SUDBURY AREA RISK ASSESSMENT

VOLUME II – CHAPTER 6: OTHER RISK ASSESSMENT ISSUES

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6.0 OTHER RISK ASSESSMENT ISSUES

While conducting the Sudbury HHRA, a number of important issues were raised which required special consideration during the risk assessment process. These include:

- Special considerations in assessing the exposure of children to the Sudbury COC and the implications of the inherent toxicity of these substances to this sensitive lifestage;
- Implications of sulphur dioxide (SO_2) and acid precipitation on the mobility and toxicity of the COC, in an area historically impacted by SO_2;
- Potential impacts of occupational exposures for GSA residents;
- A discussion of the implications of metal-metal interactions, given that the COC can be present as complex mixtures in the environment;
- A brief review of soil ingestion rates in children and recommendations to address long-term "pica" behaviour within the risk assessment;
- Comparison of the U.S. EPA IEUBK lead exposure model results with lead exposure estimated by the HHRA;
- Implications of dermal sensitization to nickel for GSA residents;
- An overview of the epidemiology and community health status for the GSA, as it pertains to the COC evaluated in the HHRA;
- A discussion of lifetime exposure, and how the elderly are addressed within the HHRA as a potentially sensitive life stage; and
- Whether Sudbury residents are at an increased risk due to COC concentrations potentially accumulating within their bodies, leading to an elevated lifetime body burden.

These issues, in the context of the Sudbury HHRA, are discussed in detail in the following chapter.

6.1 Special Considerations for the Assessment of Children's Exposure and Toxicity

6.1.1 Introduction

For the assessment of risks from exposures to environmental chemicals, children[1] cannot be considered as small adults. Throughout childhood, children are growing and developing, and may be more susceptible to adverse effects from chemicals in the environment. As such, it is vital that the current HHRA takes into account the potential sensitivity of this subpopulation within the GSA as part of the Sudbury Soils Study.

Children have heightened vulnerability to chemicals for the following reasons:

- Children have disproportionately heavy exposures to many environmental agents;
- Children's metabolic pathways, especially in fetal life and in the first months after birth, are immature;
- Developmental processes are easily disrupted during rapid growth and development before and after birth; and
- Children have more years of future life and thus more time to develop diseases initiated by early exposures (NAS, 1993).

To address these issues, Daston *et al.* (2004) proposed a children's risk assessment framework modified from standard risk assessment frameworks and guidance (Figure 6-1).

[1] For the purpose of this discussion, the word "children" is used to include all stages of development, from conception through organ maturation in adolescence.

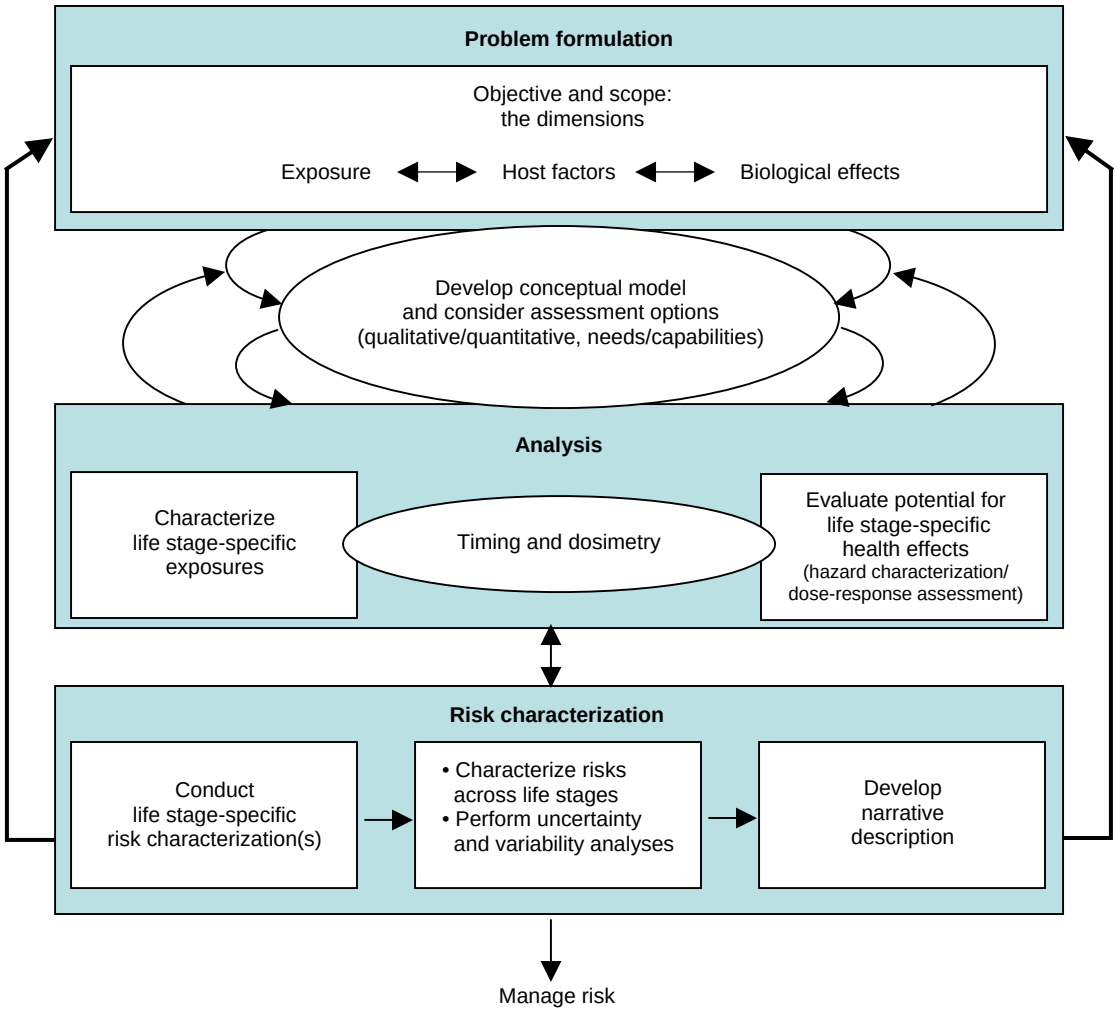

Figure 6-1 Proposed Framework for Assessing Risks to Children from Exposure to Environmental Agents (Daston *et al.*, 2004)

The issues of children's exposure and hazard, and how they have been addressed in the Study are discussed below.

6.1.2 Children's Exposure

Children's exposure to environmental chemicals is different from that of adults because their bodies and their behaviours are different. Children consume more food and water for their body mass, have higher inhalation rates for their body mass, and have higher surface area to volume ratios than adults (NAS, 1993; U.S. EPA, 2002a). In addition to factors related to their bodies, children have several unique exposure routes, and those they share with adults may be enhanced due to certain behaviours (Landrigan

et al., 2004). Uniquely, children can be exposed *in utero* and *via* breast milk (Landrigan *et al.,* 2004). In addition to these exposure routes, children play outside, play close to the ground, touch and taste objects more than adults do, all of which may increase their exposure to environmental chemicals relative to that of adults. Children may also ingest non-food items, sometimes to an extreme (*i.e.,* pica children), and may have a more limited diet than many adults due to life stage requirements or simply preference.

The exposure patterns of children may be addressed in risk assessment by estimating exposures for multiple age groups. However, the risk assessment community has not yet agreed on the most appropriate age groups for the assessment of children's exposure and/or risk (Ginsberg *et al.,* 2004; U.S. EPA, 2002a). It is likely that this is ideally determined on a case-by-case basis, as age groups can be defined based on changes in behaviour or on development of various organs and systems as is most appropriate for the assessment.

The U.S. EPA's (2002a) *Child-Specific Exposure Factors Handbook* provides data on exposure factors that can be used to assess doses from oral (dietary and non-dietary), dermal and inhalation exposures among children. The handbook provides data in the following areas:

- Breast milk ingestion;
- Food ingestion, including homegrown foods and other dietary-related areas;
- Drinking water ingestion;
- Soil ingestion;
- Rates of hand-to-mouth and object-to-mouth activity;
- Dermal exposure factors such as surface areas and soil adherence;
- Inhalation rates;
- Duration and frequency in different locations and various microenvironments;
- Duration and frequency of consumer product use;
- Body weight; and,
- Duration of lifetime.

Certain data points can also be determined by surveying a subset of the affected population. Such data have the advantage of being directly applicable to the population and account for any regional differences.

6.1.3 Children's Hazard and Risk Characterization

Internal Dose

Children's toxicokinetics (*i.e.,* adsorption, distribution, metabolism and excretion (ADME) of chemicals) differs from that of adults for four reasons:

1. Smaller body size;
2. Different ratios of fat, muscle and water within the body;
3. Higher breathing and metabolic rates per unit of body mass; and
4. The immaturity of clearance systems and enzymatic reactions (Ginsberg *et al.,* 2004).

To address differences in ADME across developmental stages, risk assessors can extrapolate from juvenile animal data and/or from data in adult humans; however, there is a need for suitable data from which to extrapolate, and for physiologically-based toxicokinetic models for children (Daston *et al.,* 2004). In many cases an incomplete database will limit risk assessors to a semi-quantitative approach using uncertainty factors (UFs).

The question to be answered in determining an appropriate child-protective UF is whether the differences between early life stages and adults can be considered as part of the overall human variability, and whether these substantial differences can be accounted for by the uncertainty factors designed to account for variability among individuals (*i.e.,* whether a child-protective UF of 1X is appropriate). As a group, children have greater variability in their toxicokinetics than a similar population of adults because they may be at different points in growth and maturation; therefore, it is more likely that variability among individual children *versus* that among individual adults will exceed typical UFs (Ginsberg *et al.,* 2004).

A survey of the recent literature indicated that the general consensus on UFs for internal dose in children should be determined on a case-by-case basis.

Toxicological Susceptibility

Children are developing and constantly changing, and they may experience different susceptibilities to chemical perturbation during organ development. A risk assessor should ask a series of questions in the problem formulation stage to determine if it's likely that children have a particular vulnerability to a chemical: Does the chemical cause known organ-specific toxicity; what organs are affected; how are

these organs potentially differentially susceptible during development; and, what are the specific time periods of concern (Daston *et al.,* 2004). If the chemical is known to affect particular organ systems, or particular processes, then critical windows of vulnerability can be identified when the organs are developing or the processes are active (Daston *et al.,* 2004). Summaries and discussions of these windows of susceptibility are available in the literature (*e.g.,* researchers listed by Daston *et al.*, 2004).

In addition to the potentially increased susceptibility of children discussed above, there is evidence in humans for the development of cancer in adults resulting from childhood exposures (U.S. EPA, 2005). There are also examples from animal studies of transplacental carcinogens and suggestions that altered development can affect later susceptibility to cancer induced by chemical exposures in adult life (U.S. EPA, 2005).

The U.S. EPA (2005) lists factors that potentially lead to increased childhood susceptibility to carcinogenic agents relative to adults:

- More frequent cell division during development can result in enhanced fixation of mutations due to the reduced time available for repair of DNA lesions, and clonal expansion of mutant cells gives a larger population of mutants;
- Some embryonic cells (*e.g.,* Brain cells) lack key DNA repair enzymes;
- Some components of the immune system are not fully functional during development;
- Hormonal systems operate at different levels during different life stages; and
- Induction of developmental abnormalities can result in a predisposition to carcinogenic effects later in life.

However, the U.S. EPA (2005) states that susceptibility differences with respect to early life stages may not be taken into consideration in the method generally used to estimate cancer risk from oral exposures based on a lifetime average daily dose.[2] In many cases, the cancer slope factors are based on effects seen following the exposures of mature animals (U.S. EPA, 2005). However, it is important to note that in some chronic animal studies, animals are segregated shortly after they are weaned (e.g., 6 to 8 weeks old for rodents), and after two weeks of acclimatization begin dosing. As such, study dosing would begin at an age that is roughly equivalent to human teenagers.

[2] Note that this method can account for differences in exposure between children and adults (U.S. EPA, 2005).

Due to this uncertainty, the U.S. EPA (2005) recommends using age-specific values for both exposure and toxicity/potency, where appropriate. They recognize, however, that age-specific slope factors are often not available, and have developed age-dependent adjustment factors (ADAFs) to be used to modify the general slope factors for chemicals with a known mutagenic mode of action (Table 6.1). The modified slope factors are to be combined with age-specific exposure information to characterize risk (U.S. EPA, 2005).

Table 6.1 Factors to Adjust the Slope Factors of Chemicals with a Known Mutagenic Mode of Action, in the Absence of an Age-Specific Slope Factor, to Account for the Generally Higher Cancer Risks Arising From Early-Life Exposures (U.S. EPA, 2005)

Adjustment	Age at Exposure
10-fold	< 2 years old
3-fold	2 to <16 years old
None	≥16 years old

Prior to the application of these adjustment factors, one must consider the mechanism of action for each chemical of concern. Adjustment of cancer potency estimates would only seem relevant for substances known to be early-acting carcinogens and those substances for which there is reason to suspect that children will act differently than adults (*i.e.,* absorption and metabolism often differs between children and adults). In these cases where clear indications are present to indicate that children may in fact be more sensitive the adjustment factors should be applied. Additionally, in cases where there is a lack of data to make this determination, it is prudent and conservative to apply these factors.

Risk Characterization

The most appropriate way to characterize children's risk is to compare age-specific exposure limits to exposure estimates derived for the same age group. Exposure limits developed specifically for a particular age group address both the differences in metabolism between children and adults, and the increased sensitivity of developing tissues. Depending on the design of the studies used to derive it, an age-specific exposure limit may also address the effects of exposure in early life on the future development of disease conditions. U.S. EPA (2005) recommends that age-specific exposure limits be used where available. Unfortunately, these limits are often not available, and other methods of addressing these issues must be used.

The U.S. National Academy of Sciences (NAS, 1993) recommended an approach to risk assessment that accounts for the heterogeneity of exposures (*i.e.,* use of exposure distributions not point estimates) and the potential for differential sensitivities at various life stages. It is standard RA practice to use an uncertainty factor to derive an RfD from a NOAEL of 100-fold, comprised of a 10-fold factor for uncertainty in interspecies extrapolation, and a 10-fold factor to accommodate variation within the human population. The NAS concluded that this factor generally provides adequate protection for children, but it may not always be sufficient to account for unique susceptibilities at particularly sensitive stages of early development. They decided then that in the absence of data to the contrary, greater risks to children relative to adults, should be presumed; and the NAS therefore recommended that a child-protective uncertainty factor of up to 10-fold be considered where there is either evidence of developmental toxicity, or data from toxicity testing relative to children are incomplete (NAS, 1993).

More recently, the U.S. EPA (2002b) described how they apply the child-protective UF in RAs of pesticides conducted under the Food Quality Protection Act (FQPA, 1996). The 10-fold child-protective UF (or a part thereof) is applied only where the adequacy and appropriateness of the toxicity assessment or the exposure assessment are judged to be insufficient. The child-protective UF is not necessary in all cases because the intent of the child-protective UF overlaps that of other 10-fold UFs (*e.g.,* the LOAEL to NOAEL, subchronic to chronic and database deficiencies factors). In most cases, these other factors are sufficient to account for risks to children. The decisions made by the U.S. EPA (2002b) to retain the 10-fold child-protective factor or to assign a different factor are informed by the conclusions of the risk characterization, that is, by all of the data concerning both the exposure and hazard of children, considered together in a "weight-of-evidence" approach. A reduced level of confidence in the hazard and exposure assessments, or any residual uncertainties in the risk characterization, indicate that a child-protective UF is necessary.

