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Derivation of biomonitoring equivalent for inorganic tin for interpreting population-level urinary biomonitoring data

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ABSTRACT

Population-level biomonitoring of tin in urine has been conducted by the U.S. National Health and Nutrition Examination Survey (NHANES) and the National Nutrition and Health Study (ENNS – Étude nationale nutrition santé) in France. The general population is predominantly exposed to inorganic tin from the consumption of canned food and beverages. The National Institute for Public Health and the Environment of the Netherlands (RIVM) has established a tolerable daily intake (TDI) for chronic exposure to inorganic tin based on a NOAEL of 20 mg/kg bw per day from a 2-year feeding study in rats. Using a urinary excretion fraction (0.25%) from a controlled human study along with a TDI value of 0.2 mg/kg bw per day, a Biomonitoring Equivalent (BE) was derived for urinary tin (26 μg/g creatinine or 20 μg/L urine). The geometric mean and the 95th percentile tin urine concentrations of the general population in U.S. (0.705 and 4.5 μg/g creatinine) and France (0.51 and 2.28 μg/g creatinine) are below the BE associated with the TDI, indicating that the population exposure to inorganic tin is below the exposure guidance value of 0.2 mg/kg bw per day. Overall, the robustness of pharmacokinetic data forming the basis of the urinary BE development is medium. The availability of internal dose and kinetic data in the animal species forming the basis of the assessment could improve the overall confidence in the present assessment.

1. Introduction

Population-level human biomonitoring programs such as the National Health and Nutrition Examination Survey (NHANES) in the United States and other national biomonitoring efforts in France, Canada and Germany are providing valuable data on the prevalence and concentration of chemicals in the general populations (Angerer et al., 2011). Measured concentrations of chemicals and their metabolites in a human biological matrix, such as blood or urine, are potentially useful quantitative markers of exposure. Biomonitoring data can provide an integrated measure of exposure through all routes (oral, dermal and inhalation), across all sources, and all bioavailable forms of the chemical in the environment.

Determining if the exposures measured in biomonitoring programs are at levels of concern for human health is impeded by the lack of tools that relate the measurements of exposure and health effects. Biomonitoring programs provide exposure data in terms of concentrations of a chemical in blood or urine, while exposure guidance values (such the tolerable daily intake level (TDI), reference dose (RfD)) are typically reported as external dose levels normalized by body weight (e.g. mg chemical/kg bw per day). In order to interpret the biomonitoring data quantitatively, forward dosimetry and reverse dosimetry approaches have been used (eg., Sohn et al., 2004; Tan et al., 2007; Georgopoulos et al., 2009; Environment Canada and Health Canada, 2014). Biomonitoring Equivalents (BEs) are forward dosimetry tools which have been developed to aid in the interpretation of biomonitoring data from population-level studies by modelling the blood or urine equivalent of a given exposure guidance value. A BE is defined as the concentration or range of concentrations of a chemical or its metabolites in a biological medium (blood, urine or other medium) that is consistent with an existing health-based exposure guidance values such as a RfD and TDI (Hays et al., 2007, 2008). BEs have already been developed for several chemicals, both organic and inorganic, and used to interpret data from human biomonitoring programs in the U.S. and Canada in a health-based context (Aylward et al., 2013;

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St-Amand et al., 2014; Environment Canada and Health Canada, 2014, 2015). Similarly, population-specific reference values or intervals have been reported for a number of trace elements and metals based on 24-hr urine from healthy adults (e.g., Sieniawska et al., 2012). However, BEs which are useful for interpretation of biomonitoring data in a health-based context have not yet been developed for a number of metals, including tin.

Tin (Sn; atomic mass = 118.71), a silver-white shiny metal, is the 49th most abundant element in earth's crust (Dopp and Rettenmeier, 2013). The major tin producing countries are China, Indonesia and Peru (USGS, 2015). The main global use of elemental tin is for alloys such as brass, bronze and pewter and some welding materials. Inorganic tin is also extensively used in cans and containers (including as a protective coating for metal food containers), construction work, transportation and for electrical uses (USGS, 2015). Inorganic tin is also found in cosmetics, dental care products, coloring agents and food additives (WHO, 2005; Dopp and Rettenmeier, 2013).

People can be exposed to organic, inorganic and elemental tin through food, drinking water, consumer products and environmental media (air, soil and dust). However, most of the tin exposure in the general population is in the form of inorganic tin from the consumption of canned food and beverages (ATSDR, 2005; WHO, 2005). There are small amounts of tin in fresh meat, cereals and vegetables but much higher concentrations of tin are found in fruits and vegetables stored in tin-lined cans (ANSES, 2011). Currently, most food storage cans contain a lacquer to reduce the migration of tin into food and this has led to a reduction of dietary intake over time (JECFA, 2005). Mean dietary intakes for tin range from <1 up to 14 mg/day (<16 up to 233 μg/kg bw per day, assuming 60 kg body weight) based on tin concentration data from the 1990s from Australia, France, Japan, the Netherlands, New Zealand, the United Kingdom and the U.S. (EFSA, 2005; JECFA, 2006). More recently, tin was measured in the general population diet in France in the Second Individual and National Food Consumption Survey (INCA 2) that took place in 2006–2007 (ANSES, 2011). The mean estimated tin intake for adults and children were 3.9 and 7.3 μg/kg bw per day, and the respective 95th percentile for the same age groups were as 17.0 and 31.9 μg/kg bw per day. The main contributors to tin exposure in both adults and children in France were compotes and fruits (ANSES, 2011). Drinking water and air are not significant sources of human exposure to inorganic tin (WHO, 2005; ATSDR, 2005).

