Analyses by other authors (Paustenbach et al., 1993; Paxton et al., 1994) with expanded periods of follow-up and altered exposure estimates have yielded slightly different results; however, the differences fall within the same range of uncertainty.

A large retrospective cohort study of benzene-exposed workers in China by Yin et al. (1987) examined 28 460 exposed workers from 233 factories and 28 257 control workers from different industries. Thirty leukaemia cases were identified (23 acute, 7 chronic) in the exposed workers compared with four cases in the unexposed controls (SMR = 574, $p < 0.01$). Exposure estimates at the time of the survey ranged from 3 to 313 ppm, with the majority of exposures in

the range of 16–157 ppm. In 1994, the cohort was expanded by Yin et al. (1994) to include 74 828 benzene-exposed workers (since 1949) and 35 805 controls from 712 factories located in 12 Chinese cities. Dosemeci et al. (1994) described the exposure assessment, which included job title and assignment to individual work units reflecting exposures of individual workers. Yin et al. (1996) reported the overall cancer findings among the expanded benzene-exposed and control worker cohorts. An increased incidence in the benzene-exposed group compared with controls was observed for leukaemia (relative risk [RR] = 2.6, 95% CI = 1.3–5.0), malignant lymphoma (RR = 3.5, 95% CI = 1.2–14.9), and lung cancer deaths (RR = 1.4, 95% CI = 1.0–2.0). Among leukaemia cases, incidence of acute myelogenous leukaemia was increased in the benzene-exposed group (RR = 3.1, 95% CI = 1.2–10.7). Significant increases were also reported for aplastic anaemia and myelodysplastic syndromes.

9.1.6 Mode of action for carcinogenesis

Benzene biotransformation results in the generation of several metabolites (see Section 8.0) that can induce cytotoxicity through different metabolic mechanisms (Smith, 1996; Ross, 2000; Snyder, 2000). These reactive metabolites include quinones that can bind to cellular macromolecules (including DNA), tubulin, histones, and topoisomerase II. Benzoquinones and other benzene metabolites can cause oxidative DNA damage, lipid peroxidation *in vivo*, formation of hydroxylated deoxyguanosine residues, and strand breaks in the DNA of bone marrow cells, implicating a role for reactive oxygen species and covalent binding in benzene-induced toxicity. The formation of DNA double-strand breaks by reactive oxygen species and other mechanisms can lead to increased mitotic recombination, chromosomal translocations, and aneuploidy (Smith, 1996). Genetic events such as these can result in proto-oncogene activation, tumour suppressor gene inactivation, gene fusions, and other changes in stem cells that can ultimately result in leukaemia.

9.2 Effects in experimental animals

9.2.1 Acute toxicity

Animals exposed to a one-time high dose of benzene have displayed narcotic effects and death. Oral LD_{50} values for rats fall in the 300–8100 mg/kg bw range. An LC_{50} of 10 000 ppm for short-term exposure to benzene in air was reported for rats, mice, rabbits, and guinea pigs (IPCS, 1993; Paustenbach et al., 1993).

9.2.2 Subchronic and chronic toxicity

Subchronic and chronic exposure of experimental animals to benzene has resulted in haematological effects similar to those observed in humans following occupational exposure. Lymphocytopenia, anaemia, leukopenia, and changes in bone marrow morphology and cellularity have been consistently reported by many authors (Snyder et al., 1978, 1984; Cronkite et al., 1985; Ward et al., 1985; Aoyama, 1986; Li et al., 1986; NTP, 1986; ATSDR, 2007). A 2-year study by the U.S. National Toxicology Program (NTP, 1986) reported haematological

effects in rats and mice (both sexes), which included lymphoid depletion of the splenic follicles (rats) and thymus (male rats), bone marrow haematopoietic hyperplasia (mice), lymphocytopenia, and associated leukocytopenia (rats and mice). Several of these effects occurred at the lowest exposure level (25 mg/kg bw per day). In animals, lymphocyte levels generally appear to fall the most in the shortest time, whereas granulocytes appear to be the most resistant of the circulating cells; anaemia does not appear to occur as frequently as lymphocytopenia (ATSDR, 2007).

In 2007, the U.S. NTP exposed groups of 15 male and 15 female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice to 0, 25, 50, 100, or 200 mg benzene/kg bw per day in corn oil by gavage 5 days per week for 27 weeks. Males exposed to 25 mg benzene/kg bw per day or greater and females exposed to 50 mg benzene/kg bw per day or greater displayed black, brown, or grey pigmentation of the feet. Thymus weights of all dosed groups of males were significantly decreased. At weeks 13 and 27, dose-related decreases in haematocrit, haemoglobin, and erythrocyte count values in all dosed males and in the 100 mg/kg bw per day or greater females were reported. Decreased leukocyte counts, primarily lymphocyte counts, resulted in a dose-related leukopenia in males and females. In males, segmented neutrophil counts were also decreased. In the bone marrow, significantly increased incidences of minimal to mild atrophy were observed in the 100 and 200 mg/kg bw per day male dose groups compared with the vehicle controls; a significantly increased incidence of lymphoid follicle atrophy in the spleen was also observed in these dose groups. The incidence of haematopoietic cell proliferation was significantly increased in the 200 mg/kg bw per day dose group males. The 100 and 200 mg/kg bw per day dosed males also displayed significantly increased incidences of atrophy of the thymus and lymph nodes (mandibular, mediastinal, and mesenteric atrophy); a significantly increased incidence of atrophy of the mediastinal lymph node was also seen in the 100 mg/kg bw per day dosed females. The incidences of skin pigmentation were significantly increased in all dosed groups of males and in females dosed with 50 mg/kg bw per day or greater.

9.2.3 Genetic toxicity

Benzene has also been shown to be genotoxic in animals. *In vitro* studies have shown benzene to exhibit mixed results, with positive findings reported for gene mutations in bacteria and inhibition of DNA or RNA synthesis in mammalian cells. Benzene metabolites such as phenolic, quinone, epoxide, and aldehyde species cause mutations in bacteria, as well as sister chromatid exchanges, micronuclei formation, DNA strand breaks, DNA adducts, and oxidative DNA damage in mammalian cells. *In vivo*, benzene induces chromosomal aberrations in lymphocytes (mice) and in bone marrow cells (rats and hamsters) and increases the incidence of micronuclei in bone marrow (mice and hamsters), peripheral erythrocytes (mice), and lymphocytes (rats). Other genotoxic effects include gene mutations and polyploidy in mouse lymphocytes, as well as sister chromatid exchanges in the mouse fetus, liver, bone marrow, and rat and mouse lymphocytes. Sperm head abnormalities have also been observed in benzene-exposed male mice (ATSDR, 2007).

9.2.4 Developmental and reproductive toxicity

Benzene has not been found to be teratogenic in animals, although embryotoxic and fetotoxic effects have been reported at airborne concentrations as low as 47 ppm in rats (a level found not to be toxic to the dams) (Tatrai et al., 1980). Haematological effects are also reported in mice exposed to low levels of benzene *in utero* (Keller and Snyder, 1986). Administration of 20 ppm benzene to pregnant Swiss Webster mice for 6 hours per day on gestational days 6–15 caused reductions in the levels of erythroid progenitor (CFU-E) cells of the fetuses, whereas 5 and 10 ppm benzene caused enhancement of these colony-forming cells. In 2-day-old neonates, CFU-E numbers in the 5 ppm group returned to control values, but the 10 ppm neonates showed a bimodal response by litter. Granulocytic colony-forming cells were enhanced in neonates exposed *in utero* to 20 ppm benzene. Some of the mice exposed to 10 ppm prenatally were re-exposed to 10 ppm as adults. Their haematopoietic progenitor cell numbers were depressed compared with controls exposed for the first time as adults. In a follow-up study by Keller and Snyder (1988), pregnant Swiss Webster mice exposed to 5, 10, or 20 ppm benzene for 6 hours per day on gestational days 6–15 showed no significant changes in erythrocyte and leukocyte counts, haemoglobin analysis, and the proliferating pool of differentiating haematopoietic cells in 16-day fetuses. In 2-day neonates, however, exposure *in utero* to all concentrations of benzene exhibited a reduced number of circulating erythroid precursor cells, and, at 20 ppm, increased numbers of hepatic haematopoietic blast cells and granulopoietic precursor cells accompanied by decreased numbers of erythropoietic precursor cells were observed. Six-week-old adult mice exposed *in utero* to 20 ppm of benzene had a similar pattern of enhanced granulopoiesis. However, this effect was not clearly evident in 6-week-old adult mice exposed *in utero* to 5 or 10 ppm.