Ginsberg *et al.* (2004) examined the 10-fold uncertainty factor to accommodate variation within the human population a bit closer. Renwick (1998) states that this 10-fold factor consists of a half-log factor (3.16-fold) for toxicokinetic variability, and another 3.16-fold factor for pharmacodynamic variability; therefore, Ginsberg *et al.* (2004) reasoned that for the default UFs to be adequate, the inter-individual variability in toxicokinetics (from genetic, lifestyle, physiologic state and age) must all fit within a 3.16-fold factor. In other words, the upper and lower bounds of the children's distribution must be contained within the adult central tendency value, plus or minus a 3.16-fold UF; otherwise a child-protective UF (or other means of accounting for children's toxicokinetics) is needed.

Similarly, the pharmacodynamic variability (*i.e.,* the different susceptibilities of individuals of all age groups) must also all fit into a 3.16-fold factor, or a child-protective UF is needed to account for differing susceptibilities.

6.1.4 Summary

For the purpose of the current assessment, the U.S. EPA recommended uncertainty adjustments for toxicological susceptibility were conservatively applied to the evaluation of potential carcinogenic/mutagenic risks to each of the relevant modelled age stages, as follows:

- Infant (0 to <0.5 years) 10-fold UF
- Preschool Child (0.5 to <5 years) 10-fold UF
- Child (5 to 12 years) 3-fold UF
- Adolescent (12 to 19 years) 3-fold UF

It is important to remember that these UF values are intended to protect against carcinogens which have a mechanism of action relevant to the sensitive early life stages of the developing child, and are not relevant to late acting carcinogens. However, due to the uncertainty present for the mechanism of action for the current COC during these early life stages, these UFs were conservatively applied for the relevant life stages in the lifetime assessment of carcinogenic risk for arsenic, cobalt, and nickel in the current assessment.

Following a detailed evaluation of the toxicological information available for each of the COC (refer to Appendix A), it was determined that none of the evaluated COC appear to have particular concern unaddressed by existing UFs already applied during the development of the toxicological regulatory limit. In fact, the regulatory exposure limit developed for lead is actually developed to be protective of the various developing child life stages, and conservatively extended for the remaining life stages (*i.e.,* adolescent and adult). As such, no further UFs (beyond those already applied above) were added to the regulatory-established exposure limits used in the current assessment.

6.2 Sulphur Dioxide (SO_2)

Sulphur dioxide (SO_2) has long been an influencing factor on the landscape of Sudbury. While SO_2 has been specifically excluded as a COC for the current assessment, it is important to carefully consider the potential effects it may pose as a modifying factor to the existing COC.

Considerable study has historically been conducted into the impacts of SO_2 as a major precursor of acid precipitation. The phenomenon of "acid rain" occurs because sulphuric acid (H_2SO_4) may be formed from sulphur dioxide on contact with water, either in the atmosphere or on the surface. The phenomenon of acid rain is often considered as having two phases: 1) pre-deposition; and, 2) post-deposition (Goyer *et al.,* 1985). The pre-deposition human health effects of atmospheric SO_2 and acid precipitation are direct effects, which are probably related to the hydrogen ion (*i.e.,* to the acidity) (Goyer *et al.,* 1985). These effects range from constriction of bronchi and increased mucous production in the respiratory tract (at >250 ppb in healthy individuals or 25 ppb in asthmatics), to immediate danger to life and health (at 100 ppm) (ATSDR, 1998). However, these direct effects are not the subject of this discussion. The indirect, or post-deposition, effects of SO_2 and acid precipitation are of interest in the Sudbury area because acidification of soil and water can affect the speciation, mobility and solubility of metals.

There is no evidence that once deposited, sulphuric acid and acid-forming sulphur species represent a direct threat to human health; however, acidification of soil and water may mobilize metals from generally fixed sites (*e.g.,* ores and insoluble deposits) and increase total human exposure to these COC (Goyer *et al.,* 1985). Cations of various elements in the soil can be replaced by hydrogen ions (or various other ions) to cause their solubilization in water (Smith, 1992; Goyer *et al.,* 1985). Once removed from the soil matrix, these soluble ions may be transferred to media that contribute to human exposure (*e.g.,* water and food) (Goyer *et al.,* 1985). They may also be transformed to more toxic or bioavailable forms (Goyer *et al.,* 1985).

Some metals of toxicological significance that are affected by pH are aluminum, arsenic, cadmium, copper, lead, manganese, mercury and selenium (Elvingson and Ågren, 2004; Smith, 1992; Gerhardsson *et al.,* 1994). The solubility, and hence the availability and mobility of many metals is increased at lower pH values (Figure 6-2). Acidification also increases leaching of calcium, magnesium and potassium from soil (Smith, 1992). There are no data available associating the post-deposition effects of acid rain with human health effects; however, there are data to support increased exposure to toxic metals resulting from acid precipitation (Gerhardsson *et al.,* 1994).

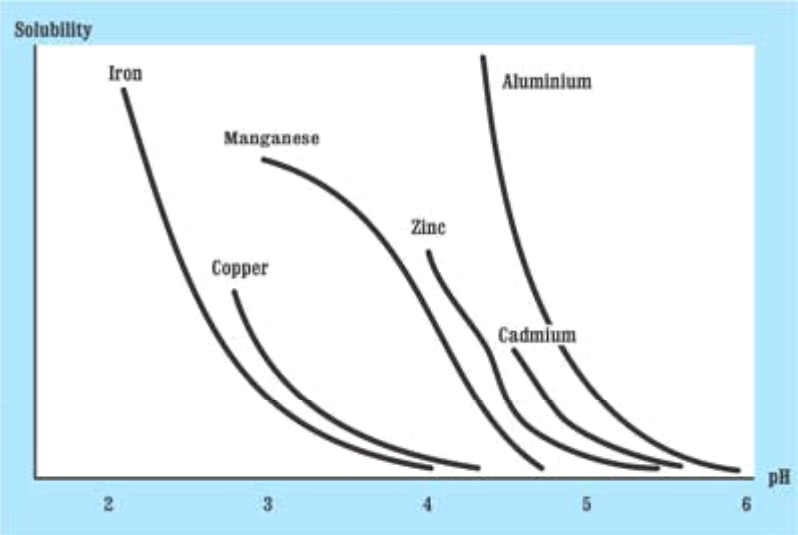

Figure 6-2 Release of Metals from Mineral Soil at Different pH Levels. [Elements with Steep Slopes in the Range Environmental pH Values, Such as Aluminum and Manganese, are Strongly Affected by Acid Precipitation (Elvingson and Ågren, 2004)]

Aluminum and manganese are particularly affected by the acidification of soil (Smith, 1992). The mobilization of aluminum can be of particular concern because it is very abundant in the earth's crust, particularly in sedimentary rocks (Goyer *et al.,* 1985). Mobilization of copper, lead and cadmium is also increased by acid precipitation, although to a lesser extent (Gerhardsson *et al.,* 1994; Goyer *et al.,* 1985). Several cases of copper storage disease in German infants were attributed to copper leached from pipes by low pH drinking water (Gerhardsson *et al.,* 1994). Acid rain contributes to human exposure to lead *via* drinking water, when lead concentrations are increased either at the source or through the distribution system (from lead solder or pipes) (Goyer *et al.,* 1985). Acid precipitation can also corrode lead paint and transfer the lead to soil and dust (Goyer *et al.,* 1985). The increase in cadmium exposure from acid precipitation can come from a variety of sources: soldered joints of copper plumbing; crops (especially tobacco and leafy vegetables) grown on soil treated with cadmium-containing fertilizers; land application of municipal sewage; and, waste dumps (Goyer *et al.,* 1985).

In samples of drinking water from the wells of farmers in Southern Sweden, a region which is partly affected by acidification, concentrations of aluminum, cadmium, copper and lead were significantly higher in low pH samples (Gerhardsson *et al.,* 1994). Concentrations of calcium and magnesium were significantly lower in the same samples (Gerhardsson *et al.,* 1994).

The mobilization of selenium into water and food is actually decreased by acidification (Gerhardsson *et al.,* 1994). The effect of this can be reduced complexation (and potential detoxification) with selenium of toxic elements following uptake (Gerhardsson *et al.,* 1994).

Another factor to consider is the extensive liming activities undertaken within the GSA as part of ecosystem regreening and restoration initiatives. Soils are typically limed to reduce the harmful effects of low pH (and plant toxicity from aluminum or manganese) and to add calcium and magnesium to the soil. As noted in Chapter 4 of Volume 1, these historical and ongoing liming activities have had a significant impact on soil pH through the GSA, playing a significant role in the incredible ecosystem recovery that has been observed to date.

Regardless, any alterations in the concentrations of copper, lead and selenium (three of the six COC that are known to be affected by acid precipitation) caused by acid rain were captured in the extensive monitoring conducted for the Sudbury Soils Study. The effect of acid precipitation is to alter exposures through existing pathways. No novel pathways of exposure are created by acid precipitation. Thus any incremental risk associated with the effects of acid precipitation on the COC was assessed as part of the total risk.

6.3 Occupational Exposures

One concern raised during the HHRA process was whether the risk assessment would consider the impacts of occupational exposures on the overall health of community members, and whether this would make workers a particularly sensitive subpopulation within the overall GSA community.

When discussing this issue, it is important to understand that the Sudbury Soils Study was not designed or intended to examine occupational exposure to metals in the workplace. There are several reasons for this. Occupational exposure is a matter addressed by the Joint Health and Safety Committee that are attended by company and union representatives, among others. Both companies, Vale Inco and Xstrata Nickel, have programs in place that examine and measure a worker's exposure to the chemicals of concern being addressed by the Study. Most importantly, different levels of "acceptable" risk are assumed for employees in the workplace compared to a resident of the general Sudbury population exposed to metals in the environment. The level of "acceptable" risk to the resident is much lower, therefore, the standards being applied in this Study are more rigorous than that would be applied in an occupational setting. Additionally, occupational concerns lie with the worker, typically a healthy male adult, while risk

assessments, by definition, protect sensitive individuals within the population (*i.e.,* children, pregnant women, the elderly, and those with compromised health).

Other concerns that may be associated with occupational contact with the COC have also been considered within the assessment. As part of the indoor dust survey and the Falconbridge Urinary Arsenic Study (see Appendices M and N of this Volume, respectively), occupational information was gathered on all members of the evaluated households. In the case of both surveys, no association between COC concentrations and employment by Vale Inco or Xstrata Nickel was noted. As such, it was concluded that improved industrial hygiene and housekeeping procedures has reduced the amount of COC, which are transported from the workplace to the home.

6.4 Chemical Mixtures: Overview of Metal-Metal Interactions

While the current HHRA evaluates health risks related to individual exposures to each of the COC, an issue that requires some attention is the potential for metal-metal interactions as a result of chemical mixtures of these COC within the environment.

6.4.1 Introduction

Under typical ambient environmental exposure conditions, humans are exposed to complex mixtures of metals (and various non-metallic substances), rather than individual compounds. Clearly, exposure to such complex mixtures can produce a broad range of health effects (U.S. EPA, 1986). There can be a variety of types of interactions between metals in environmental or dietary mixtures that can alter the overall absorption, toxicokinetics, toxicodynamics and toxicity of metals in humans and animals (Newman *et al.,* 2004). The potential for such interactions is an important consideration in the human health risk assessment of metals, as the nature of the interactions may increase or decrease the bioavailability and the toxicity of metals present within the mixture.

Goyer *et al.* (2004) noted that metal-metal interactions of multiple types routinely occur at multiple points during the processes of absorption, distribution, metabolism, and excretion. The implication of this is that the risk assessment of metals should consider exposure to multiple metals simultaneously. However, the determination of the type and direction of interaction between two or more metals is inherently difficult, as metals interaction data are limited in the scientific literature. Most of the data available is limited to studies of binary mixtures on relatively few metals, effects on relatively few organs or biological systems,

animal studies with very few human studies to corroborate findings, or primarily threshold (non-cancer) effects, and consists of mostly acute duration studies using oral or interparenteral routes (ATSDR, 2004a).

As well, many of the available studies have methodological limitations that make it difficult to clearly ascertain the potential for interactions, and/or have produced conflicting results. Thus, there is little information available that is helpful in extrapolating available interaction data to the situations of low-level chronic exposure to complex chemical mixtures that are usually the focus of human health risk assessments (ATSDR, 2004a; Krishnan and Brodeur, 1994). Even for metals where reliable interaction data exists from laboratory studies, the data usually are not adequate for predicting the likely magnitude of the interaction's impact on toxicity (U.S. EPA, 2004). Information on toxicological interactions of metals with non-metallic substances is even more limited, and in many cases, non-existent.

Complicating the assessment of metal toxic interactions is the fact that the vast majority of existing health criteria, guidelines, toxicity reference values, exposure limits, and other health-based benchmarks for metals are derived for either elemental forms of individual metals, or a few types of single metal compounds (salts, oxides, sulfides, *etc*.).

Because of this inherent limitation of the available toxicology database, regulatory agencies typically recommend that human health risk assessment of metals evaluate the individual components of the metals mixture, and then determine whether the exposures or risks for the individual metals in the mixture could reasonably be considered additive, based on the health effects associated with each metal.

The following sections outline the main types of metal-metal interactions that have been characterized, describe some existing and proposed methods that attempt to account for metal interactions (qualitatively or quantitatively) and discuss the implications of metal-metal toxic interactions in the current human health risk assessment. The emphasis for the discussion of metal-metal interactions is on the COC identified for the current HHRA, with recognition that interactions with other metals and other non-metal substances (that are not COC in the current HHRA) may be equally or more important than interactions between COC. It must also be recognized that by no means is the following review considered a comprehensive evaluation of the available and relevant scientific literature on toxic interactions between metallic substances. There is a very large body of literature that addresses these issues, and recent publications and guidance produced by ATSDR in 2004 (see http://www.atsdr.cdc.gov/iphome.html) have compiled and summarized a substantial amount of the available information on this complex topic.

6.4.2 Types of Toxicological Interactions

ATSDR (2004a) defines toxicological interactions based on deviations from the results that are expected on the basis of additivity. Interaction is said to occur when the effect of a mixture is different from additivity based on the dose-response relationships of the individual components (ATSDR, 2004a). Thus, interactions are sorted into three broad categories:

- Greater-than-additive (*i.e.,* synergism, potentiation);
- Additive (additivity, no apparent influence); and
- Less-than-additive (*i.e.,* antagonism, inhibition, masking).

Definitions for the specific types of interactions are as follows (ATSDR, 2004a):

- **Additivity**: when the effect of the mixture can be estimated from the sum of the exposure levels (weighted for potency), or the effects of the individual components.
- **No apparent influence**: when a component which is not toxic to a particular organ system does not influence the toxicity of a second component on that organ system.
- **Synergism**: when the effect of the mixture is greater than additive on the basis of the toxicities of the components.
- **Potentiation**: when a component that does not have a toxic effect on an organ system increases the effect of a second chemical on that organ system.
- **Antagonism**: when the effect of the mixture is less than additive on the basis of the toxicities of the components.
- **Inhibition**: when a component that does not have a toxic effect on a certain organ system decreases the apparent effect of a second chemical on that organ system.
- **Masking**: when the components produce opposite or functionally competing effects on the same organ system, and diminish the effects of each other, or one overrides the effect of the other.

It is important to recognize that the likelihood of a biologically significant interaction occurring is a function of at least the physical, chemical and biological properties of the chemicals involved, their modes of action, and their concentrations. Most non-additive interactions can only be demonstrated at relatively high exposures, where clear adverse effects are observed. Such interactions have not been observed or quantified at the relatively low rates of exposure typical of those associated with most

environmental or occupational situations (NAS, 1983; Krewski and Thomas, 1992), and are therefore, not typically considered in risk assessments. Additivity is generally recognized as the most plausible type of interaction that may occur in situations of chemical exposure in the ambient environment. However, it requires that the chemicals act through the same or similar mechanisms of action and/or affect the same target tissue(s). In HHRA's where the COC act *via* different mechanisms of toxic action, and affect different target tissues, it is typically assumed that no potential toxicological interactions warrant consideration and the estimated exposures and risks for the COC are considered separately.

