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Determining soil remedial action criteria for acute effects: The challenge of copper

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ABSTRACT

Gastrointestinal (GI) symptoms, the primary acute effect of the essential micronutrient copper, paradoxically occur at lower exposure levels than hepatotoxicity, the primary chronic effect. We developed a remedial action criterion (RAC) for copper to protect against GI symptoms, which primarily relate to the stomach copper concentration, and subside within an hour. Using Monte Carlo methods, we generated a distribution of RACs protective against GI symptoms for a 1 h exposure (hourly RACs) based on soil ingestion rate, volume of liquid and food in the stomach, and bioaccessibility. We then generated a distribution of daily RACs, selected as the minimum hourly RAC for each day over a year, constrained by total daily soil ingestion. Next, we identified a percentile of the distribution of daily RACs, and associated RAC, that would result in a high probability of having a minimal number of GI symptom episodes per year. Our analysis indicates that a copper concentration of 3600 mg/kg would result in a 95% probability of having fewer than five episodes of GI symptoms per year, for a child ingesting outdoor soil 180 days per year. Children residing near copper smelters are most likely to experience GI symptoms from ingestion of copper in soil.

1. Introduction

Copper, which is an essential nutrient, is unusual in that it causes acute toxicity at lower exposure levels than chronic toxicity. Acute effects of copper ingestion consist of gastrointestinal (GI) symptoms, primarily nausea, as well as abdominal pain and vomiting. The GI effects of copper generally occur immediately following exposure, and are readily reversible once exposure ceases (Araya et al., 2003a). As discussed by Olivares et al. (2001), copper interacts with mucosal cells in the stomach and triggers a vagal response. At levels of copper intake that cause GI symptoms, there is no evidence of either acute or chronic systemic copper toxicity, such as effects on the liver or the kidney. This is in part because the acute toxic response to copper occurs prior to its absorption and distribution throughout the body.

The paradox of acute effects occurring in the absence of systemic toxicity relates to copper's role as an essential nutrient. Copper is an important component of key enzymes involved in a wide range of physiological processes, including cellular energy production, anti-oxidant defense, production and metabolism of catecholamines (*e.g.*, epinephrine, norepinephrine, dopamine), development of connective tissue, and inactivation of histamines (IOM, 2001). Therefore, adverse health outcomes can result not only from the toxic effects of copper, but also from deficient copper intake. As with other essential nutrients, physiological mechanisms control levels of copper in the body to maintain homeostasis without causing adverse health outcomes due to either deficient or excess copper intake. If excess copper is ingested, such as in drinking water or soil, absorption is decreased, and excretion from the body is increased (Lopez de Romaña et al., 2011). Hence, when excess copper is ingested, acute GI effects can occur in the absence of systemic toxicity.

Observational studies/case reports involving repeated exposures to relatively high levels of copper in drinking water provide evidence regarding the reversibility and lack of systemic toxicity following acute exposure to copper. Spitalny et al. (1984) reported on three of four family members who experienced recurrent acute GI symptoms after drinking juice, coffee, or water in the morning. These symptoms subsided when the family members stopped consuming copper-containing water, and there were no other reports of permanent, systemic health effects. Knobeloch et al. (1994) similarly reported five case studies in which consumption of copper-containing drinking water was suspected of causing GI effects such as vomiting, diarrhea, and abdominal pain. These symptoms subsided when consumption of copper-containing water was discontinued, with no reports of permanent systemic effects, even following relatively long term exposures to copper in drinking water (up to 5 years).

Controlled exposure studies similarly demonstrate the reversibility and lack of systemic toxicity of copper. An acute toxicity study with single bolus dosing by Araya et al. (2003a) evaluated the incidence of GI symptoms in individuals consuming copper in

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drinking water following an overnight fast, and found that the majority of GI symptoms occurred within the first 15 min following ingestion of copper in drinking water, and subsided within an hour. Although this study by Araya et al. (2003a) did not evaluate systemic toxicity, another study by Araya et al. (2003b) evaluated both acute and chronic toxicity of copper among individuals ingesting defined concentrations of copper in their drinking water throughout the day for a period of 2 months. In this study, the frequency of study participants reporting GI symptoms increased with copper concentrations, but there was no accompanying change in indicators of copper status or liver function, as measured by blood levels of copper, ceruloplasmin, liver transaminase enzymes and other blood biomarkers.

Studies by Pizarro et al. (1999), Olivares et al. (2001), Araya et al. (2001, 2003a) indicate that the concentration of soluble copper in the stomach is an important determinant of the GI effects of copper. The study by Araya et al. (2003a) further demonstrates that the total amount or dose of copper in the stomach is also a determinant of the GI effects of copper. Thus, the most sensitive endpoint for copper toxicity in humans (acute, reversible GI symptoms) is a function of both the amount and concentration of copper in the stomach at a particular moment in time.