9.2.5 Carcinogenicity

A 2-year study by the NTP (1986) exposed F344 rats and B6C3F1 mice (50 animals per sex per group) orally (by gavage) to benzene in corn oil 5 days per week for 103 weeks. Female rats and mice were exposed to 0, 25, 50, or 100 mg/kg bw per day, and males were exposed to 0, 5, 100, or 200 mg/kg bw per day. Female rats in the mid- and high-dose groups had significantly higher incidences of cancer of the oral cavity, Zymbal gland (an auditory sebaceous gland that opens into each external ear canal; not found in humans), and uterus; in males, an increased incidence of cancers of the oral cavity, Zymbal gland, and skin was observed. Female mice were reported to have significant dose-related increases in the rate of cancer of the Zymbal gland, ovary, mammary gland, Harderian gland, and lung. In male mice, a dose-related increase in the rate of cancer of the Zymbal, preputial, and Harderian glands and lungs was also observed.

Numerous other studies have shown benzene to be carcinogenic in rats and mice. Maltoni et al. (1982, 1983, 1985, 1989) reported that benzene administered (by stomach tube) to 13-week-old Sprague-Dawley rats at 0, 50, or 250 mg/kg bw in olive oil, 4–5 times per week for 52 weeks, resulted in dose-related increases in the incidence of Zymbal gland carcinomas in female rats only. In another study by Maltoni et al. (1989), 7-week-old male and female Sprague-Dawley rats orally exposed (by stomach tube) to 0 or 500 mg benzene/kg bw in olive

oil 4–5 times per week for 105 weeks displayed significantly higher incidence (related to controls) of Zymbal gland and oral cavity carcinomas (males and females), nasal cavity and skin carcinomas (males), and cancer of the forestomach (females). Wistar rats, Swiss mice, and RF/J mice (50 animals per sex per group) orally exposed to 0 or 50 mg benzene/kg bw in olive oil 4–5 times per week for 104, 78, and 52 weeks, respectively, showed an increased incidence in cancer compared with controls (Maltoni et al., 1989). Wistar rats displayed an increased incidence of cancers of the Zymbal gland (males) and oral cavity (females); Swiss mice had an increased incidence of cancers of the Zymbal gland (males), mammary gland (females), and lung tissue (males and females); and RF/J mice were found to have a higher incidence of pulmonary tumours (males and females) and mammary gland carcinomas (females). Maltoni et al. (1982, 1983, 1985, 1989) also assessed the carcinogenic potential of benzene through inhalation studies using pregnant Sprague-Dawley rats and their offspring. Exposure to 0, 200, or 300 ppm of benzene for 15 or 104 weeks also showed increased incidences (compared with controls) of Zymbal gland cancers and mammary gland tumours in adults, with significantly higher incidences of Zymbal gland cancers and non-significant increases in cancers of the oral and nasal cavity, mammary gland, and liver also reported in the offspring. In another experiment by Maltoni et al. (1989), Sprague-Dawley rats were exposed to benzene *in utero* (via dams exposed to 0, 200, or 300 ppm) from day 12 of gestation and during lactation. Slight increases in the incidences of Zymbal gland carcinoma, oral cavity carcinoma, hepatoma, and leukaemia were reported (Maltoni et al., 1989).

Leukaemia and lymphoma have been reported in several other studies investigating benzene-mediated effects following inhalation and oral exposure. In a series of studies by Cronkite et al. (1984, 1985, 1989) and Cronkite (1986), C57BL/6 and CBA/Ca mice were exposed to 300 ppm benzene in air 6 hours daily, 5 days per week, for 16 weeks at variable intervals mimicking patterns of human occupational exposure to benzene. A significant increase in both leukaemia and lymphoma was reported in both strains of mice, as well as solid tumours (mammary and hepatoma) for CBA/Ca mice. Cronkite et al. (1989) reported a higher incidence of leukaemia in male and female CBA/CA mice exposed to 300 and 3000 ppm for 16 weeks; exposure to 3000 ppm, however, did not shorten the latency or increase the incidence compared with the 300 ppm treatment group. In a study by Farris et al. (1993), 125 male CBA/Ca mice were exposed to 300 ppm benzene for 6 hours daily, 5 days per week, for 16 weeks and sacrificed after 18 months; controls (sham-exposed, n = 125) were treated with filtered air. Significant increases in incidences of malignant lymphoma were observed in addition to preputial gland squamous cell carcinoma, lung adenoma, carcinoma of the Zymbal gland and forestomach squamous cells, as well as increased granulocytic hyperplasia of the bone marrow and spleen.

As part of an ongoing effort to determine the carcinogenic mode of action of benzene, the NTP (2007) assessed benzene's carcinogenic effects in the haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mouse model. Groups of 15 male and 15 female $p16^{Ink4a}/p19^{Arf}$ mice were administered 0, 25, 50, 100, or 200 mg benzene/kg bw per day in corn oil by gavage 5 days per week for 27 weeks. All animals except one male administered 200 mg/kg bw per day survived until the end of the study. The

incidence of malignant lymphoma was significantly increased in males exposed to 200 mg benzene/kg bw per day compared with the vehicle controls and exceeded the incidence seen in the historical controls. Malignant lymphomas were not seen in female $p16^{Ink4a}/p19^{Arf}$ mice, which suggests that benzene may be more clastogenic in males than in females. This theory was supported by the micronucleus results, which showed that males exposed to the carcinogenic dose of 200 mg/kg bw per day for 27 weeks had approximately four times the number of micronuclei compared with females.

9.2.6 Immunotoxicity

Concentrations of benzene as low as 10 ppm in air have been reported to cause immunological effects (depression of the response of B cells and T cells) in rats (Rozen et al., 1984). Mice exposed to 300 ppm benzene for 6 hours per day, 5 days per week, for 115 days showed reduced numbers of B cells in the spleen and bone marrow and T cells in the thymus and spleen (Rozen and Snyder, 1985).

10.0 Classification and assessment

Benzene has been classified as a Group 1 carcinogen (carcinogenic to humans) by Health Canada (Environment Canada and Health and Welfare Canada, 1993), the International Agency for Research on Cancer (IARC, 1987), and the U.S. EPA (IRIS, 2003). Although non-cancer effects have been observed in animals exposed to benzene either orally or through inhalation, as well as in humans exposed to benzene occupationally by inhalation, carcinogenicity is considered to be the critical health effect upon which a drinking water guideline should be based. It is important to note that both animals and humans display similar toxic effects following exposure to benzene, regardless of exposure pathway (i.e., via inhalation or ingestion). The most sensitive effects from benzene exposure in both animals and humans are the effects related to the blood-forming organs.

Epidemiological studies were deemed insufficient by Health Canada to serve as the basis for the quantitative estimation of cancer risks from exposure to benzene in the previous drinking water guideline (Health Canada, 1986). The guideline had been developed based on a 2-year cancer study in rats and mice (NTP, 1986), incorporating a surface area correction from rodents to humans and using a robust linear extrapolation model and a standard drinking water consumption rate of 1.5 L/day. Based on this approach, the unit lifetime risk associated with the ingestion of 1 µg benzene/L in drinking water was estimated to range from 6.1×10^{-7} (based on leukaemia and lymphomas in female mice) to 6.7×10^{-6} (based on oral cavity squamous cell carcinomas in male rats).

