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Guidance for Benzene in Residential Indoor Air

Science Assessment Document

Canada

Guidance for Benzene in Residential Indoor Air

Science Assessment Document

Water and Air Quality Bureau
Healthy Environments and Consumer Safety Branch

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

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LIST OF ACRONYMS AND ABBREVIATIONS

AER	Air exchange rate
AM	Arithmetic mean
AML	Acute myeloid leukemia (synonymous with ANLL, acute non-lymphocytic leukemia)
AhR	Aryl hydrocarbon receptor
ANLL	acute non-lymphocytic leukemia
ATSDR	Agency for Toxic Substances and Disease Registry
BMCL	Benchmark concentration lower confidence limit
CEPA	*Canadian Environmental Protection Act*
CMHC	Canada Mortgage and Housing Corporation
CYP2E1	Cytochrome P450 2E1
DNA	Deoxyribonucleic acid
ETS	Environmental tobacco smoke
GM	Geometric mean
IARC	International Agency for Research on Cancer
I/O	Indoor/outdoor
IPCS	International Programme on Chemical Safety
LOAEL	Lowest observed adverse effect level
MDL	Method detection limit
MRL	Minimal risk level
NHANES	National Health and Nutrition Examination Survey
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
NAPS	National Air Pollution Surveillance
P53	Protein 53
ppm	Parts per million
OEHHA	Office of Environmental Health Hazard Assessment
OR	Odds ratio
R^2	Square of the coefficient of correlation
REL	Reference exposure level
RfC	Reference concentration
RIOPA	Relationships of Indoor, Outdoor, and Personal Air study
RNA	Ribonucleic acid
SMR	Standardised mortality ratio
TC_{05}	Tumorigenic concentration associated with a 5% increase in the incidence of, or mortality due to, tumors
TEAM	Total Exposure Assessment Methodology
TWA	Time-weighted average
US EPA	United States Environmental Protection Agency
VOC	Volatile organic compound

EXECUTIVE SUMMARY

Background

Benzene is a volatile organic compound (VOC) with a relatively high vapour pressure, moderate-to-high water solubility, and low octanol/water partition coefficient that is released primarily to air. It has been identified by Health Canada as a priority indoor air contaminant through consultations with provincial and territorial health departments, as well as with key stakeholders in industrial and environmental organizations.

Exposure

Exposure of the general Canadian population to benzene is attributed predominantly to indoor air by inhalation because indoor levels generally exceed those outside, and time spent indoors is typically greater than time spent outdoors. Other routes of exposure (ingestion and dermal absorption) contribute minimally to total benzene intake (Health Canada 2009). In studies by Health Canada, the median concentrations of benzene measured in Canadian residences ranges from 0.5 to 2.2 $\mu g/m^3$ (Health Canada 2012a; Health Canada 2010b; Health Canada 2010d; Héroux et al. 2008). Indoor levels are approximately three-fold higher in homes with attached garages compared to those with detached garages, or no garages. Median outdoor concentrations are usually less than 1 $\mu g/m^3$. The ratio of indoor/outdoor levels (I/O) ranges from 1.5 to 2.4 (median) and remains above 1 at the 25% percentile, suggesting a significant contribution of indoor sources in almost all homes.

More than half of Canadian single-family homes have an attached garage. Attached garages, when present, are the major indoor source of benzene in homes because vehicle exhaust and evaporative emissions from gas-powered equipment and stored solvents in garages can enter a home (Héroux et al. 2010; Héroux et al. 2008; Jia, Batterman and Godwin 2008b; Batterman, Jia and Hatzivasilis 2007). Smoking is also a significant contributor to indoor benzene levels (Héroux et al. 2010; Héroux et al. 2008).

The known sources could not account for all benzene measured in studies and there may be other unidentified sources in homes. Some non-smoking homes without attached garages may have indoor benzene levels similar to homes with attached garages. While benzene has been detected in building materials, emission rates have generally been low ($<4\ \mu g\ m^{-2}\ h^{-1}$) with few exceptions (e.g., adhesives and caulking) (Choi et al. 2010; Won et al. 2005; Yu and Crump 1998; US EPA 1992; Wallace, Pellizzari and Leaderer 1987). Few household or consumer products have reported benzene content (Kwon et al. 2008; Kwon et al. 2007; Sack et al. 1992; US EPA 1992; Wallace, Pellizzari and Leaderer 1987) and, in the majority of studies, benzene was not associated with household products or activities (Missia et al. 2010; Héroux et al. 2008; Jia, Batterman and Godwin 2008b; Jia, Batterman and Godwin 2008b; Jia, Batterman and Godwin 2008b; Jia, D'Souza and Batterman 2008; Park and Ikeda 2006; Brown 2002; Ilgen et al. 2001c; Kim, Harrad and Harrison 2001). Therefore, a more systematic approach to identifying other sources of benzene indoors is warranted.

Another potential indoor source of benzene would be vapour intrusion if the groundwater or soil underlying the house is contaminated. In addition, if benzene is present in the domestic water supply, volatilization from water while bathing, showering, or running faucets may occur. The Health Canada drinking water guideline has been developed to account for all exposure pathways (ingestion, inhalation, dermal absorption) and thus, if a water supply complies with the drinking water guideline regarding benzene content, the health risk of such exposure would be negligible.

Health effects

Human exposure to benzene has been linked to dizziness, tremors, nausea, vomiting, headache, and drowsiness after minutes of exposure to high levels in the range of 700 to 3000 ppm (2240 to 9600 mg/m^3). Effects after subchronic to chronic exposures as low as <1 ppm (<3.2 mg/m^3) include progressive deterioration in hematopoietic function including bone marrow damage, changes in circulating blood cells and altered immune response (ATSDR 2007).

Benzene is classified as a carcinogen (US EPA 1998; Environment Canada and Health and Welfare Canada 1993; IARC 1987). Benzene affects the blood-forming system at low levels of occupational exposure $\leq$ 1 ppm (3.2 mg/m^3), and there is no evidence of a threshold. Chronic exposure to benzene has been shown to cause leukemia, a cancer of the blood or bone marrow, in occupationally exposed workers; and leukemia and lymphomas in laboratory rats and mice (Health Canada 2009; OEHHA 2001; Hayes et al. 1997; Rinsky, Young and Smith 1981). The carcinogenic mode of action for benzene is not well understood; however, a series of important biological events progressing from metabolism to development of leukemia has been proposed (Meek and Klaunig, 2010).

Health Canada and other organizations have characterized the cancer risk associated with exposure to benzene in air (Health Canada 1996; OEHHA 2001; US EPA 2000). All of these values can be expressed as an increased risk of leukemia over a lifetime. The basis for these values is epidemiological studies of occupationally exposed individuals. The derivation of any reference value requires careful consideration of many factors and the adoption of several assumptions. Differences in these key inputs are reflected in the range of published toxicological reference values for benzene. However, considering the uncertainties identified with extrapolation of risks associated with exposures at occupational levels to lower, environmentally relevant concentrations, the shape of the dose response curve and the mode of action of benzene-associated leukemia, these reference concentration values are within a similar band of uncertainty.

From the cancer risk analyses by Health Canada (1996), the United States Environmental Protection Agency (US EPA 2000) and the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA 2001), the concentrations associated with a $1x10^{-6}$ (one in one million) risk of leukemia range from 0.06 $\mu g/m^3$ (from the most justifiable unit risk identified by OEHHA (2001)) to 0.45 $\mu g/m^3$ (the upper bound of the range presented by US EPA (2000)). Guidance on benzene levels indoors has been developed by the World Health Organization (WHO 2010) and European Commission (2005). Both of these organizations suggest that benzene levels indoors should be minimized as much as possible, and neither organization has developed a numerical guideline value for benzene levels indoors.

The real cancer risk from benzene in most Canadian homes, while not always negligible, is uncertain. Environmental levels are at least three orders of magnitude lower (in $\mu g/m^3$ range) than the occupational exposure levels in the key studies (in mg/m^3 range), and conservative assumptions were used when extrapolating from the risks based on high exposures. However, the uncertainty associated with the estimation of cancer risk at environmental exposure levels may be reduced when a clear mode of action of benzene toxicity in humans is established and applied to better estimate the dose-response relationship at low exposures.

Guidance

The range of estimates of carcinogenic risks of benzene indicates that there may be a low but non-negligible risk at indoor exposure levels. On this basis, from a practical perspective, Health Canada has opted to use a qualitative approach, recommending that individuals take actions to reduce exposure to benzene indoors as much as possible. Measures to control known indoor sources may reduce benzene concentrations such that the risk to residents is very low. As further sources are identified and effective control measures developed, Health Canada will incorporate additional recommendations on reducing benzene levels in its communications to health and building professionals and the public.

While all indoor sources of benzene in Canadian homes could not be characterized, addressing the strongest predictors identified is likely to have the most significant impact on indoor levels. Exposure reduction strategies should be targeted towards these primary sources of benzene indoors over which homeowners have control, namely attached garages and indoor smoking. Indoor benzene levels may be minimized by:

- Preventing leaks from an attached garage to the house;
- Making sure that there is an appropriate seal between the home and the garage, particularly for any door that connects the two. This can be achieved by providing an appropriate air barrier and a sealed door between the garage and house and drywalling shared walls between the garage and house. These actions will also reduce the air exchange between the home and the garage;
- Installing an exhaust fan in an attached garage;
- Not idling vehicles in an attached garage;
- Not starting gas-powered equipment in an attached garage; and,
- Not smoking inside the home or the garage.

Where possible, removing solvents and gas-powered equipment, tools or engines from attached garages, since most small engines do not have emission controls on evaporative releases, may also be considered.

While there is some evidence (CMHC 2004; Ilgen et al. 2001c) to support a reduction in indoor benzene levels originating from attached garages following these exposure reduction strategies, further research is required to understand which mitigation measures are the most technically feasible and cost-effective at reducing the migration of benzene from attached garages indoors. As well, research is needed into the predictors of elevated benzene in homes with detached garages or no garages.

PREAMBLE

Health Canada assesses the health risks posed by specific indoor pollutants in residential environments and provides recommendations on how to reduce those risks. The Science Assessment Document summarizes the known health effects, pollutant sources and exposure levels in Canadian homes, and characterizes the risks to health based on the best scientific data available. Reference concentrations for short-term and/or long-term exposure to the pollutant may be developed, representing indoor air concentrations below which health effects are unlikely to occur. The Residential Indoor Air Quality Guideline for the pollutant recommends exposure limits based on the reference concentrations and on consideration of the feasibility of achieving such levels through indoor source control.

When a numerical exposure limit cannot be derived from the available scientific evidence, a Residential Indoor Air Quality Guidance Document is developed that focuses on actions to reduce exposure. Guidelines may also include recommendations to control sources or other actions to reduce exposure.

The Guidelines and/or Guidance Documents are meant to serve as a scientific basis for activities to reduce the risk from indoor air pollutants including, but not limited to:

- Assessments by public health officials of health risks from indoor air pollutants in residential, or similar, environments;
- Performance standards that may be applied to pollutant-emitting materials, products, and devices, so that their normal use does not lead to air concentrations of pollutants exceeding these guidelines; and,
- Communication products to inform Canadians of actions they can take to reduce their exposure to indoor air pollutants and to protect their health.

The Residential Indoor Air Quality Guidelines and Guidance Documents replace a series of exposure limit values for indoor air pollutants that were published in 1987 in a report titled *Exposure Guidelines for Residential Indoor Air Quality* (Health Canada 1987). In addition to updates for the substances included in the 1987 report, Guidelines or Guidance will be developed for other substances that are identified as having the potential to affect human health in the indoor environment.

The focus of this Science Assessment Document is benzene. In 1993, benzene was included in the first Priority Substances List (PSL) of 44 substances that were assessed by Health Canada and Environment Canada as part of the *Canadian Environmental Protection Act* (CEPA) Priority Substances Assessment Program. It was concluded that benzene was carcinogenic and therefore met the criteria of the original *Canadian Environmental Protection Act*, equivalent to section 64(c) of CEPA (1999) (Environment Canada and Health and Welfare Canada 1993).

The purpose of this document is to survey the scientific literature for benzene, specifically exposure, epidemiological and toxicological studies, to develop guidance for addressing benzene in residential indoor air. The present document draws on relevant studies on the exposure to, and health effects of, benzene published until the end of 2009. Key published literature associated with the derivation of reference concentrations by other organizations was evaluated. More recent articles were included on a case-by-case basis, including the replacement of references to unpublished data with published reports. Section 11 presents the search criteria in more detail. Other relevant information is drawn from three authoritative reviews: (i) *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document Benzene* published by Health Canada (Health Canada 2009); (ii) *Toxicological Profile of Benzene* published by the Agency for Toxic Substances and Disease Registry (ATSDR 2007); and (iii) the Government of Canada's *Priority Substances List Assessment Report: Benzene* (Environment Canada and Health and Welfare Canada 1993).

1.0 PHYSICAL AND CHEMICAL CHARACTERISTICS

Benzene is a colourless or light-yellow liquid chemical with a sweet smell at room temperature. It is highly flammable, has a relatively low boiling point of 80.1°C, and a high vapour pressure of 10.1 kPa–13.2 kPa at 25°C, causing it to quickly evaporate into the air. Benzene is soluble in water and miscible with most organic solvents. Its physical and chemical properties are summarized in Table 1 (Health Canada 2009; ATSDR 2007).

Table 1. Physical and chemical properties of benzene

Property	Value
Molecular formula	C_6H_6
Molecular weight	78.11 g/mol
CAS registry number	71-43-2
Density	0.878 g/cm^3 at 15°C
Vapour pressure	10.1 kPa–13.2 kPa at 25°C
Water solubility	820 mg/L–2167 mg/L at 25°C
Melting point	5.5°C
Boiling point	80.1°C
Odour threshold	4.68 ppm (15.0 mg/m^3)
Octanol/water partition coefficient	1.56–2.69
Common synonyms	Annulene, benzine, benzol, benzole, benzol coal, naphtha, cyclohexatriene, mineral naphtha, motor benzol, phenyl hydride, pyrobenzol, pyrobenzole
Conversion factors	1 ppm = 3.2 mg/m^3 at 25 C° and 1 atm (760 mm Hg) of pressure mg/m^3 = 0.31 ppm

Chemical structure

2.0 SOURCES IN THE ENVIRONMENT

The majority of benzene will partition to the atmosphere or surface waters due to its relatively high vapour pressure, moderate-to-high water solubility and low octanol/water partition coefficient (Health Canada 2009). Most benzene released into the environment is due to atmospheric releases (93%), with smaller releases to water and soil from industrial discharges, landfill leachate, and gasoline leaks from underground storage tanks (ATSDR 2007).

Canada's National Pollutant Release Inventory indicates that in 2008, on-site releases from all industrial facilities totalled 773 tonnes, of which 654 tonnes were released to air (Environment Canada 2009c). Virtually all (99.9%) of the benzene released into the environment eventually distributes itself into the air (Wallace 1989). National benzene emissions have declined 67% over the last decade as a result of government interventions to reduce benzene emissions in the oil and gas, transportation, petroleum refining, chemical manufacturing, and steel manufacturing sectors. Between 1994 and 2008, the reductions were larger in urban (-76%) than in rural (-50%) locations in Canada (Environment Canada 2009c).

Benzene naturally exists as a component of crude oil and is also a product of combustion from both natural (e.g., forest fires and volcanoes) and anthropogenic sources. Emission sources include petrochemical industries and releases during the production and use of petroleum-related products, especially in the transportation sector. Benzene is widely used in the synthesis of many chemicals (e.g., styrene, phenol, cyclohexane, aniline and alkyl benzenes), consumer products (e.g., plastics, resins and detergents), pesticides, pharmaceuticals, and in the tire and shoe industries (ATSDR 2007).

Indoors, benzene concentrations result from a limited number of sources, which can be categorized into the seven groups listed below. The influence of the more prevalent of these sources on indoor benzene levels is discussed further in Section 3.1.1.

1. Migration from attached garages: Garages often contain many VOC sources (e.g., vehicles, fuels, automotive products, solvents, lawnmowers, snow blowers) that can release benzene through both evaporative and/or combustion emissions. Gasoline is a source of benzene; the benzene content in Canadian gasoline is approximately 1% by volume or 10,000 µg/g (10,000 ppm) (Environment Canada 2009b). Temperature and air pressure gradients often favour air migration from a garage (usually colder, higher pressure) into a home (usually warmer, lower pressure) through connecting doors and gaps in the building envelope. In 2007, approximately 66% of Canadian homes had an attached garage; this percentage ranged from approximately 40% in Atlantic Canada to 75% in British Columbia and Ontario (Natural Resources Canada 2010).