With respect to metals specifically, Goyer *et al.* (2004) identifies three main classes of interactions that occur between metals:

- Interactions between essential metals;
- Interactions between nonessential metals; and
- Interactions between essential and nonessential metals.

A common interaction that applies to all three classes of metal-metal interaction during uptake or absorption is antagonism. Antagonism occurs frequently as there is considerable commonality in the uptake and/or sequestration mechanisms for metals in mammals (Goyer *et al.,* 2004). For example, two divalent metal cations may essentially compete for binding at the same receptor site on a cell surface, or to a ligand. This is often referred to as molecular or ionic mimicry in the scientific literature. There are a large number of studies that provide numerous examples of molecular or ionic mimicry of metals, where the interaction is antagonistic (Goyer *et al.,* 2004). The term "molecular" or "ionic mimicry" is often applied to situations in which a non-essential metal antagonizes an essential metal to form a complex that disrupts normal function. A well known example of molecular mimicry is lead antagonizing calcium, which can result in the body sequestering lead into bone, instead of calcium. Lead may be absorbed from the gastrointestinal tract through both passive diffusion and by replacing calcium in the active transport mechanisms involved in the cellular uptake of calcium (Goyer *et al.,* 2004). This example of mimicry may be of particular concern in individuals that are calcium-deficient. Molecular mimicry is central to aspects of uptake and biokinetics for toxic metals within the body (Goyer *et al.,* 2004).

Table 6.2 identifies which of the COC in the current HHRA are considered essential, possibly beneficial, or have no known beneficial effects.

Table 6.2 Classification of COC Based on their Role in Mammalian Metabolism (from Goyer *et al.,* 2004)

Nutritionally Essential Metals	Metals with Possible Beneficial Effects	Metals with No Known Beneficial Effects
Cobalt	Arsenic	Lead
Copper	Nickel	
Selenium		

The complex interactions that continuously occur between essential metals are related to maintaining optimal levels of these elements in the body for required biochemical and physiological processes and functions. All nutritionally essential metals have homeostatic mechanisms that maintain optimum tissue levels over a range of exposures. Metal interactions may be included among the processes involved in homeostatic regulation (Goyer *et al.,* 2004). These homeostatic mechanisms moderate situations of either excessive intake or deficiency and regulate essential biochemical and physiological functions over a wide range of intake levels for essential metals.

Much of the information that is available on interactions between non-essential metals is focused on arsenic, cadmium, and lead (lead and arsenic are COC in the current HHRA). However, none of the available data are adequate at this time for predicting the magnitude of the reported interactions (Goyer *et al.,* 2004). Depending on the endpoint, there is conflicting data as to the direction of the interactions (ATSDR, 2004c,e). Another shortcoming of the available data on interactions between non-essential metals is that most of the animal studies used commercial diets or semi-purified diets that may have higher or lower levels of essential metals than human diets (this information is often not reported). Much higher doses of the non-essential metals appear to be required to elicit effects when commercial diets are used, than when semi-purified diets are used (Goyer *et al.,* 2004). Also, at the other extreme, effects are seen at very low doses when diets deficient in essential metals are used. This creates difficulties in comparing the results of different studies.

It is generally believed that nutritionally non-essential metals, unless the exposure is overwhelming, can be antagonized by essential metals that occur naturally in the diet (Goyer *et al.,* 2004; U.S. EPA, 2004). However, a dietary deficiency of essential metals tends to increase the toxicity of non-essential metals, (Chowdhury and Chandra, 1987; Peraza *et al.,* 1998; U.S. EPA, 2004).

6.4.3 Approaches and Implications of Metal-Metal Interactions for the Assessment of Human Health Risks

The following sections outline the approaches and implications of metal-metal interactions as part of the HHRA process.

6.4.3.1 Traditional Approaches

No specific Canadian guidance on the human health risk assessment of metals mixtures was identified. The U.S. EPA has developed three separate approaches for assessing risks from exposure to chemical mixtures, with the selection of the most appropriate approach based on data availability (U.S. EPA, 2004). The preferred approach is the use of toxicity data that are based specifically on the chemical mixture of concern. Unfortunately, this type of data is rarely available, and no such toxicity data appears to exist for metal mixtures. The U.S. EPA Integrated Risk Information System (IRIS) does have mixture toxicity data for two mixtures that include some metals (but are dominated by organic chemicals such as PAHs) - emissions produced from: (i) coke ovens; and, (ii) diesel exhaust. Even if mixture data are available, it is important to recognize that chemical mixture composition can often vary considerably depending on geographical location, and the types of contaminant sources that are present. Thus, caution is warranted in applying mixture toxicity data to a different mixture without consideration of potential differences related to composition, the contaminant sources, speciation, geology, *etc*. For example, although exposure to smelting emissions may be a common occurrence worldwide, characteristics of the natural geology and smelting processes will result in emissions with distinct compositions. Therefore, despite numerous studies that may have addressed risks associated with exposure to smelter emissions, the relevance of these data for assessing mixtures within the current HHRA study may be limited.

The second approach recommended by the U.S. EPA involves using data available for a toxicologically similar mixture of chemicals. The applicability of this data should be based on the similarity to the mixture of concern (U.S. EPA, 2004). To increase confidence in using this approach, information available on a number of similar mixtures that contain the same components at different concentration ratios can be incorporated into the assessment. This will allow for the prediction of a range of risks to compensate for differences in the mixture composition (U.S. EPA, 1986). Deciding if similar mixtures are "sufficiently similar" enough to be used for assessing risks should be determined with consideration of the differences in component ratios and the presence or absence of components that may have a significant impact on the effects of exposure to the mixture. The U.S. EPA recommends that even if risks can be assessed using data on the mixture of concern or sufficiently similar mixtures, risks should also be

assessed using the toxicity of the individual components, particularly for mixtures that contain both carcinogens and non-carcinogens (U.S. EPA, 1986).

The third approach, which is also the most common approach used in the risk assessment of metals, is based on the toxicity of the individual components of a mixture. When there is no or inadequate information available on potential interactions (which is typically the case for metals mixtures), the approach taken by the U.S. EPA, and numerous other regulatory agencies is to use the "default" method of dose-addition or risk-addition. The decision for which of these two approaches is most appropriate is based on the comparison of the toxicity of the individual metals within the mixture of interest. If the metals act in the same or similar manner on the same target organ, a dose-additive approach is recommended. This can be accomplished using a Hazard Index Method, Relative Potency Factors, or Toxicity Equivalence Factors (U.S. EPA, 2004). In cases where the individual metals act in an independent manner on different organ systems (differing slopes of the dose-response curves), either a separate effect assessment is encouraged for each metal, or a response-additive approach is recommended (U.S. EPA, 1986; 2004).

The U.S. EPA's guidance for situations where there is sufficient evidence available to indicate that components of a mixture are interacting in a manner that results in effects that are either greater than, or less than additive, is that assessment of these chemicals should be conducted separately from those that are assessed in an additive manner (U.S. EPA, 1986). The U.S. EPA suggests that this could involve estimating an interaction-based Hazard Index. (U.S. EPA, 2004). The U.S. EPA (1986) also notes that prior to evaluating non-additive interactions, the potential influence of other components on this interaction should be assessed. If there is sufficient evidence to suggest that other components may be interfering with the non-additive interaction, a discussion of the synergistic or antagonistic potential may be warranted.

The response addition approach is widely recommended for the assessment of risk from mixtures of carcinogenic chemicals (U.S. EPA 1986, 2000a; NRC, 1989). The most conservative form of response addition (and one that is widely conducted) is the simple summation of the individual risks for the individual components in the mixture. However, it should be recognized that this can lead to toxicologically inappropriate summing of risks in some cases that may substantially overestimate total risk.

Dose-additivity is commonly applied in risk assessment by the calculation of a hazard index for those chemicals that produce the same or similar effects in the same organs by same or similar modes of action. U.S. EPA (2000a; 1990; 1989; 1986) guidance leans heavily towards the dose-additive approach and states that a strong case is required to indicate that two chemicals that produce adverse effects on the same organ system, even if by different mechanisms, should not be treated as dose additive. However, it should be recognized that like the response addition approach, this can lead to toxicologically inappropriate summing of exposures and risks in some cases that may substantially overestimate risk. The common hazard index approach for metals sums hazard quotients for each metal of concern and produces a hazard index (*i.e.,* Hazard Index =Σ Ei/RfDi), where Ei = exposure concentration (or intake) for the ith metal and RfDi = some effect reference concentration (or dose) for the ith metal. For chemical mixtures in which there are multiple systemic toxicants that have a different mode of action, the U.S. EPA recommends that a separate hazard index (HI) be calculated for each chemical. The hazard indices for those chemicals that produce a similar effect (*e.g.,* reproductive toxicity) can then be summed to produce a hazard index for that type of effect (U.S. EPA, 1990).

Newman *et al.* (2004) notes some issues with the hazard index in the risk assessment of metals. In the HI calculation, there is an underlying assumption of a (pseudo) linear relation between exposure concentration and effect (Newman *et al.,* 2004). An inherent problem in the hazard index approach for metals (or any chemicals for that matter) is that with more substances considered, the hazard index automatically increases regardless of toxicity. Also, because most exposure concentration–effect models are sigmoidal, the assumption of pseudo-linearity produces an upwardly biased hazard index in many cases (Newman *et al.,* 2004). Thus, these authors note that many metals which at low concentrations would have a negligible joint effect according to a sigmoidal model, in combination, will produce a large hazard index according to a pseudo-linear approximation of the exposure concentration–effect models. This "artifact" poses a problem for risk characterization of metals because many have background concentrations which are included in these summations. Moreover, some metals are essential elements and the assumption of a monotonic, pseudo-linear relationship is especially inappropriate for these (Newman *et al.,* 2004). Using the traditional hazard index approach, an essential metal present at such low concentrations as to produce a deficiency, would be handled in HI calculations as if it were having a toxic effect. However, metals at such low concentrations would presumably not be identified as chemicals of concern for the risk assessment, which would result in their exclusion from the HHRA and the HI calculation. Newman *et al.* (2004) also note that concentration summation might be plausible in some cases, but only if the metal RfD values reflected true effect thresholds, no dose/concentration–effect

models were available, and the metals of interest caused the same effect(s) by a common mechanism. Similarly acting metals could be summed, but the justification for summing metals with independent action is not clear. The authors suggest that the decision for summing metals concentrations in the hazard index requires some means of determining the metals' joint action.

It must be recognized that both the traditional response and dose-addition approaches assume that chemicals in a mixture do not affect the toxicity of one another (*i.e.,* they act independently). Thus, neither approach accounts for potential toxic interactions.

6.4.3.2 Approaches that Attempt to Account for Interactions

ATSDR (2004a) notes that although the default approach of dose additivity cannot directly account for interactions, there is empirical evidence to suggest that dose additivity may actually be a reasonable default model for the joint action of chemicals. This is based on a study by Smyth *et al.* (1969) in which LD_{50} values were predicted for 350 possible binary mixtures of 27 industrial chemicals administered in equivolume combinations, and compared to observed data. The ratio between the predicted and observed values, calculated for each pair, ranged from 0.23 to 5.09, indicating that the magnitude of deviation from dose additivity was approximately a factor of five or less. It is not known if this relationship holds for chronic toxicity data, however. Furthermore, in light of the issues raised by Newman *et al.* (2004), it is uncertain whether it is appropriate to apply the dose additivity concept to metals that have an essential or beneficial effect.

ATSDR (2004a) describes a weight-of-evidence (WOE) method that was first proposed by Mumtaz and Durkin (1992). The WOE method is considered the first systematic attempt to address the fact that HI does not incorporate information on interactions among components of the mixture. The method expands on the suggestion made by the NRC (1989) that, in recognition of the difficulties of quantifying interactions, a UF be used to account for interactions among components of a mixture. The WOE method was designed to modify the hazard index to account for interactions, using the weight-of-evidence for interactions among binary pairs of mixture components. ATSDR (2004a) describes this modification of the hazard index (H_I) as an "Interactions-based hazard index". Details and discussion are provided within ATSDR (2004a) but essentially, an uncertainty factor is modified by a normalized weight-of-evidence score. The adjustment is performed as follows, where HI_I is the interactions-based hazard index, HI_{add} is the traditional additivity-based hazard index, and UF_I is an uncertainty factor for interactions, as follows:

$$HI_I = HI_{add} \times UF_I^{WOE_X}$$

While ATSDR (2004a) notes that application of the WOE method to generate the HI_I has revealed that it does not handle changes in proportions of mixture components in a reasonable manner, the method is still considered useful for qualitative predictions of whether hazard may be more or less than indicated by the HI_{add}. The qualitative application of the WOE method evaluates data relevant to joint action for each possible pair of chemicals in the mixture in order to make qualitative binary weight-of-evidence (BINWOE) determinations for the effect of each chemical on the toxicity of every other chemical. Thus, two BINWOEs are needed for each pair evaluated: one for the effect of chemical A on the toxicity of chemical B, and another for the effect of chemical B on the toxicity of chemical A. BINWOE determinations indicate the expected direction of an interaction (*e.g.,* greater than additive, less than additive, additive, or indeterminate), and scores the data qualitatively, using an alphanumeric scheme that factors in what is known about mechanisms of action, toxicological significance, relevance of the exposure duration, sequence, bioassay (*in vitro versus in vivo*), and route of exposure. The alphanumeric terms in the classification scheme are then converted to a single numerical score, by multiplying the corresponding direction factor by the data quality weighting factor. ATSDR (2004a,c,e) note that WOE evaluations should be target-organ specific.

The qualitative BINWOE classifications approach is shown in detail in ATSDR (2004a).

While the WOE method was initially developed for assessing interactions for non-carcinogenic effects, the qualitative WOE method is equally applicable to assessing interactions for carcinogenic effects (ATSDR, 2004a). The ATSDR further notes that this method has undergone evaluation, and appears to perform well qualitatively and even quantitatively under some circumstances. The application of the method for deriving BINWOE classifications was also considered consistent by expert toxicologists who reviewed the results of exercises in which several teams of toxicologists and risk assessors independently determined BINWOE classifications for the same pairs of chemicals (ATSDR, 2004a). However, it is acknowledged that the method is impacted by uncertainties related to variability in the responses of individual test animals, small numbers of test animals per group, and limited testing of multiple dose levels of mixtures.

ATSDR (2004a) notes that a modification of the original WOE method has been further developed by U.S. EPA and adopted as part of its mixtures guidance. The modifications include a slightly different classification scheme and a different method of calculating the interactions-modified hazard index. The

modified method also encourages greater use of quantitative interaction data through the use of magnitude-of-interaction factors for each chemical pair. However, ATSDR (2004a) notes that the EPA classification scheme, while more flexible and integrated in nature, requires more judgment, and the type of quantitative interaction data required to estimate the magnitude factor is rarely available in practice. Consistency of the application of modified WOE method has not been tested to date (ATSDR, 2004a). While the modified algorithm appears to handle changes in proportions of mixture components better than the original algorithm, additional validation with respect to the accuracy of predicted *versus* observed experimental results is warranted (ATSDR, 2004a).