In 2008, data on the carcinogenic risk to humans following the ingestion of benzene are still not available. The risk to humans can be estimated by extrapolation from human occupational inhalation exposure data. However, because only summary data are available to Health Canada for estimating the unit risk of cancer from benzene exposure, and since animals and

humans display similar blood-related effects following benzene exposure, the NTP (1986) study is still deemed to be the best study with which to derive a MAC in drinking water.

Using a linearized multistage model and an allometric scaling factor (to correct for differences in metabolism between animals and humans), the estimated unit lifetime risks associated with ingestion of drinking water containing 1 µg benzene/L are estimated to range from 2.03×10^{-6} to 4.17×10^{-6} (Health Canada, 2005a). The overall unit risk associated with the ingestion of benzene in drinking water is reported as a range, given that lifetime exposure to benzene has been shown to result in more than one cancer end-point in animals. The above unit risk range has malignant lymphoma in female mice (2.03×10^{-6}) as its lower bound (least sensitive) and bone marrow haematopoietic hyperplasia (4.17×10^{-6}) in male mice as its upper bound (most sensitive). These unit risks assume 3.5 L-eq/day as the human drinking water consumption rate in order to account for additional uptake of benzene through dermal and inhalation exposure, estimated using Krishnan (2004).

Since the 1986 guideline, evidence for benzene's leukaemogenic potential in humans has been reported by many authors for workers occupationally exposed to benzene by inhalation. The Ohio Pliofilm cohort (Rinsky et al., 1981, 1987; Crump and Allen, 1984; Paustenbach et al., 1993; Paxton et al., 1994) and Chinese worker cohort studies (Yin et al., 1987, 1994, 1996; Dosemeci et al., 1994, 1996) have emerged as good studies for assessing the carcinogenic potential of benzene in humans following inhalation exposure in the workplace. In developing its public health goal for benzene in drinking water, the California Environmental Protection Agency (CalEPA) reanalysed the Ohio Pliofilm and Chinese worker cohort data (OEHHA, 2001). For the Pliofilm cohort, original data were obtained, allowing for a thorough sensitivity analysis of several outstanding issues identified in the literature, including choice of exposure matrix, start date for determining person-years at risk, worker subset, choice of model, and choice of background incidence rates for calculating lifetime risks. CalEPA was unable to obtain a full set of data for the Chinese worker cohort. As a result, grouped summary data published by the original study author (Hayes et al., 1997) were used, which did not allow for a complete analysis.

In a detailed assessment of the CalEPA analysis, Health Canada agreed with its balanced approach and thorough consideration of the outstanding issues identified above. With only summary data available to Health Canada for reassessment of the two cohort studies, no new follow-up data since the CalEPA assessment, and thorough analysis of these two cohorts by many other international authors, it was concluded that another new analysis using virtually the same approach would be redundant. The only change necessary to the CalEPA analysis would be to use Canadian standard death rates to calculate the lifetime risk of cancer instead of using U.S. or Californian death rates. Given the expected similarity of Canadian leukaemia death or incidence rates and those in the United States and California, this change would have a minimal impact on the lifetime risk estimates (Health Canada, 2005b).

In using CalEPA's estimated unit risks of leukaemia for ingestion of benzene, which were extrapolated from the Pliofilm and Chinese cohort inhalation data, Health Canada estimated the lifetime risks associated with ingestion of 1 µg/L of benzene in drinking water as 4.8×10^{-6}

(95% CI) from the Pliofilm cohort and 6.3×10^{-6} (95% CI) from the Chinese worker cohort. Once again, these estimated lifetime risks fall within the range considered to be "essentially negligible" and are comparable to the unit lifetime risks estimated from the animal data. These unit lifetime risks assume 3.5 L-eq/day as the human drinking water consumption rate (in order to account for inhalation and dermal exposure). Inhalation unit risks were converted to unit risks for ingestion using a standard body weight of 70 kg, a breathing rate of 20 m^3/day, an inhalation absorption rate of 50%, and a conversion factor of 1 ppm = 3190 µg/m^3 of air (OEHHA, 2001).

In humans, the haematopoietic cancer induced by benzene exposure is predominantly acute non-lymphocytic leukaemia; in rodents, lymphocytic leukaemia has been reported in mice (Snyder et al., 1980; NTP, 1986; Cronkite et al., 1989). The difference in induction of haematopoietic cancers in mice and humans is not yet clear; however, it may be due to differences in haematopoiesis between the two species. In mice, lymphocytes make up a larger portion of the nucleated cells in the bone marrow compared with humans (Parmley, 1988); therefore, lymphocytic leukaemia in mice could simply be the result of lymphocytes representing a larger target cell population for benzene metabolites in the bone marrow. Further research into the mechanism of lymphoma and leukaemia development in animals and humans following exposure to benzene is needed.

11.0 Rationale

The guideline for benzene is established based on cancer end-points and is considered protective of both cancer and non-cancer end-points. In establishing this guideline, the Federal-Provincial-Territorial Committee on Drinking Water also took into consideration the need for the guideline to be measurable and achievable, as well as levels of exposure from drinking water in Canada. Both animal and human epidemiological studies report similar toxic effects following exposure to benzene, regardless of exposure pathway (inhalation or ingestion). The most sensitive end-points resulting from exposure to benzene in both animals and humans are those related to the blood-forming organs.

Benzene can be found in both surface water and groundwater; in surface water, benzene tends to volatilize into the atmosphere, although ice cover may interfere with this process in winter. Benzene may enter water through petroleum seepage and weathering of exposed coal-containing strata and may enter air from volcanoes, forest fires, releases from plants, and anthropogenic sources. In Canada, levels of benzene in raw water sources have been reported as ranging between 0.02 and 0.42 µg/L, and levels in treated drinking water are generally less than 1 µg/L unless near a contamination source.

Several municipal-scale treatment processes can remove benzene from drinking water to levels below 0.005 mg/L. At the residential scale, drinking water treatment devices are available that have been certified as reducing concentrations of VOCs such as benzene to 0.001 mg/L, well below the MAC of 0.005 mg/L.

Based on the incidence of malignant lymphoma and bone marrow effects in animals following exposure to benzene by ingestion, the estimated lifetime risk associated with ingestion

of water containing benzene at the MAC of 0.005 mg/L is $1.02 \times 10^{-5} – 2.08 \times 10^{-5}$ (derived by multiplying the unit risk by the MAC). The estimated lifetime cancer risk associated with the ingestion of drinking water containing benzene at 5 µg/L is partly within the range considered generally to be "essentially negligible," although the upper level of the risk range at the MAC extends beyond that range. The guideline for a carcinogen is normally established at a level at which the increased cancer risk is "essentially negligible" when a person is exposed at that level in drinking water over a lifetime. In the context of drinking water guidelines, Health Canada has defined this term as a range from one new cancer above background levels per 100 000 people to one new cancer above background levels per 1 million people (i.e., 10^{-5}–10^{-6}) Because exposure from drinking water represents only a small fraction (1–2%) of the total exposure to benzene, this slight exceedance in risk at the MAC is deemed acceptable. The estimated unit risks from the human epidemiological data overlap those estimated from the animal data, providing additional support for a MAC of 0.005 mg/L (5 µg/L) for benzene in drinking water.

In summary, the MAC of 0.005 mg/L (5 µg/L) for benzene was established on the basis that:

- it is considered to present an "essentially negligible" risk;
- it is measurable, with an estimated PQL of 0.4 µg/L;
- treatment (both municipal and residential) is achievable at a reasonable cost.

As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area and recommend any change(s) to the guideline that it deems necessary.

12.0 References

Abernathy, D.J., Kleymenova, E.V., Rose, J., Recio, L., and Faiola, B. (2004) Human CD34+ hematopoietic progenitor cells are sensitive targets for toxicity induced by 1,4-benzoquinone. Toxicol. Sci., 79: 82–89.

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.

Aelion, C.M. and Bradley, P.M. (1991) Aerobic biodegradation potential of subsurface microorganisms from a jet fuel-contaminated aquifer. Appl. Environ. Microbiol., 57: 57–63.

