CHAPTER 6

OTHER RISK ASSESSMENT ISSUES

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6.0 OTHER RISK ASSESSMENT ISSUES

While conducting the Flin Flon/Creighton 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 Flin Flon chemicals of concern (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 Flin Flon area residents;
- A discussion of the implications of metal-metal interactions, given 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;
- An overview of the epidemiology and community health status for the Flin Flon area, as it pertains to the COC evaluated in the HHRA;
- A discussion of lifetime exposures, and how the elderly are addressed within the HHRA as a potentially sensitive life stage; and,
- Whether Flin Flon area 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 Flin Flon/Creighton 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 Flin Flon area.

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).

[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.

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).

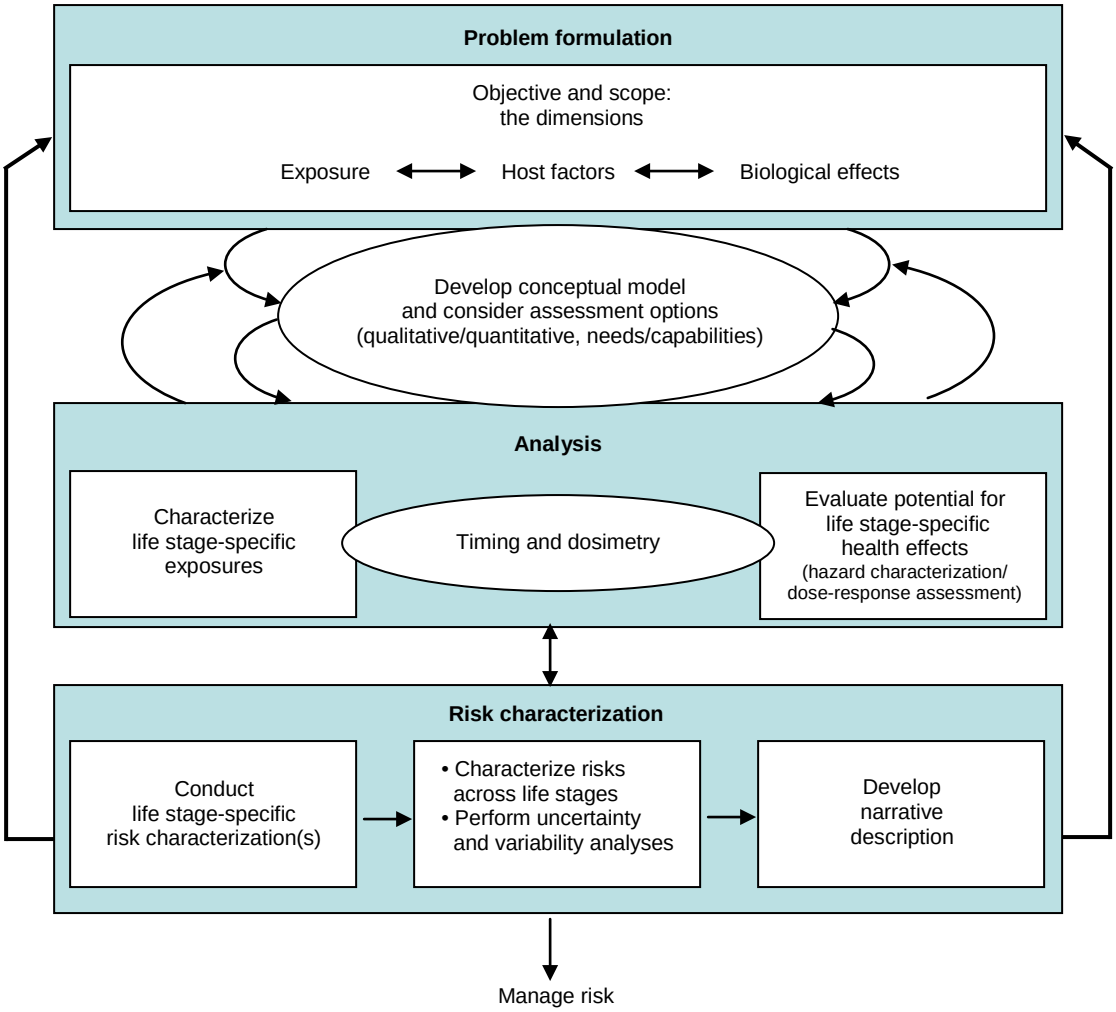

Figure 6-1 Proposed Framework for Assessing Risks to Children from Exposure to Environmental Agents (Daston *et al.*, 2004)

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 sub-set 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:

- Smaller body size;
- Different ratios of fat, muscle and water within the body;
- Higher breathing and metabolic rates per unit of body mass; and,
- 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).

