Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Benzene

Government of Canada / Gouvernement du Canada
Environment Canada / Environnement Canada
Health and Welfare Canada / Santé et Bien-être social Canada

Canada

CANADA'S GREEN PLAN

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Erratum

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p. 19, Table 6: for "Estimated Intake" - change
units to read [µg/(kg (b.w.)· day]

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PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

BENZENE

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Environment Canada
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Overview of Findings

Benzene is used in Canada in a variety of ways that result in it entering the Canadian environment. Vehicle emissions are the major source of benzene release to the environment. Releases of benzene result in measurable concentrations in the various media to which humans and other organisms may be exposed.

Except in cases of spills or occasional discharge of contaminated effluent, the highest reported mean concentration of benzene in ambient surface water in Canada is about 2000 times less than that found to induce adverse effects in the most sensitive aquatic species (leopard frog) in long-term studies. The highest mean concentration of benzene in untreated effluents released into surface water is about 80 times less than the levels found to induce adverse effects in the most sensitive aquatic species (rainbow trout) in acute studies. The highest concentration of benzene in ambient air measured in Canada is almost 240 000 times lower than the lowest concentration reported to be lethal to plants, terrestrial invertebrates, and laboratory mammals following acute exposure to benzene in air. The average concentration of benzene in rural air is more than 26 000 times lower than that found to induce adverse effects in laboratory mammals under chronic exposure conditions.

Because of its short persistence in the atmosphere, its nonhalogenated nature, and its low absorption of infrared radiation of critical wavelengths, benzene is not associated with depletion of stratospheric ozone or with global warming.

In Canada, the primary source of human exposure to benzene is ambient and indoor air; food and drinking water contribute only minor amounts to the daily intake of benzene. Benzene has been demonstrated to cause cancer in experimental animals and in humans. Benzene is, therefore, considered to be a "non-threshold toxicant", *i.e.*, a substance for which there is believed to be some chance of adverse effects at any level of exposure. For such substances, estimated exposure is compared to quantitative estimates of cancer potency in order to characterize risk and provide guidance for further action, such as analysis of options to reduce exposure.

Based on these considerations, the Minister of the Environment and the Minister of National Health and Welfare have concluded that benzene is a substance entering the environment in a quantity or concentration or under conditions that do not constitute a danger to the environment or to the environment upon which human life depends, but that may constitute a danger to human life or health in Canada. Therefore, benzene is considered to be "toxic" as defined under Section 11 of the *Canadian Environmental Protection Act*.

1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the Minister of the Environment and the Minister of National Health and Welfare to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined in Section 11 of the Act which states:

> "... a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions
>
> (a) having or that may have an immediate or long-term harmful effect on the environment;
>
> (b) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed to be "toxic" according to Section 11 may be placed on Schedule I of the Act. Consideration can then be given to developing regulations, guidelines, or codes of practice to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The assessment of whether benzene is "toxic", as defined in CEPA, was based on the determination of whether it **enters** or is likely to enter the Canadian environment in a concentration or quantity or under conditions that could lead to **exposure** of humans or other biota at levels that could cause adverse **effects**.

Data relevant to the assessment of the entry, environmental exposure, and environmental effects of benzene were identified in review documents. Information was also identified by searching commercial and government databases and indices from 1989 to 1991. These databases and indices included: AQUAREF, BIOSIS Previews, Chemical Evaluation Search and Retrieval System (CESARS), Chemical Abstracts, Chemical Hazards Response Information System (CHRIS), Cooperative Documents Project (CODOC), Enviroline, Environmental Bibliography, FATERATE, Federal Register, Hazardous Substances Data Bank (HSDB), Integrated Risk Information System (IRIS), International Register of Potentially Toxic Chemicals (IRPTC), MICROLOG, National Technical Information Service (NTIS), Pollution Abstracts, Registry of Toxic Effects of Chemical Substances (RTECS), SOLUB, TOXLINE, and TOXLIT. Additional relevant information was obtained from the United States Environmental Protection Agency (U.S. EPA) and from industrial sources including representatives of the Canadian Petroleum Products Institute (CPPI). Although much of the research on

benzene has been conducted outside Canada, available Canadian data on sources, use patterns, fate, and effects of benzene on the Canadian environment have been emphasized.

In addition to consulting review articles to identify data relevant to the estimation of exposure of the general human population to benzene and its effects on human health, computer literature searches were conducted biweekly from May 1990 to October 1991 on the MEDLINE, TOXLINE, and the NTIS databases. A search was also conducted on HSDB, RTECS, IRIS, Chemical Carcinogenesis Research Information System (CCRIS), TOXLINE, TOXLIT, and EMBASE in September 1991, to identify literature published after 1987 (date of previous extensive search).

Review articles consulted in the preparation of this report included those prepared by the Agency for Toxic Substances and Disease Registry (1989); National Institute of Public Health and Environmental Hygiene (1988); Occupational Safety and Health Administration (1987); Florida Petroleum Council (1986); U.S. EPA (1980); Austin *et al.* (1988); and Marcus (1987). Background documents prepared under contract, which were considered in the preparation of this report, included a multi-media exposure assessment of benzene for Canadian populations (Holliday and Park, 1989) and a data summary of concentrations of benzene in environmental media, human tissues, and terrestrial and aquatic organisms (Concord Scientific Corporation, 1990). Primary data included in reviews, which were not considered critical to the assessment of "toxic" to human health, were not evaluated.

Data relevant to the assessment of whether benzene is "toxic" to human health obtained after the completion of the sections of this report related to human health (*i.e.*, October 1991) were not considered for inclusion. Similarly, data relevant to the assessment of whether benzene is "toxic" to the environment obtained after May 1992 have not been incorporated.

Although review articles were consulted where appropriate, all original studies that form the basis for determining whether benzene is "toxic" under CEPA have been critically evaluated by the following staff of Environment Canada (entry, and environmental exposure and effects) and Health and Welfare (human exposure and effects on human health):

Environment Canada	Health and Welfare Canada
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L. Brownlee	
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Quantitative estimates of carcinogenic potency were provided by D. Krewski and S. Bartlett of Health and Welfare Canada.

In this report, an overview of findings concerning benzene that will appear in the Canada Gazette is presented. A summary of technical information that is critical to the assessment is presented in Section 2.0. This information is presented in greater detail in a Supporting Document which is available upon request. The assessment of whether benzene is "toxic" under CEPA is presented in Section 3.0. The effects of photochemical reaction products of benzene are not addressed in this assessment but are considered in the Federal/Provincial Management Plan for nitrogen oxides and volatile organic compounds (CCME, 1990).

Sections of the Supporting Document relevant to human exposure and effects were reviewed by B.H. Thorpe (Ontario Ministry of the Environment), E.J. Williams (Shell Canada Ltd.), D. Johnson and F. Ratpan (NOVA Corporation of Alberta), R.J. Keefe (Imperial Oil Ltd.), and E. Vernot (American Petroleum Institute). Following peer review by P. Enterline (University of Pittsburgh) and R. Irons (University of Colorado) of sections of the draft Assessment Report and Supporting Document relevant to the assessment of effects on human health, they were approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health and Welfare Canada. Environmental components of the Supporting Document were reviewed by representatives of the Canadian Petroleum Products Institute and by W.Y. Shiu and K.C. Ma (University of Toronto). The final Assessment Report was reviewed and approved by the Environment Canada/Health and Welfare Canada CEPA Management Committee.