Al-Bastaki, N.M. (2003) Treatment of synthetic industrial wastewater with UV/TiO_2 and RO using benzene as a model hydrocarbon. Desalination, 156(1): 193–197.

Alberta Department of Environment (2005) Personal communication with K. Pongar.

Allan, G. (1988) Experiences with treatment for volatile organic contaminants. J. N. Engl. Water Works Assoc., 101(1): 13–21.

Alther, G. (2002) Using organoclays to enhance carbon filtration. Waste Manage., 22(5): 507–513.

Aoyama, K. (1986) Effects of benzene inhalation on lymphocyte subpopulations and immune response in mice. Toxicol. Appl. Pharmacol., 85(1): 92–101.

APHA, AWWA, and WEF (2005) 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.

ATSDR (2007) Toxicological profile for benzene. Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA (www.atsdr.cdc.gov/toxprofiles/tp3.html).

AWWA (1991) Organics contaminant control committee report: existing VOC treatment installations; design, operation and cost. Water Quality Division, American Water Works Association, Denver, CO (Report No. 0033986).

Ball, B.R.and Edwards, M.D. (1992) Air stripping VOCs from groundwater: process design considerations. Environ. Prog., 11(1): 39–48.

Barbaro, J.R., Barker, J.F., Lemon, L.A., Gillham, R.W., and Mayfield, C.I. (1991) *In situ* cleanup of benzene in groundwater by employing denitrifying bacteria. Canadian Petroleum Products Institute, Ottawa, Ontario. 48 pp. (CPPI Report No. 91-6).

Bond, G.G., McLaren, E.A., Baldwin, C.L., and Cook, R.R. (1986) An update of mortality among chemical workers exposed to benzene. Br. J. Ind. Med., 43: 685–691.

Clark, R.M. and Adams, J.Q. (1991) Evaluation of BAT for VOCs in drinking water. J. Environ. Eng., 112(2): 247–268.

Clark, R.M., Fronk, C.A., and Lykins, B.W., Jr. (1988) Removing organic contaminants from groundwater: a cost and performance evaluation. J. Environ. Sci. Technol., 22(10): 1126–1130.

Clark, R.M., Miltner, R.J., Fronk, C.A., and Speth, T.F. (1990) Unit process research for removing volatile organic chemicals from drinking water: an overview. In: Ram, N.M., Christman, R.F., and Cantor, K.P. (eds.). Significance and treatment of volatile organic compounds in water supplies. Lewis Publishers, Chelsea, MI.

CPI (2003) CPI Product Profile for benzene. Camford Information Services Inc., Scarborough, Ontario.

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, NJ.

Cronkite, E.P. (1986) Benzene hematotoxicity and leukemogenesis. Blood Cells, 12(1): 129–137.

Cronkite, E.P., Bullis, J., Inoue, T., and Drew, R.T. (1984) Benzene inhalation produces leukemia in mice. Toxicol. Appl. Pharmacol., 75: 358–361.

Cronkite, E., Drew, R., Inoue, T., and Bullis, J. (1985) Benzene hematotoxicity and leukemogenesis. Am. J. Ind. Med., 7: 447–456.

Cronkite, E.P., Drew, R.T., Inoue, T., Hirabayashi, Y., and Bullis, J.E. (1989) Hematotoxicity and carcinogenicity of inhaled benzene. Environ. Health Perspect., 82: 97–108.

Crump, K.S. and Allen, B.C. (1984) Quantitative estimates of risk of leukemia from occupational exposure to benzene. Prepared for the Occupational Safety and Health Administration, May (OSHA Docket H-059B, Exhibit 152).

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

De Nardi, I.R., Varesche, M.B.A., Zalat, M., and Foresti, E. (2002) Anaerobic degradation of BTEX in a packed-bed reactor. Water Sci. Technol., 45(10): 175–180.

Dosemeci, M., Li, G.-L., Hayes, R.B., Yin, S.-N., Linet, M., Chow, W.-H., Wang, Y.Z., Jiang, Z.L., Dai, T.R., Zhang, W.U., Chao, X.-J., Ye, P.-Z., Kou, Q.-R., Fan, Y.-H., Zhang, X.-C., Lin, X.-F., Meng, J.-F., Zho, J.-S., Wacholder, S., Kneller, R., and Blot, W.J. (1994) Cohort study among workers exposed to benzene in China: II. Exposure assessment. Am. J. Ind. Med., 26(3): 401–411.

Dosemeci, M., Yin, S.N., Linet, M., Wacholder, S., Rothman, N., Li, G.-L., Chow, W.-H., Wang, Y.-Z., Jiang, Z.-L., Dai, T.-R., Zhang, W.-U., Chao, X.-J., Ye, P.-Z., Kou, Q.-R., Fan, Y.-H., Zhang, X.-C., Lin, X.-F., Meng, J.-F., Zho, J.-S., Blot, W.J., and Hayes, R.B. (1996) Indirect validation of benzene exposure assessment by association with benzene poisoning. Environ. Health Perspect., 104(Suppl. 6): 1343–1347.

Duarte-Davidson, R., Courage, C., Rushton, L., and Levy, L. (2001) Benzene in the environment: An assessment of the potential risks to the health of the population. Occup. Environ. Med., 58(1): 2–13.

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

Dyksen, J.E., Racsko, R.F., and Cline, G.C. (1995) Operating experiences at VOC treatment facilities. In: Proceedings of the 1995 Annual American Water Works Association Conference. American Water Works Association, Denver, CO. pp. 659–684.

Eastmond, D.A., Rupa, D.S., and Hasegawa, L.S. (1994) Detection of hyperdiploidy and chromosome breakage in interphase human lymphocytes following exposure to the benzene metabolite hydroquinone using multicolor fluorescence *in situ* hybridization with DNA probes. Mutat. Res., 322(1): 9–20.

English, C.W. and Loehr, R.C. (1991) Degradation of organic vapors in unsaturated soils. J. Hazard. Mater., 28: 55–63.

Environment Canada (2001) Ambient air measurements of benzene in Canada (1989–1998). National Air Pollution Surveillance (NAPS) Network, Environment Canada, Ottawa, Ontario (www.etc-cte.ec.gc.ca/publications/naps/benzene1989-98_e.html).

Environment Canada and Health and Welfare Canada (1993) *Canadian Environmental Protection Act* Priority Substances List assessment report: Benzene. Minister of Supply and Services Canada, Ottawa, Ontario (www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/benzene/index_e.html).

Farris, G.M., Everitt, J.I., Irons, R.D., and Popp, J.A. (1993) Carcinogenicity of inhaled benzene in CBA mice. Fundam. Appl. Toxicol., 20(4): 503–507.

Fishbein, L. (1984) An overview of environmental and toxicological aspects of aromatic hydrocarbons. 1. Benzene. Sci. Total Environ., 40: 189–218.

Fleming-Jones, M.E. and Smith, R.E. (2003) Volatile organic compounds in foods: A five year study. J. Agric. Food Chem., 51(27): 8120–8127.

Franz, T.J. (1975) Percutaneous absorption. On the relevance of *in vitro* data. J. Invest. Dermatol., 64: 190–195.

Franz, T.J. (1984) Percutaneous exposure of benzene. In: Advances in modern environmental toxicology. Vol. VI. Applied toxicology of petroleum hydrocarbons. Princeton Scientific Publishers, Princeton, NJ. pp. 61–70.

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

Graedel, T.C. (1978) Chemical compounds in the atmosphere. Academic Press, New York, NY. p. 105.

Hayes, R.B., Yin, S.N., Dosemeci, M., Li, G.L., Wacholder, S., Chow, W.H., Rothman, N., Wang, Y.Z., Dai, T.R., Chao, X.J., Jiang, Z.L., Ye, P.Z., Zhao, H.B., Kou, Q.R., Zhang, W.Y., Meng, J.F., Zho, J.S., Lin, X.F., Ding, C.Y., Li, C.Y., Zhang, Z.N., Li, D.G., Travis, L.B., Blot, W.J., and Linet, M.S. (1996) Mortality among benzene-exposed workers in China. Environ. Health Perspect., 104(Suppl. 6): 1349–1352.

