Abridged Toxicological Profiles and Related Health Issues: Inorganic Antimony, Inorganic Arsenic, Beryllium, and Cadmium
(for Physicians)

March 30, 2001

By Evert Nieboer, Professor of Toxicology (McMaster University) and Environmental Medicine (University of Tromsø, Norway)
and Glenn G Fletcher, M.Sc., Research Assistant

McMaster University
Department of Biochemistry
Health Sciences Centre
1200 Main Street Street West
Hamilton, Ontario
Canada L8N 3Z5

Phone: (905) 525-9140 ext 22048
Fax: (905) 522-9033
Email: nieboere@mcmaster.ca

Preamble

The four elements included in the MOE risk assessment and reviewed in this document are either believed not be clearly or solely related to the INCO operation (beryllium, Be; cadmium, Cd; antimony, Sb) or do not exceed the MOE soil clean-up guidelines except at a few locations (arsenic, As). The profiles presented are therefore abridged and limited to a summary of the chronic health effects, biological exposure indices, and concluding remarks. A summary page is also provided for each element stating the public and occupational health issues and exposure guidelines (including biological exposure indices).

Antimony

Updated April 11, 2001

Public Health Issues

· None identified

Chronic Occupational Health Issues

· Pustular dermatitis
· Pneumoconiosis
· Electrocardiographic abnormalities
· Gastrointestinal complaints

Chronic Iatrogenic Exposures

- Electrocardiographic exposures
- Liver function alterations
- Hemolysis
- Acidosis
- Thrombocytopenia
- Pancreatitis

Exposure Guidelines

Occupational (8-hr TLV-TWA)

• Antimony and compounds, as Sb	0.5 mg/m^3
· Antimony hydride (Stibine)	0.1 ppm (is a gas)

General Public

· Reference doses (US EPA)	0.4 µg./kg/day (total) 0.2 µg/kg/m^3 (inhalation)	
·	Ambient Air Quality Criteria (MOE)	25 µg/m^3
· Soil Remediation Criteria (MOE) (generic, residential)	13 µg/g	

Chronic Health Effects

Health effects associated with exposure to antimony during its refining and use include

electrocardiographic changes, respiratory tract irritation, gastrointestinal complaints, dermatitis and pneumoconiosis (DeWolff, 1995; Lewis, 1997). Antimony trioxide and trichloride are strongly irritating to tissues and membranes. Stibene (SbH_3) is a gaseous form of antimony that is generated under very special conditions in industry, although it is present in some marsh gases (e.g., Feldman et al, 1998). It is a hemolytic toxin. Parenteral administration of pentavalent antimony-containing medicinal preparations has been associated with eletrocardiographic changes, alterations in liver function, hemolysis, acidosis, thrombocytopenia, and pancreatitis (DeWolff, 1995).

IARC and the US EPA have not evaluated antimony and its compounds in terms of their carcinogenic potential in humans. The reference doses of 0.4 µg/kg/day (total) and 0.2 µg/m^3 (inhalation, based on antimony trioxide) have been suggested by the US EPA (EPA, 1991, 1995).

Biological Exposure Indices

Inorganic antimony appears to be rapidly excreted in urine and feces; it is not methylated, unlike inorganic arsenic, and appears to undergo some enterohepatic circulation (Lauwerys and Hoet, 1993). Biliary excretion seems to be limited to trivalent forms of antimony, while pentavalent compounds occur via the urine. Trivalent antimony is taken up by red blood cells.

Background serum, blood and urine concentrations are low: respectively, 0.5 ± 0.1 µg/L (reference interval of 0.01-1.7 µg/L); 2.16 ± 0.45 µg/L (reference interval of 0.03-3.5 µg/L); 0.79 ± 0.07 µg/L (reference interval 0.19-1.1 µg/L (Minoia et al, 1990). Urinary antimony concentrations can serve as an index to exposure.

Concluding Remarks

The adverse health outcomes described are for occupational exposures to or medicinal use of antimony compounds. Even though the estimates of maximum daily intakes at the Port Colborne site (MOE, 2001) are at or slightly above the US EPA suggested reference dose of 0.4 µg/kg/day, it is highly unlikely that antimony constitutes a health concern. Based on the MOE calculations, (MOE, 2001), the site-related intakes correspond to about 4% of the total uptake by all routes. Occupational exposures associated with the health outcomes described were well above 1 mg/m^3 (ATSDR, 1992), thus providing a safety factor of at least 80,000 (1000/0.012); with 0.012 µg/m^3
the maximum Port Colborne air concentration observed; similarly, iatrogenic intakes of pentavalent antimonial drugs (e.g., sodium stibogluconate) were substantial (≥20 mg Sb(V) /kg/day for 20 to 30 days) (e.g., Gasser et al, 1994). Interestingly, this drug is still used today for the treatment of the protozoal infection leishmaniasis (Tracey et al, 1996).