2. Environmental tobacco smoke (ETS): Tobacco smoke contains many aromatic compounds, including benzene. Benzene emission factors may range from 296 to 610 µg/cigarette (Charles, Batterman and Jia 2007). Most benzene emissions from cigarettes occur in the sidestream smoke. The contribution of ETS to indoor benzene levels depends on the number of smokers, number of cigarettes smoked, ventilation rates and other sources.

3. Off-gassing from building materials: Emission rates depend on many factors such as the age and nature of the material and testing environmental conditions (e.g., temperature, humidity, air velocity). In a five-city, multi-season European study, benzene emission rates in homes, schools and public buildings were <0.5 µg $m^{-2}h^{-1}$ and benzene made no significant contribution to emissions from building materials (Missia et al. 2010). In a review of literature from 1979 to 1990, identified sources of residential benzene emissions included adhesives, paint removers, particle board, foam insulation, inks and wood stains (US EPA 1992). In one study, a benzene emission rate of 120 ± 29 ng m^{-2} min^{-1} (7.2 ± 1.74 µg m^{-2} h^{-1}) was measured for painted gypsum board (drywall); it was not detected in glued wallpaper or glued carpet (Wallace, Pellizzari and Leaderer 1987). In another study, benzene was identified in vinyl and PVC flooring and nylon and rubber-backed carpet; however, these levels were not quantified (Yu and Crump 1998). More recently, benzene was detected in 89% of 69 building materials commonly used in Canada

(Won et al. 2005). Adhesives and caulking had the highest emission rates over 24 h with ranges of 11 to 252 and 146 to 905 $\mu g\ m^{-2}\ h^{-1}$, respectively, while emission rates were no more than 4 $\mu g\ m^{-2}\ h^{-1}$ for all other materials including solid and engineered materials and flooring materials. In a more recent survey, benzene was not detected in wallpaper, wallpaper adhesive, plywood flooring or epoxy-based flooring adhesive (Choi et al. 2010).

4. Household and consumer products: Benzene in these products is generally reported as content (%). Recent North American data were not identified. However, in an earlier American survey, 0.6% of 1159 products (selected for their potential to contain chlorinated solvents) contained benzene above the lower reporting limit of 0.1% by weight. These products were classified as automotive, fabric and leather treatments and oil, greases and lubricants. Benzene was not detected in household cleaners and polishes, paint related products, cleaners for electronic equipment, adhesives or miscellaneous products (Sack et al. 1992). In other studies, benzene was detected in spot cleaners (US EPA 1992), suspected in detergents (US EPA 1992), and not detected in cleaning agents or pesticides (Wallace, Pellizzari and Leaderer 1987). In two more recent Korean surveys of commonly purchased items (based on sales figures in the previous year), benzene was found in 2 of 59 household products (one laundry detergent and one nail polish) and 3 of 42 liquid household products (cleaning products or deodorizers), but was not identified in glues, nail colour removers, paints, pesticides or sealants (Kwon et al. 2008; Kwon et al. 2007).

5. Ambient air: Ambient benzene levels are generally lower than levels indoors. Where indoor levels are similar to outdoor levels, measured just outside the home, it suggests that much of the benzene is coming from outdoor sources (Jia, Batterman and Godwin 2008a; Edwards et al. 2001b). In Canadian studies, median indoor levels were consistently measured at higher levels than those outdoors, with the exception of Fort Saskatchewan (see Table 2 and Figure 2).

6. Vapour intrusion from benzene/gasoline contaminated ground water/soil under homes: in Canadian residential areas where there is benzene-contaminated ground water or soil, migration of benzene through unsaturated soil and into homes may potentially occur. Contamination with benzene is not a widespread problem in Canada. However, accidental releases of benzene may occur at any stage of production, storage, use and transport of isolated benzene, crude oil and gasoline (Health Canada 2009). For an assessment of potential contaminant vapour transport from the subsurface to building interiors, refer to Health Canada (2010a)

7. Volatilization of benzene from contaminated drinking water in homes: As benzene is highly volatile, exposure could occur by inhalation and dermal absorption of contaminated drinking water during bathing and showering. While contamination with benzene is extremely rare in Canada, this route of exposure was addressed in Health Canada's Guidelines for Canadian Drinking Water Quality (Health Canada 2009).

3.0 INDOOR AND OUTDOOR BENZENE CONCENTRATIONS AND PERSONAL EXPOSURE

Results from the Canadian Human Activity Pattern Survey indicate that Canadians spend approximately 90% of their time indoors (Leech et al. 2002), the majority of which occurs at home [64% (>18 years of age) to 72% (<11 years of age)] with time also spent indoors at other indoor locations such as schools, public buildings, offices, factories, stores and restaurants. Similar data have been reported for the United States (Klepeis et al. 2001) and in smaller North American studies of children (Noullett, Jackson and Brauer 2006; Koutrakis et al. 2005; Wu et al. 2005; Allen et al. 2004; Liu et al. 2003), adults (Rodes et al. 2010) and older adults (Leech and Smith-Doiron 2006; Rojas-Bracho et al. 2004; Ebelt et al. 2000; Stieb et al. 1998). Results from these other studies suggest that children spend more time indoors at locations away from home, whereas older adults and those with underlying health conditions spend more time indoors at home.

Canadian studies were not identified in which the contributions of different microenvironments to total benzene exposures were characterized. In a 12-city European study, Bruinen de Bruin et al. (2008) reported the percentage contributions to total personal exposure to benzene from indoors at homes (36.2%), at work (32.2%), outdoors at work (2.2%), and in transit (29.4%). The results from a study in Michigan suggest an even higher proportion of indoor benzene exposure can be attributed to home exposures (36.6% from indoors at home and 43.5% from attached garages) (Batterman, Jia and Hatzivasilis 2007). This study also reported exposures attributed to outdoors (3.2%), in-vehicle (4.0%), heavy traffic (3.6%), and office/factory (9.2%). When the distribution of personal exposures in urban and suburban communities in the United States was estimated using available field monitoring and modeling data, the results indicated that more than half of personal exposures of adults to benzene in the United States occurred indoors; however, the majority of exposure was accounted for by the infiltration of outdoor sources (e.g., point-, area-, mobile- or transportation-related) (Loh et al. 2007).

Canadian indoor, outdoor and personal exposure concentrations of benzene are presented in Table 2. The range of median benzene levels measured in all studies was from 0.3 to 6.9 µg/m^3 (indoors), <1.0 to 3.4 µg/m^3 (outdoors), and from 1.5 to 2.8 µg/m^3 (personal). Maximum values ranged from 6.2 to 118 µg/m^3 (indoors), 0.8 to 115 µg/m^3 (outdoors) and from 9 to 120 µg/m^3 (personal) (Table 2).

Table 2. Indoor, outdoor and personal exposure concentrations (µg/m^3) of benzene measured in Canada.

Location	Sampling period	Sampling method	Season	No. of homes	Smoking status	No. of samples	Concentration (µg/m^3)					Reference
							AM	GM	Median	95th %ile	Max	
INDOOR												
Halifax, Nova Scotia	2009	Summa canisters (7 X 24 hours)	Summer Winter	50 50	Non-smokers	331 312	2.4 3.2	0.8 1.2	0.5 0.8	9.0 8.2	85.2 89.7	Health Canada (2012a)
Regina, Saskatchewan	2007	Summa canisters (24 hours)	Summer Winter	111 106	Non-smokers Smokers Non-smokers Smokers	91 13 84 21	2.7 3.4 1.9 2.9	1.2 2.2 1.3 2.1	0.9 2.2 1.1 1.9	13.7 13.3 4.7 9.3	32.3 13.3 17.9 13.1	Health Canada (2010b)
Windsor, Ontario	2006	Summa canisters (5 X 24 hours)	Summer Winter	46 47	Non-smokers	211 224	3.8 1.6	1.8 1.3	1.4 1.2	21.0 3.6	50.1 10.4	Health Canada (2010d)
Windsor, Ontario	2005	Summa canisters (5 X 24 hours)	Summer Winter	45 48	Non-smokers	217 232	3.1 2.1	2.0 1.7	1.5 1.5	11.1 5.3	16.5 13.9	Health Canada (2010d)
Quebec City, Quebec	2005	3M passive samplers (7 days)	Winter–spring	96	Non-smokers/ smokers	94		1.2	1.2		22.4	Héroux et al. (2008)
Ottawa, Ontario	2002–2003	Active sampling tubes (100 minutes)	Winter–spring	75	Non-smokers/ smokers	75	2.9	1.8	2.2		21.0	Zhu et al. (2005)
Fort McKay, Alberta	2006	Passive samplers (7 days)	All seasons	33	Non-smokers/ smokers	33			1.9	18.9	32.0*	Alberta Health and Wellness (2008)
Fort McMurray First Nations Gregoire Lake/Anzac, Alberta	2006	Passive samplers (7 days)	All seasons	24	Non-smokers/ smokers	24			2.5	15.0	17.0*	Alberta Health and Wellness (2008)
Fort McMurray, Alberta	2005	Passive samplers (7 days)	All seasons	29	Non-smokers/ smokers	29			1.8	10.9	12*	Alberta Health and Wellness (2007)
Fort Chipewyan, Alberta	2005	Passive samplers (7 days)	All seasons	30	Non-smokers/ smokers	30			2.2	14.9	118*	Alberta Health and Wellness (2007)
Wabamun and area, Alberta	2004	Passive samplers (7 days)	All seasons	193	Non-smokers/ smokers	193			1.0	5.0	89*	Alberta Health and Wellness (2006)
Fort Saskatchewan and area, Alberta	2001	Passive samplers (7 days)	All seasons	138	Non-smokers/ smokers	138			0.3	4.4	11*	Alberta Health and Wellness (2003)
Grande Prairie and area, Alberta	2000	Passive samplers (7 days)	All seasons	132	Non-smokers/ smokers	132			0.9	4.9	19*	Alberta Health and Wellness (2002)
Fort McKay, Alberta	1999	Passive samplers (4 days)	Fall and winter	NA	NA	30			4.1			Kindzierski, Hoeksema and Cheperdak (2008)
Fort McMurray, Alberta	1997–1998	Passive samplers (4 days)	All seasons	300	Non-smokers/ smokers	300			1.7	6.6	60.0*	Alberta Health and Wellness (2000)
Ottawa, Ontario	1997	Summa canister (30-minute sample) pretests	Winter	16	Non-smokers	16 16	3.8 7.0		3.6 6.9		6.2 16.8	Graham et al. (2004)
Canada nationwide	1991	3M passive samplers (24 hours)	Winter Spring Summer Fall	754	NA	185 178 194 197	6.4 5.6 2.7 7.0					Fellin and Otson (1994)
Range							**1.6-7.0**		**0.3-6.9**	**3.6-21.0**	**6.2-118**	

Location	Sampling period	Sampling method	Season	No. of homes	Smoking status	No. of samples	Concentration (µg/m^3)					Reference
							AM	GM	Median	95th %ile	Max	
OUTDOOR												
Halifax, Nova Scotia	2009	Summa canisters (7 X 24 hours)	Summer Winter	50 50	— —	324 287	0.4 0.6	0.3 0.6	0.3 0.6	0.7 1.2	12.6 2.9	Health Canada (2012a)
Regina, Saskatchewan	2007	Summa canisters (24 hours)	Summer Winter	111 106	—	108 94	0.3 0.8	0.3 0.7	0.2 0.6	0.6 2.0	6.0 2.8	Health Canada (2010b)
Windsor, Ontario	2006	Summa canisters (5 X 24 hours)	Summer Winter	46 47	—	214 214	0.8 0.8	0.7 0.8	0.7 0.8	1.5 1.4	4.4 1.9	Health Canada (2010d)
Windsor, Ontario	2005	Summa canisters (5 X 24 hours)	Summer Winter	45 48	—	216 201	0.9 1.1	0.8 1.0	0.7 0.9	2.1 2.0	2.9 3.1	Health Canada (2010d); Stocco et al. (2008)
Windsor, Ontario	2004	Passive samplers (2 weeks)	All seasons	—	—	54	0.9		0.9		1.4	Wheeler et al. (2008)
Toronto, Ontario	2006	Passive samplers (2 weeks)	Summer	—	—	45	0.7		0.6		1.3	Su et al.(2010)
Fort McKay, Alberta	2006	Passive samplers (7 days)	All seasons	35	—	33			<MDL (0.4)	0.6	0.8*	Alberta Health and Wellness (2008)
Fort McMurray First Nations Gregoire Lake/Anzac, Alberta	2006	Passive samplers (7 days)	All seasons	24	—	24			0.2	1.3	1.5*	Alberta Health and Wellness (2008)
Sarnia, Ontario	2005	3M passive samplers (2 weeks)	Fall	—	—	37	1.0		0.8*		1.8*	Miller, Xu and Luginaah (2009)
Fort McMurray, Alberta	2005	Passive samplers (7 days)	All seasons	29	—	29			1.3	2.4	2*	Alberta Health and Wellness (2007)
Fort Chipewyan, Alberta	2005	Passive samplers (7 days)	All seasons	30	—	30			0.7	9.9	115*	Alberta Health and Wellness (2007)
Wabamun and area, Alberta	2004	Passive samplers (7 days)	All seasons	193	—	193			0.4	1.1	3.3*	Alberta Health and Wellness (2006)
Ottawa, Ontario	2002–2003	Active sampling tubes (100 minutes)	Winter–spring	74	—	74	1.2		1.3		16.9	Zhu et al. (2005)
Rural, British Columbia, Alberta and Saskatchewan	2001–2002	3M passive samplers (1 month)	All seasons	—	—	11,399	0.3	0.2	*0.2*		9.0	You et al. (2008); Burstyn et al. (2007)
Fort Saskatchewan and area, Alberta	2001	Passive samplers (7 days)	All seasons	138	—	138			0.6	1.4	1.8*	Alberta Health and Wellness (2003)
Grande Prairie and area, Alberta	2000	Passive samplers (7 days)	All seasons	132	—	132			0.5	1.6	2.2*	Alberta Health and Wellness (2002)
Fort McKay, Alberta	1999	Passive samplers (24 hours)	Fall and winter	NA	—	30			<MDL (1.0)			Kindzierski, Hoeksema and Cheperdak (2008)
Fort McMurray, Alberta	1997–1998	Passive samplers (4 days)	All seasons	300	—	300			1.3	5.5	17.0*	Alberta Health and Wellness (2000)
Ottawa, Ontario	1997	Summa canister (18–20 hours) Pre-tests	Winter	16	—	16 16	2.4 2.9		2.3 0.4		4.8 2.0	Graham et al. (2004)
Edmonton, Alberta	1991–1993	Summa canister (24 hours)	Average of winter and summer	—	—	212			2.6–3.4			Cheng et al. (1997)
Range							**0.3-2.9**		**<MDL-3.4**	**0.6-9.9**	**0.8–115**	

Location	Sampling period	Sampling method	Season	No. of homes	Smoking status	No. of samples	Concentration (µg/m^3)					Reference
							AM	GM	Median	95th %ile	Max	
PERSONAL												
Windsor, Ontario	2005	Summa canisters (24 hours)	Summer Winter	—	Non-smokers	207 225	2.8 2.1	2.0 1.7	1.6 1.5	9.2 4.6	15.3 10.9	Health Canada (2010d); Stocco et al. (2008)
Fort McKay, Alberta	2006	Passive samplers (7 days)	All seasons	—	Non-smokers/ smokers	33			1.7	16.8	28*	Alberta Health and Wellness (2008)
Fort McMurray First Nations Gregoire Lake/Anzac, Alberta	2006	Passive samplers (7 days)	All seasons	—	Non-smokers/ smokers	24			2.6	16.9	20*	Alberta Health and Wellness (2008)
Fort McMurray, Alberta	2005	Passive samplers (7 days)	All seasons	—	Non-smokers/ smokers	29			2.1	8.8	9*	Alberta Health and Wellness (2007)
Fort Chipewyan, Alberta	2005	Passive samplers (7 days)	All seasons	—	Non-smokers/ smokers	30			2.8	17.8	120*	Alberta Health and Wellness (2007)
Wabamun, Alberta	2004	Passive samplers (7 days)	All seasons	—	Non-smokers/ smokers	193			1.7	7.2	82*	Alberta Health and Wellness (2006)
Fort Saskatchewan, Alberta	2001	Passive samplers (7 days)	All seasons	—	Non-smokers/ smokers	138			1.6	7.1	120*	Alberta Health and Wellness (2003)
Grande Prairie, Alberta	2000	Passive samplers (7 days)	All seasons	—	Non-smokers/ smokers	132			1.5	7.5	36*	Alberta Health and Wellness (2002)
Fort McMurray, Alberta	1997–1998	Passive samplers (4 days)	All seasons	—	Non-smokers/ smokers	300			2.8	10.0	80.0*	Alberta Health and Wellness (2000)
Range									**1.5–2.8**	**7.1-16.9**	**9-120**	

Notes: No. of samples = total number of samples collected and analyzed; AM = arithmetic mean; GM = Geometric mean; MDL = method detection limit. Imputed values are italicized. *Estimated from graph.