Hayes, R.B., Yin, S.N., Dosemeci, M., Li, G.L., Wacholder, S., Travis, L.B., Li, C.-Y., Rothman, N., Hover, R.N., and Linet, M.S. (1997) Benzene and the dose-related incidence of hematologic neoplasms in China. J. Natl. Cancer Inst., 89(14): 1065–1071.

Health Canada (1986) Benzene. In: Guidelines for Canadian Drinking Water Quality supporting documentation. Bureau of Chemical Hazards, Environmental Health Directorate, Health Canada, Ottawa, Ontario.

Health Canada (2005a) Benzene: unit risks based on animal data. Unpublished report. Biostatistics Unit, Healthy Environments and Consumer Safety Branch, Ottawa, Ontario.

Health Canada (2005b) Benzene: unit risks based on human data. Unpublished report. Biostatistics Unit, Healthy Environments and Consumer Safety Branch, Ottawa, Ontario.

Hoffmann, K., Krause, C., Seifert, B., and Ullrich, D. (2000) The German Environmental Survey 1990/92 (GerES II): Sources of personal exposure to volatile organic compounds. J. Expo. Anal. Environ. Epidemiol., 10: 115–125.

Holliday, M.G. and Englehardt, F.R. (1984) Benzene. A criteria review. Report prepared under contract to the Monitoring and Criteria Division, Department of National Health and Welfare, Ottawa, Ontario. March 30.

Howard, P.H., Boethling, R.S., Jarvis, W.F., Meylan, W.M., and Michalenko, E.M. (1991) Handbook of environmental degradation rates. Lewis Publishers, Chelsea, MI.

HSDB (2005) Benzene CASRN: 71-43-2. Hazardous Substances Data Bank. National Library of Medicine (http://toxnet.nlm.nih.gov/).

IARC (1982) Benzene. In: Some industrial chemicals and dyestuffs. International Agency for Research on Cancer, Lyon, France. pp. 93–148 (IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Man, Volume 29).

IARC (1987) Benzene. In: Overall evaluations of carcinogenicity: An updating of IARC Monographs volumes 1–42. International Agency for Research on Cancer, Lyon, France. p. 120 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Supplement 7).

IPCS (1993) Benzene. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (Environmental Health Criteria 150).

IRIS (2003) Benzene (CASRN 71-43-2). Carcinogenicity assessment for lifetime exposure. Integrated Risk Information System, U.S. Environmental Protection Agency (www.epa.gov/iris/subst/0276.htm).

Jaques, A.P. (1990) National inventory of sources and emissions of benzene (1985). Environment Canada (EPS 5/AP/1).

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

Johansson, I. and Ingelman-Sundberg, M. (1988) Benzene metabolism by ethanol-, acetone-, and benzene-inducible cytochrome P-450 (IIE1) in rat and rabbit liver microsomes. Cancer Res., 48: 5387–5390.

Kang, J.W., Park, H., Wang, R.Y., Koga, M., Kadokami, H.K., Lee, E., and Oh, S. (1997) Effect of ozonation for treatment of micropollutants present in drinking water source. Water Sci. Technol., 36(12): 229–307.

Keller, K.A. and Snyder, C.A. (1986) Mice exposed *in utero* to low concentrations of benzene exhibit enduring changes in their colony forming hematopoietic cells. Toxicology, 42: 171–181.

Keller, K.A. and Snyder, C.A. (1988) Mice exposed *in utero* to 20 ppm benzene exhibit altered numbers of recognizable hematopoietic cells up to seven weeks after exposure. Fundam. Appl. Toxicol., 10: 224–232.

Kim, S., Vermeulen, R., Waidyanatha, S., Johnson, B.A., Lan, Q., Rothman, N., Smith, M.T., Zhang, L., Il, G., Shen, M., Yin, S., and Rappaport, S.M. (2006) Using urinary biomarkers to elucidate dose-related patterns of human benzene metabolism. Carcinogenesis, 27(4): 772–781.

Koffskey, W.E. and Brodtmann, N.V. (1983) Organic contaminant removal in Lower Mississippi River drinking water by granular activated carbon. Municipal Environmental Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH (EPA 600/2-83-032).

Krishnan, K. (2004) Development of a two tier approach for evaluating the relevance of multi-route exposures in establishing drinking water goals for volatile organic chemicals. Contract report prepared for Water Quality and Health Bureau, Safe Environments Programme, Health Canada, Ottawa, Ontario.

Lan, Q., Zhang, L., Il, G., Vermeulen, R., Weinburg, R.S., Dosemeci, M., Rappaport, S.M., Shen, M., Alter, B.P., Wu, Y., Kopp, W., Waidyanatha, S., Rabkin, C., Guo, W., Chanock, S., Hayes, R.B., Linet, M., Kim, S., Yin, S., Rothman, N., and Smith, M.T. (2004) Hematotoxicity in workers exposed to low levels of benzene. Science, 306: 1774–1776.

Li, G.L., Yin, S.N., Watanabe, T., Nakatsuka, H., Kasahara, M., Abe, H., and Ikeda, M. (1986) Benzene-specific increase in leukocyte alkaline phosphatase activity in rats exposed to vapors of various organic solvents. J. Toxicol. Environ. Health, 19(4): 581–589.

Lindstrom, A.B., Highsmith, V.R., Buckley, T.J., Pate, W.J., and Michael, L.C. (1994) Gasoline-contaminated groundwater as a source of residential benzene exposure: A case study. Government Reports Announcements & Index (Gra&I), Issue 23.

Love, T.O., 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, OH.

Lubicki, P., Cross, J., Jayaram, S., Zhao, J.S., and Ward, O. (1997) Removal of nitrobenzene and volatile organic compounds using electron radiation. IEEE 1997 annual report. Conference on Electrical Insulation and Dielectric Phenomena, Minneapolis, MN, October 19–22. Institute of Electrical and Electronics Engineers, Inc.

Lykins, B.W., Jr. and Clark, R.M. (1994) U.S. drinking water regulations: treatment technologies and cost. Drinking Water Research Division, U.S. Environmental Protection Agency, Cincinnati, OH (EPA-600/J-94/381).

Lykins, B.W., Jr., Geldreich, E.E., Adams, J.Q., Ireland, J.C., and Clark, R.M. (1984) Granular activated carbon for removing nontrihalomethane organics from drinking water. Municipal Environmental Research Laboratory, Drinking Water Research Division, U.S. Environmental Protection Agency, Cincinnati, OH (EPA-600/2-84-165).

Lykins, B.W., Jr., Clark, R.M., and Fronk, C.A. (1988) Reverse osmosis for removing synthetic organics from drinking water: a cost and performance evaluation. In: AWWA 1988 Annual Conference Proceedings, Orlando, FL. American Water Works Association, Denver, CO. pp. 1433–1457.

Mackay, D., Shiu, W.Y., and Ma, K.C. (1992) Illustrated handbook of physical-chemical properties and environmental fate for organic chemicals. Volume 1. Lewis Publishers, Boca Raton, FL.

Maibach, H.I. and Anjo, D.M. (1981) Percutaneous penetration of benzene contained in solvents used in the rubber industry. Arch. Environ. Health, 36: 256–260.

Maltoni, C., Conti, B., and Scarnato, C. (1982) Squamous cell carcinomas of the oral cavity in Sprague-Dawley rats following exposure to benzene by inhalation. Med. Lav., 4: 446–450.

Maltoni, C., Conti, B., and Cotti, G. (1983) Benzene: a multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. Am. J. Ind. Med., 4: 589–630.

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

Maltoni, C., Ciliberti, A., Cotti, G., Conti, B., and Belpoggi, F. (1989) Benzene, an experimental multipotential carcinogen: results of the long-term bioassays performed at the Bologna Institute of Oncology. Environ. Health Perspect., 82: 109–124.