The paradox of acute toxicity occurring at lower exposure levels than chronic toxicity presents a challenge for establishing acceptable exposure levels, such as soil cleanup criteria, where the aim is to protect individuals who will be exposed repeatedly on a long term basis. One scenario for which it might be necessary to develop an acceptable exposure level for copper is for soil in the vicinity of copper smelters, where copper levels can be substantially elevated relative to other contaminants. At such sites, copper in soil may be sufficiently elevated to elicit GI symptoms, particularly in young children who are more likely to engage in behavior associated with incidental soil ingestion than older children and adults. Although GI symptoms following ingestion of copper in soil have not been documented, this may be due in part to the non-specific nature of GI symptoms, which could also be caused by, and therefore misattributed to, many factors other than copper. In this analysis we present an approach for determining a remedial action criterion (RAC) for copper in soil that is protective against the gastrointestinal effects of copper.

2. Methodology

2.1. Overall approach

A RAC for copper should represent a soil concentration, in mg/kg, at which there is no appreciable risk of experiencing GI symptoms, *i.e.*, a soil concentration at which any increase in GI symptoms due to ingestion of copper from soil is indistinguishable from the typical background incidence of GI symptoms. Given that the gastrointestinal effects of copper are a function of the concentration of copper in the stomach, the RAC should be based on the concentration of soluble copper in the stomach ($C_{stomach}$), where $C_{stomach}$ represents a concentration that would not cause GI symptoms. This concentration is referred to as the Acceptable Stomach Concentration (ASC) for this analysis.

The copper concentration in the stomach is a function of the copper concentration in soil, the amount of soil ingested ($Soil_{ing}$), the bioaccessibility (B) of copper in the stomach (*i.e.*, the amount of copper solubilized from soil under physiological conditions), and the volume of food and liquid in the stomach ($V_{stomach}$).

$$RAC\,(\mathrm{mg/kg}) = \left[\frac{(ASC\,(\mathrm{mg/L}))}{\left(\frac{Soil_{ing}\,(\mathrm{mg})\times B(\mathrm{unitless})}{V_{stomach}\,(\mathrm{L})}\right)}\right] \times \left[10^6\,\frac{\mathrm{mg}}{\mathrm{kg}}\right] \quad (1)$$

As noted in the study by Araya et al. (2003a) the gastrointestinal effects of copper typically occur within 15 min following ingestion of copper in drinking water, and subside within 60 min. Hence Eq. (1) can be used to determine a RAC at which there is no appreciable risk of developing GI symptoms in any given hour. However, even if a RAC is selected such that the probability of developing GI symptoms in any given hour is low, the probability of developing GI symptoms over the course of a year may result in an unacceptably high frequency of adverse GI symptom episodes.

In order to determine a RAC that minimizes the frequency of adverse GI symptom episodes on an annual basis, we first generated a distribution of hourly RACs, using Monte Carlo simulation. We then generated a distribution of daily RACs, selected as the minimum hourly RAC for each day. Based on the distribution of daily RACs, we used a binomial probability function to identify a RAC associated with a low probability of experience a defined number of GI symptom episodes on an annual basis. Because soil ingestion rates are higher for young children (ages 1–6 years) than for older children and adults, the RAC for children would be lower than a RAC for adults. Thus we have determined RACs that would minimize the occurrence of GI symptoms in young children.

2.2. Selection of input distributions for Monte Carlo analysis

The aim of this analysis was to estimate a RAC that would be protective of 1- to 6-year-old children in the general population. Thus, we identified distributions to represent variability within the general population for the parameters in the RAC equation (Eq. (1)).

2.2.1. Acceptable stomach concentration (ASC)

We identified the ASC from the drinking water studies by Araya et al. (2001, 2003a); Olivares et al. (2001), all of which reported incidence of GI symptoms at defined concentrations of copper in drinking water. Incidence rate of GI symptoms (primarily consisting of nausea) ranged from 4% above background at a drinking water concentration of 2 mg/L copper (in the study by Araya et al., 2003a) to 30% above background at a drinking water concentration of 12 mg/L (in the study by Olivares et al., 2001). Based on the concentration–response functions from these studies, we identified 2 mg/L in drinking water as a likely threshold concentration, above which GI symptoms are expected to occur with increasing frequency. Because we are deriving a RAC based on the concentration of copper in the stomach, we divided the total amount of copper ingested in the drinking water studies by the ingestion volume (200 mL) plus the volume of gastric juice in an "empty" adult stomach, to correspond with the adult participants in the studies by Araya et al. (2001, 2003a); Olivares et al. (2001). For this analysis, we conservatively used 80 mL as a reasonable maximum upper-end value for the volume of gastric juice in an adult's empty stomach. This volume was selected based on information from the National Library of Medicine, which reports a range of 20–100 mL as the volume of gastric juice in an empty stomach (NLM, 2003) as well as a study by Cook-Sather et al. (1997), who reported a 95th percentile of approximately 1.13 mL/kg body weight for gastric fluid volume in healthy, fasted children. Assuming a similar gastric fluid volume/weight ratio in adults, 80 mL corresponds approximately with the 95th percentile for gastric fluid volume for a typical 70-kg adult.

We modeled the probability of experiencing acute GI symptoms as a function of copper concentration in the stomach, based on the concentration–response frequency observed in the drinking water studies by Araya et al. (2001, 2003a); Olivares et al. (2001), using a gamma distribution (as described in Table 1 and as shown in Fig. 1a. We used EPA Benchmark Dose Software (BMDS) to fit the model to the observed data for its three parameter values (back-