References

ATSDR, 1992. *Toxicological Profile for Antimony*. Agency for Toxic Substances and Disease

Registry, Public Health Service, US Department of Health and Human Services, Atlanta, GA.

DeWolff FA, 1994. Antimony and health. *Br Med J* **310**: 1216-7.

EPA, 1991. Antimony. *IRIS (Integrated Risk Information System Online Database)*. Available at http://www.epa.gov/iris/

EPA, 1995. Antimony trioxide. *IRIS (Integrated Risk Information System Online Database)*. Available at http://www.epa.gov/iris/

Feldmann J, Koch I, Cullen WR, 1998. Complementary use of capillary gas chromatography-mass spectrometry (ion trap) and gas chromatography-inductively coupled plasma mass spectrometry for the speciation of volatile antimony, tin and bismuth compounds in landfill and fermentation gases. *Analyst* **123**: 815-20.

Gasser RA Jr, Magill AJ, Oster CN, Franke ED, Grögl M, Berman JD, 1994. Pancreatitis induced by pentavalent antimonial agents during treatment of Leichmaniasis. *Clin Infect Dis* **18**: 83-90.

Lauwerys RR, Hoet P, 1993. *Industrial Chemical Exposure Guidelines for Biological Monitoring, 2nd ed.* Lewis Publishers, Boca Raton, FL, pp 19-21.

Lewis R, 1997. Metals. *In:* J LaDou, *Occupational and Environmental Medicine*. Appleton and Lange, Stamford, CT, pp 405-39.

Minoia C, Sabbioni E, Apostoli P, Pietra R, Pozzoli L, Gallorini M, Nicolaou G, Alessio L, Capodaglio E, 1990. Trace element reference values in tissues from inhabitants of the European Community. 1. A study of 46 elements in urine, blood and serum of Italian subjects. *Sci Total Environ* **95**: 89-105.

MOE, 2001. *Soil Investigation and a Human Health Risk Assessment for the Residential Community West of INCO: Port Colborne (2000)*. Standards Development Branch, Ministry of Environment, Toronto, ON.

Tracey JW, Webster LT Jr, 1996. Drugs used in the chemotherapy of protozoal infections. *In*: JG Hardman, LE Limbird, PB Molenoff, RW Ruddon, AG Gilman (eds), *Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed.* McGraw Hill, New York, pp 987-1008.

Inorganic Arsenic

Public Health Issues (for high level, chronic ingestion)

- Skin and internal cancers
- Skin lesions
- Neurological outcomes
- Cardiovascular disease
- Gastrointestinal disorders

Chronic Occupational Health Issues

- Lung cancer and cancers at other sites
- Cardiovascular disease
- Neurological outcomes

Exposure Guidelines

Occupational (total aerosols; 8-hr TLV-TWA)

·	Arsenic, elemental and inorganic compounds, as As	0.01 mg/m^3

General Public

·	Ambient Air Quality Criteria (MOE)	? $\mu g/m^3$
· WHO Provisional Tolerable Daily Intake (PTDI)	2.0 µg/kg-bw/day	
· Soil Remediation Criteria (MOE) (generic, residential)	20 µg/g (25 µg/g for medium and fine textured soils)	

Body Fluids Reference Values and Biological Exposure Indices

- Background Concentration
  Urine: 8 ± 6 µg As/g creatinine (inorganic arsenic and its metabolites)

· End of workweek (inorganic arsenic plus methylated metabolites) (ACGIH)	35 µg As/L

Chronic Health Effects

Dermal Effects

Hyperkeratosis, hyperpigmentation and skin cancer have been associated with the consumption of drinking water containing inorganic arsenic. These clinicopathological findings have been documented for outbreaks in Taiwan, Japan, Argentina, Bangal, and Bangladesh (Bates et al, 1992; Chen et al, 1992; Hopenhayn-Rich et al, 1996; Mazumder et al, 1998; Smith et al, 2000). Concentrations above 50 µg/L in the drinking water were common, which is clearly in excess of the WHO maximum allowable level of 10 µg/L. Concentrations > 500 µg/L were not uncommon. Similar outcomes have also been traced to the medical use of Fowler's solution during the period 1809-1950, which contained 1% of potassium arsenite (3120 µg As/L). It constituted therapy for an extensive list of diseases including nutritional disorders (e.g., anorexia), neuralgia, rheumatism, diabetes, and hematological disorders (Gorby, 1994).

