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Arsenic and its Compounds – PSL1

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Canadian Environmental Protection Act

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Notice to Readers

Pesticidal uses of arsenic were not assessed in this report. The pesticide arsenic pentoxide is subject to the provisions of the *Pest Control Products Act*, and its regulatory status as a heavy duty wood preservative is currently being re-evaluated (see Announcement A92-02: Re-evaluation of Heavy Duty Wood Preservatives, Agriculture

Canada, Food Production and Inspection Branch, July 2, 1992). As part of the pesticide re-evaluation process, Environment Canada and Health Canada will assess the potential effects on the environment and on human health resulting from these pesticidal uses of arsenic.

Synopsis

Due to the nature of the available data, this assessment of "arsenic and its compounds" focuses on "arsenic and its inorganic compounds".

Arsenic is present in the aquatic and terrestrial environments because of natural weathering and erosion of rock and soil, and human activities (including gold- and base-metal processing, the use of arsenical pesticides, coal-fired power generation and the disposal of domestic and industrial waste materials).

The highest concentrations of arsenic and its inorganic compounds in the Canadian environment occur near active and abandoned gold- and base-metal mining and ore processing facilities, and in areas affected by the use of arsenical pesticides. Mean arsenic concentrations of up to 0.3 µg/m^3 in air, 45 µg/L in surface waters, 100 to 5 000 mg/kg in sediments and 50 to 110 mg/kg in soils have been found near these sources in several regions of Canada; most (= 80%) of this arsenic is likely inorganic. In addition, an average of up to 35 mg inorganic As/kg (dry weight) may be present in the diet of fish, and 109 µg inorganic As/kg body weight per day may be present in the diet of fish-eating mammals near gold-mining areas in Canada. These concentrations of arsenic are high enough to cause, or to have the potential to cause, adverse effects in a variety of aquatic and terrestrial organisms.

Canadians are exposed to inorganic arsenic in food, drinking water, soil and ambient air, with food representing the major source of intake. Exposure to arsenic may be elevated in populations residing in the vicinity of industrial and geological sources.

Inorganic arsenic has been consistently demonstrated in numerous studies to cause cancer in humans exposed by both inhalation and ingestion. The group of inorganic arsenic compounds as a whole (since data do not permit an assessment of individual compounds within the group) is therefore considered to be a "non-threshold toxicant" (i.e., a substance for which there is believed to be some chance of adverse health effects at any level of exposure). For such substances, estimated exposure is compared to quantitative estimates of cancer potency to characterize risk and provide guidance for further action (i.e., analysis of options to reduce exposure). For inorganic arsenic, such a comparison suggests that the priority for analysis of options to reduce exposure would be moderate to high.

Based on these considerations, the Ministers of the Environment and of National Health and Welfare have concluded that the current concentrations of inorganic arsenic in Canada may be harmful to the environment and may constitute a danger in Canada to human life or health. Therefore, "arsenic and its compounds" (as specified above) are considered to be "toxic" as interpreted under section 11 of the *Canadian Environmental Protection Act* (CEPA).

1.0 Introduction

CEPA requires the Ministers of Environment Canada and of Health and Welfare Canada to prepare and publish a Priority Substances List that identifies substances, including chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires the federal Ministers of Environment Canada and of Health and Welfare Canada 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 assessed to be "toxic," as defined in section 11 of the Act, may be placed on Schedule I of the Act, which allows for the development of regulations to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Arsenic and its compounds are included in Group 1 of the Priority Substances List. Due to the paucity of data available to serve as a basis for assessment of exposure to individual organic arsenic compounds in the general environment and the effects of these substances on the environment or on experimental animals and humans, either as individual compounds or as a group, the scope of this assessment focuses on arsenic and its inorganic compounds. Upon acquisition of additional data on the speciation of arsenic in the environment, as is suggested in Section 4.0, "Recommendations for Research", it may be possible in future to assess organic arsenic compounds. With the exception of Section 2.3.1 ("Fate"), unless otherwise specified, the term 'arsenic in this report refers to "total inorganic arsenic."

For assessment of data other than those considered to be critical for the determination of whether arsenic and its compounds are "toxic" to human health under the Act, evaluations of other agencies, such as the U.S. Environmental Protection Agency and the U.S. Agency for Toxic Substances and Disease Registry, have been consulted where available and considered to be appropriate. An extensive background review of available data on the effects of inorganic arsenic on the environment and human health completed under contract by the British Industrial Biological Research Association in April, 1990, was also consulted in the preparation of this assessment. Additional relevant data were requested from the Mining Association of Canada

and its member companies. Information relevant to assessment of effects on the environment was also identified by an on-line search of the Pollution Abstracts database (1985 to 1990). To identify additional literature relevant to the assessment of the effects of arsenic on human health, which was not included in the reviews consulted, computer literature searches on the MEDLINE and TOXLINE databases were conducted throughout the period during which the assessment was prepared (October, 1990 to February, 1992). In addition, computer literature searches were conducted in January, 1991 to identify recent critical epidemiological data on MEDLINE (1984 to 1991), BIOSIS and EMBASE (1988 to 1991).

Data relevant to assessment of whether arsenic is "toxic" to human health obtained after completion of these sections of the report (i.e., April, 1992) were not considered for inclusion. Similarly, data relevant to assessment of whether arsenic is "toxic" to the environment obtained after June, 1992 have not been incorporated.

For the assessment of effects on the environment, the most sensitive end-points in the most sensitive species are emphasized in this report. Similarly, the evaluation of effects on human health addresses principally the toxicological end-point considered to be most sensitive.

Although reviews prepared by other agencies have been consulted where considered appropriate, all original studies that form the basis for the determination of "toxic" under CEPA have been critically evaluated by the staff of the Departments of Health and Welfare Canada (effects on human health) and Environment Canada (effects on the environment). Individuals involved in the preparation of this report were:

D. Boersma (Environment Canada)
R. Burnett (Health and Welfare Canada)
P. Doyle (Environment Canada)
C. Fortin (Environment Canada)
K. Hughes (Health and Welfare Canada)
J. MacLatchy (Environment Canada)
M.E. Meek (Health and Welfare Canada)

L. Shutt (Environment Canada)
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Primary data included in reviews, which were not considered critical to the assessment of "toxic" to human health, were not evaluated.

An overview of the findings that will appear in the Canada Gazette is presented. An extended summary of the technical information, which is critical to the assessment and which is included in greater detail in a Supporting Document, is presented in Section 2.0. The assessment of whether arsenic is "toxic" under CEPA is presented in Section 3.0. Recommendations for further research are presented in Section 4.0.

Technical information in the Supporting Document relating to the assessment of effects on the environment was reviewed by Dr. W. Cullen (University of British Columbia), Dr. M. Diamond (University of Toronto), Mr. A. Khosla (Proctor and Gamble Inc.), Dr. F. Michel (Carleton University), Mr. E. Paquin (Government of the Northwest Territories), Mr. B. Riddell (Allied Chemicals Canada Ltd.) and Mr. M. Sudbury (Falconbridge Ltd.). The environmental component of this Assessment Report was reviewed externally by Dr. W. Cullen (University of British Columbia), Dr. K. Reimer (Royal Roads Military College) and Dr. A. Tessier (Institut National de la Recherche Scientifique, Université du Québec).

Comments on the adequacy of coverage of the literature relevant to human health in the Supporting Document were received from Dr. A. Li-Muller and Dr. R.R. Weiler of the Hazardous Contaminants Branch of the Ontario Ministry of the Environment and Dr. I. Harding-Barlow, a consulting environmental and occupational toxicologist. Sections of the Supporting Document relevant to assessment of exposure of Canadians to inorganic arsenic in the environment, as well as the complete list of references, were forwarded to officials of the Mining Association of Canada for identification of additional pertinent data. Following peer review of the Supporting Document and Assessment Report relating to human health and exposure by staff of the British Industrial Biological Research Association, Dr. H. Gibb and Dr. C. Chen of the U.S. Environmental Protection Agency and Dr. P. Enterline and Dr. G. Marsh of the University of Pittsburgh, the

documents were approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazardous of Health and Welfare Canada.

The entire Assessment Report was subsequently reviewed and approved by the Environment Canada/Health and Welfare Canada CEPA Management Committee.

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

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2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production and Uses

Arsenic is a metalloid, belonging to Group 5 of the Periodic Table. It has an atomic number of 33 and an atomic weight of 74.92. Although usually considered to exist in oxidation states of minus III, 0, III or V, it is questionable whether arsenic is present in the minus III state in the environment (Cullen and Reimer, 1989).

Arsenic occurs occasionally in nature as a solid in the elemental state, but is found most often in compounds with sulphur, either alone or in combination with various metals (Boyle and Jonasson, 1973). Common arsenic-containing minerals include arsenopyrite (FeAsS), realgar (AsS), orpiment (As_2S_3), niccolite (NiAs) and cobaltite (CoAsS) [Boyle and Jonasson, 1973]. Arsenic can occur in the gaseous state as volatile arsenic trioxide (As_2O_3), arsine (AsH_3) and methylated arsines. In the dissolved phase, arsenic can be present as inorganic As(III) and As(V) species, as well as various methylated As(V) compounds (Cullen and Reimer, 1989).

In Canada, arsenic is produced mainly as arsenic trioxide through the roasting of arsenious gold ores. Though four gold-ore roasters operated in the 1970s, only two mines produce arsenic in 1992. Demand for arsenic has fallen sharply since the early 1980s, due to concerns about environmental effects. Because of low prices, arsenic trioxide currently produced in Canada is being stockpiled for future sale (Ignatow *et al.,* 1991).

At present in Canada, arsenic is used mainly in metallurgical applications (Environment Canada, 1991) and in the manufacture of wood preservatives. For the period 1984 to 1988, Canadian sales of arsenic (as arsenic pentoxide) for use in wood preservation fluctuated between about 650 and 1 300 tonnes per year (Brien, unpublished data). Arsenic compounds have also been used in Canada in herbicides (Brien, unpublished data), in pharmaceuticals and in glass manufacturing (CCREM, 1987).

2.2 Entry into the Environment

Arsenic is present naturally in the aquatic and terrestrial environments from weathering and erosion of rock and soil. In areas of arsenic-enriched bedrock, background concentrations can be significantly elevated. In Canada, for example, large amounts of arsenic have been reported in soil, sediment and water in the vicinity of arsenic-bearing precious metal deposits near Cobalt, Ontario, and Halifax, Nova Scotia (Boyle *et al.,* 1969; Brooks *et al.,* 1982; Bottomley, 1984). Arsenic is released naturally into the atmosphere by volcanic

eruptions and the escape of volatile methylarsines from soil (Chilvers and Peterson, 1987).