Mathews, J.M., Etheridge, A.S., and Mathews, H.B. (1998) Dose-dependent metabolism of benzene in hamsters, rats and mice. Toxicol. Sci., 44: 14–21.

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

McKone, T.E. and Knezovich, J.P. (1991) The transfer of trichloroethylene (TCE) from a shower to indoor air: experimental measurements and their implications. J. Air Waste Manage. Assoc., 41(6): 832–837.

Ministère du Développement durable, de l'Environnement et des Parcs du Québec (2005) Personal communication with C. Robert.

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.

Nakai, J.S., Chu, I., Li-Muller, A., and Aucoin, R. (1997) Effect of environmental conditions on the penetration of benzene through human skin. J. Toxicol. Environ. Health, 51(5): 447–462.

New Brunswick Department of Environment (2008) Personal communication with K. White.

Newfoundland and Labrador Department of Environment and Conservation (2005) Personal communication with M. Goebel.

Nomiyama, K. and Nomiyama, H. (1974) Respiratory retention, uptake and excretion of organic solvents in man. Int. Arch. Arbeitsmed., 32: 75–83.

Nova Scotia Department of the Environment (2005) Personal communication with J. MacDonald.

NSF/ANSI (2005) Section 7.2.4. In: Standard 58: Reverse osmosis drinking water treatment systems. NSF International and American National Standards Institute. pp. 29–30.

NSF/ANSI (2006) Section 7.2.4. In: Standard 53: Drinking water treatment units—health effects. NSF International and American National Standards Institute. pp. 39–40.

NTP (1986) Toxicology and carcinogenesis studies of benzene (CAS No. 71-43-2) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC (Technical Report Series No. 289; NIH Publication No. 86-2545; http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr289.pdf).

NTP (2007) Toxicology and carcinogenesis study of benzene (CAS No. 71-43-2) in genetically modified haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice (gavage study). National Toxicology Program, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Research Triangle Park, NC (NTP GMM 8; NIH Publication No. 08-4425; http://ntp.niehs.nih.gov/files/GMM8_web1.pdf).

OEHHA (1997) Draft hazard identification of the developmental and reproductive toxic effects of benzene. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA, September (www.oehha.ca.gov/prop65/hazard_ident/pdf_zip/benzene.pdf).

OEHHA (2001) Public health goal for benzene in drinking water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA, June (www.oehha.ca.gov/water/phg/pdf/BenzeneFinPHG.pdf).

Ollis, D.F., Pelizzetti, E., and Serpone, N. (1991) Photocatalyzed destruction of water contaminants. Environ. Sci. Technol., 25(9): 1523–1529.

Ontario Ministry of the Environment (2008) Personal communication with S. Deshpande.

Parmley, R. (1988) Mammals. In: Rowley, A.F. and Ratcliffe, N.A. (eds.).Vertebrate blood cells. Cambridge University Press, Cambridge, U.K. pp. 337–424.

Paustenbach, D.J., Bass, R.D., and Price, P. (1993) Benzene toxicity and risk assessment, 1972–1992: implications for future regulation. Environ. Health Perspect., 101(Suppl. 6): 177–200.

Paxton, M.B., Chinchilli, V.M., Brett, S.M., and Rodericks, J.V. (1994) Leukemia risk associated with benzene exposure in the Pliofilm cohort: I. Mortality update and exposure distribution. Risk Anal., 14(2): 147–154.

Pekari, K., Vainiotalo, S., Heikkila, P., Palotie, A., Luotamo, M., and Riihimaki, V. (1992) Biological monitoring of occupational exposure to low levels of benzene. Scand. J. Work Environ. Health, 18(5): 317–322.

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.

Perbellini, L., Faccini, G.B., Pasini, F., Cazzoli, F., Pistoia, S., Rosellini, R., Valsecchi, M., and Brugnone, F. (1988) Environmental and occupational exposure to benzene by analysis of breath and blood. Br. J. Ind. Med., 45: 345–352.

Rappaport, S.M., Waidyanatha, S., Yeowell-O'Connell, K., Rothman, N., Smith, M.T., Zhang, L., Qu, Q., Shore, R., Ii, G., and Yin, S. (2005) Protein adducts as biomarkers of human benzene metabolism. Chem.-Biol. Interact., 153–154: 103–109.

Rasmussen, R.A. and Khalif, M.A.K. (1983) Atmospheric benzene and toluene. Geophys. Res. Lett., 10(11): 1096–1099.

Rinsky, R., Young, R.J., and Smith, A.B. (1981) Leukemia in benzene workers. Am. J. Ind. Med., 2: 217–245.

Rinsky, R.A., Smith, A.B., Hornung, R., Filloon, T.G., Young, R.J., Okun, A.H., and Landrigan, P.J. (1987) Benzene and leukemia: an epidemiologic risk assessment. N. Engl. J. Med., 316: 1044–1050.

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, OH (EPA-600/D-83-011).

Rosenberg, E. and Gutnick, D.L. (1981) The hydrocarbon-oxidizing bacteria. In: Starr, M.P., Stolp, H., Trüper, H.G., Balows, A., and Schlegel, H.G. (eds.). The prokaryotes: A handbook on habitats, isolation, and identification of bacteria. Volume 1. Springer-Verlag, Berlin, Germany.

Ross, D. (2000) The role of metabolism and specific metabolites in benzene-induced toxicity: evidence and issues. J. Toxicol. Environ. Health, 61: 357–372.

Rothman, N., Li, G.-L., Dosemeci, M., Bechtold, W.E., Marti, G.E., Wang, Y.-Z., Linet, M., Xi, L.-Q., Lu, W., Smith, M.T., Titenko-Holland, N., Zhang, L.-P., Blot, W., Yin, S.-N., and Hayes, R.B. (1996a) Hematotoxicity among Chinese workers heavily exposed to benzene. Am. J. Med., 29(3): 236–246.

Rothman, N., Smith, M.T., Hayes, R.B., Li, G.-L., Irons, R.D., Dosemeci, M., Haas, R., Stillman, W.S., Linet, M., Xi, L.-Q., Bechtold, W.E., Wiemels, J., Campleman, S., Zhang, L., Quintana, P.J.E., Titenko-Holland, N., Wang, Y.-Z., Lu, W., Kolachana, P., Meyer, K.B., and Yin, S. (1996b) An epidemiological study of early biologic effects in Chinese workers. Environ. Health Perspect., 104(Suppl. 6): 1365–1370.

Rozen, M.G. and Snyder, C.A. (1985) Protracted exposure of C57BL/6 mice to 300 ppm benzene depresses B- and T-lymphocyte numbers and mitogen responses. Evidence for thymic and bone marrow proliferation in response to the exposures. Toxicology, 37(1–2): 13–26.

Rozen, M.G., Snyder, C.A., and Albert, R.E. (1984) Depressions in B- and T-lymphocyte mitogen-induced blastogenesis in mice exposed to low concentrations of benzene. Toxicol. Lett., 20(3): 343–349.

Rudolph, J., Jebsen, C., Khedim, A., and Johnen, F.J. (1984) Measurements of the latitudinal distribution of light hydrocarbons over the Atlantic. In: Physico-chemical behaviour of atmospheric pollutants. Proceedings of the 3rd European Symposium, Varese, Italy. D. Riedel Publishing Co., Dordrecht, Holland.

Rushton, R. and Romaniuk, H. (1997) A case–control study to investigate the risk of leukemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. Occup. Environ. Med., 54: 152–166.

Sabourin, P.J., Chen, B.T., Lucier, G., Birnbaum, L.S., Fisher, E., and Henderson, R.F. (1987) Effect of dose on the absorption and excretion of [^{14}C]benzene administered orally or by inhalation in rats and mice. Toxicol. Appl. Pharmacol., 87: 325–336.

Saskatchewan Department of Environment and Resource Management (2005) Personal communication with S. Ferris and P. Minifie.

SCC (2003) Accredited certification bodies. Standards Council of Canada (www.scc.ca/en/programs/product_cert/accredited_clients.shtml).