Internal Cancers

Epidemiological assessments of the drinking-water arsenic contamination incidents and the medicinal use of arsenite strongly suggest that ingestion of inorganic arsenic is linked to elevated risks of bladder, kidney, lung, and liver cancers (Bates et al, 1992; Chen et al, 1992). Inhalation of arsenic trioxide (As_2O_3) in copper smelters has also been associated with enhanced respiratory cancer risks and at other sites (e.g., Axelson et al, 1978; Enterline et al, 1987, 1995; Järup and Pershagen, 1991; Bates et al, 1992). Good linear relationships between lung cancer risk (standard mortality ratios, SMRs, of 100-800) and total urinary arsenic (100-1200 µg/L, corresponding to mean air levels of 200-1500 µg/m^3) have been reported (Enterline et al, 1987); the average duration of exposure was about 20 years.

IARC (1987) designates arsenic and arsenic compounds as carcinogenic to humans (Group 1).

Neurological Outcomes

Chronic exposure to arsenic by ingestion or inhalation has been associated with peripheral neuropathy, axonal degeneration and encephalopathy (Gorby, 1994; Lagerkvist and Zetterlund, 1994; Morton and Caron, 1989; Lewis, 1997; ATSDR, 1993, 2000). It appears that neurological outcomes are not seen for arsenic intakes ≤10 µg/kg/day (ATSDR, 1993, 2000).

Cardiovascular Disease

Vascular disease has been associated with occupational exposure and ingestion of arsenic. Copper smelter workers exposed to arsenic trioxide appear to have had increased risk of cardiovascular disease, although this has not been consistently found (ATSDR, 1993; Engel et al, 1994). Increased vasospastic reactivity (e.g., dependence of finger blood pressure on temperature) and the presence of Raynaud's phenomenon have also been reported (Lagerkvist et al, 1986; Engel et al, 1994). Estimates of workplace exposure levels at which this occurred were 0.05-0.5 mg As/m^3 (ATSDR, 1993). By contrast, severe peripheral vascular disease with gangrene and amputations have consistently been reported with the drinking-water contamination incidents described earlier (Engel et al, 1994; Smith et al, 2000). Ingestion rates of 14 to 65 µg As/kg/day are suspected (ATSDR, 1993, 2000).

Gastrointestinal and Hepatic Symptoms

Nausea, vomiting, diarrhea, anorexia, weight loss, hepatomegaly, jaundice, pancreatitis and liver cirrhosis have been reported for chronic intake of high levels of inorganic arsenic (Gorby, 1994). Exposure levels above 10 µg As/kg/day appear to be responsible (ATSDR, 1993, 2000).

Other Outcomes

Hematologic effects (e.g., anemia, leukopenia) appear to be common effects of chronic arsenic poisoning, while the kidney does not appear to be a major target organ (Gorby, 1994; ATSDR, 1993, 2000).

Biological Exposure Indices

Consumption of seafood can result in significant intake of arsenic because seafood contains organoarsenicals such as arsenobetaine and arsenosugars (Le et al, 1994). These compounds are considered to be nontoxic and are excreted rapidly and predominantly unchanged into the urine. Assessments of exposures to inorganic arsenic by monitoring urinary arsenic must take this into account. Consequently, chemical speciation must be considered. The major human metabolic pathway for inorganic arsenic is methylation, with dimethylarsinic acid (DMA) and monmethylarsonic acid (MMA) the major products. Consequently, these species need to be determined in urine along with unchanged inorganic arsenic consisting of arsenate and arsenite. The sum of these compounds is designated iAs-met. Typical background concentrations of iAs-met for non-exposed individuals is 8 ± 6 µg As/g creatinine (roughly equal to 10 ± 8 µg/L) (Vahter, 1986). The recommended biological exposure index for iAs-met at the end of the workweek for workers is 35 µg As/L (ACGIH, 2000).

Hair and nail arsenic concentrations also appear to be suitable indices for arsenic exposure in non-occupationally exposed individuals (Lauwerys and Hoet, 1993).

Concluding Remarks

Like lead, arsenic compounds constitute systemic poisons. The intake levels at which no noncancer adverse outcomes are known appear to be ≤10 µg/kg/day . Gastrointestinal absorption rates of inorganic arsenic are not well established, but appear to be extensive for some compounds (ATSDR, 1993, 2000). Health Canada (1996) accepts the WHO provisional tolerable daily intake (PTDI) of 2.0 µg/kg-bw/day as inorganic arsenic. Based on the measured soil arsenic concentrations of Port Colborne properties, and the low solubility expected (1-2%), this PTDI should not be exceeded by the majority of residents. The intake for the small number of highly contaminated sites may exceed it. By contrast, the extrapolated cancer risk suggest that there may be a risk for most Port Colborne sites of skin and other cancers, although the uncertainties in the numerical estimate of 3/1000 based on the indicated PTDI and the suggested slope factor of 1.5×10^{-3} $(\mu g/kg\text{-}bw/day)^{-1}$ (EPA, 1998) can be argued to be significant. In fact, about one-third of this risk may be expected to occur for the normal background intake of inorganic arsenic of 0.12-0.70 µg/kg-bw/day by Canadians (PSL, 1993), which seems unrealistic. Risks of one per million or one-hundred thousand are usually considered acceptable. This criterion cannot be met in case of arsenic for the average Canadian.