Base-metal and gold-production facilities are the principal anthropogenic sources of arsenic released into the Canadian environment. Based largely on data on emissions in 1988, MacLatchy (1992) estimated that about 15 tonnes of arsenic were released annually by Canadian base-metal smelters and refineries in liquid effluent, while 310 tonnes/year were released into the atmosphere, and 770 tonnes/year were disposed of on land as solid waste. Significant amounts of arsenic are released in liquid effluent from Canadian gold-milling operations using cyanide (Scott, 1989), as well as in stack gases from roasting of gold ores.

In 1972, about 1 750 tonnes of arsenic were emitted into the Canadian atmosphere by four gold-ore roasters (Gagan, 1979). Atmospheric releases from one of the two roasters currently operating in Canada, located in Yellowknife, NWT, are about 8.8 tonnes of arsenic per year (McCaig and Cianciarelli, 1984; Paquin, unpublished data). Weathering of acidic mill tailings, as well as waste rock and mine workings, can also result in the release of arsenic, especially at abandoned base and precious metal mine sites where leachates are not treated (Hawley, 1980; Errington and Ferguson, 1987).

Other anthropogenic sources of arsenic include the use of arsenical pesticides in fruit and vegetable production prior to 1975 (Frank *et al.,* 1976) and in wood preservation (Henning and Konasewich, 1984), coal-fired power generation (Evans *et al.,* 1985; Van Voris *et al.,* 1985) and disposal of domestic and industrial wastes (PACE, 1983; Environment Canada, 1985; 1987; OME, 1988).

2.3 Exposure-related Information

2.3.1 Fate

As Woolson (1983) has noted, the ultimate sink for most environmental arsenic is ocean sediment. Because of its reactivity and mobility, however, arsenic can cycle extensively through both biotic

and abiotic components of local aquatic and terrestrial systems, where it can undergo a variety of chemical and biochemical transformations, such as oxidation, reduction, methylation and demethylation (Cullen and Reimer, 1989).

As_2O_3 vapour is introduced anthropogenically into the atmosphere along with other high temperature gases by smelters, fossil fuel combustion and roasters. After release, As_2O_3 can be trapped on suspended particulate matter by adsorption or complexation reactions (Cullen and Reimer, 1989), or it can condense directly to a solid upon cooling (Gagan, 1979). Volatile arsine and methylarsines can also be released to the atmosphere from soil by microbial activity (NRCC, 1978). They are eventually oxidized and converted to particulate form, typically as methylated As(V) species (Parris and Brinckman, 1976).

Most atmospheric arsenic is associated with small (< 1 µm diameter) particulates, but 1-5% can be present in the vapour phase (Walsh *et al.,* 1979a). Arsenic is removed from the atmosphere by either dry deposition or rainfall, with rates of deposition typically being highest in the immediate vicinity of sources (Traversy *et al.,* 1975). The average residence time of arsenic in the atmosphere has been estimated to be about 9 days (Walsh *et al.,* 1979b).

When As_2O_3 is deposited directly into aerobic surface waters, it hydrolyses to form As(III) species, principally H_3AsO_3 ("arsenite"). Arsenite is thermodynamically unstable, and therefore tends to oxidize to dissolved As(V) species, principally $HAsO4^{-2}$ and $H_2AsO_4^-$ ("arsenates"). This oxidation is relatively slow, but can be accelerated by chemical oxidizing agents such as manganese and iron oxyhydroxides (Oscarson *et al.,* 1981; De Vitre *et al.,* 1991) or by the action of certain bacteria (Cullen and Reimer, 1989).

Arsenates are chemically reduced to arsenite under anaerobic conditions, such as those found in some deep lacustrine and marine waters, sediment pore waters, ground waters, and waterlogged soils (Peterson and Carpenter, 1983 and 1986; Korte and Fernando, 1991; Masscheleyn *et al,* 1991). Biochemical processes associated with phytoplankton blooms in oxygenated surface waters can also reduce

arsenates to arsenite, and produce small amounts of methylated arsenicals (Andreae, 1978).

Arsenic can be removed from solution by biotic uptake, absorption onto iron and manganese hydroxides or clay particles, fixation by organic matter, or, less frequently, by precipitation or coprecipitation (Frost and Griffin, 1977; Pierce and Moore, 1982; Thanabalasingam and Pickering, 1986; Korte and Fernando, 1991). As a result of these processes, dissolved arsenic is rapidly removed from most surface waters (Nriagu, 1983) and deposited in sediment with settling organic and inorganic particulates.

Results of several studies suggest that arsenic can remain relatively undisturbed in contaminated sediments for long periods of time (up to 100 years) [Mudroch and Capobianco, 1980; Nriagu, 1983; Sutherland, 1989]. Some sediment-bound arsenic can be released, however, into pore waters with the decomposition of organic matter, or the dissolution of iron/manganese hydroxides in anaerobic conditions resulting from sediment burial. Since a portion of the arsenic released can diffuse back to the water column (Nriagu *et al.,* 1987; Belzile, 1988), sediment is not always a permanent arsenic "sink."

Soils can be contaminated with inorganic arsenic (AsO_3-3 and AsO_4-3 species) or methylated arsenicals contained in herbicides. Methylated arsenicals are eventually degraded (half-lives = 0.5 to 2.9 years) to $C0_2$ and arsenate by soil microorganisms (Hiltbold, 1975). Some arsenic (both inorganic and organic forms) can also be lost to the atmosphere as a result of production of volatile methylarsines (NRCC, 1978).

Most forms of dissolved arsenic can be quickly removed from soil pore waters, principally by adsorption onto iron/manganese oxides and, to a lesser extent, clay minerals. These processes can significantly reduce the amount of arsenic reaching ground water, or which is available for absorption by plant roots. They are most effective in medium- to fine-grained, well-drained soils, which can retain added arsenic for long periods [at least several decades] (Veneman *et al.,* 1983). They are less effective in poorly drained soils, however, since arsenic can be mobilized when soils become anaerobic due to

flooding (Masscheleyn *et al.,* 1991). Application of phosphate fertilizers can also result in the mobilization of otherwise tightly bound arsenic in soil (Peryea, 1991).

Various aquatic organisms, including algae, crustaceans and fish, bioaccumulate arsenic; bioconcentration factors (BCFs) of up to several thousand have been reported (NRCC, 1978). Arsenic does not, however, biomagnify through the aquatic or terrestrial food chains (Eisler, 1988).

In freshwater aquatic plants, arsenic is present mainly as lipid and water-soluble, "lipid-related" compounds; lesser amounts of arsenite and methylated As(V) species are also present (Cullen and Reimer, 1989). Although little is known about the behaviour of arsenicals in terrestrial plants, methylation has been reported in some plants grown in nitrate- or phosphate-deficient conditions (Nissen and Benson, 1982). Methylated arsenicals are also produced in a variety of terrestrial animals, including humans (NRCC, 1978). Arsenosugars and arsenic-containing lipid compounds, as well as methylated arsenicals, have been found in marine plants (Cullen and Reimer, 1989). Arsenobetaine [$(CH_3)_3As + CH_2COO-$]) is the principal arsenic compound in marine animals (Lawrence *et al.,* 1986).

2.3.2 Concentrations

Levels of arsenic in inhalable particulates (< 10 µm diameter) in ambient air in 11 Canadian cities and one rural site monitored from 1985 to 1990 ranged from < 0.0005 to 0.017 µg/m3 (24-hour average); the mean level in most cities was 0.001 µg/m^3 (Dann, 1990; Environment Canada, 1990). Based on limited data from other relatively uncontaminated areas (Johnson and Braman, 1975; Mukai *et al.,* 1986), most (=80%) of this arsenic is probably inorganic. Higher concentrations were recorded in air near Canadian base-metal smelters and the Giant gold-ore roaster at Yellowknife, where average annual concentrations of between 0.0086 to 0.3 µg As/m^3 were measured in the 1980s and early 1990s (Paquin, unpublished data; White *et al,* 1986; Teindl, unpublished data; Noranda Mines, 1992; Murphy, unpublished data; Sudbury, unpublished data; Moulins,

unpublished data). Atmospheric arsenic near such industrial sources is typically As_2O_3 in particulate form (Cullen and Reimer, 1989). No adequate data on levels of arsenic in residential indoor air have been identified.

As indicated in Figure 1, arsenic levels in Canadian surface waters remote from point sources of contamination are typically < 2 µg/L (Bailey, 1988; Environment Canada, 1988; Belzile and Tessier, 1990; Traversy *et al.,* 1975). Elevated concentrations of arsenic have been reported in surface waters in the vicinity of gold-mining or ore-roasting operations. Mean levels of about 45 µg/L (maxima about 140 µg/L) were found near abandoned gold mines in Nova Scotia (Mitchell Brook) and Ontario (Moira Lake) during the 1980s (Brooks *et al.,* 1982; Diamond, 1990). Highest arsenic levels were found in samples of water collected from several lakes near the gold mines and roasters at Yellowknife in the mid-1970s; for example, Keg and Kam Lakes contained from 700 to 1 500 µg As/L and 1 500 to 5 500 µg As/L, respectively (CPHA, 1977; Wagemann *et al.,* 1978). Limited data from the early 1990s indicated that concentrations in these lakes had declined appreciably, to about 545 and 645 µg/L in Keg Lake and Kam Lake, respectively (Reimer and Bright, unpublished data). Most (= 80%) of the arsenic in contaminated waters, as well as in surface waters remote from point sources, is expected to be present as inorganic As(V) and to a lesser extent As(III) species (Cullen and Reimer, 1989).

Ground water normally contains higher concentrations of arsenic than are found in associated surface water (Boyle and Jonasson, 1973). Available data indicate that most Canadian ground waters contain less than 50 µg As/L (Michel, 1990; Léger, 1991); however, concentrations of arsenic have been reported to range up to 9 100 µg/L in ground water in areas with a high content of arsenic in the bedrock, such as in regions of Ontario, Quebec, New Brunswick and Nova Scotia (Boyle *et al.,* 1969; Lalonde *et al.,* 1980; Bottomley, 1984; Grantham and Jones, 1977; Meranger *et al.,* 1984; Deveau, personal communication). Gold-mining activities in Nova Scotia have been reported to contribute to high arsenic levels in local ground waters (Bottomley, 1984). High arsenic concentrations (up to 11 000 µg/L)

were also detected in ground water in the vicinity of an abandoned arsenical wood preservative facility near Vancouver, British Columbia (Henning and Konasewich, 1984). Recent studies (Masscheleyn *et al.,* 1991; Korte, 1991) in other areas suggest that arsenic in ground water is present mainly as inorganic As(III) and As(V) species.

Figure 1 Arsenic Concentrations in Canadian Surface Waters and Biological Effects at Corresponding Levels of Exposure

Data on concentrations of arsenic in Canadian drinking water from a nationwide survey have not been identified. Based on data obtained in provincial monitoring programs, levels in Canadian drinking water from both surface- and ground-water supplies are generally less than 5 µg/L (measured as total arsenic), although concentrations in some ground water supplies are greater (Environment Canada, 1989a; 1989b; 1989c; 1989d; OME, 1989; Manitoba Environment, 1989). Five percent of samples of well water from contaminated supplies in Nova Scotia contained more than 500 µg As/L (Meranger *et al.,* 1984).