Copies of this Assessment Report and of the unpublished Supporting Document are available upon request from:

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2.0 Summary of Critical Supporting Data

2.1 Identity and Physical/Chemical Properties of Substance

Benzene (CAS Registry Number 71-43-2) is a simple cyclic organic compound with molecular formula C_6H_6. It is a volatile, clear, flammable, colourless liquid at room temperature, and has an aromatic odour. Benzene is miscible in most common organic solvents. It has a relatively high vapour pressure (10.1 to 13.2 kPa at 25°C), a high water solubility (820 to 2167 mg/L at 25°C), and a low log octanol/water partition coefficient (1.56 to 2.69) (Mackay *et al.*, 1992). Benzene does not appreciably absorb light of wavelengths greater than 260 nm (Bryce-Smith and Gilbert, 1976) or infrared radiation at wavelengths of 7 to 13 μm (Sadtler Research Laboratories, 1982).

2.2 Production and Uses

Benzene can be produced commercially from petroleum, natural gas condensates, or coal. Most isolated (purified) benzene produced in Canada is derived from petroleum sources through catalytic reforming of naphtha, dealkylation of toluene, and separation of pyrolysis gasoline (Hancock, 1975; Allison and Brown, 1977).

A survey of commercial use patterns (CIS, 1991) indicates that 765 kilotonnes of isolated benzene were produced in Canada in 1990 and 131 kilotonnes were imported, for a total Canadian supply of 896 kilotonnes. Of these, 74 kilotonnes were exported, resulting in total domestic consumption of 822 kilotonnes of isolated benzene. Isolated benzene is produced at four industrial plants in the Sarnia/Corunna area in Ontario, at two plants in Alberta, and at two plants in Montreal, Quebec.

Benzene is used extensively in industry as a volatile solvent and as an intermediate in the production of many chemicals including ethylbenzene/styrene, cumene, and maleic anhydride (Jaques, 1990).

Benzene is also a natural component of petroleum (Kirk *et al.*, 1983). In gasoline, benzene acts as an octane-enhancer and an anti-knock agent. An estimated 35 000 megalitres of gasoline were consumed in Canada in 1989 (Statistics Canada, 1989). Based on an average benzene content in premium and regular unleaded gasolines of 2.15% by weight or 1.76% by volume (Madé, 1991), an estimated 540 kilotonnes of benzene are present in the gasoline sold annually in Canada; most of this benzene is burned during normal engine operation. The total yearly consumption of benzene in Canada, including both isolated benzene and benzene as a component of gasoline, is therefore estimated to be 1362 kilotonnes.

2.3 Sources and Releases

Benzene is an organic compound found naturally in the environment in low concentrations. It is a component of crude oil and is formed through incomplete combustion of organic materials. Benzene enters water and soil through petroleum seepage and weathering of exposed coal-containing strata. It enters groundwater from

petroliferous rocks, and air from volcanoes, forest fires, and releases of volatile chemicals from plants (Graedel, 1978; Westberg *et al.*, 1981; Whelan *et al.*, 1982; Fishbein, 1984; Slaine and Barker, 1990). The magnitude of emissions from natural sources is not known but, based on concentrations in rural areas, it is believed to be generally low in comparison with anthropogenic sources (Rasmussen and Khalif, 1983; Rudolph *et al.*, 1984).

Benzene can enter the environment from any stage involved in production, storage, use, and transport of isolated benzene, and crude oil and gasoline, including emissions resulting from fuel combustion.

It has been estimated that in 1985, 34 150 tonnes of benzene were released into the atmosphere in Canada (Jaques, 1990). Major sources were combustion of gasoline and combustion of diesel fuels, which together accounted for 76% of total atmospheric releases. Light-duty vehicles accounted for 61% of total releases. Other sources of release to the atmosphere included emissions during benzene production (6.5% of total releases); other chemical production (7.7%); primary iron and steel production (1.0%); solvent uses (1.5%); residential fuel combustion (4.1%); and gasoline marketing (1.9%). Total emissions of benzene to the atmosphere are expected to decline in the future, primarily because of the planned reduction of emissions of volatile organic compounds (VOCs) from light-duty vehicles and the efforts to reduce VOC emissions from a variety of other sources in order to control ground-level ozone (CCME, 1990).

Benzene can enter soil from oil and gasoline spills, leaking underground storage tanks, and seepage from waste disposal sites (U.S. EPA, 1980; Johnson *et al.*, 1989). Contamination of surface water may result from spills of chemicals and petroleum products and from discharges of industrial and municipal effluents (U.S. EPA, 1980; Ontario Ministry of the Environment, 1992). Estimates of total environmental loadings from such sources in Canada are not available.

It is estimated that every year in Canada, 34 kilotonnes of benzene are released into the atmosphere, 1 kilotonne into water, and 0.2 kilotonnes onto soil. These figures are based on proportions of benzene released to air, water, and soil in the United States (Slimak and Delos, 1983) and the Netherlands (National Institute of Public Health and Environmental Hygiene, 1988) and on data on releases to the atmosphere in Canada (Jaques, 1990).

2.4 Environmental Fate and Concentrations

2.4.1 *Fate*

Mechanisms affecting the environmental fate of benzene include photo-oxidation (Guesten *et al.*, 1981; Tully *et al.*, 1981; Besemer, 1982; Mill, 1982; Atkinson, 1985; Japar *et al.*, 1991), volatilization (Thomas, 1982), advection (Mackay *et al.*, 1992), and biodegradation (Horowitz *et al.*, 1982; Vaishnav and Babeu, 1987). The atmosphere and surface waters should be the major sinks for benzene because of its relatively high vapour pressure, high water solubility, and low octanol/water partition coefficient.

Processes in the atmosphere should play a determining role in benzene's ultimate fate in the environment (Mackay and Paterson, 1991; Mackay *et al.*, 1992).

Photo-oxidation is the major degradation pathway for benzene in air. Benzene is oxidized in reactions with hydroxyl radicals and, to a lesser extent, tropospheric ozone and nitrate radical (NO_3). Under typical urban atmospheric conditions, half-lives attributable to reactions with hydroxyl radicals were calculated to be 9 days, more than 235 days with nitrate radical, and more than 470 days with ozone (Finlayson-Pitts and Pitts, 1986). Other estimates for overall half-lives of benzene have ranged from 0.1 to 21 days (Darnall *et al.*, 1976; Atkinson, 1985; Howard *et al.*, 1991). Major products of photo-oxidation include: phenol, nitrophenol, nitrobenzene, glyoxal, butanedial, formaldehyde, carbon dioxide, and carbon monoxide (Nojima *et al.*, 1975; Finlayson-Pitts and Pitts, 1986). Since the atmospheric half-life of benzene is relatively short, long-range transport of benzene is unlikely.

Volatilization and biodegradation are the major processes involved in the removal of benzene from water. The half-life of benzene in water 1 metre deep was estimated to be 4.8 hours as a result of volatilization (Agency for Toxic Substances and Disease Registry, 1989). Reported half-lives of benzene have ranged from 33 to 384 hours for aerobic biodegradation in surface waters (van der Linden, 1978; Tabak *et al.*, 1981; Mills *et al.*, 1982; Vaishnav and Babeu, 1987). For anaerobic biodegradation in deeper waters or in groundwater, half-lives ranged from 28 days to 720 days (Horowitz *et al.*, 1982; Vaishnav and Babeu, 1987; Howard *et al.*, 1991).

The primary mechanisms responsible for loss of benzene from soil are volatilization to the atmosphere and runoff to surface water. Biodegradation also accounts for a small proportion of loss (Scheunert *et al.*, 1985; National Institute of Public Health and Environmental Hygiene, 1988). Benzene released below the soil surface, for example from leaking underground storage tanks, can leach into groundwater. With organic carbon sorption coefficients (K_{OC}s) reported for benzene ranging from 12 to 213, benzene is considered to be moderately to highly mobile in soil (Karickhoff *et al.*, 1979; Rogers *et al.*, 1980; Korte *et al.*, 1982).