3.1 Indoor Concentrations

The range of median indoor benzene concentrations in Health Canada studies was 0.5 to 2.2 µg/m^3 (Health Canada 2012a; Health Canada 2010b; Health Canada 2010d; Héroux et al. 2008). In other Canadian studies, this range was slightly wider, 0.3 to 6.9 µg/m^3 (Alberta Health and Wellness 2008; Kindzierski, Hoeksema and Cheperdak 2008; Alberta Health and Wellness 2007; Alberta Health and Wellness 2006; Zhu et al. 2005; Alberta Health and Wellness 2003; Alberta Health and Wellness 2002). In Health Canada studies that reported 95th percentiles the range in non-smoking homes were 3.6-8.2 µg/m^3 in winter and 9.0-21.0 µg/m^3 in summer, with maximums ranging from 10.4-89.7 µg/m^3 in winter and 16.5-85.2 µg/m^3 in summer (Health Canada 2012a; Health Canada 2010b; Health Canada 2010d). In general, higher concentrations were reported in studies conducted prior to 2000 (Kindzierski, Hoeksema and Cheperdak 2008; Graham et al. 2004; Alberta Health and Wellness 2000; Fellin and Otson 1994).

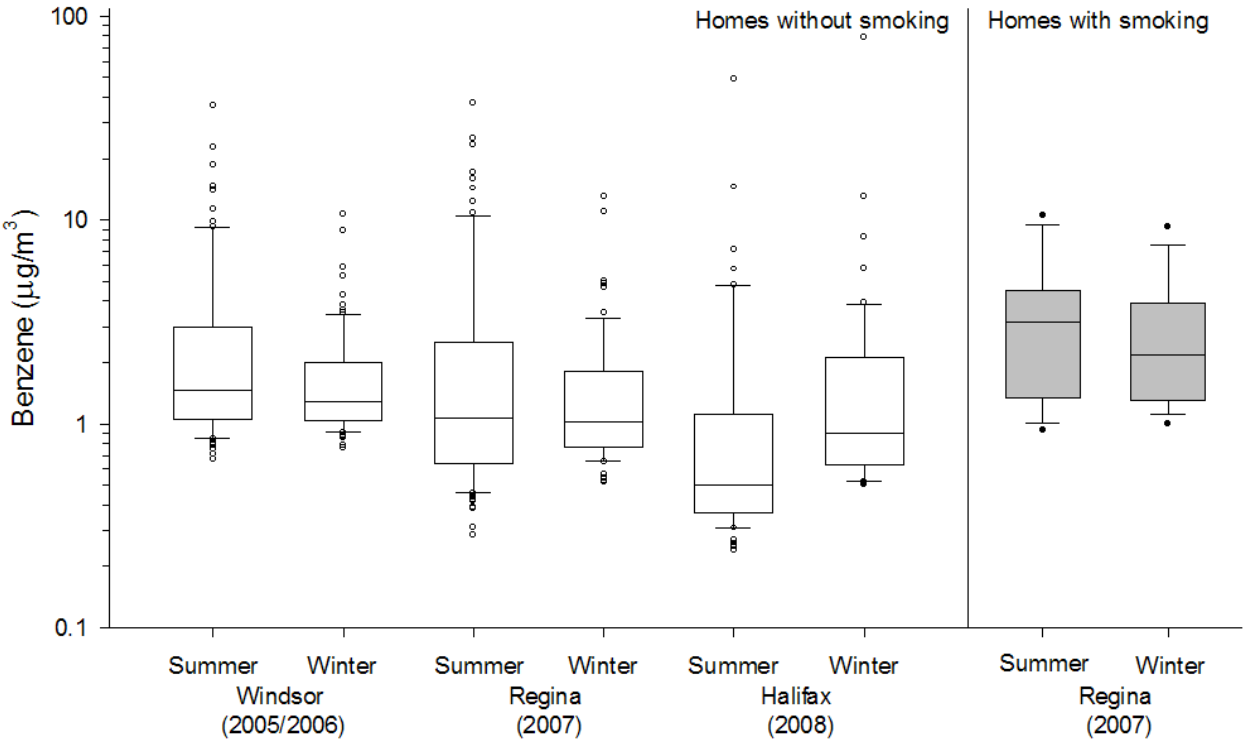
The distribution of indoor benzene concentrations in studies conducted by Health Canada is presented in Figure 1. It should be noted that for the studies in Halifax and Windsor, multiple measurements were made at each home and these values have been averaged to present one value per home, while for the Regina study a single measurement was made at each home. The distribution of indoor/outdoor (I/O) ratios for each home is presented in Figure 2. An I/O ratio compares levels of benzene measured inside a given home to levels measured directly outside the same home. Indoor/outdoor ratios were higher in the summer than the winter, except homes where smoking occurred. The observation of I/O ratios greater than 1.0 was consistent across cities and seasons, and is indicative of indoor sources of benzene. The predictors and factors affecting indoor levels of benzene are discussed in Section 3.1.1.

Median indoor benzene concentrations measured in Health Canada studies (0.5-2.2 µg/m^3) appear to be bounded by lower values than the ranges measured in more recent studies in the United States (1.2 to 4.4 µg/m^3) (Dodson et al. 2008; Jia, Batterman and Godwin 2008a; Weisel, Alimokhtari and Sanders 2008; Sax et al. 2006; Weisel et al. 2005b; Adgate et al. 2004a; Adgate et al. 2004b; Payne-Sturges et al. 2004; Sexton et al. 2004; Van Winkle and Scheff 2001; Clayton et al. 1999; Heavner, Morgan and Ogden 1995) and Europe (1.6 to 3.3 µg/m^3) (Bruinen De Bruin et al. 2008; Gallego et al. 2008; Kirchner et al. 2007; Hippelein 2004; Raw et al. 2004; Schlink et al. 2004; Topp et al. 2004; Edwards et al. 2001b; Ilgen et al. 2001a). A statistically robust comparison is not feasible given significant differences in study designs, climates, dwelling types, sample sizes and other factors.

3.1.1 Sources and factors affecting benzene in residences

Identified factors associated with indoor benzene concentrations in residences include: the presence of an attached garage; indoor smoking; ventilation rates; consumer products; and outdoor sources. These factors are discussed in the sub-sections that follow. Results from Canadian studies for which predictors were analysed by regression models are summarized in Table 3. The methodology used for the Halifax data was similar to that for Regina and Quebec City, however, these results are based on an unpublished internal analysis and are presented here for comparison purposes. These models were able to explain some of the variability associated with indoor

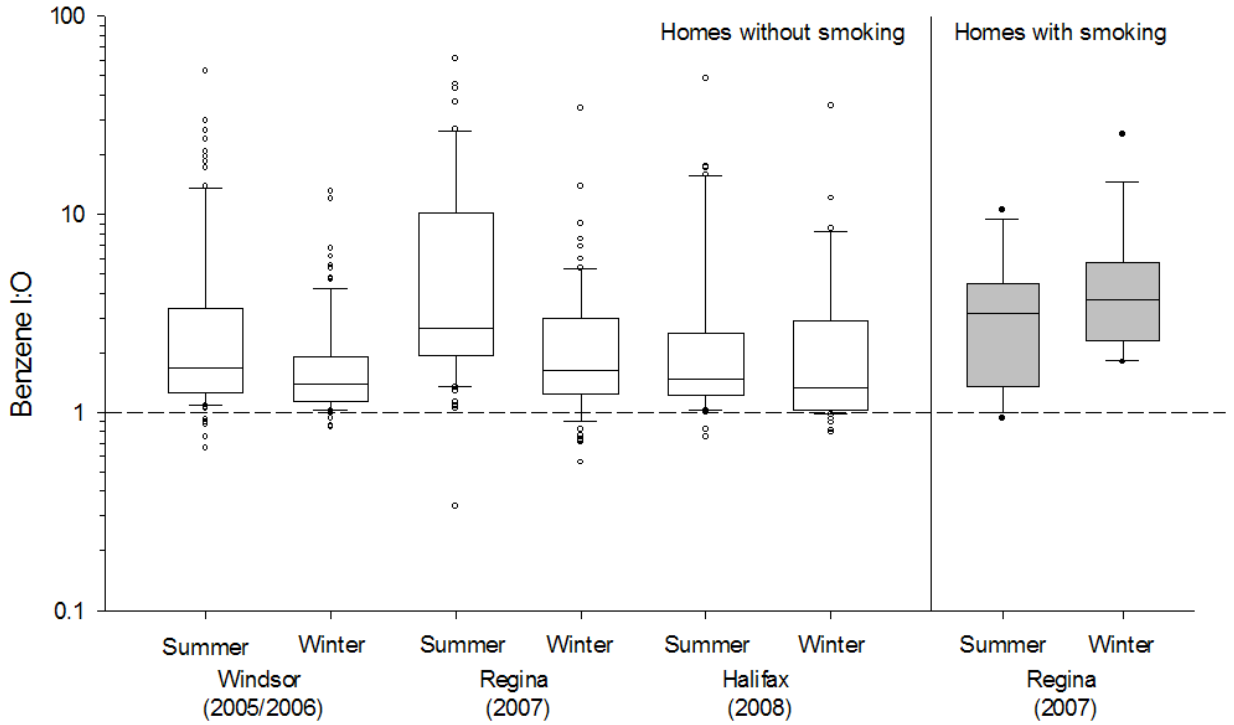
Figure 1. Distribution of indoor benzene concentrations by season across studies conducted by Health Canada



The 75th, 50th and 25th percentiles are represented by the top, middle and bottom of the boxes. The whiskers represent the 90th and 10th percentiles. Outliers are represented by open circles. Source data: Health Canada (2012a; 2010b; 2010d).

benzene concentrations (R^2= 0.26-0.59), but much of the variability was still left unexplained, suggesting that other factors also play a role in influencing indoor benzene concentrations. In the original publications, the parameter estimates associated with each predictor represented the average change in the natural logarithm of indoor benzene concentrations, in µg/m^3. However, given that these parameter estimates can be difficult to interpret, the findings in Table 3 have been presented as the fold-increase in indoor benzene concentrations. For example, in Regina in the summer, it was predicted that indoor benzene concentrations in homes with an attached garage would be 2.9 fold higher than in homes without an attached garage. It is important to note that the sample size for the presence or absence of any given predictor is relatively small for the Halifax data. Predictors with a sample size $\leq$ 5 were excluded.

Figure 2. Distribution of indoor/outdoor (I/O) ratios by season across studies conducted by Health Canada



The 75th, 50th and 25th percentiles are represented by the top, middle and bottom of the boxes. The whiskers represent the 90th and 10th percentiles. Outliers are represented by open circles. Source data: Health Canada (2012a; 2010b; 2010d).

3.1.1.1 Attached garage

Indoor levels of benzene measured as part of Health Canada studies in Windsor, ON, Regina, SK, and, Halifax, NS, stratified by garage type, are presented in Figure 3. Levels of benzene in homes with attached garages are generally higher than levels found in homes with detached garages or no garages. Looking at the lower outliers, it can be seen that it is possible for homes with attached garages to have indoor benzene concentrations similar to homes with detached garages or no garage.

An attached garage was the most consistent and often strongest predictor of indoor benzene levels in multiple regression analyses (see Table 3). These results suggest that indoor benzene levels in homes with attached garages could be 2.4 to 2.9 times higher than in homes without attached garages, after adjusting for other factors. In Halifax, an attached garage *per se* was not associated with indoor benzene levels; however, specific activities in attached garages in the summer (e.g., parking vehicles, storing gasoline, paints or solvents) had similar influences on indoor levels as attached garages did in other studies. In the winter, indoor benzene levels were predicted to be higher based on house age, which was significantly correlated with the presence of attached garages . Therefore, the influence of attached garages, in this case, may have been captured, in part, by other predictors such as house age. Other explanations for the general lack of association

Table 3. Relative increase in indoor benzene levels by predictor in Canadian studies.

Study	Regina (summer) 101 smoking and non-smoking homes (Héroux et al. 2010)	Regina (winter) 91 smoking and non-smoking homes (Héroux et al. 2010)	Quebec City (winter and spring) 96 smoking and non-smoking homes (Héroux et al. 2008)	Halifax (summer) 50 non-smoking homes (Health Canada 2012b)	Halifax (winter) 50 non-smoking homes (Health Canada 2012b)
R^2 (coefficient of determination):	0.43	0.49	0.26	0.59	0.54
PREDICTORS					
Attached garage	2.9[a]	2.4[a]	2.5[a]		
Park two or more cars in garage				3.28	
Move car into or out of garage				1.46	
Store gasoline in garage				2.04	
Presence of paints or solvents in garage				2.26	2.60
Indoor smoking	x[b]	2.0[a]	2.7[a]		
INDICATORS OF VENTILATION					
Air changes per hour				0.90	
Home ventilation system: central exhaust					2.02
Air-conditioning	1.5[a]				
House age			1.02[a]		1.99[c]
Windows open	0.68				
Average indoor relative humidity	0.98				
Average outdoor relative humidity				0.99	
Outdoor temperature				1.03	1.01
Outdoor benzene		1.6		1.24	1.66
INDOOR RELATED ACTIVITIES					
New furniture/rug (<12 months); cleaning furniture			0.36[a]		
Supplemental heating: wood fireplace					1.33

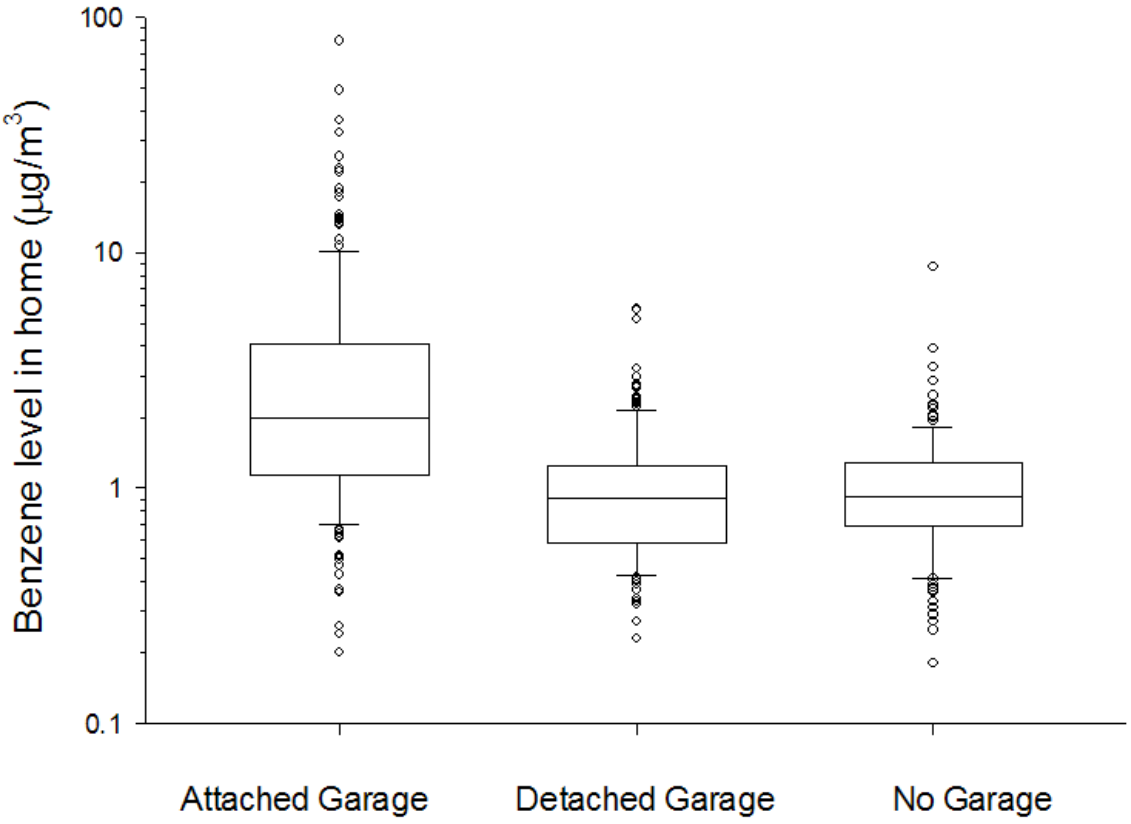
[a] Values are significant ($p<0.1$)
[b] Indoor smoking was not included in the final model because it was not associated with benzene concentrations ($p > 0.10$) in bivariate analysis.
[c] Year of construction 1961 to 1980 compared to before 1946 (reference group)

between attached garage and indoor benzene levels in the winter in Halifax may be due to city characteristics that have yet to be elucidated. The results of a similar analysis for two Michigan cities showed that the mean concentration of benzene in primarily non-smoking homes with an attached garage was 3.79 µg/m^3 higher than in homes without an attached garage, after adjusting for all other factors (Jia, Batterman and Godwin 2008b).