It is important to note that a basic assumption of both WOE methods is that interactive interference will not be significant – meaning that if chemicals A and B interact in a certain way, the presence of chemical C will not cause the interaction to be substantially different. Thus, the inherent assumption is that pair-wise interactions will dominate in the mixture and adequately represent all the interactions. This is a major area of uncertainty, as well as a major limitation of the WOE approaches, and appears to be unsupported by empirical data. It appears to be more an assumption of convenience that reflects data availability than an assumption based on science. It would seem plausible that multiple interactions would influence each other in complex and multiple ways; however, the majority of reliable data that are available on chemical interactions focus on binary mixtures. Thus, the significance of tertiary, quaternary and beyond mixtures on toxic interactions is not well understood.

Detailed guidance for deriving BINWOE determinations and evaluating joint toxic action studies is presented in ATSDR (2001). The qualitative WOE method has been used to produce the available ATSDR (2004 b,c) interaction profiles.

Another refinement to the HI described in ATSDR (2004a) is the use of the target-organ toxicity dose (TTD) method, which was designed to accommodate the assessment of mixtures whose components do not all have the same critical effect. It also takes into account the fact that most components of chemical mixtures affect other target organs at doses higher than those that cause the critical effect. Clearly, these other effects at higher doses will vary across chemicals present in the mixture, but may be important in assessing the overall health effects of the mixture (ATSDR, 2004a).

The approaches of toxic equivalency and relative potency also use the assumption of dose additivity to assess the health effects of a mixture. These approaches are typically only applied to mixtures that consist of a particular class of chemicals, and are used when health effects information for one component of the mixture (such as the TCDD congener for dioxins and furans, and benzo[a]pyrene for carcinogenic PAHs)

is deemed sufficient to derive health effects criteria for the other components of the mixture that have no or inadequate toxicity data. These approaches do not appear to have been applied to mixtures of inorganic chemicals.

ATSDR (2004a) also describe the ISS method of Woo *et al.* (1994), which like the WOE method, uses data for binary mixtures to predict the hazard from mixtures of three or more chemicals. This method is conducted using a software package. It is focused on carcinogenic chemicals and integrates three U.S. EPA and National Cancer Institute databases on binary interactions of carcinogens with other carcinogens, promoters, and inhibitors (roughly 1,000 chemicals are in the databases). The ISS calculates a weighting ratio that reflects the ratio of greater- than-additive (>1) to less-than-additive interactions (<1) for the components of a mixture. The weighting ratio is based on the interactions data for the chemical pairs in the mixture. For those pairs lacking interactions data, interactions between other similar members of the chemical classes to which the chemicals belong form the basis for the weighting ratio. The weighting ratio also incorporates some judgments regarding the relative effectiveness of the interactions. The ISS model includes four types of interactions only: synergism, promotion, antagonism, and inhibition. ATSDR (2004a) notes that a major limitation of the ISS model is that it does not consider exposure concentration or dose. Another key limitation noted is that the class-class interaction ratings for pairs of chemicals with no data tend to dominate the score. The ISS model is used by the U.S. EPA but it is also undergoing further review and development (ATSDR, 2004a). As such, it does not appear to be a well validated approach at this time.

There has also been some limited application of binary Physiologically Based Pharmacokinetic (PBPK) models to the study of chemical toxic interactions. However, to date, only organic compounds have been evaluated in this manner (ATSDR, 2004a). There are also approaches currently being developed for PBPK modeling of mixtures of three or more chemicals, but these have not progressed to the point where they could be applied in a human health risk assessment (ATSDR, 2004a).

A method to account for interactions that differs from the others noted above involves developing ways to count each result in an interaction category for each pair of chemicals, and then assess the variance of the results and the statistical significance of the observed pattern. This method was developed by Durkin. (1995) using the data in U.S. EPA's MIXTOX database, and can be used to assess the patterns of interactions between single chemicals, a chemical and a class of chemicals, or between classes of chemicals. With this approach, statistically significant interaction patterns for classes of chemicals could be used as "rules" for chemicals in those classes that lack empirical interactions data.

The approaches described above are considered to represent the major efforts to attempt to determine the nature and direction of toxic interactions in human health risk assessment of chemical mixtures. Other approaches not discussed here exist as well. Newman *et al.* (2004) and ATSDR (2004a) describe some of these. Further details on the above approaches, including strengths and weaknesses, are provided in ATSDR (2004a). This guidance document also outlines ATSDR's preferences for the assessment of the joint toxic action of chemical mixtures, which can vary depending on data availability, and provides examples of their preferred approach in several case studies of contaminant mixtures (none involve specific metals or inorganics, however).

Overall, it appears that there are few existing approaches used or proposed for the risk assessment of chemical mixtures than can adequately and reliably account for interactions between chemicals in the mixture. Those methods that do attempt to account for interactions do so almost exclusively at the binary level (two chemicals at a time). Clearly, this may not represent all the significant complex interactions that can occur with co-exposure to multiple inorganic or metallic substances. Interactions between inorganics and organics are poorly characterized and are subject to even more uncertainty than inorganic-inorganic interactions.

Furthermore, the toxic mode of action for the COC outlined in Chapter 4 and Appendix A of this volume summarizes the toxicological criteria for the chemicals of concern in the current HHRA, along with the endpoints upon which the criteria are based. It is evident from this table that with the exception of lung cancer as the endpoint for the arsenic and nickel inhalation criteria, each of the COC target different organ systems or produce different critical effects.

6.4.4 Potential Interactions between COC

Limited data on interactions between some of the COC considered in the current HHRA has been compiled and summarized in ATSDR in either interaction profiles or toxicological profiles. Brief summaries of the findings from these ATSDR profiles are provided below. Data were only identified for a few combinations of COC.

In the available interaction profiles that are relevant to the COC (ATSDR, 2004c,e), ATSDR applied the target-organ toxicity dose (TTD) and BINWOE approaches to the assessment of joint action. The interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have, if or when they occur. The interaction profiles focus on endpoints for which data exists for

both chemicals in the binary pair that is evaluated. If one endpoint lacks data for one of the chemicals in the binary pair, then ASTDR did not evaluate that endpoint for joint action.

A brief summary of ATSDR (2004a,c) findings from the interaction profiles follows. The summary provides the predicted direction of interactions between binary pairs of metals that are COC. Less than additive implies likely antagonistic, inhibition or masking interactions, and more than additive implies potential synergism or potentiation. Details and rationale for the conclusions and results of the BINWOE analysis are within the interaction profiles. Data are only available to assess joint action *via* oral exposure routes, and for only a selected number of toxicological endpoints.

Lead and Copper

- Effect of copper on lead neurological and hematological toxicity for oral exposure: less than additive.
- Effect of lead on copper hepatic toxicity for oral exposure: no effect.

Lead and Arsenic

- Effect of lead on arsenic neurological toxicity for oral exposure: more than additive.
- Effect of arsenic on lead neurological toxicity for oral exposure: more than additive.
- Effect of lead on arsenic dermal toxicity for oral exposure: indeterminate.
- Effect of lead on arsenic renal toxicity for oral exposure: less than additive.
- Effect of arsenic on lead renal toxicity for oral exposure: less than additive.
- Effect of lead on arsenic cardiovascular toxicity for oral exposure: indeterminate.
- Effect of arsenic on lead cardiovascular toxicity for oral exposure: indeterminate.
- Effect of lead on arsenic hematological toxicity for oral exposure: less than additive.
- Effect of arsenic on lead hematological toxicity for oral exposure: less than additive.

The inconsistency in the direction of interactions reflects the limited data and the high degree of uncertainty that is associated with studies of the joint action of these COC.

In individual toxicological profiles from ATSDR (http://www.atsdr.cdc.gov/toxpro2.html), limited information on interactions of the COC is also summarized. From the individual profiles on COC for this

HHRA, the following types of interactions among COC are noted. However, it must be recognized that the summaries within the ATSDR toxicological profiles are not a comprehensive review of the interactions literature, and may not reflect the most recent data available.

Copper and Lead

- Dietary copper appears to be antagonistic to the adverse effects of lead on the hematopoietic system (*i.e.*, system responsible for the formation of blood cells), growth depression, and tissue hypertrophy (Klauder and Peterini, 1975).

Cobalt and Nickel

- An interrelationship between cobalt and nickel sensitization has been reported in individuals (humans and animals) exposed to both metals (Rystedt and Fisher, 1983; Veien *et al.,* 1987; Wahlberg and Lidén, 2000). The combination of nickel sensitivity and irritant eczema appears to result in a high risk for developing an allergy to cobalt. Studies of cultured alveolar type II cells showed a synergistic response to co-exposure to cobalt and nickel chlorides (Cross *et al.,* 2001).
- There also appears to be cross-reactivity between nickel and cobalt in sensitive individuals. For example, eight patients with asthma resulting from cobalt exposure also developed an asthmatic response when challenged with nickel sulfate (Shirakawa *et al.,* 1990).

Selenium, Copper, Lead and Arsenic

- Most forms of selenium have been reported to reduce the toxicity of lead, copper and arsenic (Frost, 1972; Levander, 1969; 1982).
- Arsenic antagonizes selenium toxicity (Levander, 1969).
- There is a pronounced synergism between arsenic and two methylated selenium metabolites, trimethyl selenonium ion and dimethyl selenide (Obermeyer *et al.,* 1971).

Some important considerations when considering the limited interaction data for the COC are as follows:

- The endpoints for which an interaction was observed may not necessarily be the same endpoint as that which the TRVs are based on. As the limited data presented above illustrates, it cannot be assumed that the same interaction observed for one endpoint will occur for other endpoints. The ATSDR largely focused on the endpoints on which their Minimal Risk Levels are based, but those endpoints are not necessarily what other regulatory agency's toxicological criteria are based

on. With respect to the current COC, the BINWOE analysis conducted by ATSDR does not focus on the endpoints for binary pairs that both selected TRVs are based on; rather, the analysis reflects the available data.

- In some cases, the strongest evidence for interactions is based on effects that occur at doses higher than those which a TRV is based on. It is not clear if it can be assumed that interactions related to effects/endpoints that occur at higher doses will also occur at lower doses.

- All identified interactions data for the COC are limited to the oral route of exposure. It is not known if interactions observed *via* oral exposure routes also occur *via* the inhalation or dermal routes. There are very limited data available regarding interactions of inorganic chemicals *via* the inhalation and dermal exposure routes. The greater amount of oral interaction studies may reflect the fact that oral exposure pathways (such as diet, drinking water, soil ingestion) are typically the greatest contributors to total metal exposure in the general population.

- By only considering interactions between COC identified for a particular HHRA, other potentially significant interactions between the COC and various non-COC will be missed. For example, it could be the case that the most critical interactions are between a COC and an essential element that is not selected as a COC in the assessment.

6.4.5 Implications for the Current Assessment

As described in Section 6.4.4, each of the COC, with the exception of inhaled arsenic and nickel, produce different critical effects on different organ systems. Although ATSDR (2004c) has indicated that the interaction of lead and arsenic may produce a neurological effect that is greater than additive, the toxicological criteria for these chemicals are not based on the same critical effects, nor do they target the same biological system. This is also true for copper and lead which, when interacting, are suggested to produce a neurological effect that is sub-additive with no significant hepatic interaction (ATSDR, 2004b).

It should also be noted that when one considers the six COC in the current HHRA, there would be 15 possible binary interactions. Interactions data were only identified for six of the possible 15 binary pairs. Furthermore, there is no way to account for interactions with the COC and chemical exposures that occur every day in all environmental media and the diet, which will also interact with each other and the COC in complex ways that are poorly understood. There is no way of knowing if these interactions are more or less toxicologically significant than interactions that occur between the COC only.

Based on these considerations, the overall limited nature of the metal-metal interactions literature, and consideration of the information presented in the previous sections, it was considered most appropriate to evaluate the potential risks from exposure to arsenic, cobalt, copper, lead, nickel and selenium on an individual basis for all exposure routes assessed in the HHRA. No interaction information identified for the COC is considered adequate at this time for quantitative or even qualitative incorporation into the human health risk assessment. However, despite the uncertainties involved with this approach, given the generous uncertainty factors built into the development of each of these COC-specific toxicological reference values, it is not expected that this would result in a significant underestimation of health risks even under worst case scenarios.

6.5 Brief Review of Soil Ingestion Rates in Children and Recommendations to Address Long-Term Pica Behaviour

6.5.1 Introduction

Ingestion of contaminated soil by children may result in significant exposure to toxic substances at contaminated sites. The purpose of this discussion is to review existing methods that would help address the issue of long-term soil intake rates in children, including those considered to display "pica" behaviour (the intentional ingestion of soil).

The potential for exposure to contaminants *via* ingestion of soil is greater for children because they are likely to ingest more soil than do adults as a result of behavioural patterns present during childhood. Pica behaviour is considered to be relatively uncommon and has been estimated to be present in about 1 to 2% of the population (Calabrese *et al.,* 1989; 1990). Other studies reported earth eating and pica "dirt" eating to vary from 3 to 19% for children in a black rural community, non-black low income family children, pregnant women and non-pregnant women (Vermeer and Frate 1979; Bruhn and Pangborn 1971). (Binder *et al*., 1986; Clausing *et al*., 1987; Calabrese *et al*., 1989; Davis *et al*., 1990; van Wïjnen *et al*., 1990; Stanek and Calabrese, 1995; Thompson and Burmaster, 1991; Sedman and Mahmood, 1994). Out of over 600 children involved in eight key tracer studies (references), only one child exhibited pica behaviour.

Sections 6.5.2 and 6.5.3 provide a review of the latest research concerning soil intake rates in "normal" and pica children, respectively. A brief discussion on how to include long-term pica behaviour of children in a risk assessment is presented in Section 6.5.4.

6.5.2 Review of Soil Ingestion Rates in "Normal" Children

This section focuses on normal soil ingestion by children that occurs as a result of hand-to-mouth activity. Early study methods used hand wipes and hand-to-mouth behaviour of young children to estimate daily soil ingestion of young children. Recent methods are based on a mass-balance trace element approach. These methods measure trace elements in feces and soil that are believed to be poorly absorbed in the gut. These measurements are then used to estimate the amount of soil ingested over a specified period of time.

For children under six years of age, the U.S. EPA guidance recommends using a mean acute soil ingestion rate of 100 mg/day, and a conservative mean estimate of 200 mg/day (U.S. EPA, 2002a). These values are fairly consistent with the mean soil ingestion values reported in the key studies, which ranged from 39 to 271 mg/day with a mean of 138 mg/day. The U.S. EPA (2002a) determined that the 95th percentile values for soil ingestion, based on key studies identified in Table 6.3, ranged from 106 mg/day to 1,432 mg/day, with an average of 358 mg/day. As a result, they have recommended a 95th percentile value for an acute soil ingestion rate in children of 400 mg/day (U.S. EPA, 2002a).

However, it is important to understand the various uncertainties associated with these values:

1. Individuals were not studied for sufficient periods of time to obtain a good estimate of the usual intake. Therefore, the values presented in this section may not be representative of potential long-term exposures.

2. The experimental error in measuring soil ingestion values for individual children is also a source of uncertainty. For example, incomplete sample collection of both input (*i.e.,* food and non-food sources) and output (*i.e.,* urine and feces) is a limitation for some of the studies conducted. In addition, an individual's soil ingestion value may be artificially high or low depending on the extent to which a mismatch between input and output occurs due to individual variation in the gastrointestinal transit time.

3. The degree to which the tracer elements used in these studies are absorbed in the human body is uncertain. Accuracy of the soil ingestion estimates depends on how good this assumption is.

4. There is uncertainty with regard to the homogeneity of soil samples and the accuracy of parents' knowledge about their children's play areas.