Actual exposures to arsenic can be ascertained by measuring the inorganic arsenic and its metabolites in urine.

References

ACGIH, 2000. *2000 TLVs and BEIs*. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ATSDR, 1993. *Toxicological Profile for Arsenic (Update).* Agency for Toxic Substances and Disease Registry, Public Health Service, US Department of Health & Human Services, Atlanta, GA..

ATSDR, 2000. *Toxicological Profile for Arsenic (Update).* Agency for Toxic Substances and Disease Registry, Public Health Service, US Department of Health & Human Services, Atlanta, GA.

Axelson O, Dahlgren E, Jansson C-D, Rehnlund SO, 1978. Arsenic exposure and mortality: A case-referent study from a Swedish copper smelter. *Br J Ind Med* **35**: 8-15.

Bates MN, Smith AH, Hopenhayn-Rich C, 1992. Arsenic ingestion and internal cancers: A review. *Am J Epidemiol* **135**: 462-76.

Chen C-J, Chen CW, Wu M-M, Kuo T-L, 1992. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer* **66**: 888-92.

Engel RR, Hopenhayn-Rich C, Receveur O, Smith AH, 1994. Vascular effects of chronic arsenic exposure: A review. *Epidemiologic Reviews* **16**: 184-209.

Enterline PE, Henderson VL, Marsh GM, 1987. Exposure to arsenic and respiratory cancer: A reanalysis. *Am J Epidemiol* **125**: 929-38.

Enterline PE, Day R, Marsh GM, 1995. Cancers related to exposure to arsenic at a copper smelter. *Occup Environ Med* **52**: 28-32.

EPA, 1998. *IRIS (Integrated Risk Information System Online Database)*. Available at http://www.epa.gov/iris/

Gorby MS, 1994. Arsenic in human medicine. *In*: JO Nriagu, ed. *Arsenic in the Environment, Part II: Human Health and Ecosystem Effects (Advances in Environmental Science and Technology, Vol 27)*. John Wiley & Sons, New York, pp 1-16

Health Canada, 1996. *TDI/RDI/EDI Summary Values for Various Trace Elements*, Ottawa.

Hopenhayn-Rich C, Biggs ML, Fuchs A, Bergoglio R, Tello EE, Nicolli H, Smith AH, 1996. Bladder cancer mortality associated with arsenic in drinking water in Argentina. *Epidemiology* **7:** 117-24.
IARC, 1987. *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, IARC Monographs Supplement 7.* International Agency for Research on Cancer, Lyon, France, pp 100-106.

Järup L, Pershagen G, 1991. Arsenic exposure, smoking, and lung cancer in smelter workers–A case-control study. *Am J Epidemiol* **134**: 545-51.

Langerkvist BJ, Zetterlund B, 1994. Assessment of exposure to arsenic among smelter workers: A five-year follow-up. *Am J Ind Med* **25**: 477-88.

Langerkvist B, Linderholm H, Nordberg GF, 1986. Vasospastic tendency and Raynaud's phenomenon in smelter workers exposed to arsenic. *Environ Res* **39**: 465-74.

Lauwerys RR, Hoet P, 1993. *Industrial Chemical Exposure Guidelines for Biological Monitoring, 2nd ed.* Lewis Publishers, Boca Raton, FL, pp 21-8.

Le X-C, Cullen WR, Reimer KJ, 1994. Human urinary arsenic excretion after one-time ingestion of seaweed, crab, and shrimp. *Clin Chem* **40**: 617-24.

Lewis R, 1997. Metals. *In:* J LaDou, *Occupational and Environmental Medicine*. Appleton and Lange, Stamford, CT, pp 405-439.

Mazumder DNG, Haque R, Ghosh N, De BK, Santra A, Chakraborty D, Smith AH, 1998. Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. *Int J Epidemiol* **27**: 871-7.

Morton WE, Caron GA, 1989. Encephalopathy: An uncommon manifestation of workplace arsenic poisoning? *Am J Ind Med* **15**: 1-5

PSL, 1993. *Priority Substances List Assessment Report: Arsenic and its Compounds*. Environment Canada and Health Canada, Ottawa.

Smith AH, Lingas EO, Rahman M, 2000. Contamination of drinking-water by arsenic in Bangladesh: A public health emergency. *Bull World Health Org* **78**: 1093-1103.

Vahter M, 1986. Environmental and occupational exposure to inorganic arsenic. *Acta Pharmacol Toxicol* **59 (Suppl 7)**: 31-4.