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 colonel 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

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

acclimatization begin dosing. As such, study dosing would begin at an age that is roughly equivalent to human teenagers.

Due to this uncertainty, 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, 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;
- Toddler (0.5 to <5 years) 10-fold UF;
- Child (5 to 12 years) 3-fold UF; and,
- Adolescent (12 to 18 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 cadmium in the current assessment. The correction factor for early life exposure was not applied in the assessment of carcinogenic risk from exposure to arsenic, since the arsenic cancer slope factors are based on lifetime studies that inherently address increased susceptibility following exposures to infants, children and unborn fetuses.

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 Flin Flon. While SO_2 has not been considered 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 Flin Flon 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 (Goyer *et al.,* 1985; Smith, 1992). 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 (Smith, 1992; Gerhardsson *et al.,* 1994; Elvingson and Ågren, 2004). 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).

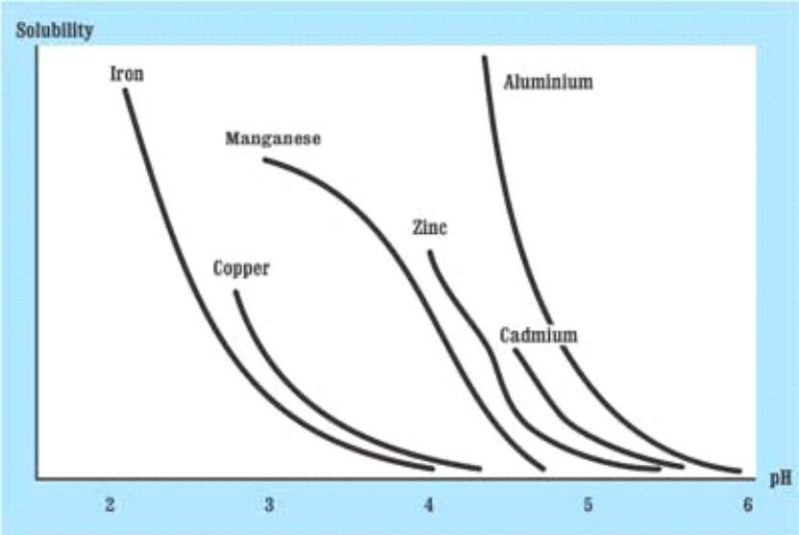

Figure 6-2 Release of Metals from Mineral Soil at Different pH Levels. [Elements with Steep Slopes in the Range Environmental pH Values, Such as Aluminum and Manganese, are Strongly Affected by Acid Precipitation (Elvingson and Ågren, 2004)]

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 liming activities undertaken within the Flin Flon area 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. These activities have a significant impact on soil pH and play a significant role in the 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 HHRA. 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 Flin Flon community.

When discussing this issue, it is important to understand that the HHRA 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. HBMS has programs in place that examine and measure a worker's exposure to the chemicals of concern being addressed by the HHRA. Most importantly, different levels of "acceptable" risk are assumed for employees in the workplace compared to a resident of the general Flin Flon 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 HHRA 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, 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 (refer to Appendix D), occupational information was gathered on all members of the evaluated households. No association between COC concentrations in house dust and employment by HBMS 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 2004a (see http://www.atsdr.cdc.gov/interactionprofiles) 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; and,
- 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***
Copper	--	Arsenic[a]
Selenium	--	Cadmium
--	--	Mercury
--	--	Lead

[a] Goyer *et al*. (2004) does not formally classify arsenic as a metal with possible beneficial effects. WHO (1996); NAS/IOM (2003) have classified arsenic as having possible beneficial effects although a critical review by NRC (1999) does not support this statement. Studies in poultry have shown that some organic compounds act as growth factors and in rats, hamsters, goats, miniature pigs and chicks, arsenic deprivation may impair growth. However, in humans, the possible benefits on metabolic functions is yet to be established (NRC, 1999).