Other North American and European studies have demonstrated that benzene emissions from sources in attached garages contribute significantly to indoor benzene levels (Dodson et al. 2008; Gallego et al. 2008; Batterman, Jia and Hatzivasilis 2007; Batterman, Hatzivasilis and Jia 2006; Isbell, Stolzberg and Duffy 2005; Adgate et al. 2004b; Graham et al. 2004; Edwards and Jantunen

2001; Ilgen et al. 2001c; Tsai and Weisel 2000; Brown and Crump 1998; Schlapia and Morris 1998). The percentage of indoor benzene levels attributable to attached garages was 65% in one study of 15 Michigan homes (less than 30% was attributed to the outdoors and less than 5% to the house) (Batterman, Jia and Hatzivasilis 2007). A smaller percentage (approximately 40%) was

Figure 3. Measured 24-hour geometric mean benzene levels stratified by garage type in studies conducted by Health Canada in Windsor, Regina and Halifax



The 75th, 50th and 25th percentiles are represented by the top, middle and bottom of the boxes. The whiskers represent the 90th and 10th percentiles. Outliers are represented by open circles. Source data: Health Canada (2012a; 2010b; 2010d) .

attributed to the presence of an attached garage in studies of 55 Boston, MA residences (Dodson et al. 2008) and 137 Anchorage, AK homes (more than half were single family homes) (Schlapia and Morris 1998).

Other analyses have identified more specific sources of benzene in garages, namely mobile sources or emissions from gas-powered vehicles and engines in garages; and, evaporative emissions (as opposed to exhaust emissions) (Weisel, Alimokhtari and Sanders 2008). Garage benzene levels were elevated after a poorly maintained emissions control device on a vehicle was simulated (compared to a properly maintained evaporative emissions control) (Tsai and Weisel 2000); and,

after hot soaks (cooling off of warm vehicle) and cold starts (turning on a cold vehicle) compared to baseline conditions (Zielinska et al. 2010; Graham et al. 2004).

Increases in garage benzene concentrations were followed by elevated indoor levels under some, but not all, scenarios. In the first study, while higher indoor levels in the living room were observed with a poorly maintained emissions control device (mean of 6.4 $\mu g/m^3$) compared to a properly functioning control system (mean of 2.0 $\mu g/m^3$), this difference was not statistically significant (Tsai and Weisel 2000). Furthermore, while Zielinski et al. (2010) reported a good correlation between garage and kitchen benzene levels, kitchen benzene levels were only elevated after a cold start (from 1.8 $\pm$ 0.8 ppbv (5.8 $\pm$ 2.6 $\mu g/m^3$) to 8.9 $\pm$ 6.0 ppbv (28 $\pm$ 19 $\mu g/m^3$)), and not under other conditions. In a third study, indoor mean benzene levels increased 4-fold after cold-start or hot-soak tests compared to pre-test values in 16 Ottawa homes (Graham et al 2004).

The placement of an attached garage or the location of parked vehicles at a house may also influence indoor benzene levels. It was reported that garages attached laterally to the first floor contributed more to indoor (living room) benzene concentrations than subterranean ones attached to the basement (Dodson et al. 2008). Schlapia and Morris (1998) reported that homes with a living area above a garage had higher indoor benzene levels compared to homes with a living area beside the garage, even if a car was not parked in the garage. In another study, indoor benzene levels were approximately two-fold higher when a car was kept near the house (attached garage or carport) compared to homes without nearby cars (e.g., no car or detached garage) (Hun et al. 2011).

Only one known report (not published in the peer-reviewed literature) compared the predictors of indoor benzene levels in homes with attached garages to homes without attached garages (Schlapia and Morris 1998). In 91 Anchorage, AK homes with attached garages, variability in benzene concentrations was explained by the inversely related collinear factors of ambient benzene concentration and ambient temperature (23% and 4%, respectively), as well as number of car trips originating from the garage (13%), type of heating system (forced-air versus hot-water boilers) (11%), living space above the garage (7%) and the opening of fuel containers within three days of sampling (4%). Conversely, in 46 homes without an attached garage, 42% of the variability was explained by ambient temperature or ambient benzene concentration.

While attached garages seem to drive benzene indoor air concentrations in many studies, a garage is not the sole source of indoor benzene and may not always be the dominant source. Other influencing factors are discussed in the following text.

3.1.1.2 Indoor smoking

The most recent data from the Canadian Tobacco Use Monitoring Survey (2005) indicated that 15% of Canadian households reported at least one person who smoked inside the home every day or almost every day. Of the remaining 85%, 86% did not allow any smoking inside the home. Forty percent of the households that did allow smoking in the home or had someone regularly smoking inside the home had some restrictions in place (Health Canada 2005).

Indoor smoking was a predictor of indoor benzene levels in studies conducted in Quebec City and Regina (winter only) (Héroux et al. 2010; Héroux et al. 2008). Results of multivariate regression

analyses suggested smoking, adjusted for other factors, elevated indoor benzene levels approximately two to three times compared to homes without indoor smoking (see Table 3). One possible explanation for the lack of association with smoking in the summer in Regina may be increased ventilation rates; however, air exchange data were only available for the winter season so this hypothesis could not be tested (Héroux et al. 2010).

In other studies, elevated benzene levels have been reported in smoking homes compared to non-smoking homes. Overall results from the Total Exposure Assessment Methodology (TEAM) study in six US cities indicated elevated levels of indoor benzene in 300 homes with smokers (median of 10.5 µg/m^3) compared to 200 homes with non-smokers (median of 7 µg/m^3) (Wallace 1989). In an analysis of Total Exposure Assessment Methodology (TEAM) data from New Jersey, North Carolina and North Dakota, the presence of a smoker was the strongest predictor in stepwise regression analyses of overnight personal air, which was considered equivalent to indoor concentrations by the authors (Wallace, Pellizzari and Hartwell 1987). In European studies, the presence of tobacco smoke indoors has also been associated with significantly higher levels of benzene (Gallego et al. 2008; Edwards and Jantunen 2001; Ilgen et al. 2001c).

Mixed results have been reported for other studies. In an analysis of a smaller dataset from the TEAM study, the presence of smokers did not result in elevated indoor benzene levels (geometric means of 6.19 µg/m^3 in non-smoking homes vs. 7.11 µg/m^3 in smoking ones) in Southern California (n = 50) (Hartwell et al. 1992). Benzene was approximately two-fold higher in 7 smoking homes compared to 39 non-smoking Anchorage, AK homes, but the difference was not statistically significant (Schlapia and Morris 1998). In the homes of children who participated in the screening level phase of the Minnesota Children's Pesticide Exposure Study, higher levels of benzene were observed in smoking (n = 52) vs. non-smoking (n = 236) homes (p = 0.016; concentrations not provided); however, in the smaller intensive phase, no difference was reported (24 smoking homes, 77 non-smoking homes) (Adgate et al. 2004b). Among 113 homes of inner city children in Minneapolis, MN, smoking was not associated with elevated indoor benzene levels, adjusted for other factors (Adgate et al. 2004a). In two other studies, benzene levels were elevated in smoking residences, but this was attributed to other (non-smoking but unidentified) indoor sources (Heavner, Morgan and Ogden 1995) in one study, while further analysis did not identify ETS as a significant source of indoor benzene in the other study (Kim, Harrad and Harrison 2001).

The difference in results across studies may be related to the observation that occupant-reported smoking status (from surveys used in the studies) may be imperfectly correlated to ETS, as well as data gaps in the collection of smoking data (e.g., differences between yes/no smoking vs. number of cigarettes smoked), differences in defining smoking households, and small sample sizes.

3.1.1.3 Ventilation (air exchange rate or air flow rate)

Air exchange rate (AER), reported as air changes per hour (h^{-1}) depends on a number of factors, including home construction practices, use of exhaust fans, geographic location, season and the extent to which windows and doors are open (Chan et al. 2005; US EPA 2004). Air exchange rate increases under the influence of indoor/outdoor temperature differences or outdoor wind speeds, both of which increase infiltration or exfiltration of air through any small openings in a building. Since homes are generally built more tightly in colder climates, AERs tend to be lower in these

homes. As well, newer homes are more likely to be built tighter than older ones. Higher AERs should lower concentrations from indoor sources (but may increase concentrations from outdoor sources), while lower AERs may encourage elevated levels from indoor sources.

Air exchange rates are generally higher in garages than homes (Batterman, Hatzivasilis and Jia 2006; Graham et al. 2004; Fugler, Grande and Graham 2002) and this difference is likely to be greater where homes are built more tightly (e.g., Canada) (Emmerich, Gorfain and Howard-Reed 2003). A more tightly built home may encourage increased migration of pollutants from the garage to the house, based on temperature/pressure gradients. In a study of air-tightness in Canadian homes, the garage-to-house interface accounted for 10 to 13% of the leakage in 67 homes (Graham et al. 2004). Modelling indicated that higher indoor benzene levels were positively correlated with the garage-to-house interface leakage area and higher leakage rates, but also positively correlated with house and garage air-tightness. Remediation methods were tested, including air sealing of the garage-to-house interface, and installation of a transfer grille in the garage and of a garage exhaust fan, and it was reported that each method reduced peak concentrations of benzene in both garages and homes, but that installing a grille did not reduce overall indoor levels (CMHC 2004).

Similarly, the average airflow from the garage to house was equal to 6.5 $\pm$ 5.3% of the house's total air exchange in a study of 15 Michigan homes (Batterman, Jia and Hatzivasilis 2007). This percentage increased in homes with lower AERs (tighter homes) and higher volumes (larger homes), although the estimated coefficients of variation were not significant for these variables. House and garage AERs explained 67% of the variation in the garage-to-house air flow fraction, although no variables reached significance in multiple regression analyses. Dodson et al. (2008) noted a higher airflow from subterranean attached garages to basements than from laterally attached garages to occupied areas, suggesting occupied areas adjacent to subterranean garages would be expected to have higher levels of benzene than the occupied areas adjacent to lateral garages.

As seen in Table 3, predictors associated with the AER and tightness of a house were also associated with changes in indoor benzene levels. Air-conditioning was predicted to elevate indoor benzene levels 1.5 fold higher than homes without air-conditioning, and open windows were predicted to result in a 0.68 fold decrease in benzene levels compared to homes without open windows (Héroux et al. 2010). In a similar analysis, summer season and open windows were predicted to result in decreased mean indoor benzene levels of 1.9 and 2 $\mu g/m^3$ compared to winter season and closed windows, respectively (Jia, Batterman and Godwin 2008b). Expressed in the reverse manner, the results of a study in Germany indicated that indoor benzene levels were higher in homes with lower ventilation measured as hours per week of open windows (Ilgen et al. 2001c). Seasonal factors are discussed in more detail below.

In Halifax, six homes had central exhaust ventilation, and while it was predicted that indoor benzene levels would be higher in homes with this type of system than homes without it, there is no obvious connection between the use of ventilation systems and increased indoor benzene concentrations in an area with low outdoor benzene levels. Any interpretation or further analysis would need to take into consideration the small sample size and marginal correlation between ventilation system and house age.

Seasonal factors

AER may be closely related to season due to homes using natural ventilation (open windows) in the summer; however, this may not be the case if air-conditioning is used in the summer. When an air conditioner is in use, windows are likely to be closed, creating a more tightly sealed house. Very low AERs may be associated with homes that use air-conditioning in the summer. In contrast, if occupants open many windows in warmer weather, the measured AER can be as high as 2 to 3 h^{-1}, or significantly higher than any period with closed windows.

The influence of season on AER may also influence the levels of benzene indoors. Seasonal differences in indoor benzene levels have been reported in Health Canada studies (Health Canada 2012b; Héroux et al. 2010) and studies in the United States and Europe (Missia et al. 2010; Dodson et al. 2008; Gallego et al. 2008; Jia, Batterman and Godwin 2008b; Isbell, Stolzberg and Duffy 2005; Topp et al. 2004; Edwards and Jantunen 2001; Ilgen et al. 2001c). Across all studies in Figure 2, I/O ratios were higher in the summer than winter in non-smoking homes, which suggests homes are more tightly sealed in the summer (perhaps due to the use of air conditioning) or that there are stronger indoor sources in the summer (perhaps due to a benzene-temperature interaction). In two European studies, outdoor benzene levels, which were highly correlated with season and/or temperature, had a strong influence on indoor levels (Gallego et al. 2008; Ilgen et al. 2001c). Indoors, concentrations of benzene were higher in the winter than the summer in rural areas. In one study, this was also true in urban areas, but Ilgen et al. reported no significant difference between summer and winter indoor benzene concentrations in urban areas. In both rural and (to a lesser extent) urban areas, a relationship between indoor benzene concentration and ambient air temperature was observed, suggesting that it was the seasonal change in ambient temperature that was driving changes in indoor levels (Ilgen et al. 2001a; Ilgen et al. 2001c). Benzene levels in garages have also been shown to be correlated with ambient temperature (Zielinska et al. 2010).

3.1.1.4 Outdoor air quality

The influence of ambient levels on indoor levels is highly variable, reflecting variation in ambient benzene both spatially and temporally. Two studies were identified in which the influence of outdoor air quality on indoor benzene levels was examined. In both studies, the I/O ratios were greater than one, and similar to the results of Canadian studies presented in Figure 2, indicating higher indoor than outdoor levels. From the American Multi-city Relationships of Indoor, Outdoor and Personal Air (RIOPA) study of approximately 300 homes in three cities it was reported that, at the median, outdoor sources (not including attached garages, which were considered an "indoor source of benzene") contributed 90% of indoor concentrations (Weisel et al. 2005b). In a later analysis of data from 114 homes, the source of elevated indoor benzene levels was reported to be driven by a mixture of tailpipe and evaporative emissions from vehicles (Hun et al. 2011). In the second study, conducted in South Korea, indoor benzene and breath concentrations were correlated, but neither were correlated with outdoor benzene concentrations. The authors suggested that indoor sources were responsible for the majority of benzene measured indoors (Jo and Moon 1999). The differences in these results are likely driven by the inclusion of smokers in the second study, as well as differences in housing characteristics, and analysis methods (e.g., AER was only considered in the RIOPA study).

3.1.1.5 Building materials and household products

There is very little evidence that benzene levels are elevated in newer homes or immediately following renovations. It has been reported that, in general, VOC levels in new homes decrease rapidly, and after about a year, concentrations do not show statistically significant changes (Park and Ikeda 2006). Elevated indoor benzene levels were reported in the only identified study of newly built homes. In the days immediately following construction of a new home or office renovations in Melbourne, Australia, benzene levels were elevated by an order of magnitude compared to 21 established buildings (geometric mean ~ 3 µg/m^3); these levels declined with time, reaching "established" levels after 20 to 35 weeks (Brown 2002). The only other evidence of elevated indoor benzene levels was reported in a study of 12 British homes, in which benzene levels in two homes were elevated after cleaning, painting, or cooking fat that was overheated (Kim, Harrad and Harrison 2001).

The results of other, larger studies, suggest building materials and household products are not strong sources of indoor benzene levels. In studies conducted by Health Canada (See Table 3) no associations between elevated benzene levels and recent renovations or new products were reported. In fact, new carpet and recent renovations were associated with lower benzene levels. The authors speculated that these unexpected results may be related to several factors, including carpets acting as a sink for VOCs, a broad definition of recent renovations that was not captured by sampling, the use of low VOC-emitting materials, renovations in rooms where sampling was not taken, or small sample size (Héroux et al. 2008).