Beryllium

Public Health Issues

· Dermatitis (remote possibility)
· Chronic beryllium disease (remote possibility)

Chronic Occupational Health Issues

· Tracheobronchitis, pneumonitis
· Granulomatous pulmonary disease
· Dermatitis (ulceration, granulomas)
· Upper airways irritant
· Lung cancer

Exposure Guidelines

Occupational (total aerosols: 8-hr TLV-TWA)

· Beryllium and compounds as Be	2 $\mu g/m^3$
· Beryllium and compounds as Be, intended change (ACGIH)	0.2 $\mu g/m^3$

General Public

· Reference dose (US EPA)	0.02 $\mu g/m^3$, non-cancer outcomes
· Unit inhalation risk (US EPA)	0.0024 $(\mu g/m^3)^{-1}$, cancer
· Ambient Air Quality Criteria (MOE)	0.01 $\mu g/m^3$
· Soil Remediation Criteria (MOE)	1.2 $\mu g/g$

Chronic Health Effects

The health effects associated with beryllium exposure have been extensively reviewed in the following sources: IPCS (1990); ATSDR (2000); IARC (1993); Lauwerys and Hoet (1993); and Lewis (1997). Only the essential features are summarized here.

Acute beryllium disease (berylliosis) develops after many years of exposure or following a single acute exposure to metallic beryllium, beryllium alloys and beryllium oxide fumes. Mining of beryl ore has not been associated with adverse health effects. The respiratory tract symptoms range from mild nasopharyngitis to a severe chemical pulmonitis. The acute form has a short induction period, is of brief duration and resembles a chemical pneumonitis (Steenland and Ward, 1991). Few cases have been seen since the 1940s. The chronic form has a much longer induction period, and constitutes a progressive granulomatous disease which often results in reduced lung volumes, dyspnea, and diffuse irregular opacities on X-rays. It resembles a pneumoconioses (Steenland and Ward, 1991). Chronic beryllium disease involves Be-specific lymphocytes (CD4+ subset). Individuals carrying a version of a gene (allele) for a cell-surface glycoprotein that participates in antigen recognition involving the Be^{2+} ion are at higher risk than

others who do not have this version of a specific major compatibility complex (MHC) class II molecule (Newman, 1993; Richeldi et al, 1993). Thus chronic berylliosis is an example in which environmental and immunogenetic factors are responsible for an occupational disease.

Chronic beryllium disease has become rare since the adoption of stringent industrial hygiene measures (IARC, 1993). There is some suggestion that chronic berylliosis can develop in individuals not occupationally exposed but living near a beryllium-using facility for which air beryllium concentrations were estimated to be 0.01-0.1 $\mu g/m^3$ (IARC, 1993; ATSDR, 2000). The MOE ambient air quality criteria for beryllium and compounds is 0.01 $\mu g/m^3$, corresponding to the lower end of this range. The MOE estimates that the air levels at Rodney Street are well below this guideline (more than 40-fold), namely 0.00024 $\mu g/m^3$.

Not surprisingly, beryllium and its compounds also evoke dermal responses, including typical contact dermatitis, localized dermal ulceration or a subcutaneous granuloma. The latter response requires penetration of the skin by way of abrasion or a cut.

IARC (1993) designates beryllium and beryllium compounds as carcinogenic to humans (Group 1). Workers with a history of acute beryllium disease were at higher risk of developing lung cancer than those diagnosed with chronic berylliosis (Steenland and Ward, 1991; Ward et al, 1992).

Other than the dermal response, inhalation of beryllium and its compounds is responsible for the health effects described.

Biological Exposure Indices

Uptake of beryllium through the gastrointestinal tract and skin absorption likely contribute little to the total body burden. Inhalation exposure results in long-term storage in lung tissue and in the skeleton, which is the ultimate site of storage (IPCS, 1990; Lauwerys and Hoet, 1993). Elimination of absorbed beryllium mainly occurs by way of urine and to a minor extent in the feces. Beryllium can be determined in blood and urine, although the relationship of the concentrations in these fluids to exposure is not well understood (Lauwerys and Hoet, 1993). For example, renal excretion appears slow and variable (Lewis, 1997); the biological half-life has been estimated to be 2 to 8 weeks (ATSDR, 2000). However, body fluid beryllium concentrations can serve as a non-quantitative index to exposure since background levels are low: serum, 0.15 ± 0.01 µg/L with a reference interval of 0.03 - 0.27 µg/L; urine, 0.40 ± 0.09 µg/L with a reference interval of 0.04-0.76 µg/L (Minoia et al, 1990).

Concluding Remarks

It is reasonable to conclude that beryllium exposure and its adverse health consequences are not an issue at the Port Colborne site. This conclusion is based on a number of lines of evidence. First, inhalation is the critical uptake pathway in terms of adverse health outcomes and the estimated air levels (0.00024 $\mu g/m^3$) are well below any health guidelines such as those issued by the US EPA (EPA, 1998) (e.g., 0.02 $\mu g/m^3$ for non-cancer effects and unit risk of 0.0024 ($\mu g/m^3$)$^{-1}$ for respiratory cancer corresponding to an absolute risk below one in a million at the estimated air concentrations). Second, the estimated air concentrations also are well below the MOEs ambient air quality criteria of 0.01 $\mu g/m^3$.