Schnatter, A.R., Armstrong, T.W., Thompson, L.S., Nicolich, M.J., Katz, A.M., Huebner, W.W., and Pearlman, E.D. (1996) The relationship between low-level benzene exposure and leukemia in Canadian petroleum distribution workers. Environ. Health Perspect., 104(Suppl. 6): 1375–1379.

Sedran, M.A., Suidan, M.T., Venosa, A., and Pruden, A. (2003) Analysis of an aerobic fluidized bed reactor degrading MTBE and BTEX at reduced EBCTs. In: Proceedings of the American Water Works Association Annual Conference. American Water Works Association, Denver, CO. pp. 1–7.

Shih, T., Wangpaichitr, M., and Suffet, M. (2005) Performance and cost evaluations of synthetic resin technology for the removal of methyl *tert*-butyl ether from drinking water. J. Environ. Eng., 131(3): 450–460.

Singh, H.B. and Zimmerman, P.B (1992) Atmospheric distribution and sources of nonmethane hydrocarbons. Adv. Environ. Sci. Technol., 24: 177–235.

Slaine, D.D. and Barker, J.F. (1990) The detection of naturally occurring BTX during a hydrogeologic investigation. Ground Water Monit. Rev., 10: 89–94.

Smith, M.R. (1990) The biodegradation of aromatic hydrocarbons by bacteria. Biodegradation, 1: 191–206.

Smith, M.T. (1996) Mechanistic studies of benzene toxicity—implications for risk assessment. Adv. Exp. Med. Biol., 387: 259–266.

Smith, M.T. and Fanning, E.W. (1997) Report on the workshop entitled: “Modelling chemically induced leukemia—implications for benzene risk assessment.” Leukemia Res., 21(5): 361–374.

Smith, M.T. and Zhang, L. (1998) Biomarkers of leukemia risk: benzene as a model. Environ. Health Perspect., 106(Suppl. 4): 937–946.

Smith, M.T., Zhang, L., Jeng, M., Wang, Y., Guo, W., Duramad, P., Hubbard, A.E., Hostadler, G., and Holland, N.T. (2000) Hydroquinone, a benzene metabolite, increases the level of aneusomy of chromosomes 7 and 8 in human CD34-positive blood progenitor cells. Carcinogenesis, 21(8): 1485–1490.

Snyder, C.A., Goldstein, B.D., Sellakumar, A., Wolman, S., Bromberg, I., Erlichman, M.N., and Laskin, S. (1978) Hematotoxicity of inhaled benzene to Sprague Dawley rats and AKR mice at 300 ppm. J. Toxicol. Environ. Health, 4: 605–618.

Snyder, C.A., Goldstein, B.D., Sellakumar, A.R., Bromberg, I., Laskin, S., and Albert, R.E. (1980) The inhalation toxicology of benzene: Incidence of hematopoietic neoplasms and hematotoxicity in AKR/J and C57BL/6J mice. Toxicol. Appl. Pharmacol., 54: 323–331.

Snyder, C.A., Goldstein, B.D., Sellakumar, A.R., and Albert, R.E. (1984) Evidence for hematotoxicity and tumorigenesis in rats exposed to 100 ppm benzene. Am. J. Ind. Med., 5(6): 429–434.

Snyder, R. (2000) Recent developments in the understanding of benzene toxicity and leukemogenesis. Drug Chem. Toxicol., 23: 13–25.

Snyder, R. and Hedli, C.C. (1996) An overview of benzene metabolism. Environ. Health Perspect., 104(Suppl. 6): 1165–1171.

Snyder, R. and Kalf, G.F. (1994) A perspective on benzene leukemogenesis. Crit. Rev. Toxicol., 24(3): 177–209.

Sobrinho, J.A.H., Thiem, L.T., and Alkhatib, E.A. (1997) Benzene removal by PAC in jet flocculation system. J. Environ. Eng., 123(10): 1011–1018.

Speth, T.F. (1990) Removal of volatile organic compounds from drinking water by adsorption. In: Ram, N.M., Christman, R.F., and Cantor, K.P. (eds.). Significance and treatment of volatile organic compounds in water supplies. Lewis Publishers, Chelsea, MI.

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.

Stallings, R.L., Rogers, T.N., and Mullins, M.E. (1985) Air stripping of volatile organics. J. Inst. Environ. Sci. Technol. (IEST), 28(3): 28–31.

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.

Stillman, W.S., Varella-Garica, M., Gruntmeier, J.J., and Irons, R.D. (1997) The benzene metabolite, hydroquinone, induces dose-dependent hypoploidy in a human cell line. Leukemia (Basingstoke), 11(9): 1540–1545.

Subrahmanyam, V.V., Ross, D., Eastmond, D.A., and Smith, M.T. (1991) Potential role of free radicals in benzene induced myelotoxicity and leukemia. Free Radic. Biol. Med., 11: 495–515.

Susten, A.S., Dames, B.L., Burg, J.R., and Niemeier, R.W. (1985) Percutaneous penetration of benzene in hairless mice: an estimate of dermal absorption during tire-building operations. Am. J. Ind. Med., 7: 323–335.

Tatrai, E., Ungvary, G.Y., Hudak, A., Rodics, K., Loerincz, M., and Barcza, G.Y. (1980) Concentration dependence of the embryotoxic effects of benzene inhalation in CFY rats. J. Hyg. Epidemiol. Microbiol. Immunol., 24: 363–371.

Taylor, J., Chen, S.S., Mulford, L.A., and Norris, D. (2000) Flat sheet, bench and pilot testing for pesticide removal using reverse osmosis. American Water Works Association Research Foundation and American Water Works Association, Denver, CO (Report No. 90808).

Thomas, K.W., Pellizzari, E.D., Clayton, C.A., Perritt, R.L., Dietz, R.N., Goodrich, R.W., Nelson, W.C., and Wallace, L.A. (1993) Temporal variability of benzene exposures for residents in several New Jersey homes with attached garages or tobacco smoke. J. Expo. Anal. Environ. Epidemiol., 3(1): 49–73.

Tiburtius, E.R.L., Peralta-Zamora, P., and Emmel, A. (2005) Treatment of gasoline contaminated waters by advanced oxidation processes. J. Hazard. Mater., B126: 86–90.

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

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 (1979) Environmental monitoring of benzene. Office of Toxic Substances,.U.S. Environmental Protection Agency, Washington, DC (EPA 560/679/006).

U.S. EPA (1985a) National primary drinking water regulations, volatile synthetic organic chemicals, proposed rule making. U.S. Environmental Protection Agency. Fed. Regist., 50(219): 46902.

U.S. EPA (1985b) Technologies and cost for removal of VOCs from potable water supplies. Science and Technology Branch, Criteria Standards Division, Office of Drinking Water, U.S. Environmental Protection Agency, Washington, DC (PB86-118213).

U.S. EPA (1990) Technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Office of Drinking Water and Ground Water, Criteria and Standards Division, 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, OH.

U.S. EPA (1991b) National primary drinking water regulations—synthetic organic chemicals and inorganic chemicals; final rule. U.S. Environmental Protection Agency. Fed. Regist., 56(30): 3526.

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

U.S. EPA (1998a) 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 (1998b) Carcinogenic effects of benzene: An update. National Centre for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC (EPA/600/P-97/001F).

U.S. EPA (2000) EPI Suite Version 3.11. U.S. Environmental Protection Agency (www.epa.gov/oppt/exposure/pubs/updates_episuite_v3.11.revised.htm).

U.S. EPA (2002a) National primary drinking water regulations; organic chemicals, sampling and analytical requirements. Code of Federal Regulations, 40 CFR Part 141, Section 141.24, Volume 19. U.S. Environmental Protection Agency. pp. 363–372.

U.S. EPA (2002b) Announcement of the results of EPA's six year review of existing drinking water standards and request for public comment. Code of Federal Regulations, 40 CFR Part 141. U.S. Environmental Protection Agency. Fed. Regist., 67(74): 19029–19090.