5. All the soil ingestion studies, with the exception of Calabrese *et al.* (1989), were conducted during the summer, when soil contact is more likely. Although the U.S. EPA (2002a) recommended that soil ingestion values be derived from studies that were mostly conducted in the summer, exposure during the winter months when the ground is frozen or snow covered should not be considered as zero. Exposure during these months, although lower than in the summer months, would not be zero because some portion of household dust comes from outdoor soil.

Several studies have investigated the use of Monte Carlo techniques to extrapolate from short-term (daily) soil ingestion to long-term average soil ingestion (Stanek *et al.,* 1998; Stanek and Calabrese, 2000; Stanek *et al.,* 2001a,b). Stanek *et al.* (2001b) estimated the long-term annual average soil ingestion distribution using daily soil ingestion estimates from children who participated in the mass-balance study at Anaconda, Montana (Calabrese *et al.,* 1997). No pica children were involved in the Anaconda study. The mean, standard deviation and percentiles of the long-term soil ingestion distribution are provided in Stanek *et al.* (2001b).

6.5.3 Review of Soil Ingestion Rates in Pica Children

Soil pica behaviour is much less prevalent then normal, inadvertent soil ingestion, thus the available data on soil ingestion rates for pica children are limited. Calabrese *et al.* (1989; 1991) estimated that upper range soil ingestion values may range from approximately 5,000 to 7,000 mg/day. This estimate was based on observations of one pica child among the 64 children who participated in the study. In the study, a 3.5 year-old female exhibited extremely high soil ingestion behaviour during one of the two weeks of observation. Intake ranged from 74 to 2,000 mg/day during the first week of observation and from 10,100 to 13,600 mg/day during the second week of observation.

Wong (1988) attempted to estimate the amount of soil ingested by two groups of children living at two locations in Jamaica. Of the 52 children studied, six displayed soil pica behaviour. A high degree of daily variability in soil ingestion was observed among the six children who exhibited pica behaviour. Three of six children showed soil pica behaviour on only one of four days. The other three ingested greater than 1,000 mg/day on two of four, on three of four, and on four of four days, respectively.

In conducting a risk assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), U.S.EPA (1984) used 5,000 mg/day to represent the soil intake rate for pica children, while U.S. EPA (2000b) used an intake rate of 10,000 mg/day. The Centers for Disease Control (CDC) also investigated the potential for exposure to TCDD through the soil ingestion route. CDC used a value of 10,000 mg/day to represent the

amount of soil that a pica child might ingest (Kimbrough *et al.,* 1984). These values are consistent with those observed by Calabrese *et al.* (1991).

Based on a review of the key tracer studies, the U.S. EPA (2002a) proposed an ingestion rate of 10,000 mg/day for use in acute exposure assessment. This value, however, was based on only one pica child observed in the Calabrese *et al.* (1989) study, where the intake ranged from 10,000 to 13,000 mg/day during the second week of observation. The Danish Environmental Protection Agency uses the same soil ingestion rate of 10,000 mg/day as U.S. EPA when conducting a risk assessment of children.

The Agency for Toxic Substances and Disease Registry (ATSDR) held an experts workshop on soil-pica behaviour in June, 2000, in Atlanta, Georgia (ATSDR, 2000b). The panellists thoroughly discussed and debated the prevalence of soil-pica behaviour, ingestion rates for soil-pica, means for identifying people with soil-pica behaviour, and additional topics. Common themes discussed throughout the workshop included the need for clear definitions of key terms, the lack of extensive research on the distribution of soil ingestion rates, and the need for additional research to fill data gaps. The experts noted that ATSDR's assumption that soil-pica children ingest 5,000 mg of soil per day appears to be supported by only a few subjects in soil ingestion studies. Referring to the soil ingestion rates presented in the literature, some experts thought that ATSDR's assumed ingestion rate for soil-pica children was high. Other experts agreed, however, that ATSDR should err on the side of being protective and should use 5,000 mg/day until more data are collected. They also stressed the need for validating the 5,000 mg/day soil ingestion rate.

ATSDR currently applies the soil ingestion rate of 5,000 mg per day for the entire duration of acute (<14 days), intermediate (14 to 365 days), and chronic exposures (>365 days) to develop screening levels. One expert noted that extrapolations of short-term analytical studies to long-term exposure scenarios may be inappropriate, as few children likely ingest 5,000 mg of soil a day throughout a year. Specifically, he explained that a statistical review of an analytical study has suggested that the likelihood of children ingesting 5,000 mg of soil every day of the year is extremely low (<1%) (Stanek and Calabrese, 1995). In the end, experts agreed that there was limited data to support this approach.

Based on the available information, a range of 5,000 to 10,000 mg/day appears to be the soil ingestion rate used to assess pica behaviour by regulatory and non-regulatory agencies. However, there is not sufficient data to determine whether such an intake occurs every day for pica children.

It is plausible that many "normal" children may exhibit some pica behaviour if studied for longer periods of time. For example, Stanek and Calabrese (1995) conducted a statistical analysis of the existing soil ingestion data and estimated that 33% of children will ingest greater than 10,000 mg of soil on one or two days per year, and 16% of children will ingest greater than 1,000 mg of soil on 35 to 40 days per year. This prediction, however, was based on a limited dataset.

6.5.4 Estimating Long Term Soil Pica Behaviour in a Risk Assessment

There are limited data for quantifying amounts of soil ingested by children, particularly by pica children. The data that exist pertain to short-term ingestion rates that may not be reflective of long-term patterns of intake. The pica ingestion rates that are proposed for risk assessment by several organizations range from 5,000 to 10,000 mg/day (10,000 mg/day based on one pica child in Calabrese *et al*., 1989; 1991). These data were derived based on limited data and expert judgment, and they err on the side of conservatism.

A central issue when conducting exposure and risk assessments is to determine the variation of soil ingestion among members of the population under consideration, or to estimate the uncertainty associated with assumed mean intake rates for representative members of a group. Many chemical risk assessments have used default values or point estimates of soil ingestion rates for risk calculations, culminating in point estimates of risk. This approach can be useful for an acute screening assessment but it is not useful for chronic type exposures. An important question to address is whether pica children actually ingest consistently large amounts of soil on a daily basis for long periods of time. ATSDR applies the soil ingestion rate of 5,000 mg/day for the entire duration of the exposure period of interest for screening assessments. However, it is more likely that pica children will ingest varying amounts of soil (albeit larger amounts on average than "normal" children) over a long period of time that may reach and even exceed the proposed default intake values from time to time. Thus, a distribution (*i.e.*, lognormal or normal) of soil ingestion rates would represent a better estimate of intake by pica children. That said, data to produce a long-term soil distribution for pica children do not exist. However, a long-term soil distribution for "normal" children was developed by Stanek *et al.* (2001b) using Monte Carlo methods. A ratio between the mean or median of the soil ingestion distribution for "normal" children and the 5,000-10,000 mg/day screening values could be applied to shift the "normal" distribution to a pica distribution. Obviously there is a lot of uncertainty in doing so, including the assumption that "normal" and pica children have similar soil ingestion distributions. Another important uncertainty is the fact that screening values are based on limited data.

The resulting long-term soil pica distribution would be very conservative. The increase in ingestion rates would range between 25 to 50 fold compared to "normal" children soil ingestion rates (if one compares the conservative mean estimate of 200 mg/day (U.S. EPA, 2002c) with the 5,000 to 10,000 mg/day screening values). Since the risk assessment will be used to drive clean-up levels, using such a conservative approach might not provide feasible and appropriate remediation goals.

Another option would be to develop a long-term ingestion rate distribution using pooled ingestion rates of "normal" and pica children from several studies. This would result in a distribution that includes mostly "normal" soil ingestion behaviour, and some pica behaviour. Obviously this distribution would be more conservative than the "normal" long-term distribution developed by Stanek *et al*. (2001b). However, it would still not be protective of children who exhibit pica behaviour on a regular basis, nor would it be protective of acute pica behaviour in "normal" children.

In summary, short-term soil ingestion rates exist for pica children and could be used in a screening assessment. These data are, however, based on limited observations. It is possible to derive a long-term soil ingestion distribution for pica children by shifting the long-term soil ingestion distribution for "normal" children by a conservative factor. This would create a distribution that is very conservative and may not help design appropriate clean-up levels.

6.5.5 Recommendations

Based upon this review, it was determined that it would be inappropriate to use the short-term, acute soil consumption values associated with pica children for a long-term, chronic assessment of potential health risks related to soil contamination. Therefore, a long-term soil ingestion distribution was developed based upon information presented in Stanek *et al.* (2001b). Based upon this distribution, a 95th percentile (or RME) total soil and dust ingestion rate for preschool children and children of 202 mg/day (91 mg/day soil, 111 mg/day indoor dust), and a 50th percentile (or CTE) total soil and dust intake rate of 53 mg/day (24 mg/day soil and 29 mg/day dust) were calculated. Refer to Chapter 4 for further details.

6.6 Dermal Sensitization to Nickel

Nickel dermatitis (also called contact or allergic dermatitis) is the most commonly observed adverse effect of nickel in the general population (ATSDR, 2003a). It is a form of allergic contact dermatitis where an inflammatory reaction is produced in the skin by contact with nickel in those who have acquired

a hypersensitivity[3] to nickel as a result of a previous exposure (Dorland, 2000; Keczkes *et al.,* 1982). Research has observed a relationship between specific human lymphocyte antigens and nickel sensitivity (Mozzanica *et al*., 1990). In sensitized individuals, exposure to nickel results in a red, itchy rash at the site of exposure (although the rash may spread). Later the area may become covered in tiny water-filled blisters, or may be dry and scaly.

Sensitized individuals are of interest in risk assessment because they may experience adverse effects at lower exposures than non-sensitized individuals. Once an individual has been sensitized to nickel, subsequent inhalation, oral or dermal exposures to low levels of nickel may cause reactivation of the dermatitis (Keczkes *et al.,* 1982). It is accepted that subsequent exposures *via* either the oral or dermal routes can reactivate nickel dermatitis; however there is no evidence that airborne nickel causes allergic reactions in the general population (ATSDR, 2003a).

Under non-occupational exposure conditions, sensitization to nickel typically occurs primarily as a result of prolonged skin contact with nickel-containing metal objects (*e.g.*, jewelry, coins, dental braces, stainless steel and metal fastenings on cloths) or when metal objects are inserted into body parts (*e.g.*, ear piercing, orthodontics and orthopaedic devices) (Menné and Maiback, 1987; Menné *et al.*, 1989; Wilkinson and Wilkinson, 1989; Dotterud and Falk, 1994; Larsson-Stymne and Widstrom, 1985; Meijer *et al*., 1995; van Hoogstraten *et al*., 1991).

ATSDR (2003a) reports that approximately 10 to 15% of the population has become sensitized to nickel. Andreassi *et al.* (1998) reported that approximately 10 to 15% of women and 1 to 3% of men living in industrialized countries are sensitized to nickel. Although nickel is classified as an allergen of moderate potency (Kligman, 1966), there is a high risk of developing nickel allergic hypersensitivity occupationally and in the general public due to the ubiquitous occurrence of nickel in all aspects of daily life (Hostynek, 2002). Due to chemical and experimental variables in addition to individual variables (*e.g.,* differences in susceptibility to nickel, age, gender, integrity of skin), Hostynek (2002) reported that a threshold value for nickel inducing sensitization cannot be developed at this time.

Recent studies have shown that acute oral exposure to nickel compounds can result in flare-ups of allergic contact dermatitis and eczema and in some cases, urticaria and respiratory symptoms in women that are sensitized to nickel (Andreassi *et al.,* 1998; Boscolo *et al.,* 1995). Cronin *et al.* (1980) reported that the lowest single dose of nickel reactivating dermatitis in sensitized individuals is approximately 0.009

[3] Sensitization is an increased susceptibility of a subject to a particular chemical agent when exposed to that chemical over time.

mg/kg/day. Other studies have shown a low incidence of allergic dermatitis responses in the dose range of 0.02 to 0.04 mg/kg/day (Burrows *et al.,* 1981; Gawkroder *et al.,* 1986; Kaaber *et al.,* 1978; Menné and Maibach, 1987). Although a dose response relationship between nickel exposure and dermatitis in sensitized individuals has been shown (Emmett *et al.,* 1988), Hostynek (2002) reported that identifying concentrations which will elicit a reaction in sensitized individuals is not possible due to chemical, experimental and individual variables. While no clear threshold value can be determined, based on a review of the data, Hostynek (2002) reported that the "best" estimate of the concentration of nickel necessary to elicit an allergic response is 0.6 ppm in aqueous solution (based on Katz and Samitz, 1975). Hostynek (2002) also notes that some dermatologists consider an acceptable limit to be 10 times less than this value (*i.e.,* 0.06 ppm).

In situations of chronic environmental exposures to nickel, low-level doses have been shown to desensitize some individuals and to prevent sensitization in others. A recent study has suggested that long-term exposure to environmental nickel may induce immunologic tolerance resulting in a lower risk of developing contact allergy to nickel (Smith-Sivertsen, *et al.,* 2002). Other studies have shown improvements in symptoms of nickel dermatitis during, and in some cases after a low-dose oral regime (Sjöwall *et al.,* 1978; Panzani *et al.,* 1995; Bagot *et al.,* 1995; Santucci *et al.,* 1994). However, some animal studies suggest that induction of tolerance requires high doses. This observation is consistent with the impression that nickel dermatitis is not a serious occupational disease in the nickel refining industry (Menné, 1994).

Without clear data on the exposure threshold for re-activation of nickel dermatitis, it is not possible to conclude whether environmental exposures to nickel will reactivate nickel dermatitis in sensitive individuals, or will have a desensitizing effect.

Due to the confounding issues outlined above and the absence of obvious health concerns related to this form of sensitization in the GSA community, nickel dermatitis has been noted as a potential uncertainty within the assessment, but will not be evaluated further as part of the Sudbury Soils Study.

6.7 Epidemiology and Selected Community Health Indicators

This section presents some data about the health of the population in the area of study in order to provide some context for the study's findings. Although this section contains epidemiological information about selected community health indicators, it should be noted that there are serious limitations and pitfalls in

comparing the potential health risks identified in a risk assessment protocol with health status as observed through health-registry based information or other epidemiologic knowledge.

To understand these limitations, it is first important to understand how a community's health status and the causes of health and disease in a community are derived through the application of epidemiological principles.

Data from health (or disease) registries and from surveys are used to describe the health of a community. Health (or disease) registries and surveys serve as effective tools in epidemiological research when certain criteria are met. The usefulness of a registry or survey is governed by the quantity, quality and completeness of the data it contains. Raw data from registries and surveys (*e.g.*, information restricted to time, gender and age) is then used in epidemiological studies or research to further investigate causes of specific diseases or health outcomes.

Beaglehole *et al.* (1993) defined epidemiology as the science that is "concerned with the causes and natural history of disease, the description of the health status of populations and the assessment of the effectiveness of interventions". The ability to establish the causes behind certain health outcomes depends on the study designs used; some are more effective in establishing causation than others. Just because an exposure is associated with a certain outcome does not mean that the exposure caused the outcome.

Secondly, it is important to understand that human health risk assessments do not measure health outcomes. The methodology behind a human health risk assessment leads to a *calculated* risk to human health posed by the actual or potential presence or release of hazardous substances, pollutants or contaminants. Pitfalls associated with attempts to translate elevated *calculated* risks into *measurable* health outcomes arise because of the following reasons (among others):

(i) The fact that potential increased risks are identified does not necessarily mean that these risks will present themselves. For example, because of the conservative nature of risk assessment the calculated exposures often over-estimate actual exposures. The purpose of a risk assessment is to identify areas where risk management may be used to reduce the calculated exposures. Clearly, when exposure is reduced, the predicted potential health risk is also mitigated.