Third, in the MOEs soil investigation report (MOE, 2001), the strong correlation between beryllium and aluminum levels in the soil clearly indicates that beryllium is associated with dust generated from rocks, soil and or even coal judging by the aluminum/beryllium content ratio observed (Bowen, 1979).

References

ACGIH, 2000. *2000 TLVs and BEIs*. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ATSDR, 2000. *Toxicological Profile for Beryllium (Update)*. Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services, Public Health Services, Atlanta, GA.

Bowen HJM, 1979. *Environmental Chemistry of the Elements.* Academic Press, London.

EPA, 1998. *IRIS (Integrated Risk Information System Online Database)*. Available at http://www.epa.gov/iris/

IARC, 1993. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 58: Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry*. International Agency for Research on Cancer, World Health Organization, Lyon, France.

IPCS, 1990. *Environmental Health Criteria Vol 106: Beryllium*. International Programme on Chemical Safety, World Health Organization, Geneva.

Lauwerys RR, Hoet P, 1993. *Industrial Chemical Exposure Guidelines for Biological Monitoring, 2nd ed.* Lewis Publishers, Boca Raton, FL, pp 29-31

Lewis R, 1997. Metals. *In*: J LaDou, *Occupational & Environmental Medicine, 2nd ed.* Appleton & Lange, Stamford, Connecticut, pp 410-12.

Minoia C, Sabbioni E, Apostoli P, Pietra R, Pozzoli L, Gallorini M, Nicolaou G, Alessio L, Capodaglio E, 1990. Trace element reference values in tissues from inhabitants of the European Community. 1. A study of 46 elements in urine, blood and serum of Italian subjects. *Sci Total Environ* **95**: 89-105.

MOE, 2001. *Soil Investigation and a Human Health Risk Assessment for the Residential Community West of INCO: Port Colborne (2000)*. Standards Development Branch, Ministry of Environment, Toronto, ON.

Newman LS, 1993. To Be^{2+} or not to Be^{2+}: Immunogenetics and occupational exposure. *Science 262*: 197-8.

Richeldi L, Sorrentino R, Saltini C, 1993. HLA-DPB1 Glutamate 69: A genetic marker of beryllium disease. *Science* **262**: 242-4.

Steenland K, Ward E, 1991. Lung cancer incidence among patients with beryllium disease: A cohort mortality study. *J Natl Cancer Inst* **83**: 1380-5.

Ward E, Okun A, Ruder A, Fingerhut M, Steenland K, 1992. A mortality study of workers at seven beryllium processing plants. *Am J Ind Med* **22**: 885-904.

Cadmium

Public Health Issues

· Renal function perturbations
· Bone fracture risk

Chronic Occupational Health Issues

· Chronic obstructive lung disease
· Reduced lung function
· Renal damage
· Bone diseases
· Lung cancer

Exposure Guidelines

Occupational (8-hr TLV-TWA)		
· Cadmium, elemental and compounds, as Cd	0.01 mg/m^3 (total) 0.002 mg/m^3 (respirable fraction)	
General Public		
·	Ambient Air Quality Criteria (MOE) (cadmium and compounds)	20 $\mu g/m^3$
· Soil Remediation Criteria (MOE) (generic, residential)	12 µg/g	
· Reference dose (US EPA)	1.0 µg/kg/day for food	
Biological Exposure Indices		
· BEIs (ACGIH)	5 µg/g creatinine in urine 5 µg/L in blood	

Chronic Health Effects

The chronic health issues associated with exposures to cadmium and its compounds are well documented in the following sources: Friberg et al, 1985, 1986; IPCS, 1992; IARC, 1993; ATSDR, 1998; EPA, 1998; Järup et al, 1998. Only the salient features are summarized below and a special focus

is provided on the public health implications.