Key data on concentrations of strong acid-extractable arsenic in Canadian sediment are presented in Figure 2. Background concentrations in relatively uncontaminated surface sediment are generally less than 20 mg As/kg dryweight; arsenic levels in deeper sediment are normally only a few mg/kg (Friske, 1985; Johnson, 1987). Arsenic accumulation (up to 65 mg/kg) has been reported in contaminated Halifax harbour sediments (Tay *et al.,* 1991). Bamwoya *et al.* (1991) found 262 mg As/kg in sediment downstream from an arsenical wood preservation facility near Elmsdale, Nova Scotia. Concentrations of arsenic are highest in sediments near base- and precious-metal mining and ore-processing operations. Average levels of 100 to 200 mg/kg (maximum 650 mg/kg) were reported near base- metal mines and smelters in several provinces (Bailey, 1988; Palmer *et al.,* 1989; Franzin, 1984). Near gold mines and an abandoned precious-metal refinery, mean concentrations in sediments ranged from about 700 to 5 000 mg As/kg (maximum 18 650 mg/kg)

[Trip and Skilton, 1985; Diamond, 1990; Reimer and Bright, unpublished data; Sutherland, 1989]. Limited data on the composition of pore waters from two areas in Canada (Reimer and Thompson, 1988; Diamond, 1990) suggest that most (> 85% of) bioavailable arsenic in sediment is present as inorganic As(III) and As(V).

Information concerning concentrations of strong acid-extractable arsenic in Canadian soils is presented in Figure 3. Based on a review of available data, mean concentrations of arsenic in several uncontaminated soil types in Canada were reported to range from 4.8 to 13.6 mg/kg dry weight (dw) [Kabata-Pendias and Pendias, 1984]. Higher concentrations were found near near base-metal smelters (mean concentrations ranged from 50 to 110 mg As/kg, with a maximum of 2 000 mg As/kg) [Temple *et al.,* 1977; Hertzman *et al.,* 1991; Brunswick Mining and Smelting Corporation, personal communication; Murphy, unpublished data; Teindl, unpublished data] and gold-mining/roasting operations (mean concentrations of 60 to 110 mg As/kg, and maximum of >10 000 mg As/kg) [Gemmill, 1977; NRCC, 1978; Hutchinson *et al.,* 1982; EBA Engineering Consultants Ltd., 1991]. Elevated arsenic levels have also been reported in soils where arsenical pesticides (including wood-preservation compounds) have been used; for example, concentrations of arsenic of up to 290 mg/kg (mean values of up to 54 mg/kg) have been detected in soil from orchards in Ontario (Boyle and Jonasson, 1973; Frank *et al.,* 1976), and up to 10 860 mg/kg (mean values of up to 6 000 mg/kg) at active wood-preservation facilities in Atlantic Canada (Bamwoya *et al.,* 1991). Highest arsenic concentrations (up to 75 000 mg/kg; typically 3 000 to 4 000 mg/kg) were found in tailings at base- and precious-metal minesites in Ontario and Nova Scotia (Hawley, 1980; Dale and Freedman, 1982). Analysis of whole-soil and soil pore water from a limited number of areas indicates that most (> 90%) of the arsenic in soils is inorganic (Woolson, 1983; Haswell *et al.,* 1985; Masscheleyn *et al.,* 1991).

Figure 2 Arsenic Concentrations in Canadian Sediments and Biological Effects at Corresponding Levels of Exposure

Figure 3 Arsenic Concentrations in Canadian Soils and Biological Effects at Corresponding Levels of Exposure

Levels of arsenic in the tissue of freshwater fish in areas remote from point sources of contamination generally range from < 0.1 to 0.4 mg As/kg fresh weight (fw) [Moore and Ramamoorthy, 1984]. Concentrations in samples of fish in Lakes Erie and Ontario in the mid1970s and in base-metal mining areas in Atlantic Canada in 1984 and 1985 were usually within this range (Traversy *et al.,* 1975; Bailey, 1988). Higher levels were reported in fish sampled near active and abandoned gold-mining operations, with maximum concentrations ranging from 2.36 to 4.77 mg As/kg (fw) [Gemmill, 1977; Azcue, 1992; Dale and Freedman, 1982]. Levels of arsenic in the tissue of freshwater macrophytes in areas remote from point sources of contamination are generally < 10 mg As/kg dw (Moore and Ramamoorthy, 1984). Concentrations of arsenic up to 538 and 206 mg As/kg dw have been detected in aquatic macrophytes growing near a gold mine in Nova Scotia in 1981 (Dale and Freedman, 1982) and a base-metal smelter in Manitoba from 1975 to 1976 (Franzin and McFarlane, 1980), respectively. Wagemann *et al.* (1978) found high levels of arsenic in aquatic macrophytes (max. 3 700 mg As/kg dw; mean 1 010 mg/kg dw) from Kam Lake, and zooplankton (max. 2 400 mg As/kg dw; mean 1 875 mg/kg dw; BCFs 53 to 80) from Keg Lake, near Yellowknife, in the mid-1970s. Results of a more recent study (1990-91) indicate that levels of arsenic in aquatic macrophytes near Yellowknife remain high (up to 4 900 mg/kg dw) [Reimer and Bright, unpublished data]. Limited data on arsenic speciation in plant and aquatic-animal tissues suggest that most arsenic is in the form of organo-arsenic compounds; however, a small amount (< 1-30%) may be present as inorganic As(III) [Cullen and Reimer, 1989].

Arsenic has been detected in most foodstuffs consumed by humans; however, the proportion of inorganic arsenic varies considerably. Much of the arsenic in fish, for example, is present in highly complexed forms that are not bioavailable, or as organic compounds

that are rapidly excreted from the body. The percentage of total arsenic that is inorganic in various foods has been determined to range from 0% in saltwater fish to 75% in milk, dairy products, beef and pork, based on limited data (Weiler, 1987). Mean concentrations of total arsenic in 10 food groups surveyed in a duplicate diet study in five cities in Canada ranged from 0.46 ng/g or µg/L (drinking water) to 60.1 ng/g (0.0601 mg/kg) [meat, fish and poultry] (Dabeka *et al.,* 1987). Based on very limited data, concentrations of arsenic in produce grown in the vicinity of industrial sources may be somewhat higher than those reported in the duplicate diet study (Teindl, unpublished data; Noranda Mines, 1992; Brunswick Mining and Smelting Corporation, personal communication; Murphy, unpublished data).

2.4 Effects-related Information

2.4.1 Essentiality and Toxicokinetics

It has been postulated that arsenic might be an essential element in animals, as there is some evidence that such essentiality is plausible, but there is no indication that arsenic is essential to humans (U.S. EPA, 1988).

The absorption of ingested inorganic arsenic in humans is largely dependent upon the solubility of the compound; greater than 95% of ingested soluble trivalent and pentavalent arsenic is absorbed by the gastrointestinal tract. The absorption of inhaled arsenic depends upon the solubility and particle size. Once absorbed, arsenic is distributed widely throughout the body (including the foetus), and eliminated rapidly from tissues, with the exception of skin and hair. Trivalent arsenic is detoxified in the liver by enzymatic methylation to methylarsonic acid and dimethylarsinic acid, which are rapidly eliminated in the urine; pentavalent arsenic must be reduced to trivalent arsenic before methylation can occur. The methylating capacity varies between individuals, and, based on the results of a short-term study in a small number of individuals, appears to be

progressively, but not completely, saturated above doses of 500 µg (Buchet *et al.,* 1981).

2.4.2 Experimental Animals and In Vitro

The acute toxicity of inorganic arsenic compounds increases with solubility in water. Soluble salts, such as sodium and potassium arsenates and arsenites, arsenic pentoxide, arsenic trichloride and arsenic acid, are highly acutely toxic to mammals, with LD_{50} s in rats, mice and rabbits ranging from 2.6 to approximately 40 mg As/kg-bw (British Industrial Biological Research Association, 1990). The reported LD_{50} s for the less-soluble arsenic trioxide and calcium arsenate, the virtually insoluble lead arsenate, and the insoluble magnesium arsenate, ranged from 2.2 to 230 mg As/kg-bw in rats, mice, rabbits and dogs, while the acute toxicity of insoluble gallium arsenide and nickel subarsenide is much lower (LD_{50}s in the rat of more than 7.8 g As/kg-bw and 1 g As/kg-bw, respectively) [British Industrial Biological Research Association, 1990].

The lowest reported no-observed-effect level (NOEL) following inhalation in limited available short-term and sub-chronic studies is 0.0013 mg/m^3 (1.3 µg/m^3) arsenic trioxide, based on the observation of slower conditioned reflexes and histological changes in the brain, liver and lungs of rats at the higher concentration (0.005 mg/m^3 or 5.0 µg/m^3) [Rozenshtein, 1970]. In studies in experimental animals, the main organs affected by repeated oral doses of arsenic compounds are the liver and kidneys, although effects have also been noted on the spleen, body weight and various haematological and biochemical parameters. The no-observed-adverse-effect level (NOAEL) for chronic ingestion of arsenic appears to be in the region of 1.5 to 3.5 mg As/kg-bw/day, based on 2-year studies in which rats and dogs were administered arsenic in the diet (British Industrial Biological Research Association, 1990); however, toxic effects, such as reduced growth and litter size and histological changes in the liver, kidney, spleen and skin, have occurred at or below 1.5 mg As/kg-bw/day when arsenic is administered in the drinking water of rats or mice for up to 2 years (Byron *et al.,* 1967; Schroeder and Balassa, 1967; Schroeder and Mitchener, 1971). For example, liver damage has been

reported in rats drinking water containing arsenic trioxide at concentrations equivalent to doses of 0.01 mg As/kg-bw/day or greater (Ishinishi *et al.,* 1980).

The results of early, limited carcinogenicity bioassays, in which experimental animals have been administered arsenic compounds by ingestion or inhalation, have been largely negative (U.S. EPA, 1984). In some more-recent studies, increases in the incidence of primarily pulmonary adenomas were observed in hamsters following weekly intratracheal instillations of calcium arsenate and arsenic trioxide for 15 weeks (Pershagen and Bjorklund, 1985; Yamamoto *et al.,* 1987), whereas in other similar studies, results for arsenic trioxide, gallium arsenide and arsenic trisulphide were negative (Ohyama *et al.,* 1988; Yamamoto *et al.,* 1987; Pershagen and Bjorklund, 1985). The results of initiation/promotion studies have provided some limited evidence that some arsenic compounds may act as tumour promoters in experimental animals (Shirachi *et al.,* 1986; 1987). Arsenic appears to induce clastogenic damage rather than gene mutations in short-term *in vitro* and *in vivo* assays, and induces transformation in mammalian cells *in vitro* (British Industrial Biological Research Association, 1990; International Agency for Research on Cancer, 1987).