Using the Level III Fugacity Modelling developed for southern Ontario (Mackay, 1991), the overall residence time in the environment was predicted to be short (3.5 days, considering both degradation and movement of benzene out of the area) and the reaction residence time was short also (9.7 days, considering loss through degradation reactions only).

Benzene does not bioconcentrate in aquatic biota to a significant degree. Relatively low bioconcentration factors (BCFs) have been reported for aquatic bacteria, algae, macrophytes, and fish. The highest reported value was for *Daphnia pulex*, with a BCF of 225 (log BCF of 2.35) (Trucco *et al.*, 1983). Once the organisms are removed from contaminated water, benzene is rapidly cleared by the organisms. For *Daphnia pulex*, 85% of accumulated benzene was removed during the 72 hours following withdrawal from contaminated water (Trucco *et al.*, 1983). The depuration of benzene in fish is also rapid. Half-lives were estimated to be less than 0.5 days in eel, *Anguilla*

japonica (Ogata and Miyake, 1978), and less than 1 day in striped bass, *Morone saxatilis* (Niimi, 1987).

2.4.2 *Concentrations*

Mean concentrations of benzene in 586 samples of ambient air in ten Canadian cities surveyed between 1988 and 1990 ranged from 1.2 to 14.6 $\mu g/m^3$, with a maximum 24-hour average concentration of 41.9 $\mu g/m^3$; the overall mean concentration was 4.4 $\mu g/m^3$ (Dann, 1991). Similar levels were reported in a more recent survey of eleven Canadian cities, while mean concentrations of benzene in three rural locations ranged from 0.6 to 1.2 $\mu g/m^3$ (Dann and Wang, 1992). Airborne concentrations of benzene at the perimeter of gasoline service stations in five Canadian cities averaged 439 $\mu g/m^3$ (maximum of 6834 $\mu g/m^3$) in the summer of 1985 (PACE, 1987) and 1383 $\mu g/m^3$ (maximum of 16 246 $\mu g/m^3$) in the winter of 1986 (PACE, 1989). Mean short-term (10 to 15 minutes) airborne concentrations during refuelling ranged from 2600 to 4400 $\mu g/m^3$ (PACE, 1987; 1989).

A major source of benzene in indoor air is cigarette smoke; smoke actually inhaled (mainstream smoke) contains 12 to 48 μg per cigarette, while amounts in smoke emitted from cigarettes (sidestream smoke) are approximately ten times greater (U.S. Department of Health and Human Services, 1986). Based on data obtained in 200 homes in the United States (Wallace, 1989), tobacco smoking is estimated to contribute an additional 3 $\mu g/m^3$ to the concentration of benzene in residential indoor air. Various household and other products appear to contribute to the concentration of benzene in residential indoor air. The contribution of these products to the benzene content of indoor air, indirectly determined from the differences in reported concentrations in indoor air in the homes of nonsmokers and the corresponding concentrations in ambient air in a survey of homes in the United States (Wallace *et al.*, 1987; Wallace, 1989), has been estimated to be 2 $\mu g/m^3$ (Holliday and Park, 1989).

Benzene has been measured in Canadian surface waters. In surveys at 10 sites along the Great Lakes and 30 water treatment facilities across Canada, benzene concentrations in untreated water were generally lower than the detection limit (0.1 or 1 $\mu g/L$, respectively); the highest reported mean concentration was 2 $\mu g/L$ (Otson *et al.*, 1982; Otson, 1987). Concentrations of benzene along a 6-km industrialized section of the St. Clair River near Sarnia, Ontario, ranged from below the detection limit (0.1 $\mu g/L$) to 4.3 $\mu g/L$ (Comba and Kaiser, 1987). Benzene levels were below the detection limit upstream from the industrialized section and returned to near or below detection levels about 1 km downstream. A mean benzene concentration of 0.45 $\mu g/L$ was calculated for the sampling stations along the industrialized section of the river. In Ontario, the highest concentrations of benzene in untreated effluents released into surface water were reported from the organic chemical manufacturing sector; the highest 12-month average concentration of benzene at one outfall was 65.3 $\mu g/L$ (Ontario Ministry of the Environment, 1992). Benzene was not reported to occur in water at concentrations above the detection limit of 1 $\mu g/L$ in other surveys of Canadian waters (NAQUADAT, 1991).

Benzene has been measured in groundwater in areas where underground storage tanks containing gasoline have leaked, and near landfill sites. In some sites, benzene concentrations in the groundwater have ranged from below the detection limit (Barker *et al.*, 1988; Intera Technologies Ltd., 1987; Water and Earth Science Associates Ltd., 1988) to 15 mg/L (Jackson *et al.*, 1985).

Few data are available on the concentrations of benzene in drinking water in Canada. Benzene was detected (quantitation limit, 1 µg/L) in 50 to 60% of potable water samples from 30 treatment facilities in a national survey conducted in 1979; mean concentrations of benzene in treated water ranged from <1 to 3 µg/L and the maximum value was 47 µg/L (Otson *et al.*, 1982). Benzene has rarely been detected in provincial monitoring programs at concentrations greater than 1 µg/L (Ayotte, 1987; O'Neill and MacKeigan, 1987a, 1987b, 1987c, 1987d; Ontario Ministry of the Environment, 1989).

Data on the occurrence of benzene in food are very limited. Although it has been detected in individual foodstuffs at concentrations of up to 2100 µg/kg, benzene was not detected in several foods representative of a "typical" U.S. diet, with detection limits ranging up to 0.66 µg/kg (Rose and Chin, 1990).

2.5 Toxicokinetics

While benzene is believed to be readily absorbed from the gastrointestinal tract, it is estimated that approximately 50% of inhaled benzene is absorbed through the lungs, and only very small amounts through the skin (Agency for Toxic Substances and Disease Registry, 1989). Absorbed benzene is distributed throughout the body, with the possibility of some accumulation in adipose tissue. Metabolism of benzene occurs largely in the liver, although some metabolism may take place in the bone marrow. The pathways of benzene metabolism appear to be qualitatively similar in humans and experimental animals, although there may be quantitative differences in the proportion of putatively toxic metabolites in various species. The pathway leading to the formation of the putatively toxic metabolites (benzoquinone and muconaldehyde) appears to be a saturable process at relatively low doses; as a result, the proportion of toxic metabolites formed is greater at low doses than at high doses (Henderson *et al.*, 1989, 1990; Medinsky *et al.*, 1989). The metabolites of benzene are largely excreted in the urine, while unmetabolized benzene is eliminated by exhalation. With absorption of increasing amounts of benzene, a greater proportion is exhaled unchanged than is excreted as metabolites in urine.

2.6 Mammalian Toxicology

Benzene is not highly acutely toxic to experimental animals. Hematological effects similar to those observed in humans have been reported in animals following short-term, subchronic, or chronic exposure to benzene. It has been consistently observed in these studies that lymphocyte levels are depressed most severely and in the shortest time, while granulocytes appear to be the most resistant of the circulating cells,

and that anemia does not occur as frequently as lymphocytopenia (Agency for Toxic Substances and Disease Registry, 1989).

In recent studies, benzene has been carcinogenic in two species of experimental animals, inducing a wide variety of tumors following inhalation (Table 1) and ingestion (Table 2). Based on the results of *in vitro* and *in vivo* studies in experimental animals, benzene appears to induce clastogenic damage to DNA rather than causing point mutations.

Benzene is not teratogenic in experimental animals, although embryotoxic and fetotoxic effects have been reported at airborne concentrations less than those observed to be toxic to the mothers (as low as 47 ppm or 150 mg/m^3 in rats) (Tatrai *et al.*, 1980). Hematological changes have also been noted in mice exposed to 5 ppm (16 mg/m^3) benzene *in utero* (Keller and Snyder, 1986).