High level chronic exposure in occupational settings has been associated with respiratory diseases (reduced lung function, chronic obstructive lung disease), kidney damage, bone lesions and lung cancer. Of these adverse health outcomes, nephrotoxicity is most relevant to public health. It involves both renal tubular dysfunction and glomerular permeability (Lauwerys and Hoet, 1993; Lauwerys et al, 1994). In cross-sectional population studies (Buchet et al, 1990; Staessen et al, 1994) and a prospective population study (Staessen et al, 1999), the renal function of residents of six districts (total population of approximately 10,000) surrounding three zinc smelters was compared to that of inhabitants of four control districts (also total population of approximately 10,000) that were more than 10 km away from the smelters and were less polluted by cadmium. "After standardization for several possible confounding factors, five variables (urinary excretion of retinol-binding protein, N-acetyl-ß-glucosaminidase, ß-microglobulin, amino acids and calcium) were significantly associated with the urinary excretion of cadmium (as a marker of cadmium body burden), suggesting the presence of tubular dysfunction" (Buchet et al, 1990). In a follow-up study (Staessen et al, 1994), these nephrotoxic markers in urine were again found to be elevated in the six polluted areas, as well as a reduction in creatinine clearance and serum zinc and an increase in serum creatinine,. "In all 10 districts, cadmium in the soil was positively correlated with cadmium in celery ($r=0.77$), in beans ($r=0.67$), and in residents' urine ($r=0.76$). The creatinine clearance was inversely correlated with cadmium in soil ($r= -0.78$), in celery ($r= -0.90$), and in beans ($r= -0.70$)" (Staessen et al, 1994). In a prospective 7-year follow-up study of the same populations, Staessen et al (1999) found that "cadmium excretion in the districts near smelters was 22.8% higher ($p=0.001$) than in other districts", and there was a significant difference in bone fracture rates in women ($p<0.007$) and a non-significant increase ($p=0.08$) of height loss in men. Across the 10 districts, mean cadmium concentrations in soil ranged 0.8 to 14.7 µg/g and 0.1 to 4.0 µg/g (dry weight) in vegetables.

Biological Exposure Indices

Cadmium concentrations in whole blood and urine are good, but different indices of exposure. Because of its unique metabolism involving the protein metallothionein, cadmium accumulates in the liver and kidneys and is released from these organs with a long half-life of ≥10 years (Friberg et al, 1985, 1986). Cadmium in urine reflects the accumulated cadmium and thus the body burden. By contrast, cadmium in blood represents more recent exposure and exhibits a half-life of 40-90 days (Nieboer et al, 1999).

For individuals with blood and urinary cadmium levels within the reference intervals established for the general Canadian population (i.e., < 2 µg Cd/g creatinine in urine and < 6 µg Cd/L in blood for smokers, compared to < 1 µg/g creatinine in urine and < 2 µg/L in blood for non-smokers) (Nieboer and Fletcher, personal assessment; also see Health Canada, 1995), the risk of cadmium-related renal dysfunction is low or nonexistent. Empirical models predict a 10% probability of subclinical renal dysfunction (e.g., micro proteinuria) for individuals with urinary cadmium in the range 1.0-2.0 µg Cd/g creatinine and blood levels ≥ 5.6 µg/L (Järup et al, 1988; Buchet et al, 1990; ACGIH, 1991). It is apparent that the largest single source of cadmium exposure is through cigarette smoking and that this alone can affect renal function. In a world-wide survey, Canadian cigarettes had the second highest cadmium content (1.57 ± 0.08 µg/cigarette) (Watanabe et al, 1987). Based on the Belgian studies reviewed, the general public may be at some minor risk in communities with zinc/cadmium mining/refining operations (past

or present) or with extensive cadmium-products use or manufacturing (Kreis et al, 1992; Staessen et al, 1994, 1999), since adverse renal function changes correlated positively with concentrations of cadmium in soil and vegetables. Some concern may also be warranted for subpopulations with unique dietary practices that include, for example, significant consumption of kidney or liver (e.g., from marine mammals or wildlife; Glooschenko et al, 1988; Crête et al, 1989) or aquatic macrophytes such as wild rice (Pip, 1993) that have a known potential for accumulating cadmium even in non-polluted environments. Consumption of fish fillet (i.e., muscle tissue) does not appear to make a significant contribution. In addition to smoking habits (past and present), age, and unique diets, statistical analysis of community-based studies must consider possible occupational exposure and environmental factors (i.e., place of residence) as predictors of cadmium levels in urine and whole blood (Nieboer, 1995; Sartor et al, 1992).

The ACGIH (2000) continues to recommend the biological exposure index (BEI) of cadmium in urine of occupationally exposed individuals as 5 µg/g creatinine (or 5 µmol/mol creatinine) and 5 µg/L in blood. In promulgating this BEI, it was concluded that even though subclinical renal changes such as micro-proteinuria remain within the normal range, they are predictive of exacerbating the age-related decline in renal function (ACGIH, 1991).

Concluding Remarks

The mean cadmium soil levels observed at the Port Colborne site (around 1.2 µg/g) are at the lower end of those in the Belgian studies reviewed. Consequently, on average the impact of cadmium exposure on renal function might be expected to be minimal. However, the maximum levels of 5.1 µg/g (depth of 0-5 cm) and 35.3 µg/g (5-30 cm) do indeed fall within the range of the Belgian concentrations reported in the 1994 study of 4.86 (0.40-70.50) µg/g corresponding to the "high exposure" contaminated sites and 0.81 (0.20-5.50) µg/g for the more remote districts designated as having "low exposure" (Staessen et al, 1994). It seems prudent therefore to consider clinical chemistry assessments involving the renal parameters mentioned for residents living on the more contaminated sites. If proximal tubule and glomerular perturbations can be discerned, the parameters assessed may be expected to be in the normal range, but shifted towards the upper end of the reference intervals for unexposed, healthy, non-smoking individuals and taking into account age.