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, and 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. However, none of the available data are adequate at this time for predicting the magnitude of the reported interactions (Goyer *et al.,* 2004), and depending on the endpoint, there is conflicting data as to the direction of the interactions (ATSDR, 2004b,c). 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

Health Canada does not have a specific guidance on the human health risk assessment of metals mixtures. In their 2004 risk assessment guidance document for contaminated sites they recommend assuming that HQs are additive for simultaneous exposure to chemicals with similar target organs, effects or mechanisms of action (HQ approach) (Health Canada, 2004). For carcinogens they recommend that the ILCR should be in 1 in 100,000 for the sum of all carcinogens with the same target organ and form of cancer.

IPCS in association with WHO is attempting to harmonize approaches to the risk assessment from exposure to chemicals. One of the areas is to focus on the methods used to assess combined exposure to multiple chemicals (aggregate/cumulative risk assessment). The draft "Framework to Consider Combined Exposures" in risk assessment has been available for public and peer review as of September, 2008 (IPCS, 2008). Currently, WHO (2006) recommends considering mixture effects only when chemicals are "present near their guideline value and have similar mechanisms of toxicity."

U.S. EPA (1986) first published a mixture guideline document. A supplementary guidance document for conducting human health risk assessment of chemical mixtures was published in 2000. In comparison to the ATSDR guidance document, it is fairly similar but with less emphasis on PBPK and PBPD modeling (Monosson, 2005). As well, similar to ATSDR, the Hazard Index for the mixture of concern is first calculated and then modified according to evidence on pairwise interactions. In terms of weight-of-evidence (WOE), the U.S. EPA requires stronger evidence for antagonism before allowing relaxation of expected toxicity (Hertzberg and Teuschler, 2002).

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 separate effect assessments are encouraged for each metal, or a response-additive approach is recommended (US 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). 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 (1986; 1989; 1990; 2000a) 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 US 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). Uncertainties associated with the formula of the HI include 1)"assumption of a common MOA might not apply because only commonality of the target organ is considered" 2) Using the lower bound on the toxicity threshold (safe level) may not be an accurate measure of the toxic potency. Weak toxicity data results in a lower safe level because of larger uncertainty factors or use of lower confidence bounds on the dose 3) "The use of RfDs as safe levels may results in an overestimate of the degree of concern because the RfD is based on one critical or most sensitive effect. Therefore, when a chemical causes multiple effects and is to be included in more than one HI calculation, the general use of its RfD is problematic. A solution to generate Target organ Toxicity Doses (TTD) for use in target organ specific HI calculations (currently recommended for oral exposures only) (U.S. EPA, 2000a).

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 developed a "Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures" in May 2004 (ATSDR, 2004a)." Generally, the approach recommended is similar to the U.S. EPA in which the method of choice utilizes the use of exposure and toxicity data on the whole mixture of concern or a similar mixture. Interaction profiles for certain chemicals that tend to occur together have been developed (http://www.atsdr.cdc.gov/interactionprofiles/). The

interaction profiles may be of use in providing targeted toxicity dose RfDs for the COC and for the WOE evaluation for pairs of COC. If whole mixture data or interaction profiles are not available, then ATSDR recommends a component-based approach. This approach only applies if exposures are high enough that the joint toxic action of the components may pose a hazard due to additivity or interaction or both.

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 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 (HI) 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 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 the 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 vs. 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) 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 U.S. 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 *vs.* 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 (2004b,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.

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, 2004b,c), 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 (2004b,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 (Table 6-3).

Table 6-3 Predicted Direction of Interactions between COC *via* Oral Exposure Routes (from ATSDR, 2004b,c)

Effect of	*Cardiovascular Toxicity*			*Dermal Toxicity*	*Haematological Toxicity*			*Hepatic Toxicity*	*Neurological Toxicity*				*Renal Toxicity*				*Testicular Toxicity*	
	As	Cd	Pb	As	As	Cd	Pb	Cu	As	Cd	Pb	MeHg	As	Cd	Pb	Hg	Cd	Pb
As	--	--	I	--	--	<A	<A	--	--	--	> A	--	--	I	<A	--	<A	--
Cd	--	--	A	I	<A	--	<A	--	--	--	> A	--	A	--	<A	--	--	>A
Cu	--	--	--	--	--	--	<A	--	--	--	<A	--	--	--	--	--	--	--
Pb	I	A	--	I	<A	A	--	NE	> A	I	--	A	<A	A	--	>A	>A	--
Hg	--	--	--	--	--	--	--	--	--	--	I	--	--	--	--	--	--	--
MeHg	--	--	--	--	--	--	--	--	--	--	A	--	--	--	--	--	--	--

-- Not specified
A Additive
< A Less than additive
>A More than additive
I Indeterminate
MeHg Methyl mercury
NE No effect

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 Petering, 1975).