Concentrations of benzene as low as 10 ppm (32 mg/m^3) have been reported to cause immunological effects (depression of the response of B cells and T cells) in rats (Rozen *et al.*, 1984). Exposure to benzene at concentrations as low as 100 ppm (320 mg/m^3) has also been associated with neurological effects and behavioural disturbances in animals similar to those caused by other petroleum hydrocarbons (Agency for Toxic Substances and Disease Registry, 1989; Dempster *et al.*, 1984).

2.7 Effects on Humans

In epidemiological studies, hematotoxic effects have been reported in several populations occupationally exposed to benzene, due to damage or depression of the hematopoietic system. Depression in bone marrow activity results from damage to or destruction of the pluripotential stem cells and/or the early proliferating committed cells. In several studies, workers occupationally exposed to benzene have developed pancytopenia which in more severe cases is referred to as aplastic anemia. Kipen *et al.* (1988) reported significant decreases in white and red blood cell counts and hemoglobin in workers exposed during the 1940s in the cohort of pliofilm workers studied by Rinsky *et al.* (1987). Additional work on the hematological effects, particularly during the early years of employment, in workers in this cohort is under way (Cody *et al.*, in press), since it has been suggested that similar decreases in blood cell counts could be found in pre-employment tests, and the correlation with benzene exposure is artifactual (Hornung *et al.*, 1989). Effects on the immune system, including decreases in T lymphocytes (Moszczynski, 1981), alterations in serum immunoglobulins and complement levels, and symptoms of benzene-induced autoimmunity and allergy, have been observed in workers occupationally exposed to benzene (Agency for Toxic Substances and Disease Registry, 1989).

Associations between leukemia and exposure to benzene in occupationally exposed populations have been observed in numerous case studies, and in the majority of epidemiological studies conducted to date (see Tables 3 and 4). In addition, there was a clear exposure-response relationship in the population for which exposure has been most extensively characterized (Rinsky *et al.*, 1987). However, information in only three

Table 1 Summary of Carcinogenicity Bioassays in Experimental Animals by Inhalation in which Treatment-related Effects were Reported (modified from Agency for Toxic Substances and Disease Registry, 1989)*

Species	Protocol	Treatment-related Effects	Reference
C57BL/6J mice	100 and 300 ppm (319 and 958 mg/m^3) lifetime	lymphocytic lymphoma (thymic involvement), myeloma, leukemia	Snyder *et al.*, 1980
CD-1 mice and Sprague-Dawley rats	100 and 300 ppm (319 and 958 mg/m^3) lifetime	acute and chronic myelogenous leukemia	Goldstein *et al.*, 1982
Sprague-Dawley rats, breeders and embryos	200 and 300 ppm (639 and 958 mg/m^3), 15 or 104 weeks, beginning at 12 days gestation; observed for 150 weeks	breeders: zymbal gland carcinoma, hepatoma, mammary carcinoma; offspring: zymbal gland carcinoma, nasal carcinoma, hepatoma, leukemia, mammary carcinoma	Maltoni *et al.*, 1985
C57BL/6 mice	300 ppm (958 mg/m^3) for 16 weeks, lifetime observation	thymic lymphoma, unspecified lymphoma	Cronkite *et al.*, 1984
Sprague-Dawley rats	100 ppm (319 mg/m^3) lifetime	zymbal gland carcinoma, liver hemangioma, hepatoma, liver hemangio-endothelioma and fibrosarcoma, chronic granulocytic leukemia, mammary carcinoma	Snyder *et al.*, 1984
CBA/Ca mice	100 and 300 ppm (319 and 958 mg/m^3) for 16 weeks, 900 days observation	leukemia	Cronkite, 1986
C57B1 mice and CD-1 mice	300 ppm (958 mg/m^3) one week in three for life, 1200 ppm 3834 mg/m^3) for 10 weeks, observed for life	300 ppm (958 mg/m^3): lung adenoma in CD-1 mice, zymbal gland carcinoma in C57B1 mice; 1200 ppm (3834 mg/m^3): lung adenoma and zymbal gland carcinoma in CD-1 mice	Snyder *et al.*, 1988

* Based on the original "author call" of possible or direct correlation, as presented in Agency for Toxic Substances and Disease Registry (1989), with the exception of Snyder *et al.* (1988) which underwent primary critical review by Health and Welfare Canada staff.

Table 2 Summary of Carcinogenicity Investigations in Experimental Animals by Ingestion in which Treatment-related Effects were Reported (modified from Agency for Toxic Substances and Disease Registry, 1989)*

Species	Protocol	Treatment-related Effects	Reference
Sprague-Dawley rats	50 and 250 mg/(kg b.w. • day), 52 weeks, observed for 144 weeks; 500 mg/(kg b.w. • day), 104 weeks, observed for 141 weeks	zymbal gland carcinoma, carcinoma of oral and nasal cavities, hemolymphoreticular neoplasms, other malignant tumors	Maltoni *et al.*, 1985
Wistar rats	500 mg/(kg b.w. • day), 100 weeks	zymbal gland carcinoma, carcinoma of oral cavity, thymoma, other hemolymphoreticular neoplasms	Maltoni *et al.*, 1985
Swiss mice	500 mg/(kg b.w. • day), 78 weeks, observed for 100 weeks	zymbal gland carcinoma, pulmonary and mammary tumors	Maltoni *et al.*, 1985
F344/N rats	25 to 200 mg/(kg b.w. • day), 2 years	carcinoma of oral cavity, zymbal gland carcinoma, skin carcinoma	National Toxicology Program, 1986
B6C3F$_1$ mice	25 to 100 mg/(kg b.w. • day), 2 years	zymbal gland carcinoma, malignant lymphoma, alveolar/bronchiolar carcinoma, alveolar/ bronchiolar adenoma, harderian gland adenoma, preputial gland carcinoma, ovarian granulosa cell tumor, mammary gland carcinoma, mammary gland carcinosarcoma	National Toxicology Program, 1986

* Based on the "author call" of possible or direct correlation, as presented by Agency for Toxic Substances and Disease Registry (1989).

Table 3 Historical Cohort Studies on the Association Between Occupational Exposure to Benzene and Leukemia (from Austin *et al.*, 1988, and Health Council of the Netherlands, 1989)

Number and Type of Subjects	Exposure Measure	Standardized Mortality Ratio for Leukemia*	Reference
38 000 petrochemical industry workers Referent: general population	Potential occupational exposure to > 1% (10 000 ppm) benzene for > 5 years	SMR = 121	Thorpe, 1974
594 benzene workers Referent: general population	Cumulative exposure (ppm-months)	SMR = 200	Ott *et al.*, 1978
259 chemical workers Referent: general population	Employment at plant that used large quantities of benzene	SMR = 682	Decouflé *et al.*, 1983
454 oil refinery workers Referent 1) general population, 2) non-exposed workers	Occupational exposure to benzene < 1 to > 10 ppm (<3.19 to >31.9 mg/m^3)	Obs = 0 Exp = 0.42	Tsai *et al.*, 1983
1 361 graphic industry workers	not specified	SMR = 250 (total leukemia)	Paganini-Hill *et al.*, 1980
13 570 rubber industry workers	not specified	SMR = 240 (lymphatic)	Monson and Fing, 1978
28 460 workers from various industries Referent: 28 257 non-exposed workers	10 to 1000 mg/m^3, 50 to 500 mg/m^3 (most areas)	SMR = 574 (total leukemia)	Yin *et al.*, 1987
33 815 rubber industry workers	"low exposure"		Parkes *et al.*, 1982
34 781 petrochemical industry workers	"low exposure"		Rushton and Alderson, 1980

* Type of leukemia specified where available.