Little recent information is available on the developmental and reproductive toxicity of arsenic. Foetotoxic effects have been observed at doses that are not maternally toxic (i.e., = 8 mg As/kg-bw/day) [Matsumoto *et al.,* 1973], but teratogenic effects have been observed only at doses that were toxic to the dams. Available data on the reproductive toxicity of arsenic are limited largely to early studies, in which the lowest concentration reported to induce effects (decreased litter size and increased ratio of male to female offspring in a three-generation study in mice) was 1.5 mg As/kg-bw/day (Schroeder and Mitchener, 1971). Adverse effects on the immune system, including increased susceptibility to bacterial and viral infection, suppressed humoral response and a reduction in the number of T lymphocytes, have been reported in several studies in which mice were exposed to arsenic by inhalation or ingestion (British Industrial Biological Research Association, 1990).

2.4.3 Humans

The acute toxicity of ingested inorganic arsenic in humans also increases with the solubility of the compound. The lethal dose in humans is estimated to be approximately 50 to 300 mg (or 0.8 to 5 mg/kg-bw) of arsenic trioxide, although severe effects have been reported following ingestion of as little as 20 mg, and persons have survived oral doses of approximately 10 g (British Industrial Biological Research Association, 1990).

Chronic ingestion of arsenic has been associated with adverse effects on the skin, including hyperkeratoses of the palms and soles, and hyperpigmentation in several epidemiological studies. There has been an exposure-response relationship between concentrations of arsenic in drinking water supplies and the prevalence of non-cancerous dermal lesions in studies in Taiwan and Chile (Tseng, 1977; Tseng *et al.,* 1968; Borgono *et al.,* 1980; Borgono *et al.,* 1977; Borgono and Greiber, 1972). Similar dermatological effects have been reported in several studies in workers occupationally exposed to airborne arsenic (British Industrial Biological Research Association, 1990).

Ingestion of arsenic in drinking water has been associated with an increased prevalence of "Blackfoot disease," a peripheral vascular disease leading to gangrene of the toes and feet, in a population of 40 421 residents in Taiwan whose well water contained up to 1.82 ppm (1,820 µg/L) arsenic (Tseng *et al.,* 1968; Tseng, 1977). This effect has not been observed, however, in populations ingesting drinking water containing high concentrations of arsenic in other countries, and it has been suggested that other compounds in the water supply may play a role in the development of the disease (Lu, 1990a; 1990b; Chen *et al.,* 1988). Mixed results have been obtained in numerous epidemiological studies designed to investigate the association between exposure to arsenic and mortality due to cardiovascular and cerebrovascular causes (British Industrial Biological Research Association, 1990; Wu *et al.,* 1989), although in most studies in which an increase in mortality due to these causes was reported (Lee and Fraumeni, 1969; Lubin *et al.,* 1981; Wall, 1980; Welch *et al.,* 1982),

there was no relationship between excess mortality and average concentration of arsenic or duration of exposure.

There is no conclusive evidence that arsenic causes any adverse reproductive effects in humans, based on several very limited studies (Aschengrau *et al.,* 1989; Beckman and Nordstrom, 1982; Nordstrom *et al.,* 1978a; 1978b; 1979a; 1979b). Although slight neurological effects were reported in a small group of individuals in Nova Scotia whose well water contained more than 0.05 ppm (50 µg/L) arsenic (Hindmarsh *et al.,* 1977), no adverse neurological effects were observed in two larger studies of populations exposed in some cases to higher concentrations (Kreiss *et al.,* 1983; Southwick *et al.,* 1983). Haematopoietic effects have been reported following occupational exposure to unspecified concentrations of arsenic, although these effects appear to be reversible (U.S. EPA, 1984; Yoshida *et al.,* 1987). Possible impairment of the immune system has been reported in an unconfirmed study of a small number of individuals drinking water containing 0.39 mg/L (390 µg/L) of arsenic (Ostrosky-Wegman *et al.,* 1991).

An association between inhalation of inorganic arsenic and respiratory cancer has been observed in several case reports and numerous analytical epidemiological investigations of workers in smelters and arsenical pesticides production facilities. Sufficient information on exposure to serve as a basis for quantitative estimation of the excess risk of respiratory cancer has been presented, however, in studies for only three cohorts of smelter workers. These studies involve workers at the Tacoma smelter in Washington (Enterline *et al.,* 1987a), the Anaconda smelter in Montana (Higgins *et al.,* 1986) and the Ronnskar smelter in Sweden (Jarup *et al.,* 1989). The weight of evidence obtained in analytical epidemiological studies of populations in other than these smelters is summarized in Table 1.

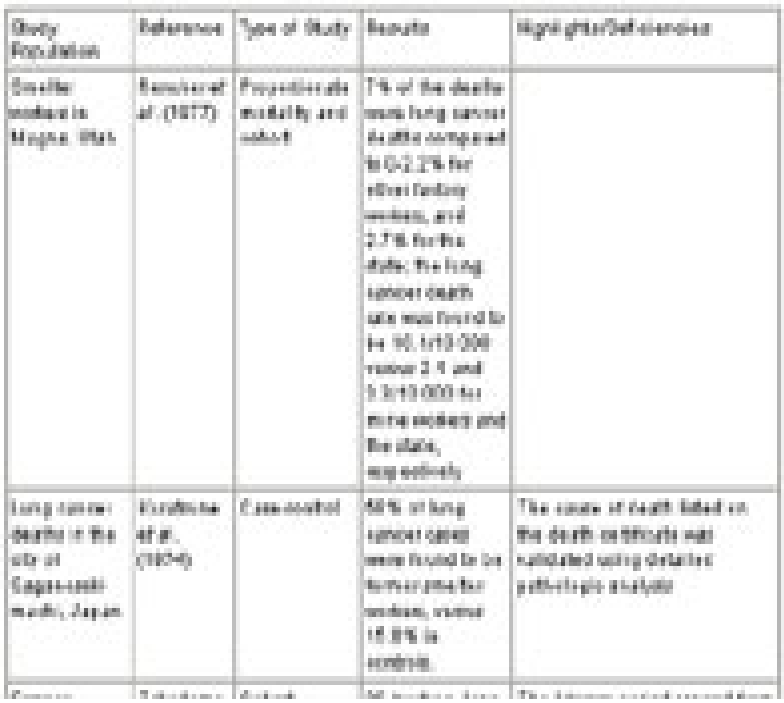
In the cohort of 2 802 employees at the Tacoma smelter investigated by Enterline *et al.* (1987a), the standardized mortality ratios (SMRs) for respiratory cancer increased with an increase in cumulative exposure to arsenic. The shape of the exposure-response curve was concave downwards, which, the authors speculated, was due to a decrease of bioavailable arsenic at higher concentrations, since

urinary arsenic levels increased non-linearly with airborne levels. Although no information was available on the smoking habits of these subjects, the excess in respiratory cancer did not appear to be related to sulphur dioxide exposure, based on the results of a comparison of mortality due to respiratory cancer between two departments, both with high arsenic concentrations and differing sulphur dioxide levels in an earlier follow-up of the same cohort (Enterline and Marsh, 1982).

Higgins *et al.* (1986) investigated the mortality of 8 044 workers at the Anaconda smelter. Deaths due to respiratory cancer in this cohort increased with estimated exposure to arsenic based on time-weighted average, 30-day ceiling and cumulative exposure, in a manner similar to that observed in the Tacoma cohort studied by Enterline *et al.* (1987a). No data were available on the smoking habits of these workers or their exposure to sulphur dioxide.

Mortality due to lung cancer was examined in a cohort of 3 916 men employed at the Ronnskar smelter (Jarup *et al.,* 1989). Although there appeared to be no exposure-response relationship at the lower exposures, the overall trend was highly significant. The excess of lung-cancer deaths appeared to have been related more to intensity than to duration of exposure, and there was no exposure-response relationship between sulphur dioxide and lung cancer mortality.

Table 1 Epidemiological Studies of Occupationally Exposed Populations (Modified from U.S. Environmental Protection Agency, 1984; Additional Recent Studies Have Also Been Included)



Potential interaction between occupational exposure to airborne arsenic and cigarette smoking in the induction of respiratory cancer has not been extensively investigated. Welch *et al.* (1982) found little difference between the SMRs for respiratory cancer for smokers and non-smokers in a study of 1 800 employees at the Anaconda smelter, although only a small proportion of the cohort were non-smokers (i.e., 18.4%). In a nested case-control study within the cohort of Ronnskar smelter workers, Jarup and Pershagen (1991) determined that the interaction between exposure to arsenic and smoking was intermediate between that predicted by an additive and multiplicative model. In a study of employees at eight copper smelters, Enterline *et al.* (1987b) reported that both exposure to arsenic and smoking were associated with increased mortality due to respiratory cancer.

Although the relationship between inhaled arsenic and cancers at sites other than the lungs has not been extensively investigated, it has been suggested that inhalation of arsenic is also associated with an excess risk of cancer of the gastrointestinal tract and the urinary system (Gibb and Chen, 1989).

An excess of lung-cancer incidence or mortality has been reported in a few limited ecological correlationals and one proportionate mortality

study in populations residing in the vicinity of point sources of arsenic emissions (Newman *et al.,* 1976; Blot and Fraumeni, 1975; Pershagen *et al.,* 1977; Matanoski *et al.,* 1976; 1981; Cordier *et al.,* 1983; Arizona Department of Health Services, 1990); however, no association between cancer rates and proximity to the source of emissions was found in three inherently more sensitive case-control studies (Frost *et al.,* 1987; Rom *et al.,* 1982; Lyon *et al.,* 1977).

A clear exposure-response relationship between the prevalence of skin cancer in 40 421 individuals from 37 villages in Taiwan and the concentration of arsenic in the drinking water was reported (up to 1.82 ppm or 1 820 µg/L). There were no cases of skin cancer in a similar comparison population whose water contained = 0.017 ppm (= 17 µg/L) arsenic, although three cases would have been expected (Tseng *et al.,* 1968; Tseng, 1977). In addition, an increase in the prevalence or mortality due to skin cancer has been reported in the majority of epidemiological studies of populations exposed to elevated concentrations of arsenic in drinking water in Argentina (Bergoglio, 1964; Biagini *et al.,*1974), Mexico (Cebrian *et al.,*1983), Chile (Zaldivar, 1974; 1977) and England (Philipp *et al.,*1983). Such effects have not been observed in smaller populations exposed to arsenic in drinking water in the United States (Southwick *et al.,*1983; Morton *et al.,*1976); however, this may be attributable to shorter exposure periods, lower waterborne concentrations or the insensitivity of the study designs.