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); and,
- 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. However, since data for lower doses is not available, in order to remain protective of the population the information for a higher dose was used and represents a worst-case scenario;
- 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; and,
- 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. Similar to Table 6-3, Table 6-4 summarizes joint action between COCs and no-COCs *via* oral exposure routes for a selected number of toxicological endpoints that have been summarized by ATSDR (2004b,c). The summary provides the predicted direction of interactions between binary pairs of metals in which one is the COC and the other is a non-COC.

Table 6-4 Predicted Direction of Interactions between COC and Non-COC *via* Oral Exposure Routes (from ATSDR, 2004b,c)

Effect of	***Haematological Toxicity***		***Hepatic Toxicity***	***Neurological Toxicity***		***Dermal & other Non-Renal Toxicity***	***Renal and Non-Renal Toxicity***	***Renal Toxicity***
	Pb	Zn	Cu	Mn	Pb	As	Cr (VI)	As
Cr (VI)	--	--	--	--	--	>A	--	<A
Cu	--	P	--	--	--	--	--	--
Mn	>A	--	--	--	>A	--	--	--
Pb	--	NE	--	A	--	--	--	--
Zn	<A	--	<A	--	<A	--	--	--
As	--	--	--	--	--	--	<A	--

-- Not specified
A Additive
< A Less than additive
>A More than additive
P Protective

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, 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, cadmium, copper, lead, mercury 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 behavioral 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 (Bruhn and Pangborn 1971; Vermeer and Frate 1979). (Binder *et al*., 1986; Clausing *et al*., 1987; Calabrese *et al*., 1989; Davies *et al*., 1990; van W'ijnen *et al*., 1990; Thompson and Burmaster, 1991; Sedman and Mahmood, 1994; Stanek and Calabrese, 1995). 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, 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. U.S. EPA (2002a) determined that the 95th percentile values for soil ingestion, based on key studies identified ranged from 106 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:

- 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;

- 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;
- 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;
- There is uncertainty with regard to the homogeneity of soil samples and the accuracy of parents' knowledge about their children's play areas; and,
- 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 behaviur 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 behavior. A high degree of daily variability in soil ingestion was observed among the six children who exhibited pica behavior. 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, 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's (ATSDR) held an experts workshop on soil-pica behaviour in June, 2000, in Atlanta, Georgia (ATSDR, 2000). The panelists thoroughly discussed and debated the prevalence of soil-pica behavior, ingestion rates for soil-pica, means for identifying people with soil-pica behavior, 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 by 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 to 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 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 behavior, and some pica behavior. 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. Furthermore, the evaluation of short-term risks considering pica behaviours is highly uncertain and as such this has not been quantitatively evaluated.

6.6 Community Health Status Assessment: Flin Flon and Creighton

A Community Health Status Assessment of Flin Flon and Creighton was completed by public health officials from Manitoba Health and Healthy Living and the Saskatchewan Ministry of Health concurrently with the Flin Flon and Creighton HHRA study. The study aimed to provide an assessment of the overall health status of the combined populations of Creighton, SK, Flin Flon, SK and Flin Flon, MB (FF/CR) in comparison to Manitoba, Saskatchewan, the NOR-MAN Health Region, and the Mamawetan Churchill River (MCR) Health Region. The assessment was not designed to replace the need for the HHRA, but rather to provide information to complement the work of the HHRA.

This study reviewed a number of common health conditions and health determinants over a 10 year period, from 1996 through 2005, using information collected from various sources including the Vital Statistics Agency of Manitoba, the Vital Statistics Registry of Saskatchewan, the Saskatchewan Cancer Registry, the Manitoba Cancer Registry, the Canadian Community Health Survey conducted by Statistics Canada and Census Canada.