In a European five-city, multi-season study of indoor levels in homes, schools and public buildings, no significant contribution to indoor benzene levels from building materials was reported (Missia et al. 2010). Benzene levels were not associated with redecorating, painting or varnishing, building materials, or storage of hobby materials in a German study of 115 homes (Ilgen et al. 2001c). Similarly, in a study of 159 Michigan homes, VOC levels in general were not influenced by flooring, stove type, air fresheners or arts-and-crafts hobbies. Benzene, in particular, was also not associated with renovations, paints, adhesives, furniture or cleaning products. It should be noted that some high VOC concentrations were associated with model building, furniture and auto repair, but small numbers precluded statistical analyses, and elevated benzene levels were not specifically reported (Jia, D'Souza and Batterman 2008).

3.1.1.6 Wood-burning appliances

Benzene is a component of wood smoke. In a controlled human exposure study, benzene concentrations were 0.54 to 1.7 µg/m^3 for clean air exposures and 21 to 30 µg/m^3 for wood smoke exposures (Sällsten et al. 2006). However, the available evidence does not suggest wood-burning appliances are a source of elevated indoor benzene levels. In one Australian study, no differences in indoor benzene levels were observed between homes without wood heaters, homes with wood heaters compliant with the Australian Standard for wood heaters, and homes with non-compliant wood heaters (Galbally et al. 2009). The authors reported that wood-smoke emissions to the outdoors may contribute to elevated indoor levels as a result of infiltration back indoors. In a Swedish community, homes with daily use of wood-burning appliances did not have significantly elevated one-day levels of indoor benzene compared to referent homes, but seven-day median concentrations were marginally higher (3.0 vs. 2.5 µg/m^3; $p = 0.05$). In regression analyses,

benzene was not associated with any characteristics of wood-burning appliances or behaviours (Gustafson et al. 2007). In contrast to all of these studies, supplemental heating with a wood fireplace was predicted to result in a 1.33 fold increase in indoor benzene levels in Halifax in the winter time (see Table 3) compared to homes that did not use wood as a supplemental heating source.

It is possible that season, sample size and participant activity (frequency and duration of use) may make it difficult to study the contribution of wood-burning appliances to indoor benzene levels. Conversely, properly installed and maintained appliances vent most pollutants to the outdoors and contribute very little to indoor levels regardless of frequency or duration of use.

3.1.2 Time trends of indoor benzene concentrations

Although the data are limited, the results of Canadian (Kindzierski, Hoeksema and Cheperdak 2008; Zhu et al. 2005) US (Hodgson and Levin 2003) and European (Rehwagen, Schlink and Herbarth 2003) studies indicate that benzene levels in residences have decreased over the past several decades. These declines may be explained by a number of factors, although their influence on indoor benzene levels has not been quantified

- Reduced ambient levels (Dann and Wang 2000), reflecting improved mobile source control measures (mainly aimed at reducing ozone precursors);
- Reduced VOC-content in building materials, furnishings and consumer products used indoors;
- Reduced levels of indoor tobacco smoking (Health Canada 2010c); and,
- Reduced emissions from vehicles parked in attached garages, reflecting lower evaporation and permeation rates of fuel, changes in vehicle technology (e.g., fuel injection systems), and reductions in the benzene content of fuel (Government of Canada 1997).

3.2 Residential Outdoor Concentrations

In recent studies conducted by Health Canada, median daily outdoor benzene concentrations ranged from 0.2 to 0.9 $\mu g/m^3$ (Health Canada 2012a; Health Canada 2010b; Health Canada 2010d). Considering all Canadian studies, median residential outdoor benzene levels ranged from 0.2 $\mu g/m^3$ to 3.4 $\mu g/m^3$, with some samples below an MDL of 0.42 $\mu g/m^3$ (see Table 2).

Outdoor benzene concentrations in the United States and Europe are similar to Canadian data. The ranges of median outdoor concentrations since 1990, excluding rural and remote areas, were 0.9 to 3.1 $\mu g/m^3$ in the United States (Jia, Batterman and Godwin 2008a; Sax et al. 2006; Weisel et al. 2005b; Adgate et al. 2004a; Adgate et al. 2004b; Payne-Sturges et al. 2004; Sexton et al. 2004) and less than 1.1 to 3.1 $\mu g/m^3$ in Europe (Bruinen De Bruin et al. 2008; Gallego et al. 2008; Kirchner et al. 2007; Topp et al. 2004; Rehwagen, Schlink and Herbarth 2003; Edwards et al. 2001b; Ilgen et al. 2001a). In one US study (Clayton et al. 1999) and one European study (Kim, Harrad and Harrison 2001), median levels greater than 5 $\mu g/m^3$ were reported.

The Canadian, US and European studies identified several common factors that influenced outdoor benzene concentrations, including season (Gallego et al. 2008), community type (Sexton et al. 2004), traffic (Su et al. 2010; Gallego et al. 2008; Jia, Batterman and Godwin 2008b; Wheeler et al. 2008; Janssen et al. 2001) and industrial sources (Su et al. 2010; Jia, Batterman and Godwin 2008b; Wheeler et al. 2008).

3.2.1 Time trends of ambient benzene concentrations

Canadian annual ambient concentrations of benzene are reported by the National Air Pollution Surveillance (NAPS) network of Environment Canada for rural and urban sites, including sites near industrial or point sources, which have been shown to have an impact on ambient levels (Burstyn et al. 2007). Between 1990 and 1998, ambient benzene concentrations decreased by about 5% annually (total of 34%) (Dann and Wang 2000). A 44% decline in the annual mean benzene concentration at urban sites was reported from 1994-1996 (2.5 µg/m^3) to the period 2000-2004 (1.4 µg/m^3) (Environment Canada 2009a). By 2008, average levels were below 1 µg/m^3 at urban sites, and below 0.5 µg/m^3 at rural sites (Environment Canada 2009a). Decreasing concentrations have also been observed in the US and in Europe since the 1990s (McCarthy et al. 2007; Rehwagen, Schlink and Herbarth 2003).

3.3 Personal Exposures

The available Canadian data show a limited range of personal exposures (see Table 2). Personal benzene levels were reported in only one study of non-smokers (median of 1.6 µg/m^3) (Health Canada 2010d; Stocco et al. 2008). In all studies (smokers and non-smokers), the range of median personal benzene concentrations was 1.5 to 2.8 µg/m^3 (Health Canada 2010d; Alberta Health and Wellness 2008; Stocco et al. 2008; Alberta Health and Wellness 2007; Alberta Health and Wellness 2006; Alberta Health and Wellness 2003; Alberta Health and Wellness 2002; Alberta Health and Wellness 2000). Indoor levels exceeded personal levels in the study of non-smokers, while personal levels often exceeded indoor levels in studies that included both smokers and non-smokers.

Measures of personal exposure in US and European studies were similar to Canadian studies. In US studies of non-smokers, mean personal benzene concentrations were <4 µg/m^3 (Sax et al. 2006; Weisel et al. 2005a), whereas in studies in which means were reported for non-smokers and smokers combined, or for subjects exposed and not exposed to ETS, mean personal benzene concentrations were > 4 µg/m^3 (Jia, D'Souza and Batterman 2008; Sax et al. 2006; Weisel et al. 2005a; Adgate et al. 2004a; Adgate et al. 2004b; Payne-Sturges et al. 2004; Sexton et al. 2004; Clayton et al. 1999). In European studies, mean personal exposure to benzene in non-smokers ranged from 2.0-9.4 µg/m^3, whereas non-smokers exposed to ETS had measured concentrations from 2.5 to 4.03 µg/m^3, and smokers, in one study, had average personal measurements of 5.09 µg/m^3 (Saborit et al. 2009; Bruinen De Bruin et al. 2008; Gonzalez-Flesca et al. 2007; Edwards et al. 2001b; Ilgen et al. 2001b).

Measures of personal exposure to VOCs are generally highly correlated with indoor concentrations. Thus, determinants of indoor benzene are likely to strongly affect personal exposures. Indeed, personal exposure levels can be predicted in part by area sampling results (Stocco et al. 2008; Payne-Sturges et al. 2004; Sexton et al. 2004). In one study, time-weighted

indoor concentration explained more of the variability in personal benzene exposures than any other factor except for an attached garage (Adgate et al. 2004b). In another study, 50% of the variance in personal benzene exposure was explained by residential indoor concentrations (Adgate et al. 2004a).

Other determinants of personal exposure to benzene that have been identified include an attached garage (Stocco et al. 2008; Adgate et al. 2004b), ETS (Adgate et al. 2004a; Wallace 1989; Wallace, Pellizzari and Hartwell 1987; Wallace et al. 1987), other automobile or traffic related factors (Edwards et al. 2001a; Wallace 1989) and outdoor concentration (Stocco et al. 2008). In Helsinki, living in areas with low vehicle traffic (thus, lower outdoor benzene) was not associated with lower personal exposure to benzene as exposures were more than offset by increased commuting time in vehicles (Edwards and Jantunen 2001).

There may be additional sources of exposure for certain individuals, including hobbies/activities that use solvents or fuels, such as small engine repair, evaporative emissions from gasoline contamination of outerwear, and refilling and maintenance of gasoline-powered equipment (e.g., lawn mowers, snowblowers), but no information on the personal levels associated with these activities was found in the literature.

4.0 ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

Benzene is absorbed into the systemic circulation by all routes of exposure. Experimental, occupational, and environmental exposure studies suggest that humans absorb approximately 50% of the benzene inhaled (Wallace, Pellizzari and Gordon 1993; Pekari et al. 1992; Perbellini et al. 1988). Absorption is highest during the initial minutes of exposure and declines with time (Nomiyama and Nomiyama 1974; Srbova, Teisinger and Skramovsky 1950). The results of studies in dogs and rodents also confirm that benzene is rapidly absorbed through the lungs (Sabourin, Chen and Lucier 1987; Schrenk, Yant and Pearce 1941).

Benzene distribution after oral, inhalation, and dermal routes of exposure in animals has been extensively characterized. Results from animal studies indicate that absorbed benzene after inhalation exposure is distributed throughout several body compartments, including blood, bone marrow, fat, kidney, liver, lung, brain and spleen; however, as a lipophilic compound, it accumulates more in fatty tissues and bone marrow (ATSDR 2007).

Benzene is metabolized mostly in the liver, but also in other tissues including the bone marrow, which is considered to be critical in the development of leukemia (Environment Canada and Health and Welfare Canada 1993). The conversion of benzene to benzene oxide by cytochrome P450 is the first step in its metabolism, followed by further metabolism via one of three pathways. In the first, benzene oxide spontaneously rearranges to phenol, which may be subsequently metabolised to hydroquinone and benzenetriol and further to benzoquinones, semiquinones and free radicals. In the second pathway, the benzene oxide is converted to benzene dihydrodiol by epoxide hydrolase and can subsequently form catechol. The third pathway involves open ring forms of benzene leading to the formation of trans, trans-muconaldehyde (Health Canada 2009).

Although animal studies show a linear increase in total metabolite production with oral exposure level, the dose related production of benzene metabolites in humans is not thoroughly understood, specifically at low levels of exposure (Health Canada 2009). The metabolism of benzene in 250 benzene-exposed workers and 139 control workers in Tianjin, China was studied by Kim et al. (2006). The urinary concentrations of unmetabolized benzene and all major metabolites (phenol, E,E-muconic acid, hydroquinone, and catechol), as well as the minor metabolite, S-phenylmercapturic acid, were found to be consistently elevated when the median air benzene levels were at or above the following concentrations: 0.2 ppm (0.64 mg/m^3) for E, E-muconic acid and S-phenylmercapturic acid; 0.5 ppm (1.6 mg/m^3) for phenol and hydroquinone; and 2 ppm (6.4 mg/m^3) for catechol. The dose-related production of E, E-muconic acid, phenol, hydroquinone, catechol, and total metabolites reportedly declined 2.5- to 26-fold as the median air benzene levels increased from 0.027 to 15.4 ppm (0.086 to 49.3 mg/m^3). Reductions in metabolite production were found to be most pronounced for catechol and phenol at levels below 1 ppm (3.2 mg/m^3), indicating that metabolism favoured the production of the toxic metabolites, hydroquinone and E, E-muconic acid, at low exposures. 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 (0.24-1050 mg/m^3) was investigated by Rappaport et al. (2005). At approximately 500 ppm (1600 mg/m^3) benzene, both benzene oxide and 1, 4-benzoquinone levels plateaued, suggesting that cytochrome CYP2E1 became saturated at this point. Thus, benzene metabolism may be much more effective at low levels of benzene and exposure to levels of benzene above 500 ppm (1600 mg/m^3) may result in smaller biologically effective doses, since benzene metabolism becomes substantially saturated at this level. These results suggest that exposure to levels of benzene below 50 ppm (1600 mg/m^3) may produce the maximum amount of metabolites per unit of benzene exposure (Health Canada 2009).

Most metabolites of benzene are excreted in the urine, while unmetabolized benzene is eliminated by exhalation (Environment Canada and Health and Welfare Canada 1993). The percentage of benzene exhaled has been reported to be time-dependent, with the greatest excretion in the first hour after exposure, followed by slower elimination phases. The exhalation of benzene is also influenced by concentration with larger percentages of unmetabolized benzene exhaled at higher concentrations (e.g., >850 ppm (2720 mg/m^3) vs ≤130 ppm (416 mg/m^3)) (ATSDR 2007).

5.0 HEALTH EFFECTS

The animal and human toxicology and health effects of benzene have been thoroughly reviewed in several authoritative assessments including: (i) the Government of Canada's *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document Benzene* (Health Canada 2009); and, (ii) the Agency for Toxic Substances and Disease Registry's *Toxicological Profile of Benzene* (ATSDR 2007). A brief summary of the toxicology of benzene is included in this section. The reader is referred to these previous assessments for detailed analyses of the health effects of benzene. More recent literature pertinent to the endpoints identified in these assessments, as well as studies with measurements of benzene indoors, was reviewed. This literature supports previous findings and elaborates on some endpoints, such as the toxicity of benzene metabolites, but does not change the conclusions of previous Health Canada and ATSDR assessments. Studies of chronic benzene poisoning, studies in environments dissimilar to Canada (e.g., schools in Southeast Asia) and exposures by routes other than inhalation were not considered, unless other

routes provided novel insights into the mode of action of benzene. It is important to note that both animal toxicological and humans epidemiological studies report similar toxic effects following exposure to benzene, regardless of exposure pathway (i.e., via inhalation or ingestion).

5.1 Indoor Air Studies and Pulmonary Health Effects

The health effects (particularly asthma) of a suite of VOCs found indoors, including benzene, have been examined in a limited number of studies. Interpretation of the results of these studies is difficult due to the high degree of correlation between different VOCs that limits the ability to identify substance-specific effects. In an Australian case-control study, 88 cases (61 males) discharged from the emergency room with asthma and 104 controls (64 males) without an asthma diagnosis were studied (Rumchev et al. 2004). The homes of children (six months to three years) diagnosed with asthma had two-fold higher levels of benzene (p=0.000) (8-h median: 24.8 µg/m^3), relative to controls (8-h median 11.8 µg/m^3). A 10 µg/m^3 increase in benzene was associated with an increased risk of having asthma (OR=2.922 (95% CI: 2.250, 3.795)). This association remained significant after other VOCs showing significant individual effects were entered into the model (OR=1.09 (95% CI: 1.06, 1.12)). Caution should be taken when interpreting the results for any one substance due to the high degree of correlation between VOCs and the relatively small observed increase in risk for a substantial increase in benzene concentration (10 µg/m^3).

Two studies of subsets of adult subjects from the National Health and Nutrition Examination Survey (NHANES) in the United States did not measure indoor concentrations of benzene *per se* but did consider personal exposure measurements or a marker of benzene exposure. In one cross-sectional study (n=550; 268 males), personal exposure to benzene over 48 to 72 hours (average: 1.21 µg/m^3) was associated with physician-diagnosed asthma (OR=1.33 (95% CI: 1.13, 1.56)) and three or more wheezing attacks in the previous 12 months (OR=1.85 (95% CI: 1.13, 3.04)), but not one to two wheezing attacks in subjects without asthma (Arif and Shah 2007). In the second study, blood benzene concentrations (medians of 0.7 and 0.06 µg/L in 421 males and 322 females, respectively) were not associated with changes in pulmonary function after adjusting for smoking habits (Elliott et al. 2006).