There is also more-recent epidemiological evidence for an association between the mortality due to various cancers of internal organs and the ingestion of arsenic-contaminated water. Increased risks of, principally, bladder, kidney, liver and lung cancer have been observed in several ecological correlational studies of exposed populations, with some indication of an exposure-response relationship (Chen *et al.,* 1985; Wu *et al.,* 1989). In the most sensitive analytical (case-control) study, the odds ratios of developing bladder, lung and liver cancers for those who had used artesian wells containing high concentrations of arsenic (0.35 to 1.14 ppm) for 40 or more years were 3.90, 3,39 and 2.67, respectively, as compared to those who had never used artesian well water. There was an association for mortality

due to all three cancer types with duration of exposure, and the odds ratios were not changed significantly when several other risk factors were taken into consideration in logistic regression analysis (Chen *et al.,* 1986). There has also been some evidence of an association between ingestion of arsenic in drinking water and lung cancer in a recent analytical epidemiological (case-control) study in Japan, in residents of the Niigata Prefecture whose drinking water had contained up to 3.0 ppm (3 000 µg/L) arsenic from 1954 to 1959. When smoking was taken into account, however, the relationship was no longer clear (Tsuda *et al.,* 1989). A rare tumour of the liver, hepatic angiosarcoma, has also been observed in patients ingesting arsenicals (arsenite as Fowler's solution) for medicinal purposes (Falk *et al.,* 1981; Popper *et al.,* 1978; Lander *et al.,* 1975; Regelson *et al.,* 1968; Roat *et al.,* 1982). Similarly, lung cancer has been reported in patients ingesting arsenic medicinals (Robson and Jelliffe, 1963).

2.4.4 Ecotoxicology

There is an extensive data base on effects of inorganic arsenic on aquatic organisms. Results of studies suggesting particular sensitivity to dissolved arsenic are summarized in Figure 1. The most sensitive response to dissolved arsenic was observed in the marine alga *Skeletonema costatum,* in which productivity was reduced by 20-40% after exposure for 4 hours to 5 µg inorganic As(III) or As(V)/L and phosphate levels within the normal range for ocean waters (Sanders, 1979). Growth was reduced by about 40% in the freshwater alga *Scenedesmus obliquus* maintained for two weeks in a solution containing 10 µg of inorganic As(V)/L (Vocke *et al.,* 1980). Harmful effects of As(V) were diminished when phosphate concentrations were increased (Sanders, 1979; Thursby and Steele, 1984).

Adverse effects on estuarine and marine invertebrates have been reported at arsenic levels of 100 µg/L and above. A 15-day exposure to 100 µg As(V)/L as sodium arsenate significantly ($p < 0.05$) reduced (by about 25%) the survival of juvenile *Eurytemora affinis* (copepod); exposure to 50 µg As(V)/L produced no significant effect on survival (Sanders, 1986). The 96-h LC_{50} of arsenic trioxide for zoea larvae of

the Dungeness crab, *Cancer magister,* was 232 µg As(III)/L, while the 48-h EC_{50} of sodium arsenite for abnormal development for embryos of the Pacific oyster, *Crassostrea gigas,* was found to be 326 µg As(III)/L (Martin *et al.,* 1981).

Adverse effects have been observed in freshwater invertebrates exposed to over 500 µg As/L. Exposure to 520 µg As(V)/L as sodium arsenate for three weeks caused a 16% impairment in reproduction in *Daphnia magna,* while the 21-day LC_{50} was 2 850 µg As(V)IL (Biesinger and Christensen, 1972). The 48-h EC_{50} of arsenic trioxide for immobilization in the midge, *Chironomus tentans,* was 680 µg As(III)/L (Khangarot and Ray, 1989), while the 96-h LC_{50} of sodium arsenate to the cladoceran, *Bosmina longirostris,* was 850 µg As(V)IL (Passino and Novak, 1984).

Exposure for six months to 300 µg As(III)/L as arsenic trioxide resulted in a small but statistically significant reduction ($p = 0.05$) in smolt out-migration (from 91% to 80%) of coho salmon, *Oncorhynchus kisutch* (Nichols *et al.,* 1984). The 7-day LC_{50} for goldfish eggs (*Carassius auratus*) was reported to be 490 µg inorganic As(III)/L, while the 21-day LC_{50} for rainbow trout eggs *(Oncorhynchus mykiss)* was 540 µg inorganic As(III)/L (Birge, 1978). Acute LC_{50} s for other species of fish (both young and adults) have been reported to range from 1 100 to 28 500 µg As(III)/L. Rainbow trout (*Oncorhynchus mykiss*) fed 30 mg As(III)/kg as sodium arsenite in the diet for eight weeks had lower blood-haemoglobin levels (reduced by 25%) and weights (reduced by 30%) than controls (Oladimeji *et al,* 1984).

Amphibians may be quite sensitive to arsenic, with concentrations as low as 40 µg As(III)/L (as sodium arsenite) causing death (after 7-day exposure) in 50% of exposed embryo-larvae of the toad *Gastrophryne carolinensis* (Birge, 1978). An 8-day LC_{50} of 4 450 µg inorganic As(III)/L was reported for embryo-larvae of the marbled salamander *Ambystoma opacum* (Birge *et al.,* 1978).

Information on effects of exposing benthic organisms to sediment-bound arsenic (typically measured after strong-acid extraction) is summarized in Figure 2. A decline in sediment microbial populations has been observed at concentrations exceeding 100 mg inorganic

As(III)/kg (Huysmans and Frankenberger, 1990). Luminescence was reduced in the marine bacterium *Photobacterium phosphoreum* ($p < 0.05$; Microtox test), at concentrations above 700 mg As/kg in contaminated sediment from Puget Sound, in Washington State (Tetra Tech Inc., 1986). Based on comparison of field data on the presence (or absence) of benthic species at various sites to concentrations of arsenic in associated sediment, the Ontario Ministry of the Environment has estimated that the majority of freshwater benthos in the Great Lakes region are adversely affected by 33 mg As/kg dw of sediment (Jaagumagi, 1990). Significant reductions ($p = 0.05$) in the abundance of higher level benthic infauna (Polychaeta, Mollusca, Crustacea) were noted in marine sediment from Puget Sound at concentrations above 57 mg As/kg dw (Barrick *et al.,* 1988). Significant increases ($p = 0.05$) in mortality of amphipods (*Rhepoxynius abronius*) [10-d exposure] and oyster (*Crassostrea gigas)* larvae abnormalities (48-hr exposure) were reported in Puget Sound sediment at concentrations above 93 and 700 mg As/kg dw, respectively (Tetra Tech Inc., 1986). Toxic effects have also been reported in marine benthos in Commencement Bay, Washington, and San Francisco Bay, California, at concentrations in the 50 to 60 mg As/kg range and higher (Long and Morgan, 1990).

Effects of exposure to arsenic in soil on selected terrestrial organisms are summarized in Figure 3. In one study with earthworms, 100% mortality was reported for *Eisenia fetida* exposed to sodium arsenite at a nominal concentration of 200 mg As(III)/kg for 14 days in an artificial soil; 100 mg As(III)/kg had no effect on survival (Bouche *et al.,* 1987).

Some vascular plants are also quite sensitive to soil arsenic; for example, growth was reduced by 40-60% in green beans *(Phaseolus vulgaris)* in soil containing 10 mg As(V)/kg and 25 mg As(III)/kg [nominal or strong acid-extractable values] (Jacobs *et al.,* 1970; Woolson, 1973). Spinach plants (*Spinacia oleracea)* exhibited a growth reduction of about 40% when exposed to a nominal concentration of 10 mg As(V)/kg (Woolson, 1973). Adverse effects were more highly correlated with weak than with strong acid-extractable arsenic content of soil (Woolson, 1973).

Birds are most sensitive to arsenic in early life stages. For example, sodium arsenite was found to be extremely toxic in chicken (*Gallus gallus*) eggs, reducing hatchability by 65% at injected concentrations of 0.001 mg As(III)/kg egg yolk, and causing 50% mortality at about 0.05 mg As(III)/kg egg yolk (Birge and Roberts, 1976). Teratogenicity was observed when eggs were dosed at or above 0.05 mg As(III)/kg-bw. Inorganic arsenite poisoning in nestlings and adult birds is marked by muscular debilitation and incoordination, fluffed and huddled position, immobility and seizures (Eisler, 1988). Camardese *et al.* (1990) found that one-day-old Mallards (*Anas platyrhynchos*) fed a diet containing 300 mg As(V)/kg added as sodium arsenate for ten weeks showed increased resting times, which could increase susceptibility to predators in the wild. Oral LD_{50} values were reported to be about 25, 185 and 220 mg As(III)/kg-bw as sodium arsenite for the California Quail (*Lophortyx californicus*), Mallard Duck and Ring-necked Pheasant (*Phaisianus colchicus*), respectively (Hudson *et al.,* 1984).

Arsenic ingestion has also been shown to adversely impact some hormonally mediated behaviours in mammals. Mortalities were recorded in white-tailed deer (*Odocoileus virginianus*) following consumption of browse contaminated with arsenical pesticides (Swiggart *et al.,* 1972; Mathews and Porter, 1989).

3.0 Assessment of "Toxic" under CEPA

3.1 CEPA 11(*a*): Environment

As described in Section 2.3.2, arsenic has been detected in Canadian air, surface and ground waters, sediment, soil and biota. Most of the bioavailable arsenic in these media, with the exception of that in plant and animal tissue, is expected to be present as inorganic As(III) or As(V) species.

In order to determine if environmental levels of arsenic are sufficiently elevated to adversely affect Canadian wildlife, two scenarios were developed. As arsenic does not biomagnify in food chains, species exposed to high concentrations in the atmosphere or water are at greatest risk. The first scenario, therefore, focuses on areas near base-metal smelters, which can emit significant amounts of airborne arsenic. The second scenario examines exposure to arsenic near inactive gold mines with arsenic leaching into surface waters adjacent to tailings piles. In both cases, results of toxicological investigations with laboratory animals were extrapolated to small terrestrial mammals.

Based on experiments in which female rats were exposed to airborne arsenic (as arsenic trioxide) continuously for 3 months, the lowest reported NOAEL is 1.3 µg As/m^3. This value was divided by 10 to account for interspecies differences and differences between laboratory and field conditions, resulting in a tolerable concentration of 0.13 µg/m^3. The maximum annual mean concentration of arsenic measured in air near two Canadian base metal smelters is 0.30 µg As/m^3, which is more than double the estimated tolerable concentration. Thus, airborne arsenic has the potential to cause harmful effects in small mammals in regions of Canada where concentrations in air are elevated.