Confidence Intervals ("Error Bars")

Ninety-five percent confidence intervals (CI) were used in this study where appropriate to demonstrate information on the range in which results will most likely be found. This is necessary because for survey information, only a sample of the population is surveyed and thus by chance the people selected may not accurately reflect the whole population. The 95% CI indicates the range that the whole population answers will be true 95% of the time (*i.e*., correct 19 times out of 20). Specifically, this measure was used to compare the rates of cancer incidence and vital statistics between populations.

Population

Population age structure can make a difference when comparing health status between groups. Population groups with younger age structures for example, would be expected to have lower rates of some illnesses such as cancer and chronic conditions (*e.g*., diabetes and heart disease) than populations with older age structures. Differences in the population age between FF/CR and the four comparison populations were thus considered and found notably different. Appropriate statistical adjustments (called 'age standardization') were conducted so that comparison between populations was possible.

Health Determinants – "The Things That Determine or Influence Our Health"

Health status is determined by a combination of factors including, incomes and social status, education, employment, the natural and human-made environment, social supports, early childhood development, health services and health behaviors.

The Creighton and Flin Flon communities have similar (or slightly higher) education, employment, and income measures compared to Manitoba and Saskatchewan populations, as well as fairly similar housing conditions in terms of crowding. For some of the non-medical health determinants however, current information is not available for Creighton and Flin Flon, while it is available for the MCR and NOR-MAN Health Regions.

For off-reserve populations in NOR-MAN and MCR Health Regions, there are higher rates of people who are overweight and obese, are heavy drinkers, and are more exposed to second-hand smoke compared to the general population in Saskatchewan and Manitoba but the

differences are not statistically significant. In the MCR Heath Region rates of smoking are significantly higher than in Saskatchewan, and in the NOR-MAN Health Region rates of smoking are significantly higher compared to Manitoba.

For purposes of comparison, the Manitoba population most closely resembles the FF/CR population based on the population and health determinants indicators, followed by Saskatchewan, and subsequently the NOR-MAN Health Region.

Vital Statistics

a) Mortality

For all causes of death combined, the death rate in FF/CR is lower than the death rates in NOR-MAN and slightly lower than in Manitoba and Saskatchewan. In assessing the death rates by age group, generally there is little difference between populations for most age groups. Mortality rates in FF/CR are lower than MCR Health Region in the 20 to 35 year age group and lower than NOR/MAN Health Region, Manitoba and Saskatchewan in the 35 to 65 year age group. For over 65 years of age, death rates in FF/CR are roughly the same as the provincial rates, less than those in NOR-MAN and higher than in MCR Health Region;

Death rates associated with circulatory disease are lower in FF/CR compared to NOR-MAN, Saskatchewan and Manitoba, as are death rates for cancers compared to NOR-MAN and Manitoba;

Death rates associated with respiratory disease are higher in FF/CR than in Manitoba and Saskatchewan but lower than in NOR-MAN Health Region. Death rates for injuries and violent deaths are also higher in FF/CR than in Manitoba and Saskatchewan but lower than NOR-MAN and MCR Health Regions;

The most common causes of premature deaths in FF/CR, NOR-MAN and MCRHR, as indicated by potential years life lost, are injuries followed by cancer and circulatory disease. Premature death rates for males and females combined are lower in FF/CR than in Manitoba, and NOR-MAN and MCR Health Regions, while premature death rates from injuries are higher in FF/CR than the provinces. Premature death rates from respiratory disease in FF/CR are lower than in Manitoba, Saskatchewan, and NOR-MAN and MCR Health Regions; and,

Respiratory deaths tend to be more of an issue in FF/CR for the oldest age groups as is demonstrated by the fact that the overall death rate from respiratory disease in FF/CR is higher compared to other health regions, while premature deaths from respiratory issues are lower than other regions.

b) Cancer

Cancer has multiple causes (‘risk factors’) including tobacco, diet and obesity, which are thought to cause about 60% of the cancer causing death in developed countries. This study of cancer incidence could not determine the cause of specific types of cancers seen in Creighton and Flin Flon;

When considering all cancers combined, with the exception of non-melanoma skin cancer, there is no significant difference in the cancer rate for females in FF/CR

compared to those in Manitoba, NOR-MAN or MCR Health Regions, or in the cancer rate for males compared to all health regions. Incidence of skin cancer could not be included within this assessment due to differences in nomenclature between the Provinces of Manitoba and Saskatchewan. Given that one of the most common forms of cancer associated with arsenic exposure is skin cancer, the results of the Community Health Status Assessment may not have captured increased incidence in arsenic-related cancers in the Flin Flon area population relative to the provincial averages; and,