References

ACGIH (American Conference of Governmental Industrial Hygienists), 1991. Notice of intended changes–cadmium, methyl isobutyl ketone, and trichloroethylene. *Appl Occup Environ Hyg* **6**: 703-11.

ACGIH, 2000. *2000 TLVs and BEIs*. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ATSDR, 1998. *Toxicological Profile for Cadmium (Update)*. Agency for Toxic Substances and Disease Registry, US Public Health Service, Atlanta, GA.

Buchet JP, Lauwerys R, Roels H, Rernard A, Bruaux P, Claeys F, Ducoffre G, de Plaen P, Staessen J, Amery A, Lijnen P, Thijs L, Rondia D, Sartor F, Saint Remy A, Nick L, 1990. Renal effects of cadmium body burden of the general population. *Lancet* **336**: 699-702.

Crête M, Nault R, Walsh P, Benedetti J-L, Lefebvre MA, Weber J-P, Gagnon J, 1989. Variation of cadmium content of caribou tissues from northern Québec. *Sci Total Environ* **80**: 103-12.

EPA, 1998. *IRIS (Integrated Risk Information System Online Database)*. Available at http://www.epa.gov/iris/

Friberg L, Elinder C-F, Kjellström T, Nordberg GF (eds), 1985/86. *Cadmium and Health: A Toxicological and Epidemiological Appraisal. Volume 1: Exposure, Dose, and Metabolism; Volume II: Effects and Response*. CRC Press, Boca Raton, FL.

Glooschenko V, Downes C, Frank R, Braun HE, Addison EM, Hickie J, 1988. Cadmium levels in Ontario moose and deer in relation to soil sensitivity to acid precipitation. *Sci Total Environ* **71**: 173-86.

Health Canada, 1995. *A Handbook for Health Professionals*. Great Lakes Health Effects Program, Health Protection Branch, Health Canada, Ottawa, ON.

IPCS, 1992. *Environmental Health Criteria Vol 134: Cadmium.*. International Programme on Chemical Safety, World Health Organization, Geneva.

IARC, 1993. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 58: Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry*. International Agency for Research on Cancer, World Health Organization, Lyon, France.

Järup L, Berglund M, Elinder CG, Nordberg G, Vahter M, 1998. Health effects of cadmium exposure - a review of the literature and a risk estimate. *Scand J Work Environ Health* **24 (Suppl 1):** 1-51.

Järup L, Elinder CG, Spång G, 1988. Cumulative blood-cadmium and tubular proteinuria: A dose-response relationship. *Int Arch Occup Environ Health* **60**: 223-9.

Kreis IA, Wijga A, van Wijnen JH, 1992. Assessment of the lifetime accumulated cadmium intake from food in Kempenland. *Sci Total Environ* **127**: 281-92.

Lauwerys RR, Hoet P, 1993. *Industrial Chemical Exposure Guidelines for Biological Monitoring, 2nd ed.* Lewis Publishers, Boca Raton, FL, pp 32-8.

Lauwerys RR, Bernard AM, Roels HA, Buchet J-P, 1994. Cadmium: exposure markers as predictors of nephrotoxic effects. *Clin Chem* **40**: 1391-4.

Nieboer E, 1995. Unpublished results.

Nieboer E, Fletcher GG, Thomassen Y, 1999. Relevance of reactivity determinants to exposure assessment and biological monitoring of the elements. *J Environ Monit* **1**: 1-14.

Pip E, 1993. Cadmium, copper and lead in wild rice from central Canada. *Arch Environ Contam Toxicol* **24**: 179-81.

Sartor FA, Rondia DJ, Claeys FD, Staessen JA, Lauwerys RR, Bernard AM, Buchet JP, Roels HA, Bruaux PJ, Ducoffre GM, Lijnen PJ, Thijs LB, Amery AK, 1992. Impact of environmental cadmium pollution on cadmium exposure and body burden. *Arch Environ Health* **47**: 347-53.

Staessen JA, Lauwerys RR, Ide G, Roels HA, Vyncke G, Amery A, 1994. Renal function and historical environmental cadmium pollution from zinc smelters. *Lancet* **343**: 1523-7.

Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vagronsveld J, Fagard R, 1999. Environmental exposure to cadmium, forearm bone density, and risk of fractures: Prospective population study. *Lancet* **353**: 1140-4.

Watanabe T, Kasahara M, Nakatsuka H, Ikeda M, 1987. Cadmium and lead contents of cigarettes produced in various areas of the world. *Sci Total Environ* **66:** 29-37.