Mink (*Mustela vison),* a semi-aquatic opportunistic carnivore, was selected as a model species in a second wildlife scenario, based on exposure conditions near an abandoned gold mine on Mitchell Brook, near Waverley, Nova Scotia. Arsenic levels in tailings at this mine (typically about 4 000 mg/kg) are comparable to those reported in tailings from similar gold mines elsewhere in Canada. As indicated in Table 2, data on the mean arsenic content of air, water and fish along a 1.5 km stretch of Mitchell Brook were used to estimate a total daily intake of 109 µg inorganic As/kg-bw by local mink. The Lowest-Observed-Adverse-Effect level (LOAEL) reported to induce reproductive effects (reduced litter size) in chronically exposed mice is 1 500 µg inorganic As(III)/kg-bw [calculated by British Industrial Biological Research Association (1990) from data of Schroeder and Mitchener (1971)]. This LOAEL was divided by a factor of 100 (10 to

account for conversion from a LOAEL to a NOAEL, and 10 to account for interspecies differences and differences between laboratory and field conditions). This results in an estimated tolerable, daily intake (TDI) of 15 µg As/kg-bw, which is almost eight times lower than the estimated total daily intake (109 µg inorganic As/kg-bw) for mink. Therefore, exposure to inorganic arsenic has the potential to reduce populations of mink and possibly other fish-eating mammals near Canadian mines with arseniferous tailings that exhibit acidic drainage.

Table 2 Estimated Total Daily Intake of Inorganic Arsenic for a 1 Kg Adult Mink Living along M Waverley, Nova Scotia

Table 1 Footnotes

Table 3 Footnote a

Mean air concentration for Halifax area from Dann (1990); mean water and fish (*Fundulus dia* Freedman (1982); fraction of inorganic arsenic in freshwater fish (i.e., 0.23) estimated from da

Return to Table 3 Footnoteareferrer

Table 3 Footnote b

Rate of daily consumption data from Stahl (1967), for water from Calder and Braun (1983), ar that fish comprise 75% of mink diet.

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Medium	**Concentration** Table 2 Footnotea	**Daily Rate of Consumption** Table 2 Foo
Air	0.001 µg/m^3	0.55 m^3
Water	80 µg/L	0.1 L
Fish	2,784 x 0.23 = 640 µg/kg	0.158 kg
Total		

As indicated in Figure 1, the most sensitive chronic responses to inorganic arsenic reported in pelagic freshwater organisms are a 7-day LC_{50} of 40 µg As(III)/L for the narrow-mouthed toad (embryo-larval stage), and reduced growth in the alga *Scenedesmus obliquus* exposed for 14 days to a concentration of 10 µg As(V)/L. The highest mean concentrations recently reported for arsenic in Canadian

freshwater, about 45 µg/L (in Moira Lake, Ontario and Mitchell Brook, Nova Scotia), are above these chronic toxicity thresholds. It is likely, therefore, that pelagic organisms are adversely affected by exposure to arsenic in some Canadian freshwaters.

The data summarized in Figure 2 indicate that the lowest reported chronic effect level of sediment-bound arsenic on benthic freshwater organisms is 33 mg/kg (strong acid-extractable), which is expected to have a severe detrimental effect on species diversity. Average strong acid-extractable levels above this effect threshold, and up to 5 300 mg As/kg, have been reported recently in sediment from Canadian lakes near several precious-metal (principally gold) and base-metal mining and ore-processing facilities. It is likely, therefore, that benthic aquatic organisms are adversely affected by exposure to arsenic in freshwater sediment in Canada.

As shown in Figure 3, the most sensitive chronic response to inorganic arsenic in soil reported for terrestrial organisms is reduced growth in green beans at 10 mg As(V)/kg and 25 mg As(III)/kg (strong acid-extractable or nominal values). Soils contaminated with inorganic arsenic in Canada, including those near gold-mining and ore-roasting facilities, base-metal smelters, in orchards which had been treated with arsenical pesticides, and at a wood-preservation plant, have been reported to contain average strong acid-extractable arsenic concentrations of more than 25 mg As/kg and up to 6 240 mg As/kg. While samples from some contaminated areas were collected as many as 20 years ago, because arsenic binds strongly to iron oxides and clays (Frost and Griffin, 1977; Pierce and Moore, 1982; Korte and Fernando, 1991), concentrations are not expected to have changed appreciably during this time interval.

Terrestrial organisms are therefore expected to be adversely affected by exposure to arsenic in some Canadian soils.

The lowest reported effect level for arsenic in food for aquatic organisms was 30 mg inorganic As(III)/kg dw, which reduced weight gain in rainbow trout by 30% after exposure for 8 weeks. Given a dissolved arsenic level in Keg Lake of 545 µg/L in 1990, a reported bioconcentration factor of about 64 for arsenic in Keg Lake

zooplankton, and assuming that the water content of zooplankton is in the 90-95% range, the arsenic content in zooplankton in Keg Lake in 1990 is expected to have been in the 350 to 700 mg/kg dw range. If it is assumed, based on the limited data available, that only 5% of this arsenic was present as inorganic As(III), concentrations of inorganic As(III) in zooplankton near Yellowknife could have been as high as 35 mg/kg dw, which is above the 30 mg/kg dw effect threshold for rainbow trout. Thus, fish that regularly consume zooplankton in Keg Lake, and perhaps elsewhere, could be adversely affected by exposure to inorganic As(III).

Therefore, since organisms are exposed to inorganic arsenic in Canadian air, surface waters, sediments, soils and biota, at concentrations that are sufficiently high to cause, or to have the potential to cause, harmful effects, arsenic and its inorganic compounds are "toxic" as defined in paragraph 11(*a*) of CEPA.

3.2 CEPA 11(*b*): Environment on Which Human Life Depends

Because it occurs primarily in particulate form and at low concentrations in the atmosphere (typically about 0.001 µg/m^3), arsenic is not expected to contribute to global warming, depletion of stratospheric ozone, or other recognized environmental processes that could adversely affect human health.

Therefore, arsenic and its inorganic compounds are not considered to be "toxic" as defined in paragraph 11*(b)* of CEPA.

3.3 CEPA 11(*c*): Human Life or Health

The assessment of whether arsenic and its compounds are "toxic" to human life or health is considered to apply to the group of inorganic arsenic compounds as a whole, since available data did not permit an assessment of the risks posed by individual compounds on human health.

3.3.1 Population Exposure

Estimated daily intakes (on a body weight basis) of inorganic arsenic from environmental media by various age groups in the Canadian population are presented in Table 3. Ingestion in food represents the principal route of inorganic arsenic intake for all age groups, followed by dirt and soil in infants and children, and water and air for all age groups. Based on limited data on the relative proportion of inorganic arsenic in various foodstuffs, average daily intake from food ranges from < 0.02 to 0.6 µg/kg-bw/day. Intake in soil is estimated to range from 0.001 to 0.004 µg/kg-bw/day in adults to 0.03 to 0.08 µg/kg-bw/day in infants. Based on the limited monitoring data on the concentration of arsenic in the drinking water of Canadians, average daily intake of arsenic, which in surface-water supplies is predominantly in the pentavalent inorganic form, in this medium by each age group is usually less than 0.5 µg/kg-bw; however, intake of inorganic arsenic (both As(III) and As(V)) from drinking water may be higher from some ground water supplies. Average daily intake of arsenic from ambient air is estimated to range from 0.0003 to 0.0004 µg/kg-bw/day. Total daily exposure to inorganic arsenic from environmental sources ranges from 0.1 to 2.6 µg/kg-bw/day, with the greatest exposure being in young children. Cigarette smoking may contribute an additional 0.01 to 0.04 µg/kg-bw/day.

Intake of inorganic arsenic may be higher, however, in communities near point sources such as smelters, tailings areas, geological sources and areas with a history of arsenical pesticide application. Estimated intakes of inorganic arsenic for populations living near such point sources are presented in Table 4. These estimates are based on monitoring data from various geographical locations, and represent a highly unlikely "worst-case scenario," in which an individual is assumed to be exposed to contaminated air, water and soil. While data on levels of arsenic in ambient air and soil near smelters were obtained for several locations, only limited information was available on concentrations in drinking-water supplies. Although it is possible that intake in food may also be elevated for populations residing in the vicinity of industrial sources, available data were considered insufficient to quantitatively estimate intake from this medium for

populations under such conditions. Based on the estimates presented in Table 4, total daily intake of inorganic arsenic in such areas ranges from < 0.1 to 35 µg/kg-bw-day. Ingestion represents the principal route of exposure to arsenic, with contaminated ground water, soil and dust as well as food in the vicinity of point sources, contributing significant amounts to the daily intake of arsenic, particularly in children.

3.3.2 Effects

Based on available data, carcinogenicity is considered to be the most sensitive endpoint for assessment of "toxic" for arsenic under CEPA. Although non-cancerous dermatological effects, possibly peripheral vascular diseases and neurotoxic effects (occupational), have been observed in epidemiological investigations of occupationally exposed populations or those ingesting drinking water containing high concentrations of arsenic, such effects have generally only been observed at levels associated with estimated large excess risks of cancer. Similarly, although not generally considered to be a good model for some arsenic-induced effects in humans, adverse effects have been observed in animal species only at concentrations greater than those associated with estimated large excess risks of cancer in humans.

Excesses in mortality due to lung cancer have been associated with exposure to arsenic in numerous analytical epidemiological studies of workers in smelters and arsenical pesticide production facilities, with considerable evidence of an exposure-response relationship. Where it was possible to investigate the influence of possible confounders, such as concomitant exposure to sulphur dioxide or cigarette smoke, these factors have not explained this excess. In addition, in the populations for which exposure has been the most extensively characterized (i.e., three cohorts of workers employed at smelters in Washington, Montana and Sweden), there was a clear exposure-response relationship between airborne arsenic levels and mortality due to lung cancer (Enterline *et al.,* 1987a; Higgins *et al.,* 1986; Jarup *et al.,* 1989). Although not as well studied, there is also evidence that cancers at sites other than the lung, including the

stomach, colon, liver and urinary system, may be associated with occupational exposure to arsenic (Gibb and Chen, 1989).

Table 3 Estimated Average Daily Intake of Inorganic Arsenic by Canadians

Table 1 Footnotes

Table 3 Footnote a

Assumed to weigh 6 kg, breathe 2 m^3 of air per day and drink 0.1 L of water per day (EHD, 19 based on data from van Wijnen *et al* (1990), in which 0-1 year olds ingested approximately 70

Return to Table 3 Footnoteareferrer

Table 3 Footnote b

Assumed to weigh 13 kg, breathe 5 m^3 of air per day, drink 0.8 L of water per day (EHD, 1988 reported by Binder *et al*., 1986; Calabrese *et al.*, 1989; Clausing *et al.*, 1987; van Wijnen *et al.*

Return to Table 3 Footnotebreferrer

Table 3 Footnote c

Assumed to weigh 27 kg, breathe 12 m^3 of air per day and drink 1.1 L of water per day (EHD, midpoint between value for 1-4 year olds (50 mg/day) and that for adults (20 mg/day), i.e., 35

Return to Table 3 Footnotecreferrer

Table 3 Footnote d

Assumed to weigh 55 kg, breathe 21 m^3 of air per day, drink 1.1 L of water per day (EHD, 198 adults).