Table 4 Case-control Studies on Benzene Exposure and Leukemia (from Austin *et al.*, 1988)

Observation Period	Number and Type of Subjects	Exposure Measure	Relative Risk for Leukemia*	Reference
1966 to 1969	257 leukemia cases 124 hospital controls	occupational or household exposure to solutions with benzene or toluene	RR = 3.3 (acute leukemia) RR = 4.1 (chronic lymphocytic leukemia) RR = 1.8 (myelocytic leukemia)	Girard *et al.*, 1970
1945 to 1967	303 adult leukemia cases 303 controls	potential occupational exposure to benzene or X-rays	RR = 2.5	Ishimaru *et al.*, 1971
1955 to 1974	138 adult leukemia cases 276 controls	medical record of benzene exposure	RR = 3.3	Linos *et al.*, 1980
1950 to 1975	Oil refinery workers 36 cases 216 controls	low, medium, or high occupational benzene exposure	RR = 2.0 (high or medium vs. low)	Rushton and Alderson, 1981
1964 to 1973	Rubber workers 15 lymphocytic leukemia cases 30 controls	primary exposure from job involving direct use of benzene	RR = 4.5 (lymphocytic leukemia)	Arp *et al.*, 1983
1964 to 1973	11 lymphocytic leukemia cases 1 350 controls	occupational exposure in work areas where benzene was used	RR = 2.5 (lymphocytic leukemia)	Checkoway *et al.*, 1984

* Type of leukaemia specified where available.

studies (Bond *et al.*, 1986; Wong, 1987a, 1987b; Rinsky *et al.*, 1987) is considered sufficient to form the basis of a quantitative assessment of carcinogenic potency, although the numbers of deaths due to leukemia were small in each investigation. The other studies are less relevant owing to limitations that include poor characterization or description of the basis for estimation of exposure, concomitant exposure to substances other than benzene, and/or the low number of observed cases. For example, although 25 deaths due to leukemia were reported in the historical cohort study of workers in various industries by Yin *et al.* (1987), the published report did not include sufficient information to form the basis for characterization of individual exposure.

In the cohort of 956 chemical workers studied by Bond *et al.* (1986), there was a nonsignificant excess of deaths due to leukemia compared to national rates (4 versus 2.1). However, the observed and expected numbers of deaths due to leukemia (observed:expected = 3:1.9, when individuals exposed to arsenic, asbestos, or vinyl chloride were excluded) were small. Although there was a significant excess of deaths due to skin cancer in the cohort excluding those exposed to arsenic, asbestos, or vinyl chloride, all of these cases occurred in the group with the lowest estimated cumulative exposure to benzene. There was no relationship between the excess of deaths due to leukemia and area of work, duration of employment, or cumulative exposure, which may be attributable to the small numbers observed.

In the cohort of 7676 workers at seven chemical plants examined by Wong (1987a, 1987b), there was also an excess of deaths due to leukemia when compared to national rates (not statistically significant). Again, however, the total number was small (observed:expected = 6:4.43 in the continuously exposed group). Mortality due to lymphatic or hematopoietic cancer was significantly increased in the intermittently and continuously exposed groups combined, compared to unexposed workers (19 versus 3), as was the number of deaths due to leukemia (7 versus 0). This may be attributable, however, to a deficit of deaths due to leukemia in the latter group (*i.e.*, 0 observed, 3.4 expected). There was an increasing trend in the standardized mortality ratios (SMRs) for lymphopoietic cancer, leukemia, and non-Hodgkin's lymphopoietic cancer with cumulative exposure in the group that had experienced continuous exposure to benzene. None of the observed leukemias in this cohort was the type most often observed in workers exposed to benzene, *i.e.*, acute myelogenous leukemia.

Rinsky *et al.* (1987) examined the mortality of a cohort of 1165 pliofilm workers exposed to benzene, which was the only hematotoxic solvent to which employees were exposed in the workplace. Compared to national rates, there was a significant increase in deaths due to all lymphatic and hematopoietic neoplasms (observed:expected = 15:6.6) as well as from leukemia (observed:expected = 9:2.66; seven of the observed cases were acute myelogenous leukemias, one was chronic myelogenous leukemia, and one was an unspecified myelogenous leukemia; see Table 5). There was a strongly positive trend in mortality due to leukemia with increasing cumulative exposure (SMRs of 109, 322, 1186, and 6637, with increasing exposure) but no pattern between exposure and latency period. In a nested, matched case-control analysis, the average duration of exposure was longer for cases than controls (8.7 versus 2.6 years). There were four deaths in the cohort due to multiple myeloma (compared to one expected). Three of these deaths occurred in the lowest exposure group and all had a minimum latency period of 20 years. Although the numbers of observed and expected cases of leukemia in this study were rather small, additional deaths due to this cause have occurred according to the most recent (to December 1987) follow-up of a portion of this cohort, which has not been published (Rinsky, 1991).

Structural and numerical chromosomal aberrations have also been consistently reported in lymphocytes of workers exposed to benzene. Metabolites of benzene have been demonstrated to disrupt microtubule assembly *in vitro*, and also cause aneuploidy

Table 5 Description of Leukemia Deaths in Pliofilm Cohort (from Rinsky *et al.*, 1987)

Case Number	Latency* (years)	Cause of Death**	Plant Location; Duration of Employment
1	17	Monocytic leukemia (204)	Location 1; 1.5 years
2	2	Chronic myelogenous leukemia (204)	Location 1; 1 month
3	13.5	Acute myelocytic leukemia (204)	Location 2; 11.5 years
4	15.5	Acute myelogenous leukemia (204)	Location 2; 14 years
5	22	Di Guglielmo's acute myelocytic leukemia (204)	Location 2; 13 years
6	20	Acute granulocytic leukemia (204)	Location 2; 20 years
7	15	Acute monocytic leukemia (204)	Location 2; 5 years
8	3.5	Myelogenous leukemia (204)	Location 1; 1.5 years
9	37	Acute myeloblastic leukemia (204)	Location 2; 14 years

* Latency was defined as the length of time from the date of first exposure until death.

** In parentheses is the International Classification of Disease code as determined by a nosologist from information on the death certificate.

and chromosomal non-disjunction in human lymphocytes. This may be significant in light of the fact that cytogenetic abnormalities involving the loss of all or part of chromosomes 5 and 7 have been associated with therapy-related myelodysplastic syndrome and leukemia (Irons *et al.*, 1984; Lebeau *et al.*, 1986).

Although it has been demonstrated that benzene crosses the placenta in humans, no effects on the fetus (with the exception of chromosomal abnormalities; Funes-Cravioto *et al.*, 1977) and no increase in the incidence of birth defects have been associated with exposure to benzene in a few limited studies (Heath, 1983; Budnick *et al.*, 1984; Olsen 1983a, 1983b; Axelsson *et al.*, 1984). Although some reproductive effects have been reported in women in earlier limited studies, these observations have not been confirmed

(Vara and Kinnunen, 1946; Michon, 1965; Pushkina *et al.*, 1968; Mukhanetova and Vozovaya, 1972).

Neurotoxic effects similar to those caused by other petroleum hydrocarbons have been observed in workers exposed to benzene in combination with other industrial chemicals (Agency for Toxic Substances and Disease Registry, 1989).

2.8 Effects on the Environment

The information available on the acute and chronic toxicity of benzene includes data for species from a number of trophic levels, from bacteria and protozoa through to fish and amphibians in the aquatic environment. Information on toxicity to terrestrial species is limited to laboratory studies on plants, invertebrates, and mammals. No field studies on wild species were available.