Over the 10 year period, lung, breast, colorectal and prostate cancers were the most common types in FF/CR. This is similar to cancer trends in Canada, Manitoba, Saskatchewan, NOR-MAN and MCR Health Regions. Observations regarding particular cancer types can be summarized as follows:

- There is no significant difference in lung, colorectal, brain, bladder, kidney, non-Hodgkin's lymphoma and leukemia cancer rates in FF/CR compared to the Manitoba, Saskatchewan, NOR-MAN or MCR Health Regions;
- Lung cancer rates for males are higher in NOR-MAN Health Region compared to Manitoba, and in MCR Health Region compared to Saskatchewan;
- Breast cancer incidence rates for women in FF/CR are lower than rates for women in Manitoba; and,
- Prostate cancer incidence rate in FF/CR males is lower than for males in Saskatchewan but similar to males in Manitoba and Canada.

Conclusions and Notable Differences

Generally, the overall health status of the FF/CR population is as good if not better than the provincial averages for most of the indicators studied. Overall death rates and overall premature mortality rates are lower in FF/CR than in Manitoba and Saskatchewan, as are overall death rates for circulatory disease and premature deaths due to respiratory conditions. Like the other populations studied, the major causes of death in Flin Flon and Creighton are circulatory diseases and cancer.

Most early deaths in Flin Flon and Creighton are due to injuries and more premature deaths due to injuries occur in FF/CR compared to Manitoba and Saskatchewan. The overall death rates due to respiratory disease were also higher than the provincial rates, due largely to death rates associated with respiratory conditions for the oldest age groups. Early deaths due to respiratory disorders actually occur significantly less in the FF/CR communities than in the other populations studied. Information regarding present and past community smoking levels was not available for this study.

For men and women combined, overall and premature death rates due to cancer are lower in Flin Flon and Creighton, compared to the NOR-MAN Health Region, Manitoba and Saskatchewan. When considered separately, cancer incidence rates for men and women were not elevated in Flin Flon and Creighton, compared to the Manitoba and NOR-MAN Health Region rates. Also, there were no specific types of cancer determined to have significantly higher rates in these communities compared to the provinces.

6.7 The Elderly and Lifetime Exposures in Risk Assessment

6.7.1 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 potential sensitive group. When discussing the fact that a subpopulation may be considered sensitive, it is important to note the distinction 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 toddler 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 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 report.

Arsenic

In their review, ATSDR (2008a) did not locate any studies regarding unusual susceptibility of any human subpopulation, including the elderly, to arsenic. ATSDR (2008a) did not identify the elderly as a specific subpopulation with potentially high arsenic exposures.

Cadmium

In general, the bone has been found to be a sensitive target area of cadmium toxicity (Staessen *et al*., 1999; Alfven *et al*., 2000; 2002; 2004; Nordberg *et al*., 2002; Aoshima *et al*., 2003; Wang *et al*., 2003; Jin *et al*., 2004; Zhu *et al*., 2004; Akesson *et al*., 2005). Epidemiology studies have suggested that the elderly are more susceptible than younger adults, however, animal studies show that younger are more susceptible than the elderly (Ogoshi *et al*., 1989; ATSDR, 2008b). Kagamimori *et al*. (1986) found that in human elderly individuals consuming a diet high in cadmium showed disorders of the cardiac conduction system which resulted in lower blood pressure and decreased frequency of cardiac ischemic changes. Elderly Japanese women who were exposed to large amounts of cadmium through dietary sources during World War I and World War II and low levels of cadmium through agricultural produce were found to have Itai-Itai (bone disease) and half of the elderly women had osteomalacia (bone brittleness) as well (Kagamimori *et al*., 1986).

Copper

ATSDR (2004e) 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 (2007) found that although children are the subpopulation at greatest risk of lead-induced health effects, the elderly may also be a potentially vulnerable subpopulation. Two recent studies found an association between decreased neurobehavioral 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 (refer to Appendix A). 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 (2007) as a specific subpopulation with potentially high lead exposure.