5.2 Noncarcinogenic Toxicological Effects

5.2.1 Acute toxicity

The effects of benzene in humans by inhalation and other routes of exposure include effects to the central nervous system, causing dizziness, tremor, nausea, vomiting, headache, and drowsiness after acute exposure to high levels (700-3000 ppm (2240-9600 mg/m^3)). Acute inhalation by animals to single, high doses of benzene (approximately 10,000 ppm (32000 mg/m^3)) has resulted in central nervous system effects and death (ATSDR 2007; Paustenbach, Bass and Price 1993).

5.2.2 Subchronic and chronic toxicity

In humans, the most commonly reported non-cancer effects from chronic exposure to inhaled benzene at or below 1 ppm (3.2 mg/m^3) include blood disorders, such as aplastic anemia, pancytopenia, thrombocytopenia, granulocytopenia, and lymphocytopenia. (ATSDR 2007; IPCS 1993). These effects on blood cells suggest that benzene and/or its metabolites target the bone

marrow or early progenitor cells and there is some evidence for this. In a study of 250 shoe workers in China, a significant dose-dependent decrease in colony formation of progenitor cells with increasing benzene exposure was reported (Lan et al. 2004). The authors of this study concluded that early progenitor cells are more sensitive to the haematotoxic effects of benzene than mature blood cells.

Exposure of humans to <5 ppm (<16 mg/m^3) benzene can result in hematologic suppression (Ward et al. 1996). Decreased white blood cell count was reported in petrochemical workers exposed to <10 ppm (<32 mg/m^3) benzene (Zhang 1996) and it was reported that depressions in blood cell counts in benzene-exposed Chinese workers were not only exposure dependent, but also significantly different in the lowest exposed group ($\leq$ 0.25 ppm [0.8 mg/m^3]) compared with unexposed subjects (Qu et al. 2002).

Benzene in air has also been shown to cause immunological effects (decrease in lymphocytes) in occupationally exposed workers at levels $\leq$1 ppm (3.2 mg/m^3) (ATSDR 2007).

There is a wealth of animal toxicological data to support these findings. Moderate and long-term inhalation or oral exposure of different species to benzene at various doses (<1-3000 ppm (<3.2-9600 mg/m^3)) have resulted in progressive deterioration in hematopoietic function including bone marrow damage, changes in circulating blood cells (leukopenia, erythrocytopenia, lymphocytopenia, thrombocytopenia, pancytopenia and aplastic anemia), and alterations of the immune response (ATSDR 2007; IPCS 1993). In mice, intermediate exposures to levels as low as 10 ppm (32 mg/m^3) resulted in decreased spleen weight and decreases in circulating leukocytes (ATSDR 2007). One of the benzene metabolites, hydroquinone, was shown to have immunosuppressive properties in vitro (Cho 2008).

5.2.3 Reproductive and developmental toxicity

There is insufficient epidemiological evidence to draw conclusions with respect to the potential reproductive or developmental toxicity of benzene (ATSDR 2007). Benzene was not shown to be teratogenic in toxicological studies, but there is evidence that benzene is embryotoxic and fetotoxic at levels >47 ppm (150 mg/m^3) (Health Canada 2009). In mice, in utero exposure to benzene via maternal inhalation or intraperitoneal exposure has resulted in haematological and hematopoietic effects and oxidative stress (Badham et al. 2010; Badham and Winn 2009; Health Canada 2009; Wan and Winn 2008). Sperm head abnormalities have also been observed in benzene-exposed male mice (Health Canada 2009; Chen et al. 2008; ATSDR 2007). In one recent study, neurobehavioural deficits were observed in adult male progeny of pregnant rats exposed subcutaneously to benzene (Lo Pumo et al. 2006).

5.3 Genotoxicity

Benzene is clastogenic in humans with effects including aneuploidy, polyploidy, micronuclei, chromosomal deletions, translocations, and rearrangements (ATSDR 2007; Zhang et al. 2007; IARC 1987). Structural (chromatid and/or chromosome breaks) and/or numerical chromosomal aberrations in mitogen-stimulated peripheral lymphocytes were reported in exposed workers (ATSDR 2007).

In toxicological animal studies, benzene has been shown to be genotoxic in vivo and to a lesser extent, in vitro. Gene mutations in bacteria and inhibition of DNA and RNA synthesis in mammalian cells have been shown in in vitro studies. In vivo, benzene induces chromosomal aberrations in lymphocytes (mice) and bone marrow cells (rats and hamsters); and, increases the incidence of micronuclei in lymphocytes (rat), bone marrow (mice and hamsters), and peripheral erythrocytes (mice). 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 (Health Canada 2009; ATSDR 2007).

While there is clear evidence that benzene is genotoxic, there is limited data to describe dose-response relationships at low doses (e.g., <32 mg/m^3). The doses tested in most toxicological assays are higher than concentrations that would be observed in indoor residential environments. In epidemiological studies, genotoxicity results are often compared between groups of exposed and unexposed workers. These types of studies have limited use in describing dose-response relationships. There is some evidence of dose-related increases in chromosomal aberrations in the lymphocytes of Chinese workers occupationally exposed to benzene (OEHHA, 2001).

5.4 Carcinogenicity

Benzene has been classified as a human carcinogen by Health Canada (Environment Canada and Health and Welfare Canada 1993), the United States Environmental Protection Agency (US EPA 2003) and the International Agency for Research on Cancer (IARC 1987).

The evidence for benzene's leukaemogenic potential comes from chronic toxicological bioassays in animals and studies of humans exposed to benzene by inhalation. Exposure to 100-200 ppm (320-640 mg/m^3) for up to 104 weeks has resulted in carcinomas of the Zymbal gland and oral cavity in rats, as well as leukemia in the offspring of exposed pregnant dams. After exposure to 100 - 300 ppm (320-960 mg/m^3), thymic lymphoma, myelogenous leukemia and carcinomas of the Zymbal gland, ovaries and lungs were observed in mice (Farris et al. 1993; Cronkite et al. 1989; Maltoni et al. 1989; Cronkite, Drew and Bullis 1985; Maltoni et al. 1985; Cronkite et al. 1984; Maltoni, Conti and Cotti 1983; Maltoni et al. 1982). The results of a toxicology study of the dose-response of benzene-induced acute myeloid leukemia (AML) in transgenic mice lacking p53 suggested that differences in DNA repair capability may affect the appearance of tumours at low doses, while a decrease in the appearance of tumours at high concentrations may be related to apoptosis and loss of neoplastic target cells. Strain differences were also noted (Kawasaki et al. 2009).

The association between occupational exposure to benzene and carcinogenicity is best expressed in the results of studies from occupational cohorts that have been analyzed by several authors and regulatory organizations.

The Ohio Pliofilm has the fewest reported co-exposures to other possible carcinogenic substances in the workplace. The cohort initially included 748 male workers in three facilities in Ohio exposed to benzene in the manufacture of rubber hydrochloride (Pliofilm), employed between 1940 and 1949 and followed until the end of 1981 (Rinsky, Young and Smith 1981). They were exposed to a wider range of estimated benzene concentrations (100 ppm (3200 mg/m^3) in 1941 to 10 ppm (32 mg/m^3) (8-hour TWA) in 1949) than were workers in other cohort studies (US EPA

1998). Exposure to benzene was associated with a statistically significant increase in mortality due to malignancies of the lymphatic and haematopoietic tissue (standardized mortality ratio [SMR] = 330; $p < 0.01$), with seven of the deaths due to leukemia (SMR =560; $p < 0.001$). Workers exposed for longer than 5 years had an SMR due to leukemia of 2100. The cohort was later expanded to include 1165 white males who had worked at least one day between 1940 and 1965 with person-years at risk starting in 1950, as well as individual estimates of personal exposure (Rinsky, Smith and Hornung 1987). 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 leukemia mortality was seen with increasing exposure to benzene; a statistically significant increase was observed for all lymphatic and haematopoietic cancers compared with that expected in the general population (SMR = 227; 95% CI: 127–376). For total leukemia deaths (n=9), the SMR was 337 (95% CI: 159–641). An increased risk of multiple myeloma (n=4) was also reported (SMR = 398; 95% CI: 110–1047).

Further analysis of the Pliofilm cohort with extended follow-up data from 1981 through 1996 was published by Rinsky et al. (Rinsky et al. 2002). The purpose of this analysis was to determine whether risks remained elevated with increasing time since plant shutdown. The results of this analysis indicated five new leukemia cases in benzene-exposed white males, but the summary SMR for this group declined from 3.37 (95% CI: 1.54–6.41) to 2.56 (95% CI: 1.43–4.22). In regression models, cumulative exposure was significantly associated with elevated relative risks for leukemia mortality. Four new multiple myeloma deaths occurred, three of which were in workers judged to be unexposed. These findings reaffirm the leukemogenic effects of benzene exposure, but suggest that excess risk diminishes with time.

A second cohort of benzene-exposed workers included 28,460 benzene-exposed workers from 233 factories in China and 28,257 control workers from different industries employed from 1972 through 1981 (Yin, Li and Tain 1987). In this study, thirty leukemia cases were identified in the exposed workers compared with four cases in the unexposed controls (SMR = 574; $p < 0.01$). The exposure assessment included job title and assignment to individual work units reflecting exposures of individual workers. Exposure estimates at the time of the survey ranged from 3 to 313 ppm (9.6 to 1002 mg/m^3), with the majority of exposures in the range of 16–157 ppm (51-502 mg/m^3). This cohort was further expanded to include 74,828 benzene-exposed workers (employed since 1949) and 35,805 controls from 712 factories in 12 Chinese cities (Yin et al. 1994). 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 (RR = 2.6; 95% CI: 1.3–5.0) and specifically for AML (RR = 3.1; 95% CI: 1.2-10.7). Significant increases were also reported for malignant non-Hodgkin lymphoma, aplastic anaemia and myelodysplastic syndromes. These studies of Chinese workers found evidence for hematopoietic cancer at lower levels (< 10 ppm (<32mg/m^3) average and < 40 ppm (<128 mg/m^3)-years cumulatively) than previously reported in studies of the Pliofilm cohort. A relatively modest dose-response relationship with proportionately smaller increases in risk at increasing levels of exposure was found.

In a third nested-case control study, exposure to benzene at lower concentrations than had previously been reported and increased leukemia risk was observed in Australian petroleum industry workers (Glass et al. 2003). Each of 79 cases of leukemia identified between 1981 and 1999 were matched to five control subjects. Exposures, determined using a task-based algorithm

specific to each subject, ranged from 0.005 to 57.3 ppm-years (0.02 to 183 mg/m^3-years) with a mean of 4.9 ppm-years (16 mg/m^3-years). Both cumulative exposure and intensity of exposure were associated with increased risk of leukemia. When cumulative exposure was treated as a continuous variable, the OR for leukemia was 1.65 (95% CI: 1.25-2.17). Treated categorically, cumulative exposures >8 ppm-years (26 mg/m^3-years) were associated with a significant increased risk in leukemia, with a trend of increasing risk above 1 ppm-years (3.2 mg/m^3-years). In a later analysis, short-term, high-exposure events were considered, and cumulative exposure to benzene treated as a continuous variable or categorically at the highest exposure (>16 ppm-years (51 mg/m^3-years)) continued to be associated with a increased risk of leukemia. The odds ratios were smaller than in the initial analysis, in part because the lowest cumulative exposure categories were combined and, the authors speculated, because consideration of high-exposure events reduce the risk per ppm-year when leukemia risk is associated with higher exposures (Glass et al. 2005).

Recent meta-analyses have concluded that there is an association between benzene and leukemia in general (Vlaanderen et al. 2011; Khalade et al. 2010; Kaufman, Anderson and Issaragrisil 2009; Lamm et al. 2009; Miller et al. 2009; Wang, Zhang and Shen 2009; Costantini et al. 2008; Steinmaus et al. 2008; Whitworth, Symanski and Coker 2008; ATSDR 2007; Vineis, Miligi and Costantini 2007). Newer data led to changes in the most recent evaluation of benzene by IARC (Baan et al. 2009). It was concluded that there is limited evidence for benzene to cause acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple myeloma and non-Hodgkin lymphoma, and sufficient evidence for acute non-lymphocytic leukemia (ANLL). Other groups have investigated potential biomarkers of increased risk of lymphoma or multiple myeloma such as chromosome translocations (McHale et al. 2008) and genetic variants (Lincz et al. 2007).

Childhood leukemia has been the focus of several studies; however, no studies were identified that evaluated the cancer risk from exposure to benzene in residential settings (i.e., at environmentally relevant concentrations). Some studies have considered the risk of childhood leukemia associated with use of paints, solvents or hobbies; or, with proximity to gas stations or traffic; however, no quantitative exposure measurements have been taken. From a limited number of studies, there is no strong evidence for an association between benzene-related products or associated activities and childhood leukemia, for example paints, solvents, hobbies (e.g., model building, artwork using solvents, furniture stripping) (Scélo et al. 2009; Infante-Rivard 2008; Infante-Rivard et al. 2005; Crosignani et al. 2004; Visser, Van Wijnen and Van Leeuwen 2004; Reynolds et al. 2003; Reynolds et al. 2002; Freedman et al. 2001; Raaschou-Nielsen et al. 2001; Pearson, Wachtel and Ebi 2000; Harrison et al. 1999; Lowengart, Peters and Cicioni 1987). In contrast, the association between childhood leukemia and proximity to gas stations or traffic has been investigated in several studies. The author of a review of the majority of these studies concluded that the weight of evidence suggested no association, although results were not entirely consistent (Infante-Rivard 2008). In one recent study, results similar to an earlier study were reported, which suggested that childhood leukemia is elevated in census tracts with the highest concentrations of benzene or other hazardous air pollutants (Whitworth, Symanski and Coker 2008). In studies in which exposure to traffic was stratified, positive results were reported for exposure to high-traffic only (Crosignani, 2004; Pearson, Wachtel and Ebi 2000). In one other recent French study, residence near a gas station or repair garage was associated with elevated childhood leukemia cases (Brosselin et al. 2009) .

A number of studies have identified an increased risk for childhood acute lymphocytic leukemia (ALL) associated with maternal occupational exposure to benzene (Shu et al. 1999; Feingold, Savitz and John 1992; Shu et al. 1988; Van Steensel-Moll, Valkenburg and Van Zanen 1985). However, other studies did not detect a relationship between benzene exposure and the development of ALL, thus this association remains controversial (Infante-Rivard et al. 2005; Kwa and Fine 1980).

5.5 Mode of Action

Benzene is genotoxic and there is no clear evidence of a threshold (Glass et al. 2004; Glass et al. 2003). No evidence of a threshold for hematotoxic effects of benzene has been observed and it has been suggested that exposure to <5 ppm (16 µg/m^3) benzene could result in hematologic suppression (Ward et al. 1996; Zhang 1996). The specific adverse effects of benzene are dependent upon the concentration and duration of exposure. A causal link between chronic benzene exposure and leukemia is established; however, the shape of the exposure-response relationship at low environmental concentrations is still controversial. All exposures may carry some risk in a linear (if not supralinear) or additive fashion. No accepted animal model of benzene induced leukemia exists at the present time.

A mode of action of benzene induced leukemia was hypothesized by Meek and Klaunig (2010) based on the following five key events: (1) metabolism of benzene by Cytochrome P4502E1 in liver; (2) interaction of the benzene metabolite with target cells in the bone marrow (bone marrow stem cells or precursor cells); (3) the formation of initiated, mutated bone marrow target cells (the mutation arises either by direct interaction with genomic DNA, and subsequent mutation through misrepair, or indirectly, occurring spontaneously following epigenetic influences on the target cell or tissue); (4) the selective clonal proliferation of these mutated cells as a result of disruption to the normal cell cycle and/or changes to the normal apoptotic process; and, (5) the formation of the neoplasm (leukemia), usually resulting from additional mutations and chromosome damage.

Metabolism plays an important role in benzene toxicity. There is a shift to greater production of metabolites via the ring-opening pathway and hydroquinone than phenol at lower exposures, including into the environmental range (Rappaport et al. 2010; Weisel et al. 2003). It is generally agreed that benzene-induced myelotoxicity and genotoxicity results from a synergistic action of phenol with hydroquinone, mucoaldehyde or catechol. The metabolism of phenol and hydroquinone to benzoquinone, semiquinones, and free radicals, which can bind to cellular macromolecules including DNA, can lead to oxidative DNA damage (Smith and Fanning 1997; Smith 1996; Snyder and Hedli 1996; Valentine et al. 1996; Johansson and Ingelman-Sundberg 1988). However, the molecular mechanisms by which exposure to benzene and its metabolite(s) cause injury by binding to cell proteins and DNA, which leads ultimately to leukemic and preleukemic conditions, remain uncertain (Ontario Ministry of the Environment 2011; ATSDR 2007). Future work that could further the understanding of benzene-induced leukemia includes defining a target cell in the bone marrow and elucidating the role of oxidative stress in the development of leukemia (Meek and Klaunig 2010).