Return to Table 3 Footnotedreferrer

Table 3 Footnote e

Assumed to weigh 70 kg, breathe 20 m^3 of air per day, drink 1.5 L of water per day, and inges

Return to Table 3 Footnoteereferrer

Table 3 Footnote f

Based on a mean concentration of 5 µg/L; levels in most Canadian surface drinking-water sup concentrations in ground water often exceed 5 µg/L (Environment Canada, 1989a; 1989b; 198

Return to Table 3 Footnotefreferrer

Table 3 Footnote g

Estimates for age groups 0-0.5, 0.5-4, 5-11 and 12-19 years based on concentrations in various consumption patterns data (Nutrition Canada, 1977). Estimated intake for 20-70 year olds fron content of food is inorganic; although the percentages of total arsenic which is inorganic were determine the contribution of each food group to total dietary intake of inorganic arsenic, as th duplicate diet survey of Dabeka *et al.* (1987). Insufficient data were identified to estimate inta

Return to Table 3 Footnotegreferrer

Table 3 Footnote h

Based on the mean airborne arsenic concentration of 0.001 µg/m^3 in most Canadian cities surv

Return to Table 3 Footnotehreferrer

Table 3 Footnote i

Based on range of mean arsenic levels in various Canadian soil types of 4.8 to 13.6 ppm (Kab
arsenic present in soils is inorganic.

Return to Table 3 Footnoteireferrer

Table 3 Footnote j

Based on estimated arsenic content of mainstream cigarette smoke ranging from 40 to 120 ng
day.

Return to Table 3 Footnotejreferrer

Medium	**Estimated Daily Intake (µg/kg-bw/day)**	
	0-0.5 yr Table 3 Footnotea	**0.5-4 yr** Table 3 Footnoteb
Water Table 3 Footnotef	0.08	0.3
Food Table 3 Footnoteg	< 0.04-2.4	< 0.05-2.0
Air Table 3 Footnoteh	0.0003	0.0004
Soil/Dirt Table 3 Footnotei	0.03-0.08	0.02-0.05
Total	**0.1-2.6**	**0.3-2.4**
Tobacco Smoking Table 3 Footnotej	--	--

Table 4 Estimated Daily Intake of Inorganic Arsenic by Canadians Living Near Point Sources

Table 1 Footnotes

Table 3 Footnote a

Assumed to weigh 6 kg, breathe 2 m^3 of air per day and drink 0.1 L of water per day (EHD, 19
based on data from van Wijnen *et al.* (1990), in which 0-1 year olds ingested approximately 7

Return to Table 3 Footnoteareferrer

Table 3 Footnote b

Assumed to weigh 13 kg, breathe 5 m^3 of air per day, drink 0.8 L of water per day (EHD, 198
reported by Binder *et al.*, 1986; Calabrese *et al.*, 1989; Clausing *et al.*, 1987; van Wijnen *et al.*

Return to Table 3 Footnotebreferrer

Table 3 Footnote c

Assumed to weigh 27 kg, breathe 12 m^3 of air per day and drink 1.1 L of water per day (EHD, midpoint between value for 1-4 year olds (50 mg/day) and that for adults (20 mg/day), i.e., 35

Return to Table 3 Footnotecreferrer

Table 3 Footnote d

Assumed to weigh 55 kg, breathe 21 m^3 of air per day, drink 1.1 L of water per day (EHD, 198 adults).

Return to Table 3 Footnotedreferrer

Table 3 Footnote e

Assumed to weigh 70 kg, breathe 20 m^3 of air per day, drink 1.5 L of water per day, and inges

Return to Table 3 Footnoteereferrer

Table 3 Footnote f

Based on range of concentrations of arsenic of < 5 to 500 µg/L found in drinking-water suppli had concentrations above the upper end of this range (Bergeron, personal communication; Bru communication; Meranger *et al.*, 1984).

Return to Table 3 Footnotefreferrer

Table 3 Footnote g

Estimates for age groups 0-0.5, 0.5-4, 5-11 and 12-19 years based on concentrations in various consumption patterns data (Nutrition Canada, 1977). Estimated intake for 20-70 year olds fron content of food is inorganic; although the percentages of total arsenic which is inorganic were determine the contribution of each food group to total dietary intake of inorganic arsenic, as th duplicate diet survey of Dabeka *et al.* (1987). Insufficient data were identified to estimate inta concentrations of arsenic in foods consumed near point sources are insufficient to determine if above that of the general population.

Return to Table 3 Footnotegreferrer

Table 3 Footnote h

Based on the range of mean airborne arsenic concentrations near industrial point sources in re unpublished data; Noranda Mines, 1992; Paquin, unpublished data; Teindl, unpublished data;

Return to Table 3 Footnotehreferrer

Table 3 Footnote i

Based on range of recent concentrations of 3 to 500 mg/kg measured in soil, humus, peat or ho Frechette, 1987; Binder *et al.*, 1987; Brunswick Mining and Smelting Corporation, personal co data; Teindl, unpublished data; Zoltai, 1988) weighted to account for possible higher concentr concentrations of more than 10 000 mg/kg have recently been reported in soil near two arsenic to be a source of exposure for the community.) It was assumed that all of the arsenic present in

Return to Table 3 Footnoteireferrer

Table 3 Footnote j

It should be noted that these estimates are based on monitoring data from several different geo which the individual is assumed to be exposed to contaminated air, water and soil.

Return to Table 3 Footnotejreferrer

Medium	Estimated Daily Intake (µg/kg-bw/day)

	0-0.5 yr Table 4 Footnotea	**0.5-4 yr** Table 4 Footnoteb	**5-11 yr** Table Footnotec
Water Table 4 Footnotef	< 0.08-8.3	< 0.3-31	< 0.2-2
Food Table 4 Footnoteg	< 0.04-2.4	< 0.05-2.0	< 0.03-
Air Table 4 Footnoteh	0.003-0.07	0.003-0.085	0.004-(
Soil/Dirt Table 4 Footnotei	0.02-3.0	0.01-1.9	0.004-(
Total	**< 0.1-14**	**< 0.4-3.5**	**< 0.2-2**

Associations between the ingestion of arsenic in drinking water, or in the form of a medicinal, and skin cancer have also been observed in numerous case studies, case series and epidemiological investigations in Taiwan (Tseng, 1977; Tseng *et al.,* 1968; Chen *et al.,* 1985), Central and South America (Bergoglio, 1964; Biagini *et al,* 1974; Cebrian *et al.,* 1983; Zaldivar, 1974; 1977) and England (Philipp *et al.,* 1983). In the largest and most sensitive epidemiological study, which was conducted in Taiwan, there was an exposure-response relationship between the arsenic concentration of drinking water and the prevalence of skin cancer (Tseng, 1977; Tseng *et al.,* 1968). In addition, there is also more recent evidence of an association between the ingestion of drinking water containing high concentrations of arsenic and increased mortality due to various cancers of internal organs, including the bladder, kidney and lung, in exposed populations in Taiwan (Chen *et al.,* 1986; Wu *et al.,* 1989). Hepatic angiosarcoma (a rare tumour of the liver) and lung cancer have also been reported in patients ingesting arsenic medicinals (Falk *et al.,* 1981; Popper *et al.,* 1978; Lander *et al*., 1975*;* Regelson *et al.,* 1968; Roat *et al.,* 1982; Robson and Jelliffe, 1963).

The results of carcinogenicity bioassays, in which experimental animals have been administered arsenic compounds by ingestion or

inhalation, have been largely negative. Many of these studies, however, are considered to be inadequate by present-day standards, mainly due to insufficient numbers of exposed or control animals (British Industrial Biological Research Association, 1990). In some recent studies, increases in the incidence of primarily pulmonary adenomas were observed in hamsters following weekly intratracheal instillations of calcium arsenate for 15 weeks (Pershagen and Bjorklund, 1985; Yamamoto *et al,* 1987), whereas in other similar studies, results for arsenic trioxide, gallium arsenide and arsenic trisulphide were negative (Ohyama *et al,* 1988; Yamamoto *et al,* 1987; Pershagen and Bjorklund, 1985). Although not mutagenic, arsenic has been clastogenic in *in vitro* and *in vivo* bioassays and induces transformation in mammalian cells *in vitro.*

On the basis of documented carcinogenicity in human populations by more than one route of exposure (i.e., both inhalation and ingestion), "the group of inorganic arsenic compounds as a whole" 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, 1989).

For substances classified in Group I, where possible 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 tumours to characterize risk and provide guidance for further action (i.e., analysis of options to reduce exposure). These values, along with a brief discussion of the studies selected to form the basis for the quantitative estimation of carcinogenic potency and of the limitations of the estimates, are presented below. These issues are discussed more extensively in the Supporting Document.

The data considered most relevant to the quantification of the excess cancer potency associated with exposure to inorganic arsenic in the general environment are those obtained in epidemiological studies in humans. There is compelling evidence of the carcinogenicity of arsenic by more than one route of exposure in humans (inhaled in the

occupational environment and principally ingested in populations exposed in the general environment), whereas there is little evidence of carcinogenicity in experimental animals, possibly owing to the inadequacy of the investigations conducted to date or to the lack of a good animal model, particularly for arsenic-induced dermal lesions. In addition, use of the results of epidemiological studies to quantitatively estimate cancer potency obviates the need for interspecies extrapolation (which appears to be inappropriate in this case).

The studies that provide sufficient information to serve as a basis for quantitative estimation of the potency of arsenic to induce lung cancer are those of workers at the Tacoma copper smelter in Washington (Enterline *et al.,* 1987a), the Anaconda smelter in Montana (Higgins *et al.,* 1986) and the Ronnskar smelter in Sweden (Jarup *et al.,* 1989). These investigations involved fairly large cohorts (n = 2 802-8 044) of exposed workers, for which there was considerable information to serve as a basis for estimates of exposure. It should be noted, however, that no attempt has been made to validate the estimates of individual worker exposure provided in the accounts of these studies based on review of original records.

The study considered to be the most appropriate to provide a basis for quantification of the potency of arsenic to induce cancer following ingestion is that in which the prevalence of skin cancer was investigated in 40 421 individuals from 37 villages in Taiwan whose drinking water contained up to 1.82 ppm arsenic (Tseng *et al.,* 1968; Tseng, 1977). This study was based on a large number of individuals exposed to arsenic in the general environment, with prevalence rates being reported by exposure and age groupings. Sufficient information was reported such that an estimate of the average exposure in each group and the average age could be determined.

Detailed descriptions of the mathematical models employed for the quantification of cancer potency associated with exposure to arsenic via inhalation or ingestion are presented in the Supporting Document. A negative exponential growth curve was used to describe the concave-downward relationship between concentrations of arsenic in air and mortality due to respiratory cancer among workers for the Tacoma and Anaconda cohorts. This curve models the difference

between a linear effect in exposure and a negative exponential term. A linear model was used to describe the relationship between exposure to arsenic and lung-cancer mortality for the Ronnskar cohort. The predicted curves for the three cohorts are presented in Figure 4. Excess risk of respiratory cancer was obtained using the predicted curves and age-adjusted lung-cancer mortality rates for the Canadian population. The cancer potency was estimated by determining the constant concentration, which corresponds to a 5% increase in mortality due to respiratory cancer.