Acute toxicity studies are available for several species at various trophic levels. The 3-hour EC_{50} for inhibition of photosynthesis in the alga *Chlorella vulgaris* was 312 mg/L (Hutchinson *et al.*, 1980). The most sensitive freshwater invertebrates include nymphs of the damselfly, *Ischnura elegans*, with a 48-hour LC_{50} of 10 mg/L (Sloof, 1983), and the water fleas, with 48-hour LC_{50}s of 15 mg/L for *Daphnia pulex* (Trucco *et al.*, 1983) and 31.2 mg/L for *Daphnia magna* (Bobra *et al.*, 1983). The most sensitive fish species tested were salmonids, including rainbow trout, *Oncorhynchus mykiss*, with a 96-hour LC_{50} of 5.3 mg/L for juveniles (DeGraeve *et al.*, 1982), and coho salmon, *Oncorhynchus kisutch*, with a 96-hour LC_{50} of 9 mg/L for fry (Moles *et al.*, 1979). Benzene is toxic to a range of insects following topical or inhalation exposure; lethal effects were reported following exposure to air concentrations of 10 000 to 210 000 mg/m^3 (Miller *et al.*, 1976). Acute effects of benzene on terrestrial plants have been reported at atmospheric concentrations greater than 10 000 mg/m^3 (Miller *et al.*, 1976).

Black *et al.* (1982) investigated the chronic toxicity of benzene to the early life stages of rainbow trout, leopard frog (*Rana pipiens*), and northeastern salamander (*Ambystoma gracile*). Eggs of each species were exposed continuously to benzene from within 30 minutes of fertilization (embryos) on through to 4 days post-hatch (larvae). This resulted in continuous exposures of 27 days for rainbow trout, 9 days for leopard frog, and 9.5 days for northeastern salamander. The LC_{50}s for continuous exposure were 8.3 mg/L for rainbow trout, 3.7 mg/L for leopard frog, and 5.2 mg/L for northeastern salamander.

Although no data were available on the effects of benzene on wild mammals, the toxicity of benzene to these organisms can be assessed by extrapolation from toxicity studies conducted using laboratory mammals (see Subsection 2.6). Benzene is not highly acutely toxic to mammals exposed by inhalation or ingestion (Agency for Toxic Substances and Disease Registry, 1989). A 4-hour inhalation LC_{50} of 44 500 mg/m^3 has been reported for rats (Drew and Fouts, 1974), while a 7-hour LC_{50} for rats was 32 500 mg/m^3 (NIOSH, 1987). The acute oral LD_{50}s in the rat and mouse are 3306 and 4700 mg/kg b.w., respectively (NIOSH, 1987). As stated in Subsection 2.6,

hematological effects have been reported in mice exposed *in utero* to 16 mg/m^3, although these effects may not be strictly relevant to wildlife. Other responses noted in laboratory mammals include immunological effects in rats noted at 32 mg/m^3, and neurological effects and behavioural disturbances at 320 mg/m^3. No data are available on the effects of exposure to benzene on birds.

Gases involved in enhanced global warming strongly absorb infrared radiation, especially wavelengths of 7 to 13 µm, enabling them to trap and re-radiate a portion of the earth's thermal radiation (Wang *et al.*, 1976; Ramanathan *et al.*, 1985). Since benzene does not absorb at these wavelengths (Sadtler Research Laboratories, 1982), it is not considered to be a direct contributor to global warming. Substances involved in depletion of stratospheric ozone are generally halogenated, insoluble in water, and persistent in the atmosphere allowing movement to the stratosphere. In the stratosphere, they are degraded only by high energy, short wavelength ultraviolet radiation (Firor, 1989). Since benzene is a non-halogenated, water-soluble molecule of low persistence in the atmosphere, it is not associated with depletion of stratospheric ozone.

3.0 Assessment of "Toxic" Under CEPA

As described in the Introduction, the following assessment will consider the entry of benzene to the environment, the exposure of humans and other biota to benzene, and potential harmful effects in humans and other biota.

3.1 Entry

Benzene enters into the Canadian environment primarily through atmospheric releases. Approximately 34 150 tonnes are released yearly to the atmosphere. The major source of release is from combustion of gasoline and diesel fuels, which together account for more than 76% of total atmospheric releases. Light-duty vehicles alone account for 61% of total releases. Benzene is released to the soil from spills, leaking underground storage tanks, and in leachate from contaminated waste disposal sites. Release to water occurs through spills and discharge of contaminated effluents. Benzene has been measured in Canada in the atmosphere and in certain samples of drinking water, surface water, groundwater, industrial effluents, and leachate from waste disposal sites.

3.2 Exposure

Benzene does not persist in water or soil because it biodegrades and volatilizes rapidly to the atmosphere. It also does not persist in the atmosphere because it undergoes rapid photo-oxidation. Benzene does not appreciably absorb ultraviolet light at wavelengths passing through the upper atmosphere, or infrared radiation at wavelengths of 7 to 13 μm.

Airborne concentrations of benzene in rural areas of Canada are generally below 1.2 $\mu g/m^3$. Mean concentrations at urban sites have ranged from 1.2 to 14.6 $\mu g/m^3$, with an overall mean concentration of 4.4 $\mu g/m^3$ and a maximum 24-hour average recorded at one site of 41.9 $\mu g/m^3$.

Concentrations of benzene in Canadian surface waters are generally less than 1 μg/L. The mean concentration in untreated water measured in one study was 2 μg/L. The highest reported mean concentration of benzene in effluents has been 65.3 μg/L, measured at an outfall from an organic chemicals industry.

Accumulation of benzene is not expected to be important in any terrestrial or aquatic organism and there are no reports indicating any significant bioconcentration in organisms or biomagnification in the food chain. The main route of exposure for terrestrial biota is, therefore, inhalation rather than exposure via the food chain.

Estimated average daily intakes (on a body weight basis) of benzene from environmental media by various age groups in the general population in Canada are presented in Table 6. These estimates are based on mean concentrations of benzene found in environmental media. Elevated exposure resulting from spills, contaminated groundwater supplies, or other localized conditions were not considered. Ambient air is the main source of exposure to benzene for the general human population, with estimated

Table 6 Estimated Daily Intake of Benzene by Canadians

Medium	Estimated Intake (g/(kg b.w. • day)				
	Age (years)				
	0 to 0.5[a]	0.5 to 4[b]	5 to 11[c]	12 to 19[d]	20 to 70[e]
Ambient air[f]	1.5	1.7	2.0	1.7	1.3
Drinking Water[g]	0.02	0.06	0.04	0.02	0.02
Food[h]	0.07	0.06	0.05	0.03	0.02
Automobile-related activities[i]	-	-	-	0.9	0.7
Household products[j]	0.5	0.5	0.6	0.5	0.4
Total intake	**2.1**	**2.3**	**2.7**	**3.2**	**2.4**
Cigarette smoking					
Active[k]	-	-	-	33.0	26.0
Passive[l]	1.0	1.2	1.3	1.1	0.9

a Assumed to weigh 6 kg, breathe 2 m^3 of air per day, and drink 0.1 L of water per day (Environmental Health Directorate, 1988).

b Assumed to weigh 13 kg, breathe 5 m^3 of air per day, and drink 0.8 L of water per day (Environmental Health Directorate, 1988).

c Assumed to weigh 27 kg, breathe 12 m^3 of air per day, and drink 1.1 L of water per day (Environmental Health Directorate, 1988).

d Assumed to weigh 55 kg, breathe 21 m^3 of air per day, and drink 1.1 L of water per day (Environmental Health Directorate, 1988).

e Assumed to weigh 70 kg, breathe 20 m^3 of air per day, and drink 1.5 L of water per day (Environmental Health Directorate, 1988).

f Based on an average concentration of benzene in ambient air of 4.4 µg/m^3 (Dann, 1991).

g Based on a concentration of benzene in drinking water of 1.0 µg/L, determined from data in Otson *et al.* (1982) and provincial monitoring programs.

h Estimate for adult intake of benzene in food from Holliday and Park (1989), based on the assumption that benzene in food is in equilibrium with air, an average airborne level of benzene of 4 ppb (12.8 µg/m^3), and estimated partition coefficients for the components of the diet; estimates for other age groups modelled after Holliday and Park (1989). Food consumption patterns obtained from Nutrition Canada (1977).