Dose response relationships are generally not characterised in human genotoxicity studies as discussed in the Section 5.3. Molecular targets for the action of hydroquinone and benzoquinone metabolite(s) include tubulin, histone proteins, topoisomerase II and other DNA associated

proteins. Damage to these proteins would potentially cause DNA strand breakage, mitotic recombination, chromosomal translocations, and inversions leading to aneuploidy. These types of genetic events can result in proto-oncogene activation, tumour suppressor gene inactivation, gene fusions, and other changes in stem cells that can ultimately result in leukemia (Health Canada 2009). Occupational exposure to benzene and in vitro assays of benzene metabolites using human cell cultures have resulted in chromosomal changes that are characteristic of AML; however, these single events are insufficient to induce leukemia. Further specific gene mutation or chromosome changes are required (Smith 2010). Epigenetic effects of benzene metabolites on the bone marrow stroma and possibly stem cells could foster development of leukemia (US EPA 1998). The aryl hydrocarbon receptor (AhR) may be involved in benzene-induced hematotoxicity given its role in the regulation of hematopoietic stem cells (Smith 2010; Yoon et al. 2002). In addition, polymorphisms in genes involved in benzene metabolism may influence individual susceptibilities to benzene at various levels of exposure (Smith 2010; Dougherty et al. 2008).

As all leukemia arises in the stem and progenitor cells of the bone marrow that are damaged by benzene, there is a biologically plausible basis for suggesting benzene as a causal factor for all kinds of myeloid and lymphoid malignancies including their prestages (Beelte et al. 2009). The most recent assessment by IARC confirms that benzene's leukemogenic potential extends beyond acute myeloid leukemia, to include acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple myeloma and non-Hodgkin lymphoma (Bann et al. 2009).

6.0 CHARACTERIZATION OF RISK

6.1 Characterization of Dose-response

Benzene is a carcinogen based on convincing human evidence, as well as supporting evidence from animal studies. Most regulatory agencies have relied upon evidence from occupational exposures to derive reference values for benzene. Epidemiologic studies provide clear evidence of a causal association between exposure to benzene and AML and also limited evidence for associations with chronic lymphocytic leukemia, multiple myeloma and non-Hodgkin's lymphoma (Baan et al. 2009). Benzene-induced leukemia is considered to be the critical effect and most sensitive endpoint upon which to derive a long-term (chronic) risk specific reference concentration.

Numerous risk analyses of the key epidemiological studies, specifically the Pliofilm cohort and to a lesser extent, the Chinese Worker cohort, have been conducted to assess the carcinogenic risks from exposures to benzene (Environment Canada and Health and Welfare Canada 1993, Health Canada 2009; US EPA 2000; OEHHA 2001). The approaches used to determine this risk have resulted in variable risk estimates.

Benzene was assessed as a priority substance by Environment Canada and Health and Welfare Canada (1993). It was classified as a carcinogen and its cancer potency was assessed using a tumorigenic concentration associated with a 5% increase in mortality due to tumors (TC_{05}). Using data from the Pliofilm cohort, a TC_{05} for AML was calculated to be 15 mg/m^3 (Health Canada 1996). While it was decided to express cancer potency in this way (in or close to the experimental range as opposed to using low-dose extrapolation methods), it is possible to compare

concentrations associated with this cancer potency to those associated with unit risks derived by other organizations. Linear extrapolation[1] from the TC_{05} gives a range of concentrations associated with risk levels of $1x10^{-6}$ to $1x10^{-5}$, equal to 0.3 - 3.0 $\mu g/m^3$.

In Health Canada's assessment in support of the Drinking Water Guideline for Benzene (Health Canada 2009), the cancer risk analysis conducted by the OEHHA (2001) was critiqued. In reviewing the OEHHA analysis, Health Canada (2009) agreed with its balanced approach and thorough consideration of 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. OEHHA (2001) concluded that data from the Pliofilm cohort and Chinese Worker cohort were suitable as the basis for risk assessment for the general population. Individual exposure data were obtained for members of the Pliofilm cohort, but only summary data were available for the Chinese Worker cohort. As part of the risk assessment process OEHHA made several decisions that affected the final risk estimates including definition of the target population, use of incidence vs mortality, pattern of leukemia risk over time, lag time between exposure and disease and source of background rates of leukemia incidence. Considering all the analyses performed, from the Pliofilm cohort OEHHA (2001) derived a reasonable range of risk estimates of 0.010 – 0.048 ppm^{-1} (0.0031 - 0.015 $(mg/m^3)^{-1}$). Similarly a range was derived for the Chinese Worker cohort equal to 0.0054 - 0.087 ppm^{-1} (0.0017 – 0.027 $(mg/m^3)^{-1}$). To develop a Public Health Goal for Benzene in Drinking Water the geometric mean of the most justifiable unit risks from the Pliofilm cohort (0.044 ppm^{-1} (0.014 $(mg/m^3)^{-1}$) and the Chinese Worker cohort (0.056 ppm^{-1} (0.018 $mg/m^3)^{-1}$) was selected, namely 0.050 ppm^{-1} (0.016 $mg/m^3)^{-1}$ based on total leukemia incidence.

US EPA published its latest cancer risk analysis for benzene in 2000. While US EPA also used data from the Pliofilm cohort, its approach differed in several ways. US EPA did not conduct a re-assessment of the lifetime cancer risks from exposure to benzene for the general population. Instead a range of risk estimates was selected from the maximum likelihood estimates generated by Crump (1992, 1994) based on low-dose linearity of the Pliofilm cohort data. All exposure data (as opposed to OEHHA which only considered exposures < 400 ppm-yr) were considered; and mean cancer mortality risk estimates were used (as opposed to OEHHA's approach to select upper 95% confidence bound estimates for total leukemia incidence). US EPA recommended the maximum likely values as a range of estimates of risks, each having equal scientific plausibility to estimate risk at low environmental exposures. Considering all models, using different exposure matrices, disease endpoints, additive or multiplicative models, linear or non-linear exposure response relationships and cumulative or weighted exposure measurements an initial range of units risks was identified ($8.6x10^{-5}$ to $2.5x10^{-2}$ $(ppm)^{-1}$ [$2.6\ x10^{-8}$ to $7.8\ x10^{-6}$ $(\mu g/m^3)^{-1}$]. The risk estimates would fall in the lower region of this range if the dose-response curve were sub-linear and in the higher region if the dose-response curve were supra-linear at low exposures. Therefore, the true risk could be either higher or lower. The final range of risk estimates was based on the use of a default low-dose linear extrapolation in the absence of convincing evidence for use of any other model. This resulted in a range of unit risks of $2.2\ x\ 10^{-6}$ to $7.8\ x\ 10^{-6}$ $(\mu g/m^3)^{-1}$ (US EPA, 2000).

[1] Calculated by ratio: 15 $\mu g/m^3$ (for five percent; 0.05) divided by 500 (for one in one hundred thousand; 0.0001) or 5000 (for one in one million; 0.00001).

The Health Canada (1996), OEHHA (2001) and US EPA (2000) approaches determined cancer potency values based on scientifically supported rationales, with uncertainties clearly identified. It is important to recognize the considerable uncertainty associated with these derived values, including: (1) the uncertainties or limitations with the occupational exposure data from the epidemiologic studies used in the analysis; (2) the lack of knowledge of the shape of the dose-response curve at both high and low environmental exposure levels; and (3) the lack of knowledge of the mode of action by which benzene exerts its carcinogenic effects. Although these uncertainties cannot be quantified, they would be expected to result in at least an order of magnitude uncertainty in the estimated value. The range of concentrations associated with risks per $1x10^{-6}$ considering the three different analyses, is 0.06 µg/m^3 (from the geometric mean of the most justifiable unit risks derived by OEHHA 2001) to 0.45 µg/m^3 (from the upper bound presented by US EPA 2000). At a $1x10^{-5}$ risk level this range is 0.6 to 4.5 µg/m^3. As such, the risk estimates of the Health Canada (1996)**,** OEHHA (2001) and US EPA (2000) cannot be considered as significantly different.

6.2 Risk Characterization for the Canadian Population Indoors

In the past decade, Health Canada has completed several exposure studies in multiple Canadian cities. The results of these studies include residential indoor and outdoor VOC concentrations. Overall, the results from these studies are similar to other Canadian studies conducted after 2000; in general, higher concentrations were reported in studies conducted prior to 2000. The results of Health Canada studies are considered the most recent data available for quantifying levels of exposure in Canadian homes. Therefore, these data are used in the risk characterization. Median benzene levels measured in Canadian homes in Health Canada studies range from 0.5 to 2.2 µg/m^3 (see Table 2). In studies in which 95th percentiles were reported (Halifax, Regina and Windsor) the range in homes was 3.6 to 21.0 µg/m^3.

In Section 6.1 a range of concentrations associated with specific risk levels for leukemia based on cancer risk analyses from Health Canada (1996), US EPA (2000) and OEHHA (2001) were presented. The range of concentrations associated with a risk level of $1x10^{-6}$ was 0.06 to 0.45 µg/m^3. For a risk level of $1x10^{-5}$ the range was 0.6 to 4.5 µg/m^3.

When the concentrations of benzene measured in Canadian homes is compared to the ranges of concentrations associated with $1x10^{-5}$ or $1x10^{-6}$ risk levels, it can be observed that median levels in Canadian homes fall within, or below the concentration range associated with a $1x10^{-5}$ risk level. When considering the range of 95th percentiles of indoor benzene levels, while the lower end of measured values fall within the concentrations associated with a $1x10^{-5}$ risk, there are some values that are more than four times greater than the upper end of the range of concentrations associated with a 1 in 100,000 risk ($1x10^{-5}$). As Figures 1 and 3 suggest, the presence of smoking in the home or an attached garage has been associated with an increase in benzene concentration. Therefore, the population living in homes where smoking is present or with an attached garage may potentially be at higher risk.

The estimated cancer risks were calculated using conservative assumptions, and the actual risks to Canadians may well be lower than the estimated risks. Environmental exposure levels are at least three orders of magnitude lower (in µg/m^3 range) than occupational exposure levels (in mg/m^3 range) and there is considerable uncertainty associated with extrapolating risks observed at high

concentrations for the estimation of risks at lower exposure levels. This and other sources of uncertainty in this risk assessment are summarized in Section 6.3.

6.3 Uncertainties

Uncertainties in the cancer risk assessment for benzene at environmentally relevant exposures include
1) The understanding of the molecular mechanisms by which exposure to benzene and its metabolites exert their toxic and carcinogenic effects as discussed in Section 5.5. There is also limited genotoxicity dose-response data at environmental concentrations. It is likely that more than one mechanistic pathway may be responsible for the toxicity of benzene contributing to the leukemogenic process.
2) Associations with other forms of leukemias (other than AML) in workers, the general population and children are less established.

7.0 GUIDANCE FOR THE MITIGATION AND CONTROL OF INDOOR BENZENE

Health Canada may choose to develop a quantitative residential exposure guideline, together with recommendations on source control, or produce qualitative guidance alone, without specifying a numerical guideline. As discussed in the preamble to this assessment, the decision to recommend a numerical exposure limit for residential indoor air considers both the characterization of the health risks and the feasibility of achieving a health-based exposure limit through the control of indoor sources.

The range of estimates of carcinogenic risks of benzene indicates that there may be a low but non-negligible risk at indoor exposure levels. On this basis, from a practical perspective, Health Canada has opted to use a qualitative approach, recommending that individuals take actions to reduce exposure to benzene indoors as much as possible. Measures to control known indoor sources may reduce benzene concentrations such that the risk to residents is very low. As further sources are identified and effective control measures developed, Health Canada will incorporate additional recommendations on reducing benzene levels in its communications to health and building professionals and the public.

In most residential situations, identifying potential sources and remedial measures is more informative and cost-effective for improving indoor air quality than is air testing and comparison of measured concentrations to quantitative guideline values. Nonetheless, the quantitative dose-response characterization of low-level benzene exposure, as presented in section 6.1, is relevant to risk management. For example, in the development of benzene emission standards for building materials and consumer products, the concentration range associated with negligible risk may be used to set target emission factors for different products under different scenarios of use.

To date many steps have been taken to reduce benzene content in gasoline, building materials and consumer products and to reduce levels of smoking indoors. These changes have likely contributed to the decreasing trend in ambient and indoor benzene levels. However, benzene is still present in Canadian homes, and across Canada, median indoor concentrations of benzene are consistently

higher than outdoor levels, suggesting that there are indoor sources of benzene. The range of median indoor concentrations in Health Canada studies was 0.5 to 2.2 µg/m^3 indoors compared to 0.2 to 0.9 µg/m^3 outside homes. Further reductions in indoor benzene levels may require changes in behaviours and housing characteristics.

Several studies have indicated that, in homes with attached garages, the major source of benzene indoors generally comes from the migration of benzene from sources in the garage. Therefore, any steps to minimize migration of volatile compounds from attached garages into residential environments should be explored, including preventing leaks between the garage and house (e.g., at wall-to-wall or wall-to-floor junctions), sealing all penetrations between the house and garage (e.g., wiring, central vacuum exhaust) and installing an exhaust fan. Where possible, removing potential sources of benzene (e.g., paints, solvents, gasoline storage containers, gasoline powered tools) from the garage may also be considered. Removal of these sources from inside homes that do not have an attached garage may also reduce indoor benzene levels. There is evidence from a limited number of studies in a small number of homes that such measures can reduce indoor levels of benzene (CMHC 2004; Ilgen et al. 2001c). The reader is referred to CMHC (2009) and CMHC (2004) for further information on these strategies.

Smoking indoors was the second most frequent predictor of indoor benzene levels (Héroux et al. 2010; Héroux et al. 2008). However, there have been mixed results in Canadian and American studies published since 2001 with respect to whether levels of benzene in homes with smokers are elevated compared to homes without (Héroux et al. 2010; Héroux et al. 2008; Jia, Batterman and Godwin 2008b; Adgate et al. 2004a; Adgate et al. 2004b; Kim, Harrad and Harrison 2001). Cessation of smoking indoors may lower residential levels of benzene and will also provide other positive impacts on indoor air quality and health with regard to other pollutants found in cigarette smoke.

Other predictors of indoor benzene levels include variables associated with ventilation, such as air conditioning, season and window opening. The tighter a house is built or kept, the more likely it is that indoor pollutants will remain indoors resulting in elevated indoor concentrations. In general, it is important that individuals take measures to ensure their homes are well ventilated. Proper ventilation is intended to ensure that tightly-built houses have adequate air exchange rates to remove contaminants and excess humidity. The reader is referred to CMHC (2010) for more information. No data were identified that associated the use of specific ventilation strategies or products with reduced indoor benzene levels. However, irrespective of the degree to which a well-ventilated home may contribute to reduced indoor benzene levels, proper ventilation is overall beneficial to both indoor air quality and the health of occupants.

Studies that have identified predictors of benzene levels have been able to determine between 26 and 59% of the variability in benzene concentrations. While the strongest and most consistent predictors (attached garages and indoor smoking) have been identified, there may be other sources of benzene that account for additional variability in benzene levels. Therefore, there may be a number of other unknown factors that, collectively, contribute to indoor benzene levels.

In conclusion, there are measures that Canadians can take to reduce their exposure to benzene in residential environments. A reduction in exposure to benzene may be expected to have a public health benefit by decreasing the associated risks of leukemia. In addition, by addressing attached

garages and smoking indoors as the primary sources of benzene in homes, levels of other contaminants that can migrate from garages, or that are emitted from cigarettes, may also be reduced. The results of this science assessment document highlight the need for future research into effective strategies to reduce migration of pollutants from attached garages indoors.

The foregoing recommendations are consistent with previous Health Canada guidance to homeowners, in that the focus is first on identifying the potential sources of contaminants in the home, and then on improving air quality through the control of sources, by improved ventilation, or other remedial measures.

8.0 RECOMMENDATIONS FOR FUTURE RESEARCH

Areas for future research that have been identified by this assessment include

- Characterization of migration of benzene from attached garages under different scenarios;
- Effectiveness of interventions aimed at minimizing indoor exposure to benzene by reducing the migration of benzene from garages indoors (e.g., exhaust fans in garages, sealing of cracks and leaks);
- The development of building standards or codes that address attached garages and migration of volatile substances from garages into homes;
- Characterization of other potential sources of indoor benzene, including vapor intrusion, as well as the sources that drive indoor benzene levels in homes without smoking and without attached garages;
- Epidemiological studies of leukemia incidence at low exposure levels relevant to indoor environments; and,
- Epidemiological studies of non-leukemic hematopoietic incidences (e.g. decreased blood cell count) at low benzene exposure levels relevant to indoor environments.