(ii) The magnitude of the predicted impact determines the ability to detect it above the background disease rate. Some calculated risks and background disease rates are so small that detecting

additional cases of disease is not practically possible. Specific calculations are required to establish whether detecting additional cases over the background rate of disease can be done.

(iii) Statistical differences in disease rates (prevalence or new cases) may well have alternative explanations when all known risk factors are considered, beyond a potential chemical exposure.

(iv) Conversely, not finding additional cases/elevated rates does not mean that the predicted risk does not exist., as there may be a long lag time before cases present after an exposure.

(v) As mentioned above, it is recognized that sources of health status information have certain limitations in describing the health of communities. For example, hospital discharge rates may be misleading in terms of establishing specific disease rates as numbers are affected by factors such as access to the health care system and multiple admissions for the same diagnosis. As well, individuals that utilize a given hospital may reside outside of the catchment area of interest.

Therefore, translating calculated risks into real (experienced) health outcomes is challenging and should be avoided, especially when calculated risks are of small magnitude. Validation of HHRA predicted findings with epidemiologic observations requires research exercises of sophisticated design. Furthermore, it would be non-scientific to use epidemiologic observations to offset observed risks, thereby possibly minimizing the need for HHRA management steps to reduce exposure. Elevated risks established in an HHRA process are preventable and amenable to mitigation by strategies effective at reducing exposures, or such risks may be publicly acceptable. Consequently, the community health status summarized in this section is not intended to be evidence to validate or negate any predicted elevated health risks in the current HHRA. The health status information is provided to readers as contextual information about the health of the communities near the area of study.

Assessment of the health of a particular community or geographic population can be done with two frameworks of analysis: one with a theoretical perspective which calculates the risk of outcomes relevant to measured or calculated exposures (*i.e.,* using risk assessment methodologies or HHRA), and another, with a direct measure of the health experience of a population considering not just disease status, but also risk factors and social determinants of health through analysis of collected data or collection of new data. While both measures are descriptive, each provides a different evaluation of overall community health. A new epidemiological investigation is outside the scope of the current study, but data collected by the SDHU and other agencies do provide useful collaborative information on health status for comparison with expectations of health risks from the HHRA.

For example, the purpose of a human health risk assessment may be to provide estimates of potential risk of adverse health effects which may occur from exposure to the substances (*e.g.,* the COC) released to the environment from specific industrial activity (*i.e.,* smelting and mining in Sudbury). While based upon a variety of site-specific data, these calculated risks are still theoretical even if based on actual environmental measures of contaminants, in part because they are based on evaluations of health risks to hypothetical individuals within the community. The purpose of a community health status assessment is to ground truth the theory of the risk assessment with reality. How does a community compare to other communities with respect to its health experience? If the health experience is different, is this difference potentially related to environmental contamination (*e.g.,* COC) from industrial activities? Or is the difference related to the distribution of risk factors or social determinants unrelated to environmental pollution? While the description of selected health indicators is not able to attribute a specific excess of disease to a particular environmental contaminant, it is useful to look at potentially associated outcomes and see how the community fares compared to a suitable comparison. Where possible, the comparison used here is the province of Ontario.

It is important to note that the selected health measures are not intended to be in any way interpreted as directly related to environmental contamination. Indeed, the HHRA demonstrates that the risk of outcomes related to the COPCs is extremely low.

In describing the health of the community with the tools in hand (*e.g.*, census data, vital statistics, surveys of self report of health, surveys of chronic disease prevalence, hospital separation data, disease registry data, reproductive outcomes, *etc*.), we can see that they reflect health resulting from a complex set of factors. Environmental contamination may be only one of many influences.

This section summarizes some of the work that has been done in the Sudbury area to describe the health of the population. The 2001 Canadian Census[4] provides the most recent data on population characteristics as the next census will be taken in 2006. The Indian Registry System records[5] information about the aboriginal population; the information is collected annually. The source material used for aboriginals was the most recently available information as of December 2002 for aboriginals. Other specific sources are referenced if different from those specifically mentioned above.

[4] Statistics Canada, Canadian Census 2001. http://www12.statcan.ca/english/census01/home/index.cfm

[5] Indian and Northern Affairs Canada . Indian Registry System (IRS) / Certificate of Indian Status (CIS) http://www.ainc-inac.gc.ca/gol-ged/irs-cis_e.html

Data are collected by census geographic areas. In the *Sudbury & District Health Unit area*, there are three census divisions: i) Regional Municipality of Sudbury, ii) District of Sudbury; and, iii) District of Manitoulin. In 2001, the City of Greater Sudbury was formed from the amalgamation of the former Regional Municipality of Sudbury and unincorporated townships to form a new census division – the Greater Sudbury Division. This includes the City of Greater Sudbury and Wahnapitei First Nation. A map depicting these geographic areas is depicted in Figure 6-3 (Sudbury & District Health Unit Catchment Area).

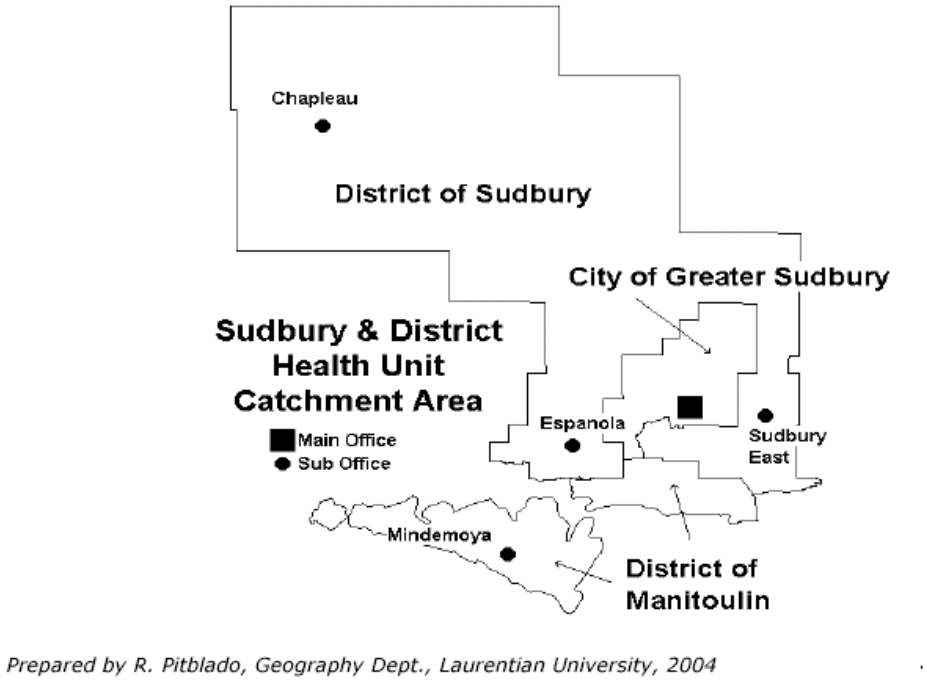

Figure 6-3 Map of the Sudbury & District Health Unit Catchment Area in 2001

Epidemiological data are generally sorted by predefined geographic areas, as for the SHDU; usually political divisions such as municipalities or census tracts, rather than ecosystem divisions such as watersheds or point source air emissions impact areas. In order to study specific impacts from a point source on populations, which are not defined exactly by geographic/political data collection units, different methodologies may be required other than analysis of data by political boundaries. Community health status is a high-level analysis while more detailed environmental-population impact requires more sophisticated epidemiologic approaches.

In order to interpret the rates of characteristics in a particular area, comparisons are made with a reference population. This allows one to determine whether there are any statistical differences between the subject population and the reference population. Generally, health outcome assessments compare a particular community with the rest of the population in the province where the community resides. Provincial rates can also be compared to overall national rates, and therefore, get a good picture of how communities fare across the country. Such exercises help to focus public health and community efforts into the areas which make the most sense to improve health status and to manage local public health resources. All of the data presented here are already published in various reports or have been provided by the SDHU. Only highlights have been selected.

Demographic Profile[6]

The majority of the population of the SDHU (81%) lives in the City of Greater Sudbury. The entire SDHU area experienced a 5% decrease in population from the 1996 to 2001 census. Francophones compose 28% of the SDHU area population, with 2% in Manitoulin District, and 30% in the Greater Sudbury Division, and 33% in Sudbury District. Sex differences are evident primarily in the over 65 age group where females predominate. Eight percent of the SDHU area population identified themselves as aboriginal. The aboriginal population figure is considered an underestimate, a reflection of undercounting in aboriginal communities. Aboriginals number 37% in Manitoulin District, 11% in Sudbury District, and 5% in Greater Sudbury Division.

The linguistic and correspondingly culturally different composition of this Region may be reflected in differences of some health statistics as compared with other regions, and must be considered in the interpretation of differences, if found. Similarly, any differences in Aboriginal group statistics must consider special social, economic, and other characteristics. This report does not attempt to analyze how differences in health outcomes may be attributable to linguistic, cultural, or other differences in health determinants unless these have been previously attributed in available publications.

[6] Resources, Research, Evaluation and Development Division, Sudbury & District Health Unit, December, 2004

Determinants of Health

The determinants of health are typically categorized as twelve broad variables(Health Canada, 2003):

- income and social status
- social support networks
- education and literacy
- employment/working conditions
- social environments
- physical environments
- personal health practices and coping skills
- healthy child development
- biology and genetic endowment
- health services
- gender
- and culture

An exhaustive disc

ussion of these for Northern Ontario and other communities has been published[7,8] and only some salient differences between provincial average characteristics and the SDHU areas will be mentioned here (also see PHRED, 2001; 2003a,b; 2005).

Household Income

The median household income (year 2000) was $43,706 for the SDHU area as compared to $53,626 for Ontario as a whole. Average incomes in Manitoulin District are lower overall, regardless of category of household by working adults. 9

Household Composition

Sixteen percent of families are lone parent families, mostly (82%) headed by females. Percentages vary across Manitoulin (20%), Sudbury District (17%), and Greater Sudbury Division (20%). Overall, about 57% of families consist of four or fewer family members.[10]

Education

Residents age 20 and over with Trades or College certificates or diplomas number at 38%, higher than the Ontario provincial average of 34%. Residents of the Regional Municipality of Sudbury are less likely to

[7] Public Health Agency of Canada http://www.canadian-health-network.ca/

[8] Health Canada. "Toward a Healthy Future: Second Report on the Health of Canadians" 1999.

[9] Sudbury & District Area Demographic Profile. Resources, Research, Evaluation and Development Division, Sudbury & District Health Unit. December 2004

[10] Sudbury & District Area Demographic Profile. Resources, Research, Evaluation and Development Division, Sudbury & District Health Unit. December 2004

have completed university (18%) than residents of the province (24%). Sudburians are more likely to have completed a trade certificate, diploma or other non-university education (31%) than residents of the province (28%).[11] At 38%, area residents age 20 and over with Trades or College certificates or diplomas make up the largest proportion of the population by education level.[12]

Employment

About the same proportion of females and males in Sudbury/Manitoulin are workers as compared to Ontario. Females are primarily in sales and services, while males predominate in trades, transport and equipment operators and related occupations. Unemployment rates are 7% for Ontario and 8 % for North Eastern Ontario, but 8.6 % for Greater Sudbury.[13] Inco and Falconbridge are the primary industrial employers of the area, followed by health care (Sudbury Regional Hospital), education (school boards, universities), city government, service industry and private sector employers.

Self-reported Health Status

Self-rated health is an indicator of overall health status. It can reflect aspects of health not captured in other measures, such as incipient disease, disease severity, aspects of positive health status, physiological and psychological reserves and social and mental function.

Adult health

Fifty two percent of adults over 18 in SDHU area reported excellent or very good health[14].

Children's health

For children's health, the majority of mothers in Northern Ontario (including SDHU areas) felt that their child's health was either good (21%) or very good (73%).[15] Based on parent's self-reported weights and heights of their child almost one-third (30%) of Northern Ontario children age two to six appear to be

[11] Kennedy, E. (August 2001). *Workers' Health Status Report: Sudbury/Manitoulin Area*. Sudbury: Sudbury & District Health Unit, Public Health Research, Education and Development (PHRED) Program.

[12] Resources, Research, Evaluation and Development Division, Sudbury & District Health Unit, December, 2004

[13] Kennedy, E. (August 2001). *Workers' Health Status Report: Sudbury/Manitoulin Area*. Sudbury: Sudbury & District Health Unit, Public Health Research, Education and Development (PHRED) Program.

[14] Statistics Canada, Canadian Community Health Survey, 2003; CANSIM Table_SDHU_HealthIndicators.htm

[15] Malaviarachi, D. (July 2001). *Key Health Indicators Including Diseases and Risk Behaviours: Sudbury/ Manitoulin District and the City of Greater Sudbury Compared to Ontario: Summary Fact Sheets*. Sudbury: Sudbury & District Health Unit, Public Health Research, Education and Development (PHRED) Program.

overweight. A further 17% are at risk of being overweight, while 9% are classified as underweight. Less than half (43%) are classified as being at a normal body mass index-for-age.[16]

Mortality

Premature mortality is higher in the Regional Municipality of Sudbury-City of Greater Sudbury than in Canada as a whole (crude rate 555 *versus* 325.16 per 100,000). The leading causes of death in the SDHU areas are cardiovascular disease, cancer, respiratory diseases, injuries and poisonings, and "other". The leading causes of illness also reflect the mortality statistics. Potential years of life lost (PYLL), a figure which reflects premature mortality, parallels mortality causes, and is highest for cardiovascular diseases followed by cancer, injury and poisoning, and other causes[17]. In both of these statistics, we see the role that cardiovascular disease plays in the mortality experience of the region, as compared to cancer, for example, which is often of primary concern with industrial emissions. The figures for SDHU and for Sudbury District reflect provincial rates except for injuries and poisonings which are higher than the province in males and females in all areas of SDHU; some of these comparisons are not statistically significant, however. Manitoulin District experienced the SDHU area's highest rates of respiratory disease deaths in males and females; these rates are higher than the province of Ontario. Smoking and other risk factors may contribute to these higher rates. The "Other causes" of death were higher in Manitoulin for females only.

The Manitoulin District experienced higher potential years of life lost (PYLL) for cardiovascular disease in males and females than the province, the Sudbury District, and the Regional Municipality of Sudbury. Similarly, the experience for all neoplasms (all cancers) paralleled the PYLL for cardiovascular disease in Manitoulin District as did the experience for injuries and poisoning, and "other causes". In short, the Manitoulin District had higher rates of death for most categories and higher premature mortality for the major causes of death than all districts of the SDHU area. Some of these differences in rates were not statistically significantly, however. The Regional Municipality of Sudbury-City of Sudbury experienced higher rates than the province for the following: cardiovascular disease in males and females; injuries and poisonings in males and females; and, premature cardiovascular mortality and cancer for both males and females.

[16] Malaviarachi, D. (July 2001). *Key Health Indicators Including Diseases and Risk Behaviours: Sudbury/ Manitoulin District and the City of Greater Sudbury Compared to Ontario: Summary Fact Sheets*. Sudbury: Sudbury & District Health Unit, Public Health Research, Education and Development (PHRED) Program.

[17] Other causes include infectious diseases, dementia, and other lesser contributors to overall mortality other than those mentioned as major contributors, such as cancer and cardiovascular disease.

Morbidity

Morbidity is the illness experience of a population. One important readily available measure of illness experience is the hospitalization rate of a population as measured by disease-specific hospital discharge rates. While this also reflects characteristics of the health care system and many other factors, it is readily available and can be compared to other areas or to the province as a whole.