i Based on estimated intake of 40 µg/day while travelling in an automobile, and 10 µg/day while refuelling at a self-service gas station (Wallace, 1989).

j Based on estimation by Holliday and Park (1989) of the contribution to indoor air concentration of benzene of 2 µg/m^3 from household products, indirectly determined from the differences in reported concentrations in indoor air in the homes of non-smokers and the corresponding outdoor levels in the TEAM study (Wallace, 1989; Wallace *et al.*, 1987) (Holliday and Park, 1989) and an average of 17 hours per day spent indoors (Environmental Health Directorate, 1988).

k Based on estimated intake of 1800 µg/day through cigarette smoking (Wallace, 1989a).

l Based on average additional indoor air concentration of 3 µg/m^3 of benzene due to tobacco smoke in homes of smokers (Wallace, 1989).

intakes ranging from 1.3 to 3.0 μg/(kg b.w. • day). Automobile-related activities are estimated to contribute an additional 0.7 to 0.9 μg/(kg b.w. • day), while use of household products, indirectly estimated from the difference between the concentration of benzene in outdoor and indoor air in the homes of nonsmokers, is estimated to increase intake by 0.4 to 0.6 μg/(kg b.w. • day). Estimated intake from food and drinking water is considerably less, ranging from 0.02 to 0.07 μg/(kg b.w. • day) and 0.02 to 0.06 μg/(kg b.w. • day), respectively. Total daily intake from these sources for five different age groups in the general population is estimated to range from 2.1 to 3.2 μg/(kg b.w. • day). Cigarette smoking may contribute an additional 26 to 33 μg/(kg b.w. • day) to the daily intake of benzene, while passive smoking may contribute 0.9 to 1.3 μg/(kg b.w. • day).

3.3 Effects

3.3.1 *Human Health*

On the basis of available data, carcinogenicity is potentially the most sensitive endpoint for the assessment of "toxic" to humans for benzene under CEPA. In numerous case studies, and in the majority of epidemiological studies conducted to date, associations between leukemia and exposure to benzene in occupationally exposed populations have been observed (see Tables 3 and 4). In addition, there was a clear exposure-response relationship in the population for which exposure has been the most extensively characterized (Rinsky *et al.*, 1987). Benzene has also been consistently clastogenic in occupationally exposed populations, inducing both structural and numerical chromosomal aberrations in human lymphocytes (Agency for Toxic Substances and Disease Registry, 1989; Occupational Safety and Health Administration, 1987). In recent studies, benzene has also been carcinogenic in two species of experimental animals, inducing a wide variety of tumours following inhalation (Table 1) and ingestion (Table 2). Available data on the mechanisms of action of benzene also indicate that induction of leukemia by this compound is biologically plausible. Benzene has been classified, therefore, in Group I ("Carcinogenic to Man") of the classification scheme developed by the Bureau of Chemical Hazards for use in the derivation of the "Guidelines for Canadian Drinking Water Quality" (Health and Welfare Canada, 1989b).

3.3.2 *Environment*

For aquatic biota, the leopard frog was the most sensitive organism identified in long-term tests. The reported LC_{50} was 3.7 mg/L for continuous 9-day exposure of the embryo-larval stages. Rainbow trout was the most sensitive aquatic species in acute tests, with a 96-hour LC_{50} of 5.3 mg/L for juveniles.

Acute effects have been reported for terrestrial invertebrates and plants for concentrations of benzene in air greater than 10 000 mg/m^3. Data on effects resulting from chronic exposure are not available.

The effect levels reported for laboratory mammals are considered to be relevant for wild mammals. The inhalation LC_{50} for rats exposed to benzene for 7 hours was 32 500 mg/m^3. The concentration observed to cause immunological changes in laboratory rats was 32 mg/m^3.

Since benzene does not appreciably absorb radiation at wavelengths from 7 to 13 µm, it is not associated with global warming. Because benzene is not halogenated and is of low persistence in the environment, it is not associated with depletion of stratospheric ozone.

3.4 Conclusions

Benzene is used in Canada in a variety of applications that lead to its entry into the Canadian environment. This entry results in measurable concentrations of benzene in the various media to which humans and other organisms may be exposed.

3.4.1 *Effects on the Environment (Paragraph 11(a))*

The most sensitive response reported for exposure to benzene in an aquatic organism is a 9-day LC_{50} of 3.7 mg/L for the leopard frog, the most sensitive aquatic species in chronic or subchronic studies. This value can be multiplied by a factor of 0.05 to convert the LC_{50} to a chronic no-observed-effect concentration (NOEC) for a non-persistent, non-bioaccumulative substance and to account for differences in species sensitivity and extrapolation from laboratory to field conditions. This yields an estimated effects threshold of 185 µg/L for long-term exposure. The highest reported mean concentration of benzene in ambient freshwater in Canada is 2 µg/L; this is 1850 times lower than the LC_{50} for the leopard frog and 93 times lower than the estimated effects threshold. Therefore, benzene is not considered to be "toxic" to freshwater organisms exposed to ambient surface water.

The most sensitive acute response reported for exposure to benzene in an aquatic organism is a 96-hour LC_{50} of 5.3 mg/L for the rainbow trout. This value can be multiplied by a factor of 0.1 to account for differences in species sensitivity and extrapolation from laboratory to field conditions. This yields an estimated effects threshold of 530 µg/L for short-term exposure. The highest reported mean concentration of benzene in undiluted effluents is 65.3 µg/L; this is 81 times lower than the LC_{50} for rainbow trout and 8 times lower than the estimated effects threshold for short-term exposure. Therefore, benzene is not considered to be "toxic" to freshwater organisms exposed under conditions approximating a worst-case scenario.

Acute effects have been reported for terrestrial invertebrates, plants, and laboratory mammals at benzene concentrations in air greater than 10 000 mg/m^3. The highest 24-hour average concentration measured in cities is 41.9 µg/m^3, which is almost 240 000 times lower than the effects threshold of 10 000 mg/m^3. The concentration at which immunological changes were noted in rats under conditions of long-term exposure is 32 mg/m^3; other effects, including neurological and behavioural changes, occurred at

concentrations at least ten times higher. The average concentration of benzene reported in rural areas (1.2 $\mu g/m^3$) is 26 667 times lower than the effects threshold of 32 mg/m^3. Benzene is therefore not considered to be "toxic" to populations of wild mammals and other terrestrial biota as a result of exposure by inhalation.

Benzene is of low acute oral toxicity to mammals (LD_{50} of 3306 mg/kg b.w. for rats). Given the ability of most organisms to metabolize or excrete benzene and benzene's low potential for bioaccumulation, wild mammals are not likely to be exposed to deleteriously high concentrations of benzene in food.

Therefore, on the basis of available data, benzene is not considered to be "toxic" as defined under Paragraph 11(*a*) of CEPA.

3.4.2 *Effects on the Environment on which Human Life Depends (Paragraph 11(b))*

Benzene will not contribute directly to global warming because of its short residence time in the troposphere and because it does not appreciably absorb radiation within the critical wavelengths (7 to 13 μm). Benzene is not expected to contribute to depletion of stratospheric ozone because of its short persistence in the atmosphere and non-halogenated nature. Benzene is not suspected of being associated with other known direct effects on the environment on which human life depends.

Therefore, on the basis of available data, benzene is not considered to be "toxic" as defined under Paragraph 11(*b*) of CEPA.

3.4.3 *Effects on Human Life or Health (Paragraph 11(c))*

Benzene has been classified in Group I ("Carcinogenic to Man") of the classification scheme developed by the Bureau of Chemical Hazards for use in the derivation of the "Guidelines for Canadian Drinking Water Quality" (Health and Welfare Canada, 1989b), based on its documented carcinogenicity in humans and experimental animals.