Mercury

ATSDR (1999) has indicated that the elderly subpopulation is one of the groups that is more susceptible as compared to healthy young adults to mercury toxicity. Reasons are that in elderly individuals, there is declining organ function, and generally higher levels of heavy metals present in the body which may accumulate in the kidney, liver and brain. In addition, some elderly individuals may have pre-existing conditions such as neurological or renal disorders that may increase their susceptibility to mercury toxicity (ATSDR, 1999).

Selenium

ATSDR (2004d) 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 (2004d) as a specific subpopulation with potentially high selenium exposure.

6.7.2 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, US 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, U.S. EPA (1997) has recommended moving towards use of a lifetime of 75 years for the general population. The current assessment used the Health Canada recommended lifetime of 80 years. Given that the current assessment assumed that receptors would spend their entire lifetime living within the Flin Flon area, increasing the averaging time will not result in lower risk estimates.

6.7.3 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 toddler was selected as the most sensitive receptor lifestage for evaluation of non-carcinogenic risk for the current assessment. A lifespan of 80 years was conservatively selected for the evaluation of lifetime cancer risks for the current assessment.

6.8 COC Lifetime Body Burden

Some concern has been raised by members of the Flin Flon community that long-term exposures to the COC being evaluated in the Flin Flon 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 compounds (*e.g.,* PCBs, dioxins and furans, *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. In the case of lead, which can accumulate in bone tissue, it will typically stay bound up and unavailable for toxic effect, unless the body undergoes significant deossification or demineralization (ATSDR, 2007). ATSDR (2008b) indicates that cadmium is accumulated in the liver and kidneys of exposed individuals.

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.

6.8.1 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, metabolic daughter products can be more toxic, or have implicit toxicity at a different site within the body, than the parent compound. For example, there are *in vitro* studies that suggest that methylated daughter products of arsenic may be more toxic than the inorganic form.

6.8.2 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 nutrients 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.

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

Two of the COC (*i.e.*, 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 COC (*i.e.*, arsenic, cadmium, copper, and lead) 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 is 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, and, cadmium is accumulated in the liver and kidneys of exposed individuals.

The following section provides an overview of the uptake, 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, 2008a). Various estimates of arsenic retention and elimination have been reported. Based on a variety of studies reviewed by ATSDR (2008a), 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 of inorganic arsenic (AsH_3), 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.

Cadmium

Once absorbed, cadmium is distributed to all tissues however; the liver and the kidney contain approximately 40 to 80% of the entire body burden (ATSDR, 2008b; Sumino *et al.*, 1975; Chung *et al.,* 1986; WHO, 2000). The placenta acts as a partial barrier to fetal exposure to cadmium; although levels of exposure have been found to vary (Kuhnert *et al*., 1982; Roels *et al.,* 1978; Truska *et al.,* 1989). Cadmium levels in cord blood are half of what is present in the maternal blood (Lauwerys *et al.,* 1978; Kuhnert *et al.,* 1982; Truska *et al.,* 1989). Human milk contains 5 to 10% of the cadmium levels that are in the blood (Radisch *et al.,* 1987).

In terms of metabolism, cadmium does not undergo oxidation, reduction or alkylation (ATSDR, 2008b). Cadmium (+2) does bind to proteins such as albumin and metallothionein to circulate in the plasma (Nordberg *et al.,* 1985; Roberts and Clark, 1988; Foulkes and Blanck, 1990). Cadmium blood levels in the general population are generally < 0.5 µg/100 mL (WHO, 2000). Much of the cadmium that enters the body is excreted in the feces or urine (Kjellstrom and Nordberg, 1978).

Copper

Copper is also an essential element, and therefore its uptake, metabolism and excretion are physiologically regulated to maintain copper homeostasis (ATSDR, 2004e). 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, 2004e). Bile is the major pathway for copper excretion (ATSDR, 2004e). 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, 2007). 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, 2007). Excretion rates are highly variable, and the data suggest that the fraction of absorbed lead that is retained by humans decreases with age (ATSDR, 2007). 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. ATSDR (2007) indicates that lead concentrations in bone increase with age throughout the lifetime, indicative of a relatively slow turnover of lead in adult bone.