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APPENDIX A: SEARCH STRATEGIES

Overview

Generating a database of benzene-related documents was accomplished in two phases. First, a search for previously prepared toxicological reviews and air quality guideline documents was completed. By consulting reputable sources, it was possible to obtain recent reviews and guideline documents for benzene prepared up to 2007. Utilizing reviews from the US-EPA, ATSDR and the Government of Canada Drinking Water document, it was decided that a comprehensive review would not be required prior to 2006 (the approximate cut-off date for the Drinking Water Document), as these documents are thorough and/or from reputable sources.

Secondly, a search of the scientific literature was completed that spanned the period between 2006 (the approximate cut-off date for the Drinking Water Document) to the end of 2009 (the cut-off date for this review). Articles published on-line or in press during this time period were included. In addition, a search for relevant research by Canada Housing and Mortgage Corporation was conducted on their website, http://www.cmhc-schl.gc.ca/en/. Finally, papers identified during the external peer review process were considered for inclusion on a case-by-case basis regardless of date of publication.

The basis of Section 2. Sources in the Environment, and Section 3. Indoor, Outdoor and Personal Concentrations, was a 2009 contract completed by Chunrong Jia and Stuart Batterman titled "Critical Review of the Sources and Exposure Levels of Benzene, Toluene, Xylene and Naphthalene Relevant to Canadian Residential Indoor Environments".

Primary data sources

To search for previously prepared reviews and guideline documents, the following sites and documents were reviewed:

Government of Canada http://www.hc-sc.gc.ca
Guidelines for Canadian Drinking Water Quality: Guideline Technical Document for Benzene, 2009: http://hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/water-eau/benzene/benzene-eng.pdf

Agency for Toxic Substances and Disease Registry http://www.atsdr.cdc.gov/toxprofiles/index.asp
Toxicological Profile for Benzene, 2007:
http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14

United States Environmental Protection Agency http://cfpub.epa.gov/ncea/iris/index.cfm
Benzene-Related Documents:
http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nmbr=0276

World Health Organization http://www.who.int/ipcs/en/
Air Quality Guidelines for Europe, 2nd edition, 2000:
http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf

European Union http://ec.europa.eu/health/index_en.htm
Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU - The INDEX Project, 2005:
http://ec.europa.eu/health/ph_projects/2002/pollution/fp_pollution_2002_frep_02.pdf

Other important documents

Government of Canada
Canadian Environmental Protection Act Priority Substances List Assessment Report: Benzene, 1993: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl1-lsp1/benzene/benzene-eng.pdf

World Health Organization - International Programme on Chemical Safety
Benzene, Environmental Health Criteria 150, 1993:
http://www.inchem.org/documents/ehc/ehc/ehc150.htm

National Toxicology Program
Toxicology and Carcinogenesis Studies of Benzene (CAS No.71-43-2) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies) (TR-289, 1986): http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr289.pdf

Scopus search
The following groupings of keywords and combinations strategies were used to search for publications in Scopus (http://www.scopus.com/) using the "Advanced" search box. Each keyword was searched in the title, abstract or keyword fields. The results were filtered to cover the period 2006 to the end of 2009. In addition to database searches, references of relevant papers were also reviewed.

Keyword groupings
An asterisk (*) is a wildcard symbol representing any number of characters. A question mark (?) is a wildcard symbol representing just one character.

GROUP 1: CHEMICAL COMPOSITION
71-43-2, benzene, Annulene, benzine, benzol, benzole, benzol coal, naphtha, cyclohexatriene, mineral naphtha, motor benzol, phenyl hydride, pyrobenzol, pyrobenzole

GROUP 2: CARDIOVASCULAR ENDPOINTS
aort*, arrhythm*, arterial, artery, atherosclero*, arteriosclero*, bradycardia, cardiac, cardio*, clotting factor, coagulation, ECG, electrocardiogram, electrocardiographic, endothel*, fibrin*, fibrosis, haematolog*, heart, HRV, hematolog*, hypertensi*, ischem*, myocard*, platelet, thrombosis, thrombus, vascular, vasopressor, ventricular

GROUP 3: RESPIRATORY ENDPOINTS
airway, allergy, allergen, alveoli, alveolus, alveolar, asthma*, bronchiole, bronchus, bronchoalveolar, edema, oedema, emphysema, epithelia, epithelial, epithelium, expiratory, fibroblast, fribronectin, fibrosis, fibrotic, fibroproliferative, forced vital capacity, hyperreactive, hyperreactivity, hyperplasia, inflammation, inflammatory, interstitial, interstitium, irritation,

lactate dehydrogenase, lavage, lung, mucociliary, nasal, oxygen saturat*, phagocyt*, pulmonary, respiratory, responsiveness, somatosensory, spirometry, sputum, or thoracic

GROUP 4: MOLECULAR AND IN-VITRO ENDPOINTS
albumin, antioxidant*, chemoattractant*, chemokine*, CINC, cytokine, cytotoxic*, eosinophil*, ICAM-1, Ig*, IL-*, in vitro, leukocyte*, lymphocyte*, macrophage*, MAPK, MIP-2, monocyte*, neutrophil*, ovalbumin, oxidative stress, phagocyt*, PMN, red blood cell, ROS, reactive oxygen species, TNF*, tumor necrosis factor, white blood cell

GROUP 5: SUSCEPTIBILITY ENDPOINTS

infecti*, mutant, polymorphism, resistance, sensitization, rhinitis, susceptibility, genotype, phenotype, compromised

GROUP 6: CARCINOGENICITY ENDPOINTS

aneuploidy, base-pair substitution, cancer, carcino*, DNA adduct, frameshift, gene deletion, gene translocation, genotox*, malignan*, micronuclei, mutagen*, mutation, revertant, S9 activation, sister chromatid exchange, transversion, leukemia

GROUP 7: CHEMICAL SPECIFIC ENDPOINTS

developmental, immunotox*, neurotoxic*, neurologic*, ototoxic*, neurobehavioral*, reproduc*, teratogen*

GROUP 8: EPIDEMIOLOGICAL ENDPOINTS

(cohort, panel, camp, human, clinical, field) and (study, studies, trial, data, analysis, case-crossover, case control, population-based, cardiovascular, cardio-respiratory, respiratory, lung, inflammation, pulmonary, disease, asthma, health effects, copd, chronic obstructive pulmonary disease, lbw, low birth weight, sudden infant death syndrome, sids, crib death, mortality, death, morbidity, toxic, toxicity, epidemiology, cytoxicity, DNA damage, health problems, health consequences)

GROUP 9: INDOOR STUDIES

indoor, resident*, dwell*, person*, human, garage

GROUP 10:
woodsmoke, wood smoke, fireplace

GROUP 11: EXCLUSION TERMS

vegetation, photosynthesis, stomata, corrosion, erosion, forest, cereal?, plant?, lake?, leaf, "climate change", herbicide?, pesticide?, insecticide?, soybean?, foliage, conifer?, foliar, cultivar?, tree?, stoma, aquatic, green?house?, grassland?, chloroplast?, pine needle

Search combinations

Combination	*Grouping*
1	*(GROUP 1* AND *GROUP 2)* NOT *GROUP 11*
2	*(GROUP 1* AND *GROUP 3)* NOT *GROUP 11*
3	*(GROUP 1* AND *GROUP 4)* NOT *GROUP 11*
4	*(GROUP 1* AND *GROUP 5)* NOT *GROUP 11*
5	*(GROUP 1* AND *GROUP 6)* NOT *GROUP 11*
6	*(GROUP 1* AND *GROUP 7)* NOT *GROUP 11*
7	*(GROUP 1* AND *GROUP 8)* NOT *GROUP 11*
8	*(GROUP 1* AND *GROUP 9)* NOT *GROUP 11*
9	*(GROUP 1* AND *GROUP 10)* NOT *GROUP 11*
10	*(GROUP 1* AND *GROUP 2)* NOT *GROUP 11*
11	*(GROUP 1* AND *GROUP 3)* NOT *GROUP 11*

APPENDIX B: INTERNATIONAL GUIDELINES AND STANDARDS

Guidelines or reference values for benzene in air were identified from seven national or international organizations based on non-carcinogenic and carcinogenic effects. Guidelines based on carcinogenic endpoints will be protective of non-carcinogenic long term effects (summarized in Table 4).

European Union

The Joint Research Centre of the European Commission carried out the *"Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU" (INDEX)* (European Commission 2005). Available European exposure data were compared to cancer risk estimates derived from the WHO unit risk of 6×10^{-6} $(\mu g/m^3)^{-1}$, the European Union annual ambient limit value for the protection of human health of 5 $\mu g/m^3$ and to a non-cancer NOAEL identified by OEHHA. It was decided not to develop a guideline value for benzene. It was concluded that "as benzene is a human carcinogen, its concentration in indoor air should be kept as low as reasonably achievable." It was further recommended that benzene concentrations indoors should not exceed outdoor levels. Risk management options were proposed that included: sources emitting benzene should not be allowed indoors; the permissible benzene content in any building material and consumer product could be lowered and reporting of known benzene levels could be provided also when below permissible levels; and raising public awareness and information available to the public about the sources, nature and levels of risk of benzene in indoor air.

Agency for Toxic Substances and Disease Registry

In "*Toxicological Profile of Benzene*", the Agency for Toxic Substances and Disease Registry derived acute (1-14 days), intermediate (15-364 days) and chronic (365 days and longer) minimal risk levels (MRL) for humans exposed to benzene by inhalation. An acute inhalation MRL for benzene was derived from a lowest observed adverse effect level (LOAEL) of 10.2 ppm (32.6 mg/m^3) for reduced lymphocyte proliferation from a study in mice (Rozen, Snyder and Albert 1984). The LOAEL was adjusted for exposure duration of less than a day (i.e., by multiplying by 6 h/24 h), converted to a human equivalent concentration based on the ratio of the blood: gas partition coefficients of animals and humans (default value of one) and divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies variation and 10 for intra-individual variation). This led to the derivation of an acute MRL of 0.009 ppm (30 $\mu g /m^3$). An intermediate inhalation MRL for benzene was derived from a LOAEL of 10 ppm (32 mg/m^3) for significantly-delayed splenic lymphocyte reaction to foreign antigens *in vitro* following exposure of mice to benzene (Rosenthal and Snyder 1987). This LOAEL was adjusted for exposure duration (i.e., by multiplying by 6 h/24 h), converted to a human equivalent concentration using the default value of one, and divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for interspecies variation and 10 for intra-individual variation). This led to the derivation of an intermediate MRL of 0.006 ppm (20 $\mu g/m^3$). A chronic MRL was derived for benzene from a benchmark dose analysis of decreased counts of B-lymphocytes in occupationally exposed individuals (Lan et al. 2004). From this analysis, the point of departure (0.1 ppm (0.3 mg/m^3)) was adjusted for exposure duration (i.e., from 8 h to continuous exposure using the US EPA default occupational minute

value) and divided by an uncertainty factor of 10 for intra-individual variation. This led to the derivation of a chronic MRL of 0.003 ppm (10 µg/m^3) (ATSDR 2007).

Health Canada

A tumorigenic concentration associated with a 5% increase in incidence (TC_{05}) equal to 15 mg/m^3 was developed by Health Canada under the Priority Substances program (Health Canada 1996). The TC_{05} was based on the incidence of leukemia in occupationally-exposed humans in the Pliofilm cohort (Rinsky et al. 1987).

California Environmental Protection Agency (CalEPA)

The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (CalEPA) derived an acute reference exposure level (REL) (6h) based on a NOAEL of 129.6 mg/m^3 for reduced fetal weight in rats in a study by Coate et al. (1984). This value was divided by an uncertainty factor of 100 (10 for interspecies differences and 10 for intraspecies variability) to give a REL of 1300 µg/m^3 (OEHHA 1999). The development of a chronic REL was based on a NOAEL of 0.53 ppm (1.7 mg/m^3) for lowered red and white blood cell counts in occupational exposed humans (Tsai et al. 1983). After adjusting for continuous exposure and intraspecies variability (uncertainty factor of 10), the chronic REL was 60 µg/m^3 (OEHHA 2000). The California Department of Health Services (1988) recommended a unit risk of 2.9 x 10^{-5} (µg/m^3) derived from the upper 95% confidence bound estimate of data deemed the most credible by US EPA (1979). As the unit risks derived by OEHHA (2001) for benzene in drinking water approximated this earlier value when expressed as a potency value (~ 0.1 (mg/kg-d)$^{-1}$), no new unit risk was adopted (OEHHA 2009).

European Parliament

The European parliament set an annual limit value of 5 µg/m^3 for ambient benzene. Limit values are based on scientific knowledge, taking into account relevant World Health Organisation standards, guidelines and programmes and the most recent research data. The aim of limit values is to avoid, prevent or reduce harmful effects on human health and/or the environment as a whole, and should be attained within a given period and not exceeded once attained. It was recognized that "Benzene is a human genotoxic carcinogen and there is no identifiable threshold below which there is no risk to human health" (European Parliament 2000).

United States Environmental Protection Agency

The US EPA derived an inhalation reference concentration (RfC) for non-carcinogenic effects from a benchmark dose analysis of decreased lymphocyte count in an occupational epidemiological study (Rothman et al., 1996). The 95% lower confidence limit (benchmark concentration lower confidence limit (BMCL) of 7.2 ppm was converted to mg/m^3, adjusted for exposure duration (from 8h/d to continuous) and standard breathing rate to give an adjusted value of 8.2 mg/m^3. This was the point of departure for the RfC derivation. Divided by a total uncertainty factor of 300 (comprised of 3 for effect-level extrapolation, 10 for human variability, 3 for subchronic to chronic and 3 for database deficiencies) resulted in an RfC of 30 µg/m^3. In deriving an inhalation unit risk based on leukemia, US EPA assumed low dose linearity in

extrapolating from published studies of the Ohio Pliofilm cohort (Crump 1994; Paustenbach, Bass and Price 1993; Paustenbach et al. 1992; Rinsky, Smith and Hornung 1987; Crump and Allen 1984; Rinsky, Young and Smith 1981) to obtain a unit risk range of 2.2 x 10^{-6} to 7.8 x 10^{-6} per 1 µg/m^3 (US EPA 2003).

World Health Organization

The *WHO Guidelines for Indoor Air Quality* concluded that no safe level of exposure can be recommended for benzene as it is a genotoxic carcinogen, and indoor exposures should be reduced to as low as possible. In addition, there is no reason to suggest indoor guidelines should differ from ambient guidelines. As such, the unit risk of 6 x 10^{-6} per 1 µg/m^3 calculated for the WHO ambient guideline based on the Pliofilm cohort studies is recommended (World Health Organization 2010).

Table 4. Summary of other benzene air guidelines and standards

Reference	Metric	Averaging time	Concentration		
			µg/m^3	Unit risk (µg/m^3)$^{-1}$	µg/m^3 per 1x10^{-6} to 1x10^{-5} risk
NON-CARCINOGENIC ENDPOINTS					
Agency for Toxic Substances and Disease Registry (2007)	Ambient	Acute (1-14 d)	30		
		Intermediate (15-364 d)	20		
		Long term (365+d)	10		
Office of Environmental Health Hazard Assessment California Environmental Protection Agency (2000; 1999)	Ambient	Acute (6 hr)	1300		
		Long term	60		
United States Environmental Protection Agency (2003)	Ambient	Long term	30		
CARCINOGENIC ENDPOINTS					
European Commission (INDEX Project) (2005)	Indoor	Long term	As low as reasonably achievable; should not exceed outdoor concentrations		
European Parliament (2000)	Ambient	Long term	5		
Health Canada (1996)	Ambient	Long term (TC_{05})	15000		0.3 to 3
Office of Environmental Health Hazard Assessment California Environmental Protection Agency (OEHHA 2009)	Ambient	Long term		2.9 x 10^{-5}	0.034 to 0.34
United States Environmental Protection Agency (2000)	Ambient	Long term		2.2 x10^{-6} –7.8 x 10^{-6}	0.13 to 4.5
World Health Organization (2010; 2000)	Indoor	Long term	Reduce to as low as possible: adopt same unit risk as ambient		
	Ambient	Long term		6 x 10^{-6}	0.17 to 1.7