U.S. EPA (2003a) Analytical feasibility support document for the six year review of existing National Primary Drinking Water Regulations (reassessment of feasibility for chemical contaminants). Targeting and Analysis Branch, Standards and Risk Management Division, Office of Groundwater and Drinking Water, U.S. Environmental Protection Agency, Washington, DC (EPA 815-R-03-003).

U.S. EPA (2003b) Water treatment technology feasibility support document for chemical contaminants; in support of EPA six-year review of National Primary Drinking Water Regulations. Targeting and Analysis Branch, Standards and Risk Management Division, Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency (EPA 815-R-03-004).

U.S. FDA (2006) Data on benzene in soft drinks and other beverages. Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (www.cfsan.fda.gov/~dms/benzdata.html).

Vaishnav, D.D. and Babeu, L. (1987) Comparison of occurrence and rates of chemical biodegradation in natural waters. Bull. Environ. Contam. Toxicol., 39: 237–244.

Valentine, J.L., Lee, S.S.T., Seaton, M.J., Asgharian, B., Farris, G., Corton, J.C., Gonzalez, F.J., and Medinsky, M.A. (1996) Reduction of benzene metabolism and toxicity in mice that lack CYP2E1 expression. Toxicol. Appl. Pharmacol., 141(1): 205–213.

Wallace, L.A. (1987) The TEAM study: Summary and analysis. Volume 1. U.S. Environmental Protection Agency, Washington, DC (EPA 600/6-87/002a; NTIS PB 88-100060).

Wallace, L.A. (1989a) Major sources of benzene exposure. Environ. Health Perspect., 82: 165–169.

Wallace, L.A. (1989b) The exposure of the general population to benzene. Cell Biol. Toxicol., 5(3): 297–314.

Wallace, L. (1996) Environmental exposure to benzene: an update. Environ. Health Perspect., 104(Suppl. 6): 1129–1136.

Wallace, L., Pellizzari, E., and Gordon, S. (1993) A linear model relating breath concentrations to environmental exposures: application to a chamber study of four volunteers exposed to volatile organic chemicals. J. Expo. Anal. Environ. Epidemiol., 3(1): 75–102.

Ward, C.O., Kuna, R.A., Snyder, N.K., Alsaker, R.D., Coate, W.B., and Craig, P.H. (1985) Subchronic inhalation toxicity of benzene in rats and mice. Am. J. Ind. Med., 7(5–6): 457–473.

Weber, W.J. and Pirbazari, M. (1982) Adsorption of toxic and carcinogenic compounds from water. J. Am. Water Works Assoc., 74(4): 203–209.

Westberg, H., Sexton, K., and Flyckt, D. (1981) Hydrocarbon production and photochemical ozone formation in forest burn plumes. J. Air Pollut. Control Assoc., 31: 661–664.

Whelan, J.K., Tarafa, M.E., and Hunt, J.M. (1982) Volatile C1–C8 organic compounds in macroalgae. Nature, 299: 50–52.

Whittaker, H. and Szaplonczay, T. (1985) Reverse osmosis at the Gloucester landfill. In: Proceedings of the 2nd Annual Technical Seminar on Chemical Spills, Toronto, Ontario. Sponsored by Technical Services Branch, Environmental Protection Service, Environment Canada. pp. 141–161.

WHO (2004) Chemical aspects. In: Guidelines for drinking-water quality. 3rd edition. Volume 1. World Health Organization, Geneva, Switzerland. p. 24 (www.who.int/water_sanitation_health/dwq/gdwq3_8.pdf).

Witz, G., Zhang, Z., and Goldstein, B.D. (1996) Reactive ring-opened aldehyde metabolites in benzene hematotoxicity. Environ. Health Perspect., 104(Suppl. 6): 1195–1199.

Wong, O. (1987) An industry-wide study of chemical workers occupationally exposed to benzene. Br. J. Ind. Med., 44: 382–395.

Yin, S.N., Li, G.L., Tain, F.D., Fu, Z.I., Jin, C., Chen, Y.J., Luo, S.J., Ye, P.Z., Zhang, J.Z., Wang, G.C., Zhang, X.-C., Wu, H.-N., and Zhong, Q.-C. (1987) Leukaemia in benzene workers: a retrospective cohort study. Br. J. Ind. Med., 44(2): 124–128.

Yin, S.-N., Linet, M.S., Hayes, R.B., Li, G.-L., Dosemeci, M., Wang, Y.-Z., Chow, W.H., Jiang, Z.L., Wacholder, S., Zhang, W.U., Dai, T.-R., Chao, X.-J., Zhang, X.-C., Ye, P.-Z., Kou, Q.-R., Meng, J.-F., Zho, J.-S., Lin, X.-F., Ding, C.-Y., Kneller, R., and Blot, W.J. (1994) Cohort study among workers exposed to benzene in China: I. General methods and resources. Am. J. Ind. Med., 26(3): 383–400.

Yin, S.-N., Hayes, R.B., Linet, M.S., Li, G.-L., Dosemeci, M., Travis, L.B., Li, C.Y., Zhang, Z.N., Li, D.G., Chow, W.H., Wacholder, S., Wang, Y.Z., Jiang, Z.L., Dai, T.R., Zhang, W.Y., Chao, X.J., Ye, P.Z., Kou, Q.R., Zhang, X.C., Lin, X.F., Meng, J.F., Ding, C.Y., Zho, J.S., and Blot, W.J. (1996) A cohort study of cancer among benzene-exposed workers in China: Overall results. Am. J. Ind. Med., 29(3): 227–235.

Yue, Z., Mangun, C., Economy, J., Kemme, P., Cropek, D., and Maloney, S. (2001) Removal of chemical contaminants from water to below USEPS MCL using fiber glass supported activated carbon filters. Environ. Sci. Technol., 35(13): 2844–2848.

Zhang, L., Venkatesh, P., Creek, M.L.R., and Smith, M.T. (1994) Detection of 1,2,4-benzenetriol induced aneuploidy and microtubule disruption by fluorescence *in situ* hybridization and immunocytochemistry. Mutat. Res., 320: 315–327.

Zhang, L., Rothman, N., Wang, Y., Hayes, R.B., Bechtold, W., Venkatesh, P., Yin, S., Wang, Y., Dosemeci, M., Li, G., Lu, W., and Smith, T. (1996) Interphase cytogenetics of workers exposed to benzene. Environ. Health Perspect., 104(Suppl. 6): 1325–1329.

Zhang, L., Rothman, N., Wang, Y., Hayes, R.B., Li, G., Dosemeci, M., Yin, S., Kolachana, P., Titenko-Holland, N., and Smith, M.T. (1998) Increased aneusomy and long arm deletion of chromosomes 5 and 7 in the lymphocytes of Chinese workers exposed to benzene. Carcinogenesis, 19(11): 1955–1961.

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.

Appendix A: List of acronyms

ALARA	as low as reasonably achievable
ANSI	American National Standards Institute
AOP	advanced oxidation process
BTEX	benzene, toluene, ethylbenzene, xylenes
bw	body weight
CalEPA	California Environmental Protection Agency (U.S.A.)
CI	confidence interval
CYP2E1	cytochrome P4502E1
DNA	deoxyribonucleic acid
EBCT	empty bed contact time
EPA	Environmental Protection Agency (U.S.A.)
GAC	granular activated carbon
K_p	skin permeability coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
L-eq	litre-equivalent
MAC	maximum acceptable concentration
MDL	method detection limit
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NOM	natural organic matter
NSF	NSF International
NTP	National Toxicology Program (U.S.A.)
PAC	powdered activated carbon
PBPK	physiologically based pharmacokinetic
ppm	parts per million
ppt	parts per trillion
PQL	practical quantitation limit
PTA	packed tower aeration
RNA	ribonucleic acid
RR	relative risk
SCC	Standards Council of Canada
SMR	standardized mortality ratio
TEAM	Total Exposure Assessment Methodology
TWA	time-weighted average
U.S. EPA	United States Environmental Protection Agency
UV	ultraviolet
VOC	volatile organic compound
v/v	by volume