Excess risk of skin cancer due to ingestion of arsenic in drinking water was obtained from the Taiwanese cohort using a multistage model, which is a linear-quadratic function of arsenic exposure and a power function of age. This model included a term to describe the cancer-induction period (9 years for females and 7 years for males). Skin-cancer rates for the Canadian population and an average daily consumption of drinking water of 1.5 L/day were used to determine excess risk. The cancer potency was estimated to be the concentration corresponding to an increase in the prevalence of skin cancer of 5%.

Figure 4 Exposure-response Relationship for Inhaled Arsenic and Respiratory Cancer in Smelter Workers

[Relative risk (Observed/Expected) is plotted against cumulative lifetime arsenic exposure in air (*µ*g/m3-yrs) for the Ronnskar, Anaconda and Tacoma smelter. Relative risks are denoted by symbols and the predicted curves are denoted by solid lines.]

Based on data for the cohorts of Anaconda, Tacoma and Ronnskar smelter workers, estimates of respiratory cancer potency ($TD_{0.05}$s) for inhaled arsenic were 7.83, 10.2 and 50.5 µg/m ^{3}, respectively. Calculated exposure/potency indices for the mean concentration of arsenic reported in ambient air in several Canadian cities (0.001 µg/m^{3}) [Dann, 1990] are 1.3 x 10^{-4}, 9.8 x 10^{-4} and 2.0 x 10^{-5}. The priority for further action (i.e., analysis of options to reduce exposure) is, therefore, considered to be moderate to high. The

exposure/potency indices are higher, however, for residents in the vicinity of industrial sources, such as smelters. Based on the potency estimates for the three cohorts of smelter workers and the range of reported mean airborne arsenic concentrations in the vicinity of industrial sources of 0.0086 to 0.22 µg/m^3 in recent years, the estimated exposure/potency indices for these populations (the size of which was not determined for this assessment) are 1.1 x 10^{-3} to 2.8 x 10^{-2}, 8.4 x 10^{-4} to 2.2 x 10^{-2} and 1.7 x 10^{-4} to 4.4 x l0^{-3}. The priority for further action (i.e., analysis of options to reduce exposure) is, therefore, considered to be high.

Based on data obtained from the epidemiological investigation in the Taiwanese population, estimates of skin-cancer potency ($TD_{0.05}$s) were 906 and 844 µg/L for men and women, respectively.Calculated exposure/potency indices for a concentration of 5 µg/L (concentrations in most drinking-water supplies in Canada are below this value), are 5.5 x 10^{-3} and 5.9 x 10^{-3} for men and women, respectively. The priority for further action (i.e., analysis of options to reduce exposure) is, therefore, considered to be high. In areas with drinking-water supplies containing concentrations of arsenic up to 500 µg/L, such as have been measured in ground water supplies in some areas of Canada, the calculated exposure/potency indices are up to 5.5 x 10^{-1} and 5.9 x 10^{-1} for men and women, respectively. It should be noted, however, that only a very small proportion of the Canadian population is exposed to these high concentrations of arsenic in drinking water.

Intake of inorganic arsenic by the general population is greater in food than in drinking water. Estimated exposure/potency indices for intake in food cannot be presented, due to insufficient data on relative bioavailability of arsenic in food versus drinking water.

There are several limitations of the critical studies of occupationally exposed populations that should be borne in mind when interpreting the quantitative estimates of cancer potency associated with inhalation of arsenic. For example, concomitant exposure to sulphur dioxide was only addressed in two of the three studies (Enterline *et al.,* 1987a; Jarup *et al.,* 1989), and information on the smoking habits of the subjects was not presented in any of these studies. In addition, although the estimated potencies for the Tacoma and Anaconda

cohorts were similar, they were approximately five times smaller than that estimated on the basis of the Ronnskar study, owing largely to variations in standardized mortality ratios, particularly for the categories of lower cumulative exposure. This variability may be due to possible inaccuracies in exposure estimates (particularly in the lower exposure categories) and/or a different background rate of lung cancer in the United States compared to Sweden (Gibb, personal communication).

Similarly, the potency estimates for skin cancer associated with ingestion of arsenic in drinking water calculated above on the basis of the Taiwanese study (Tseng *et al.,* 1968; Tseng, 1977) may be overestimated, because of several methodological weaknesses, concomitant exposure to other compounds in the water in Taiwan which may have played a role in the etiology of skin cancer, possible dietary deficiencies of the Taiwanese population and intake of arsenic from other sources. In addition, it should be noted that based on data from the United States and Taiwan, < 1 to 14.7% of skin cancers are fatal, with the percentage for the U.S. being close to the lower end of the range. In the United States, less than 2% of patients with nonmelanoma skin cancer die from the disease (U.S. EPA, 1988). This must be borne in mind when comparing estimated potencies of skin cancer (based on the Taiwanese study) with those of more fatal internal cancers. Additional limitations of the quantitative aspects of the estimates of potency of skin cancer associated with ingestion of arsenic in water have been summarized by the U.S. EPA (1988).

It has also been hypothesized that there may be a threshold for the development of cancer in humans due to arsenic exposure, and that extrapolation of risks or potencies based on a model that is linear at low doses may be inappropriate (Marcus and Rispin, 1988). This supposition is based largely on limited results of short-term studies in four human volunteers, which indicate that methylation (i.e., detoxification) of inorganic arsenic is progressively, though not completely, saturated when daily intake exceeds approximately 500 µg (Buchet *et al.,* 1981). Only limited data concerning dose-dependent variations in metabolism following chronic exposure to arsenic in humans are available which, with the exception of one study for which

the results were unduly influenced by the assumption of zero for non-detectable values (Farmer and Johnson, 1990), indicate that even at background concentrations, methylation is far from complete (Smith *et al.,* in press). Moreover, available data indicate that humans may develop tolerance to high levels of arsenic in the occupational environment following long-term exposure, with the percentages of methylated metabolites being similar to those in the general population (Vahter, 1986). In addition, based on analysis of the results of available studies, it has been concluded that the inorganic arsenic content of the urine is relatively constant (approximately 20%), regardless of the level of exposure (Smith, personal communication).

It has also been suggested, on the basis of very weak evidence, that arsenic may act as an indirect gene-inducing carcinogen, for which linear extrapolation to estimate risks or potencies at low concentrations is inappropriate (Stohrer, 1991). Indeed, one of the principal arguments for this supposition has been the absence of adverse effects, such as cutaneous lesions or skin cancer, in small populations exposed to relatively low concentrations of arsenic in drinking water in the United States (Southwick *et al.,* 1983; Morton *et al.,* 1976). The lack of detection of effects in such studies is, however, consistent with the magnitude of the skin cancer risks estimated, based on the Taiwanese study. The hypothesis that arsenic acts as an indirect carcinogen is consistent with the observation that it is not mutagenic in *in vitro* or *in vivo* bioassays and with limited evidence that some compounds may act as tumour promoters in experimental animals (Shirachi *et al.,* 1986; 1987). It is not, however, consistent with the observation that arsenic induces damage in chromosomes. Based on data from the Anaconda and Tacoma smelters and application of the multi-stage theory of carcinogenesis, Brown and Chu (1983) and Mazumdar *et al.* (1989) have suggested that arsenic acts at a late stage in the carcinogenic process, although the possibility of an effect at an earlier stage could not be ruled out (Mazumdar *et al.,* 1989). Available data are insufficient, therefore, to support the hypothesis that arsenic acts as an indirect carcinogen.

Since "the group of inorganic arsenic compounds as a whole" is classified as "carcinogenic to man" (i.e., as non-threshold

toxicants, substances for which there is considered to be some probability of harm for the critical effect at any level of exposure), it is concluded that arsenic and its compounds (as specified here) are "Toxic" as defined under paragraph 11(*c*) of CEPA.

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 Conclusions

It is concluded that organisms are exposed to arsenic and its inorganic compounds in Canadian surface waters, sediments, soils and biota at concentrations which may be sufficiently high to cause harmful effects. "The group of inorganic arsenic compounds as a whole" has been documented to be carcinogenic in humans. Therefore, on the basis of available data, arsenic and its compounds (as specified here) are considered to be "toxic" under paragraphs 11(*a*) and 11(*c*) of CEPA.

4.0 Recommendations for Research and Evaluation

1. Collection of additional information on the historical exposure of workers to arsenic and potential confounders (e.g., cigarette smoking) in the occupationally exposed cohorts used as a basis for quantitative estimates of cancer potency could possibly improve the accuracy of the estimated potencies associated with inhalation of arsenic. Similarly, collection of information on exposure of the Taiwanese population to arsenic from sources other than drinking water, as well as information on the species of arsenic present in the Taiwanese drinking water, might also

improve the accuracy of the estimated cancer potencies associated with ingestion of arsenic.

2. It is also recommended that there be additional work to characterize more fully the risks of internal cancers associated with inhalation of arsenic in the occupational environment and with ingestion in drinking water in the general environment.
3. To permit a more accurate assessment of exposure of the Canadian popula tion to inorganic arsenic, better characterization of the relative proportions of inorganic and organic arsenic in various foodstuffs is desirable. As well, it would be desirable to collect additional data on the species of arsenic present in environmental media to which humans are exposed in Canada.
4. Owing to limitations of the existing data, most of which were obtained in early studies that are not acceptable by today's standards, it would be desirable to conduct additional reproductive/developmental studies in exposed human populations and experimental animals, as well as carcinogenicity bioassays in animal species, although the priority for this research is considered to be low.
5. It would be desirable to conduct additional research concerning arsenic methylation and its relationship to genetic, dietary or other lifestyle factors, particularly in the Taiwanese population, which served as a basis for the quantitative estimate of carcinogenic potency for ingestion.
6. It would be desirable to further investigate in analytical epidemiological studies the increase in the proportionate mortality ratio for lung cancer observed for men residing in the vicinity of the smelter in Rouyn-Noranda (Cordier *et al.,* 1983). Additional quantitative characterization of the exposure of the cohort of Ontario gold miners studied by Kuziak *et al.* (1991) to arsenic and other compounds would also be desirable.
7. To permit a more complete evaluation of the environmental effects of exposure to arsenic, it would be desirable to obtain additional data on the effects of different chemical forms of dissolved arsenic on aquatic organisms (particularly

amphibians), the effects of sediment-bound arsenic on benthic organisms and the effects of inhaled arsenic on birds.

8. In order to further evaluate the exposure of organisms to arsenic in the environment, it would be desirable to obtain additional information on the amounts, chemical forms and fate of arsenic in ores and waste material at Canadian mining and metallurgical operations, as well as data on the chemical forms of arsenic and their rates of production and degradation in Canadian water, soil, sediment and biota, particularly in contaminated areas.

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