Cardiovascular disease contributes the highest proportion to hospitalization experience in the SDHU area Diabetes contributes to a higher rate of hospitalization than the province in Sudbury District, Manitoulin District and the City of Greater Sudbury. The rate of hospitalization for diabetes in Manitoulin District is about twice the rate for Sudbury District in males and females. Hospitalizations for all cancers are higher than the province in the Sudbury District and the City of Greater Sudbury, but slightly lower in Manitoulin district. No statistical significance is attached to these rates.

Cancer Incidence and mortality

Looking at Cancer Mortality rates from 1980 to 1989 and 1990 to 1999, the only cancer site with a significantly (based on non-overlapping 95% Confidence Intervals for rates) higher mortality rate in the SDHU area compared to the province over both periods was lung cancer. Smoking is the most significant risk factor associated with lung cancer, and SDHU smoking rates are higher in northern Ontario than the province overall. [18]

Cancer incidence tends to be higher in northern communities than in Southern Ontario. The exact causes of these differences are not altogether known, but tobacco smoking and diet are known to play a role in lung and colorectal cancer, respectively. Bladder cancer is associated with many industrial chemicals as well, and among the environmental chemicals, arsenic exposure has been associated with bladder cancer.

Incidence rates for lung cancer and colorectal cancer were significantly higher in the Regional Municipality of Sudbury (RMS), SDHU area and Northern Ontario compared to the province over the period 1987 to 2001. Modifiable risk factors, smoking and diet are the risk factors most often associated with these types of cancer. The incidence rates for All Cancers combined for all three northern areas were significantly higher than the province over 1992 to 1996 and 1997 to 2001.[19]

[18] Source: Ontario Cancer Registry (2003) as provided by SDHU Epidemiologist.

[19] Source: Ontario Cancer Registry (2003) as provided by SDHU Epidemiologist

Incidence rates for bladder cancer in the RMS, the SDHU area and Northeast Ontario were also significantly higher compared to the province in the last period 1997 to 2001. As with lung cancer, the most important risk factor is tobacco smoking.[20]

Personal Health Practices and Risk Factors

Cancer Screening

Women 18 years and older participate in cervical cancer screening at similar rates in SDHU area and the province overall. Slightly longer time elapses between screenings in SDHU area women than in the province (five or more year lapse - 12.5 *versus* 11%, respectively); all other lapsed periods were similar (1996 data; 2003 data not included in CCHS 2003 publications).

Slightly higher proportions of women participate in breast cancer screening in SDHU area than the province (66 *versus* 60%). [Note that breast cancer incidence is higher than the province in all but Manitoulin district.] (1996 data; 2003 data not included in CCHS 2003 publications).

Smoking

Thirty-four percent report smoking status as daily (30.2%) or occasional (3.8%) This rate is higher than Ontario as a whole. Fewer residents than in the province live in houses with no smokers. Of non-smokers (former and never), almost one-third (31.3%) are exposed to second-hand smoke on most days; of this group, 80.2% were exposed in public places (*e.g.*, bars, restaurants, shopping malls, arenas, bingo halls, bowling alleys). [21]

Alcohol

Twenty-eight percent report heavy drinking (*i.e.*, five or more drinks on one occasion, 12 or more times a year).[22] However, results of the most current survey indicate that over 70% of the population of the Sudbury & District Health Unit area aged 20 and over drink alcohol in quantities considered to be low risk. Almost one-third (28.2%) of males aged 20 and over are considered to be heavy drinkers as compared to one in five in Ontario.

[20] Source: Ontario Cancer Registry (2003) as provided by SDHU Epidemiologist

[21] Canadian Community Health Survey, 2003 (CCHS)

[22] Canadian Community Health Survey, 2003 (CCHS)

Obesity and Physical Inactivity

Obesity and physical inactivity are important risk factors for cardiovascular disease and premature mortality.

Obesity

The prevalence overall in the SDHU area of overweight adults is about 35% *versus* 28% for the province (1996 data). In 2003, 36% reported overweight with body mass index 25.0 to 29.9 (18 years and over) and 18.4% reported obese, body mass index 30.0 or higher (18 years and over**).** (No statistical significance is attached to these statistics.)

Exercise

SDHU area residents tend to be more active than the rest of the province in most age categories (1996 data). However, in 2003, 52% reported leisure-time physically active or moderately active.

Worker Health

Information from the Ontario Health Survey was complied for the Sudbury & District Health unit in a 2001 Report. These data reflect status to 1999. Salient results are listed below.[23]

A higher proportion of non-workers tends to be overweight as compared to workers.[24] Workers also tend to rate their health as better than non workers.

When Sudbury/Manitoulin area workers were compared with Sudbury/Manitoulin area non-workers the trend was clearly towards better health status for the working population. Some key results include:

- Sudbury/Manitoulin area non-workers (69%) are more likely than Sudbury/Manitoulin area workers (59%) to suffer from a chronic condition.
- Sudbury/Manitoulin area workers (61%) are more likely than Sudbury/Manitoulin area non-workers (55%) to be a healthy weight.
- Sudbury/Manitoulin area workers (68%) are more likely than Sudbury/Manitoulin area non-workers (56%) to rate themselves in excellent/very good health. Sudbury/Manitoulin area non-

[23] Kennedy, E. (August 2001). *Workers' Health Status Report: Sudbury/Manitoulin Area*. Sudbury: Sudbury & District Health Unit, Public Health Research, Education and Development (PHRED) Program.

[24] Ontario Health Survey 1996-7

workers (20%) are more likely than Sudbury/Manitoulin area workers (6%) rate themselves in fair/poor health.

- Sudbury/Manitoulin area workers are in poorer health compared to Ontario workers. Examples include:
    - Sudbury/Manitoulin area workers are more likely (8%) than Ontario workers (5%) to feel that health care was needed but not received.
    - Sudbury/Manitoulin area workers are more likely (31%) than Ontario workers (24%) to be regular smokers. Sudbury/Manitoulin area workers are less likely (67%) than Ontario workers (72%) to be non-smokers.
    - Sudbury/Manitoulin area workers are more likely (59%) than Ontario workers (53%) to suffer from a chronic condition.

Environmental Factors

Transportation

Only 4% of the population in the SDHU area use public transit as main mode of transport to work compared to 13% in Ontario as a whole.

Potential relationship of health status to COC

The relationship of specific health characteristics, especially specific diseases such as cancer, can only be directly attributed to environmental exposures if actual exposure can be documented in the population experiencing the higher rate of disease, and if the rate of disease is higher in the exposed population as compared to the unexposed population. Exposure is then the critical parameter which will distinguish among those whose disease is attributable to exposure. The outcome of interest would vary with the contaminant in question. Table 6.3 below shows the COC considered in the current HHRA and the corresponding epidemiologic outcome measures which could apply. For example, for arsenic, the relevant outcomes could be lung cancer (arsenic inhalation exposure), cardiovascular disease, skin lesions or non melanoma skin cancer, bladder cancer and gastrointestinal cancer (by ingestion).

Exposure assessments and analytic epidemiologic studies would be necessary to examine these outcomes more carefully and to be able to attribute some proportion of the outcomes to environmental exposure commitments. However, it is the historical exposures that would be relevant to current cancer measures

because of the need to consider length of the period of exposure as well as intensity. Therefore, current exposure calculations (such as those conducted in the HHRA) would not be useful in making inferences about historical exposures and current or historical disease relationships.

There are many known risk factors for cancer. Some risk factors for cancer are not modifiable (*e.g.,* age, gender, genetic predisposition). Modifiable risk factors include smoking (lung cancer), poor diet (colorectal cancer), and sunlight (skin cancer). Tobacco use is the cause of an estimated 30% of fatal cancers in Canada and the overwhelming cause of lung cancer. Smoking is also a risk factor for cardiovascular disease morbidity and mortality and for low birth weight babies. The causes of all of these outcomes tend to be multi-factorial, and cannot be assessed by either community health status review of data alone or human health risk assessment alone. Smoking rates now, if similar or lower than past rates, do suggest that the lung cancer burden is attributable to smoking. Smoking is also associated with other cancers.

Occupation-related cancers are part of the statistic of population cancer incidence and mortality. In order to examine the occupational component of the total community statistic, it is necessary to carry out analytic studies to examine the multiple potential factors influencing the rates experienced. Some of these factors are direct (*i.e.,* smoking habits, diet and occupation) or indirect. On the positive side, self perception of health is generally favorable for adults and for children as reported by parents.

The HHRA and community health status together form a picture of potential exposures (and calculated risk) and a picture of actual health experience. The relationship between the two can be explored in various ways, but no conclusions can be made on attribution of outcomes to specific environmental exposures from the two separate analyses.

Table 6.3 Evaluation of Sudbury COC and Potentially-Related Human Health Outcomes Which Can Be Examined Through Administrative Data Systems or Special Surveys

COC	Associated Health Outcomes	Available Indicators of Health Status	Data Representative of Rate of outcome	Risk measures derived from HHRA and the reference values for risk	Is there an excess rate of outcome in Sudbury?
Arsenic	***Oral exposure*** Skin Cancer		No readily available data for skin cancer	RfD 0.3 µg/kg/day Based on hyperpigmentation, keratosis and possible vascular complications in human studies	There are no data for skin cancer.
	Oral exposure Vascular disease	Possible data from mortality statistics on cardiovascular disease	May be possible to dissect out attribution to exposure if exposure is high enough		There are no data for prevalence of skin pigmentation. Cardiovascular disease mortality is higher than in the province, but also there are higher rates of several risk factors for cardiovascular disease in Sudbury area such as smoking, diabetes and obesity.
	Inhalation exposure Lung Cancer	Lung Cancer especially in occupational groups	Lung cancer data available from Ontario Cancer Registry (Cancer Care Ontario)	SF_i 0.015 (:g/kg/day)$^{-1}$ [4.3e^{-3} (:g/m^3)$^{-1}$]	Rates for lung cancer tend to be higher in northern communities, as is smoking, the major risk factor. The contribution of occupation cannot be discounted but cannot be assessed by review of routinely collected data.
	Oral exposure Bladder Cancer	Cancer Registry Data	Complete data for Ontario in the Ontario Cancer Registry (Cancer Care Ontario)	RfD 0.3 :g/kg/day Based on hyperpigmentation, keratosis and possible vascular complications in human studies	Specific rates for bladder cancer are not reported in the SDHU health status report. Ontario rates for men and women have been decreasing. Pre-invasive carcinomas are not reported. Ontario has the lowest rates of bladder cancer in Canada. Other potential causes of bladder cancer besides arsenic are highly prevalent, such as smoking and some products of chlorination in drinking water.

Table 6.3 Evaluation of Sudbury COC and Potentially-Related Human Health Outcomes Which Can Be Examined Through Administrative Data Systems or Special Surveys

COC	Associated Health Outcomes	Available Indicators of Health Status	Data Representative of Rate of outcome	Risk measures derived from HHRA and the reference values for risk	Is there an excess rate of outcome in Sudbury?
	GI Cancer esophagus; stomach; SI; pancreatic;	Cancer Registry data for esophagus, stomach; small intestine	Complete for Ontario in the Ontario Cancer Registry (Cancer Care Ontario)	RfD 0.3 :g/kg/day Based on hyperpigmentation, keratosis and possible vascular complications in human studies	No data
	Cardiovascular peripheral vascular disease	Hospital Discharge data	Incomplete (not all events are hospitalized)	RfD 0.3 :g/kg/day Based on hyperpigmentation, keratosis and possible vascular complications in human studies	No data
	Non- cancer effects Skin lesions (palmar and solar cornification)	No data	N/A	RfD 0.3 :g/kg/day Based on hyperpigmentation, keratosis and possible vascular complications in human studies	No data on skin changes.
	Peripheral Neuropathy	No data	N/A	None	No data
	Reproductive Effects	Data available on birth weight and small for gestational age infants; from the Ontario birth registry.	Reported in SDHU Health Status Report	Data on toxicity are from animal studies Chronic REL	No data
Cobalt	Required for normal metabolism.	No data applicable	No data available to assess	MDR (minimum daily requirements)	No data on cobalt status.
Copper	Required for normal metabolism.	No data applicable	No data available to assess	Oral RfD 91 :g/kg/day Inhalation 1 :g/m^3	No data on copper status or on prevalence of Wilson's disease in the population.

Table 6.3 Evaluation of Sudbury COC and Potentially-Related Human Health Outcomes Which Can Be Examined Through Administrative Data Systems or Special Surveys

COC	Associated Health Outcomes	Available Indicators of Health Status	Data Representative of Rate of outcome	Risk measures derived from HHRA and the reference values for risk	Is there an excess rate of outcome in Sudbury?
Lead	1. blood lead levels in children 2. blood lead levels in newborns 3. blood lead levels in pregnant women Blood lead levels at various stages of development are associated with deficiencies in several neurocognitive measures in children (IQ and other more subtle neurocognitive measures).	No Sudbury-specific data; good Ontario data but not current.	No data available to assess in SDHU areas. Conservative measures of exposure can be estimated from HHRA.	1.85 :g/kg/day under 10 :g/dL in blood for children under 6 years	No data on lead exposure in children.
Nickel	Occupational exposures to specific nickel compounds associated with lung cancer and nasal sinus cancer.	Registry data for lung cancer and sinus cancer. Occupational studies have been done and there is continued surveillance of the workforce. Probably not a community exposure cancer outcome.	Complete data for cancer in Ontario; need to adjust lung cancer rates to account for smoking status and occupational exposure to nickel compounds status.	Oral RfD 20 :g/kg/day Inhalation SF 2.0×10^{-5} $(:g/m^3)^{-1}$ RfC 0.1 $:g/m^3$ [nickel oxide]	No data

Table 6.3 Evaluation of Sudbury COC and Potentially-Related Human Health Outcomes Which Can Be Examined Through Administrative Data Systems or Special Surveys

COC	Associated Health Outcomes	Available Indicators of Health Status	Data Representative of Rate of outcome	Risk measures derived from HHRA and the reference values for risk	Is there an excess rate of outcome in Sudbury?
Selenium	Selenosis associated with ingestion of selenium-rich grass in cattle, rare in humans.	Clinical selenosis	No data available to assess outcomes. Clinical selenosis is rare areas of non-selenium rich soils.	UIL 5.00 :g/kg/day Upper Intake Level (UIL) - maximum level of daily nutrient intake that is likely to pose no risk of adverse health effects	No data on selenosis.

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6.8 The Elderly and Lifetime Exposures in Risk Assessment

6.8.1 The Elderly as a Sensitive Subpopulation

Children as a sensitive subpopulation in risk assessment have been the subject of intensive research and methodological development in recent years, while less focus has been given to the elderly as another potentially sensitive group. When discussing the fact that a subpopulation may be considered sensitive, it is important to note the distinct between those who may be considered "sensitive" because they are more "highly exposed" than other portions of the overall populace *versus* those that are specifically sensitive from a biological or toxicological point-of-view (*e.g.*, asthmatics).

Although many risk assessment paradigms describe the elderly as a sensitive subpopulation, specific methodologies for the assessment of risks to the elderly have not been developed. That child-specific risk assessment paradigms have been developed is, in part, a reflection of the general protective attitude of society toward the young. In addition, several of the factors which make children more vulnerable to chemical toxicants do not apply to the elderly:

- Children have disproportionately heavy exposures to many toxicants (*i.e.*, "highly exposed") due to a combination of behavioural and physical parameters (*e.g.,* time spent playing close to the ground, hand-to-mouth behaviours, higher breathing rates and higher surface area to body mass ratios) which the elderly do not share;

- Children, but not the elderly, are in a phase of rapid growth and development in which developmental processes are easily disrupted (*i.e.*, sensitive); and

- Children have more years of future life than the elderly, and thus more time to develop diseases initiated by early exposures.