Mercury

Metallic mercury is quite lipophillic, therefore it is readily distributed throughout the body and can cross blood-brain and placental barriers after inhalation (Hursh *et al*., 1976; Clarkson, 1989). In the blood, metallic mercury is oxidized to the divalent forms of which the non diffusible form is predominant and binds to proteins such as albumin and globulin (Clarkson *et al*., 1961; Berlin and Gibson, 1963; Cember *et al*., 1968; Halbach and Clarkson, 1978). Overall, the kidney is the major organ for mercury deposition since it contains metallothionein which is stimulated by mercury (Rothstein and Hayes, 1964; Piotrowski *et al*., 1973; Cherian and Clarkson, 1976). Distribution of organic mercury is similar to that of metallic or inorganic mercury (ATSDR, 1999). Metabolism of mercury involves an oxidation-reduction cycle, whereby the mercury is oxidized to the divalent inorganic cation in the red blood cells and lungs. It can be reduced to the metallic or monovalent form (ATSDR, 1999). Ultimately, mercury can be excreted *via* the urine, feces or expired air; as well it can be excreted through breast milk (ATSDR, 1999).

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, 2004d). 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.

6.8.4 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 Flin Flon 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.

6.9 The Effects of Limited Sunlight and Vitamin D Deficiency

Vitamin D is a fat-soluble vitamin that is essential for helping the body use calcium and phosphorus to build and maintain strong bones (Health Canada, 2009; ODS-NIH, 2008). The

primary source is exposure to sunlight, which is limited as compared to the majority of the North American population. Other lesser sources of vitamin D are food items such as fatty fish, beef liver, egg yolk and Vitamin D supplemented milk (ODS-NIH, 2008; Tufts, 2009). Too little vitamin D will cause calcium and phosphorus levels in the blood to decrease which causes calcium to leave the bones to balance the calcium levels in the bloodstream (Health Canada, 2009; ODS-NIH, 2008). Therefore, vitamin D deficiency may cause rickets in children and osteomalacia which is softening of the bones or osteoporosis which is characterized by brittle bones leaving them prone to fracture in adults (Health Canada, 2009; ODS-NIH, 2008; Ontario Ministry of Health, 2009; Tufts, 2009). Too much vitamin D will cause calcium to be deposited onto various tissues of the body thereby causing calcification of the kidney and other tissues (Health Canada, 2009).

In order for vitamin D to be used by the body it needs to be converted to its active form which is 1,25 $(OH)_2D$ (calcitriol or 1,25-dehydroxyvitamin D). The active form stimulates the synthesis of osteocalcin which is a protein constituent of the bone which helps in bone mineralization (ATSDR, 2007). This conversion requires that vitamin D undergo two hydroxylations. First, vitamin D is hydroxylated in the liver to form 25(OH)D (25-hydroxyvitamin D or calcidiol) which is then hydroxylated in the kidney to form $1,25(OH)_2D$ which is the biologically active form (ODS-NIH, 2008; Tufts, 2009). Effects on vitamin D metabolism resulting from exposure to arsenic, cadmium, copper, lead, mercury and selenium may occur but specific information was only located for cadmium and lead. ATSDR (2007; 2008b) has extensively reviewed the literature of the human health effects caused by cadmium and lead and has found effects to vitamin D metabolism resulting from exposure to these two metals.

Cadmium has been reported to have effects on the musculoskeletal system (ATSDR, 2008b). High exposure to cadmium from occupational or dietary sources has been associated with calcium deficiency and bone diseases such as rickets in children and osteoporosis and osteomalacia in adults (ATSDR, 2008b). Concentrations of cadmium may cause damage on the kidneys where hydroxylation of 25(OH)D to $1,25(OH)_2D$ occurs. Interferences with this process will result in decreased vitamin D metabolism which results in less of the biologically active forms of vitamin D (ATSDR, 2008b; Health Canada, 2009; Tufts, 2009).

Review of the literature by ATSDR (2007) indicated that lead has an inhibitory effect on $1,25(OH)_2D$. In children with elevated blood lead levels (greater than 33 µg/dL), decreased serum vitamin D levels have been seen along with decreased calcium levels. Children who have sufficient diets and are only moderately exposed to lead have not been reported to have decreased serum vitamin D levels. Lead appears to disrupt the conversion of the vitamin D to its active form, however, high concentrations of calcium appear to protect against decreased $1,25(OH)_2D$ and do not allow for such great absorption of lead from the GI tract (ATSDR, 2007; Cheng, *et al*., 1998; Kemp *et al*., 2007; Smith *et al*., 1981).

6.10 References

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