For compounds classified in Group I, where data permit, the estimated total daily intake or concentrations in relevant environmental media are compared to quantitative estimates of carcinogenic potency (expressed as the concentration or dose that induces a 5% increase in the incidence of, or mortality due to relevant tumors) in order to characterize risk and provide guidance for further action under the Act. Issues critical to the quantitative assessment of carcinogenic potency are discussed briefly in the following text. A more extensive discussion of these issues is presented in the Supporting Document.

It has been hypothesized that there may be a threshold for the development of leukemia in humans resulting from exposure to benzene. This is based on the

supposition that leukemia results from progression of a precursor condition such as pancytopenia, for which there may be a threshold. However, available data in humans and experimental animals are insufficient to firmly support a relationship between pancytopenia or other precursor damage to bone marrow and benzene-induced leukemia. It is generally presumed, therefore, that there is an exposure-response relationship between induction of leukemia and exposure to benzene even at low levels.

The data considered most relevant to the quantification of the carcinogenic potency of benzene are those obtained in epidemiological studies in humans. There is considerable uncertainty in the extrapolation to humans of exposure-response relationships obtained in studies in animals, based on available information on the pharmacokinetics and metabolism of benzene. The toxicity of benzene is believed to be due to a metabolite or metabolites; however, though the principal routes of metabolism appear to be similar in all species studied, there are considerable differences in the contribution made by each pathway. There is also a paucity of information on the metabolism of benzene in the species of interest, i.e., humans. Moreover, there is evidence in three species of experimental animals, including primates, that the proportion of putative toxic metabolites formed decreases with increasing exposure.

The study considered most suitable for estimating the leukemogenic potency of benzene is that of Rinsky *et al.* (1987). In this study, the largest number of observed deaths due to leukemia was reported in an exposed population for which there was sufficient information on exposure to benzene to serve as a basis for quantitative risk assessment. In addition, benzene was the only hematotoxic solvent to which employees in this cohort were exposed in the workplace. Although the numbers of observed and expected cases of leukemia reported in the published account of this study, in which workers were followed up to 1981, were rather small (Rinsky *et al.*, 1987), there have been additional deaths due to this cause in the most recent follow-up of a portion of this cohort (to December 1987), which has not been published (Rinsky, 1991). Moreover, there was a strongly positive trend in mortality due to leukemia with increasing cumulative exposure. In the nested case-control analysis, the average duration of exposure was longer for cases than controls (8.7 versus 2.6 years).

The type of leukemia most commonly associated with occupational exposure to benzene is acute myelogenous leukemia. However, persons with chronic myelogenous leukemia may suffer a terminal "blast crisis", with transformation to acute myelogenous leukemia. The cause of the death could subsequently be recorded as acute myelogenous leukemia (Robbins and Angell, 1971; Stewart, 1991). Though the clinical presentation of chronic myelogenous leukemia is different than that of the acute variety, owing to the occasional difficulty in distinguishing the cause of death from the two disease states on death certificates and since, to date, only two of the nine cases in the cohort studied by Rinsky *et al.* (1987) were chronic or unspecified myelogenous leukemias, the quantitative assessment of potency would ideally include estimates based on acute myelogenous leukemia, and acute, unspecified and chronic myelogenous leukemias combined. Since data on the background rates of chronic and unspecified leukemia were not available, however, and there is lack of convergence of the maximum likelihood

estimation procedure, potency estimates based only on acute myelogenous leukemia are presented here.

Although there were four deaths in the pliofilm cohort due to this cause (versus one expected), multiple myeloma is not included as an endpoint in the quantitative assessment of potency, since it is not possible on the basis of available data to conclude unequivocally that multiple myeloma is causally related to benzene exposure.

Attempts to quantify exposure of the workers in the cohort examined by Rinsky *et al.* (1987) have been relatively extensive (Rinsky *et al.*, 1987; Crump and Allen, 1984; Paustenbach *et al.*, 1991). However, the estimates of exposure for different job categories vary considerably among the different authors. These variations are principally a result of differences in the methods used to extrapolate from existing data to fill gaps. The extent of consideration of factors, such as peak and dermal exposures, the quality of earlier monitoring data, the effect of modifications to ventilation systems, and extended work weeks during the war, has also contributed to variations in exposure estimates.

Although the exposure estimates developed by Paustenbach *et al.* (1991) are based on additional information which was not available to either Crump and Allen (1984) or Rinsky *et al.* (1987), it has not been possible to independently estimate exposure of the workers in the critical study. Estimates of cancer potency presented here are based on the exposure estimates of Crump and Allen (1984), owing to the lack of availability of sufficient data for those of Paustenbach *et al.* (1991) and Rinsky *et al.* (1987).

The age-specific death rate for acute myelogenous leukemia was assumed to be a linear-quadratic function of the total biologically effective dose, which is additive to the death rate for the general population assumed not to be exposed to benzene. The total biologically effective dose is based on the assumption that there is a lag between the time of exposure and the time of onset of acute myelogenous leukemia. This has been modelled using a gamma density function.

The increase in probability of death due to constant lifetime exposure to benzene has been determined assuming a constant exposure for a period equal to the median survival time of 75 years and that there are no competing causes of death. The concentration that corresponds to a 5% increase in mortality due to acute myelogenous leukemia (toxic dose $_{0.05}$ or $TD_{0.05}$), based on the data on mortality in the follow-up of the pliofilm cohort to 1981 (Rinsky *et al.*, 1987), estimates of exposure developed by Crump and Allen (1984) and a linear-quadratic model for the exposure-response relationship (Thorslund and Farrar, 1992), is 14.7×10^3 µg/m^3. Based on an average concentration of benzene in ambient air (the principal source of exposure for humans) in Canadian cities of 4.4 µg/m^3 (Dann, 1991), the calculated corresponding exposure/potency index for benzene is 3.0×10^{-4}. The priority for further action (i.e., analysis of options to reduce exposure) is, therefore, considered to be high.

If accessible data permit, additional estimates for the carcinogenic potency, based on the partial follow-up of the pliofilm cohort to 1987 and the estimates of exposure developed by Rinsky *et al.*(1987) and Paustenbach *et al.* (1991), will be derived and released separately at a later date.

Since on the basis of available data, benzene is classified as carcinogenic to humans (*i.e.*, as a non-threshold toxicant - a substance for which there is considered to be some probability of harm for the critical effect at any level of exposure), it is considered to be "toxic" as defined under Paragraph 11(*c*) of the *Canadian Environmental Protection Act*.

This approach is consistent with the objective that exposure to non-threshold toxicants should be reduced wherever possible and obviates the need to establish an arbitrary *de minimis* level of risk for determination of "toxic" under the Act.

3.4.4 *General Conclusions*

On the basis of available data, benzene is not considered to be "toxic" as defined under Paragraphs 11(*a*) and 11(*b*) of CEPA. Benzene is considered to be "toxic" as defined under Paragraph 11(*c*) of CEPA.

4.0 Recommendations for Research

1. Since indoor air appears to contribute considerably to the exposure of the general population to benzene, it is recommended that sources of benzene in indoor air in Canada should be better characterized. This is considered a matter of high priority.

2. Since no data are available for toxicity to wild mammals resulting from chronic oral exposure to benzene, studies to obtain such data are desirable to permit the assessment of potential effects on wild mammals. This research is considered to be of medium priority.

3. Since no data are available for toxicity to birds resulting from acute or chronic exposure to benzene, studies to obtain such data are desirable to permit the assessment of potential effects on wild birds. This research is considered to be of low priority.

4. Additional data on the effects of chronic exposure to benzene on growth, survival, and reproduction of sensitive freshwater fish are desirable to better estimate the potential harm that could result from continuous exposure to low concentrations of benzene. This research is considered to be of low priority.

5.0 References

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