One factor that contributes to the vulnerability of children to chemicals does have a parallel in the elderly. Children's metabolic pathways are immature and they may not be able to clear toxicants in the same way as adults. In the elderly, liver and kidney function is impaired with age, limiting the body's ability to detoxify chemicals (Iyaniwura, 2004). In addition to the physical factors influencing the vulnerability of the elderly to chemical toxicity, the mental, social, psychological and economic changes associated with aging may also increase vulnerability to chemical toxicity (Iyaniwura, 2004).

Given the unique factors that can enhance their vulnerability, young children are generally considered to be the most sensitive subpopulation with regard to chemical toxicity. In particular, the female preschool child is generally selected as the most sensitive receptor life stage in the assessment of non-carcinogenic risk because they consume more food and water for their body mass, have higher inhalation rates for their body mass, and have higher surface area to volume ratios than other gender-specific life stages (U.S. EPA, 2002a). In other words, they are considered sensitive due to their propensity to be more highly exposed to COC than other lifestages.

However, since the exposure pattern and mode of action varies for each chemical, current toxicological reviews were consulted to confirm that the elderly do not have any significant vulnerabilities to the COC. The ATSDR has conducted detailed toxicological reviews of each of the COC, and was used to evaluate whether the elderly, as a subpopulation, has demonstrated any potential sensitivity towards exposure to the assessed COC. Further details are also provided for each COC in the detailed toxicological profiles in Appendix A of this volume.

Arsenic

In their review, ATSDR (2000a) did not locate any studies regarding unusual susceptibility of any human subpopulation, including the elderly, to arsenic. ATSDR (2000a) did not identify the elderly as a specific subpopulation with potentially high arsenic exposures.

Cobalt

ATSDR (2004b) did not identify the elderly as a subpopulation that is unusually susceptible to cobalt; however, those who have been previously sensitized to cobalt and those with ongoing respiratory illness may be unusually susceptible, and these conditions may be more prevalent among the elderly than in the general population. The elderly were not identified by ATSDR (2004b) as a specific subpopulation with potentially high cobalt exposure; however implants or prosthetic devices made of cobalt-containing alloys may contribute to elevate cobalt exposures (ATSDR, 2004b). Again, there may be a higher prevalence of implants and prosthetic devices in the elderly than in the general population.

Copper

ATSDR (2004d) did not identify the elderly as a subpopulation that is unusually susceptible to copper, nor were they identified as a specific subpopulation with potentially high copper exposure.

Lead

In their review, ATSDR (1999) found that although children are the subpopulation at greatest risk of lead-induced health effect. However, the elderly may also be a potentially vulnerable subpopulation. Two recent studies found an association between decreased neurobehavioural performance and blood lead levels in elderly subjects with blood lead levels of approximately 5 µg/dL (Muldoon *et al.,* 1996; Payton *et al.,* 1998), similar to the threshold identified for sensitive children (see Appendix A of this volume). Animal data also support the conclusion that the elderly may be particularly vulnerable to lead. However, following a detailed review of the scientific data, the elderly were not identified by ATSDR (1999) as a specific subpopulation with potentially high lead exposure.

Nickel

ATSDR (2003a) did not identify the elderly as a subpopulation that is unusually susceptible to nickel; however those who have been previously sensitized to nickel may be unusually susceptible. The elderly were not identified by ATSDR (2003a) as a specific subpopulation with potentially high nickel exposure; however, patients with nickel-containing joint prostheses, sutures, clips, and screws for fractured bones; dialysis patients; and, patients receiving transfusions may have elevated nickel exposures. There may be a higher prevalence of such medical devices and procedures in the elderly than in the general population.

Selenium

ATSDR (2003b) did not identify the elderly as a subpopulation that is unusually susceptible to selenium; in fact, the elderly may be less susceptible to adverse effects from selenium and more prone to selenium deficiencies. Similarly, the elderly were not identified by ATSDR (2003b) as a specific subpopulation with potentially high selenium exposure.

6.8.2 Evaluation of Lifetime Cancer Risks

In assessments of cancer risk, the length of an individual's life is an important factor, because the dose estimate is averaged over the individual's lifetime. In the Exposure Factors Handbook, U.S. EPA (1997) discusses lifetime in the context of risk assessment. Since the averaging time is found in the denominator of the dose equation, shorter estimates of lifetime result in higher risk estimates, while longer lifetimes result in lower risk estimates (U.S. EPA, 1997). U.S. EPA (1997) encourages risk assessors to use lifetime values that most accurately reflect the exposed population. Traditionally a 70 year lifespan has been assumed for use in both the development of cancer slope factors, as well as exposure averaging

times. However, based on life expectancy data from the U.S. Census, the U.S. EPA (1997) has recommended moving towards use of a lifetime of 75 years for the general population, and if males and females are evaluated separately in the risk assessment, they recommend using a lifetime of 72.1 years for males, and 78.9 years for females.

When using lifetime values other than 70 years, risk assessors should consider whether the dose-response relationships used were derived by assuming a lifetime of 70 years (U.S. EPA, 1997). To avoid introducing inconsistencies, a dose-response relationship that assumes a lifetime of 70 years can be adjusted by multiplying by the ratio of the population lifetime over 70 (U.S. EPA, 1997).

While the typical lifespan of a Canadian is now greater than 70 years, it is more conservative to use a lifetime value of 70 years (as discussed above) than to adopt the revised values recommended by the U.S. EPA (1997). Use of a 70-year lifespan is also the typical approach currently taken in most risk assessments conducted in Ontario and Canada, as a whole.

6.8.3 Recommendations

No evidence was identified to indicate that the elderly may be more vulnerable to any of the COC than a young child. As such, the female preschool child was selected as the most sensitive receptor lifestage for evaluation of non-carcinogenic risk for the current assessment.

A lifespan of 70 years was conservatively selected for the evaluation of lifetime cancer risks for the current assessment.

6.9 COC Lifetime Body Burden

Some concern has been raised by members of the Sudbury community that long-term exposures to the COC being evaluated in the Sudbury HHRA, over an individual's lifetime, could result in an accumulation of these COC leading to potential health risk with age. While this could be a concern for certain organic compounds (*e.g.,* PCBs, dioxins and furans, methyl mercury, *etc*.) which can bioaccumulate in the body's tissue, this is not the case for the COC under study in the current human health risk assessment. This is largely because the COC in question do not bioaccumulate, resulting in very little body burden over time. It is also important to note that three of the six COC are actually essential elements needed by the body for proper health.

The following section will provide background information on the implications of body burden, bioaccumulation, and essentiality of the particular COC on long-term health of an individual as they age.

6.9.1 Body Burden

An individual's body burden of a particular substance is the total amount of that substance in the individual's body, based upon the amount absorbed, mobile within the body, or ultimately stored for a period of time. As such, the body burden for a substance is equal to the amount taken up minus the amount eliminated *via* metabolism and/or excretion. However, it is important to note that in the case of many metals metabolism is not a relevant component of elimination because the metal itself cannot be broken down to a non-toxic form. The human body has evolved mechanisms to deal with the wide variety of chemical elements it is faced with on a daily basis. As a result of this evolution, pathways and mechanisms are present by which the COC may be safely removed from the body to prevent the possible bioaccumulation of the COC. Typically this is achieved by making them more polar so that they may be eliminated in urine. However, it is important to note that metabolism will not necessarily make a xenobiotic less toxic. In many cases (though not for the current COC), metabolic daughter products can be more toxic, or have implicit toxicity at a different site within the body, than the parent compound.

6.9.2 Potential Bioaccumulation

Bioaccumulation is the process whereby a substance collects in the body at concentrations greater than those found in the environment. Bioaccumulation is an essential process that allows organisms to obtain adequate nutrition from an environment in which many nutrient are present at low concentrations, but it can be of concern for certain toxic substances. For bioaccumulating substances, elimination of the substance does not keep pace with uptake, and the body burden increases as long as exposure continues. In general, substances that are quickly eliminated are not bioaccumulated. Substances may be attracted to certain sites, bind to proteins or dissolve in fats, and be temporarily stored, thus preventing or slowing its elimination from the body. While elimination of tightly bound substances is limited, if uptake slows or discontinues, or if the chemical is not very tightly bound, the body can eventually eliminate the chemical over time.

6.9.3 Overview of COC-Specific Uptake, Distribution, Storage and Elimination

Three of the COC (*i.e.*, cobalt, copper and selenium) are essential elements, meaning that a certain body burden must be maintained to prevent deficiencies and to maintain good health. Homeostatic

mechanisms ensure that levels of the element are adequate for the body's needs, but do not reach toxic levels. These mechanisms are generally effective, but may be impaired or missing (which can lead to chronic poisoning), or they can be overwhelmed by high doses (*i.e.,* acute poisoning). For the essential elements, uptake, distribution, storage and elimination are all strongly dependent on the nutritional status of the individual as the body seeks to maintain ideal concentrations.

The remaining three COC (*i.e.*, arsenic, lead and nickel) have no known functions in the body (though there is some evidence that arsenic may be beneficial at very low doses). As stated previously, strongly bound substances are less available for elimination, and tend to be those that bioaccumulate. Arsenic and nickel are not stored or bound in such a way that they are unavailable for elimination. However, lead that is not excreted is sequestered in bone tissue. It should be noted that this stored lead is unavailable for either elimination or toxicity until it is released from the bone stores.

The following section provides an overview of the update, distribution, storage and elimination of each COC within the human body. Please refer to the detailed toxicological profiles in Appendix A for an in-depth discussion of this topic.

Arsenic

Once it has been absorbed *via* any route, arsenic is eventually distributed evenly between various body tissues, with slight elevations in nails and hair (Liebscher and Smith, 1968; Kurttio *et al.,* 1998). It is eliminated from the body primarily through urinary excretion. Most arsenic is promptly released in the urine (ATSDR, 2000a). Various estimates of arsenic retention and elimination have been reported. Based on a variety of studies reviewed by ATSDR (2000a), the percentage of an administered dose excreted in urine in the first one to three days after exposure is 45 to 85% for oral exposures, 30 to 65% for inhalation exposures and 50% for dermal exposures. Other studies have noted a pattern of triphasic elimination. Pomroy *et al.* (1980) calculated half lives for inhaled arsenic in humans of 2.1 days for 66% of the dose, 9.5 days for an additional 30% of the dose and 38 days for the remaining 4% of the dose. Similarly, Apostoli *et al.* (1997) estimated a half life of four days for 75% of an ingested dose, and 10 days for the remaining 25%. In general, the retention and elimination of arsenic depends on the chemical species. Following inhalation exposure, the most rapidly eliminated species is As^{V} with a half life of 27 hours, while arsenobetaine was the slowest species to be eliminated among those tested at 86 hours (Apostoli *et al.,* 1997). Arsenic is not bioaccumulated within the body.

Cobalt

As a component of vitamin B_{12}, cobalt is an essential element (ATSDR, 2004a). It is found in many tissues of individuals with no known occupational or environmental exposures to cobalt, with the highest concentrations found in the liver, where vitamin B_{12} is stored (ATSDR, 2004a). Cobalt elimination depends on the dose, chemical species and the nutritional status of the subject. For example, fecal elimination of an oral dose can range from 3 to 99% of the dose (Harp and Scoular 1952; Paley *et al.,* 1958; Smith *et al.,* 1972; Sorbie *et al.,* 1971; Valberg *et al.,* 1969). Foster *et al.,* (1989) reported that six months after an inhalation exposure to cobalt oxide, 61% of the initial lung burden had been eliminated (33% in urine and 28% in feces). Bailey *et al.,* (1989) reported that greater than 96% of an ingested dose of Co_3O_4 was quickly eliminated in several lab species. Cobalt does not bioaccumulate within the body.

Copper

Copper is also an essential element, and therefore its uptake, metabolism and excretion are physiologically regulated to maintain copper homeostasis (ATSDR, 2004d). The copper content of the human body is maintained at approximately 100 to 150 mg, a level which avoids both copper deficiency and toxicity (WHO, 1998). Copper homeostasis is disrupted in individuals with genetic defects that impair copper homeostatic mechanisms, such as Wilson's disease. Chronic copper toxicity is associated mainly with liver effects and is almost exclusive to individuals with these defects (ATSDR, 2004d). Bile is the major pathway for copper excretion (ATSDR, 2004d). Normally, 0.5 to 3% of daily copper intake is excreted into the urine (Cartwright and Wintrobe, 1964). Following oral administration of copper acetate, 72% of the dose was excreted in feces (Bush *et al.,* 1955). Copper does not bioaccumulate within the body.

Lead

On absorption, lead is initially widely distributed to plasma and soft tissues, and then it is redistributed and accumulates in bone (ATSDR, 1999). Typically, 90% or more of the body burden of inorganic lead is stored in bone tissue. This can be a significant source of lead when bone tissue is undergoing significant deossification or demineralization, such as during pregnancy, lactation or menopause (IARC, 2004). Mobilization of lead from bone varies greatly with age, health status, nutritional state and physiological state. Lead that is not retained by the body is excreted principally by the kidney as salts, or through biliary clearance into the gastrointestinal tract (ATSDR, 1999). Excretion rates are highly variable, and the data suggest that the fraction of absorbed lead that is retained by humans decreases with

age (ATSDR, 1999). Infants (birth to two years of age) retain 31.7% of the total amount of lead absorbed (Ziegler *et al.,* 1978), while adults retain only 1% of the absorbed dose (Rabinowitz *et al.,* 1977). Lead can accumulate in bone tissue, but it will typically stay bound up and unavailable for toxic effect, unless the body undergoes significant deossification or demineralization.

Nickel

Retained nickel in non-occupationally exposed individuals accumulates in the skin, adrenal glands and intestines (ATSDR, 2003a). If the individual was exposed *via* inhalation then nickel also tends to accumulate in the lungs (ATSDR, 2003a) because deposited particulated of low water solubility are cleared quite slowly in humans. For example, a half-life estimate of 3.5 years has been calculated for welders and nickel workers exposed to nickel *via* inhalation (Nieboer *et al.*, 1999). Absorbed nickel is excreted in the urine, while nickel that is not absorbed from the gastrointestinal tract is excreted in the feces (ATSDR, 2003a). After 4 days, 26% of a dose given in water was excreted in urine and 76% was excreted in feces, while nearly all of a dose given in food was excreted in feces (Sunderman *et al.,* 1989). The average elimination half life for absorbed nickel was 28 ± 9 hours (Sunderman *et al.,* 1989). In another study, 51 to 82% of the nickel dose was excreted in urine within five days (Patriarca *et al.,* 1997). Nickel does not bioaccumulate within the body.

Selenium

Selenium is an essential element which is used in the body to form selenoproteins, it is also believed to have a protective effect against certain types of cancer. It accumulates in many organ systems, but is generally highest in the liver and kidneys, followed by the spleen, pancreas, blood, plasma, erythrocytes, skeleton, muscle and fat. Selenium is primarily eliminated in urine, feces and expired air (ATSDR, 2003b). Excretion of selenium is dependent on the level of intake, the type of diet from which selenium is absorbed, and the form in which the selenium was absorbed. Thomson and Stewart (1973) found that <6% of a trace dose of selenium (0.01 mg) as sodium selenite was excreted in urine within one day, while 64 to 73% of a larger dose (1 mg selenium as sodium selenite) was excreted in the same time period. Selenium does not bioaccumulate within the body.

6.9.4 Conclusions

While the potential for accumulation of certain environmental contaminants is a concern for many risk assessments, none of the COC being evaluated in the Sudbury HHRA are prone to significant accumulation within the body over an individual's lifespan. In fact, most of the COC have a very short half-life within the body, and in some cases are essential nutrients for good health. As such, even long-term exposure to the COC in question would not have any additional risk other than that which is already evaluated using the selected toxicological limits.

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