The current analysis focused on the efforts to interpret biomonitoring data for inorganic tin by deriving a BE for existing exposure guidance value. The objectives of this work are twofold: (1) to assemble population-level biomonitoring data to identify the concentrations of urinary tin across the general population; and (2) to derive a urinary BE for inorganic tin, in view of interpreting the urinary biomonitoring data for inorganic tin in the general population.

2. Methods

2.1. Biomonitoring data

A search was conducted for tin concentrations in urine and blood in national or population-based biomonitoring programs such as those in the U.S., Canada and Europe. Tin concentrations in urine were measured as part of the National Health and Nutrition Examination Survey (NHANES) in the U.S. (http://www.cdc.gov/nchs/nhanes.htm) and the French National Nutrition and Health Study (ENNS– Étude nationale nutrition santé; http://www.invs.sante.fr/publications/2011/exposition_polluants_enns/plaquette_eng_exposition_polluants_enns.pdf). In a small scale study, Sieniawska et al. (2012) reported tin levels in 24-hr urine samples of 111 healthy, British subjects. No measurement of tin in blood was found in the above data sources.

Urinary tin has been suggested as a possible biomarker of long-term exposures to inorganic tin (ATSDR, 2005). The published data in animals and humans indicate that inorganic tin absorbed through gastrointestinal tract is excreted primarily in urine (WHO, 2004; Gad, 2005; RIVM, 2009). The geometric mean and the upper bound (95th) percentile value of urinary inorganic tin concentrations from biomonitoring studies can be compared with the BE (developed as described below) to understand the current levels of population exposure relative to the existing health-based exposure guidance values (St-Amand et al., 2014).

2.2. Derivation of biomonitoring equivalent (BE)

The process of deriving a BE requires the analysis of relevant information regarding (i) toxicity and exposure guidance values, as well as (ii) pharmacokinetic data and models for the chemical under consideration.

2.2.1. Toxicity and exposure guidance value

Inorganic tin is generally considered to exhibit low order of toxicity, mainly due to its low absorption, low tissue accumulation and rapid fecal excretion without absorption from gastrointestinal (GI) tract (Milne, 1984; WHO, 2004; JECFA, 2011; Dopp and Rettenmeier, 2013; Ostrokovitch, 2015). In both humans and animals, GI tissue irritation is the main effect associated with the ingestion of tin (JECFA, 2011). In humans, nausea, abdominal cramps, vomiting and diarrhoea have been reported in individuals who consumed canned beverages and food contaminated with tin at 150 mg per kg of canned beverages and 250 mg per kg of canned food (WHO, 2004). In contrast, no adverse effects were reported in some volunteers who consumed canned foods with tin content ranging from 250 to 700 mg/kg (WHO, 2004). Evidence from animal studies suggest that elemental and inorganic tin can interfere with copper, iron, zinc and calcium status, presumably due to impaired absorption (The Nordic Expert Group, 2002; WHO, 2005).

The chronic systemic effects for oral exposure to inorganic tin have been evaluated by ATSDR (2005), WHO (2005) and RIVM (1993, 2009). RIVM (2009) derived a tolerable daily intake (TDI) of 0.2 mg tin/kg bw per day based on a no observed adverse effect level (NOAEL) of 20 mg/kg bw per day from a 2-year feeding study in rats in which a small increase in tin accumulation in bones and a decrease in feed efficiency were observed at 40 mg/kg bw per day. RIVM (2009) applied an uncertainty factor of 100 (10 each for inter- and intra-species variation) to derive a TDI (Table 1). Exposure guidance values for chronic exposure to inorganic tin were not established by IPCS (2005), ATSDR (2005) and JECFA (2011) due to insufficient data or limitations in hazard database.

2.2.2. Pharmacokinetic data & models

A review of the pharmacokinetic data indicates that the absorption of inorganic tin from the GI tract, which appears to be mediated by passive diffusion, is low in humans and laboratory animals, including rats, mice, rabbits, cats and dogs (IPCS, 2005). While most studies have reported less than 5% GI absorption of inorganic tin, some report absorption as high as 20% (WHO, 2004). In humans and laboratory animals, more than 90% of an ingested dose of inorganic tin is recovered in the faeces (Blunden and Wallace, 2003). The available data in humans suggest that GI absorption of inorganic tin decreases with increasing intake (ATSDR, 2005). The GI absorption of inorganic tin is influenced by the oxidation state where tin(II) has a greater absorption than tin(IV) (2.8% and 0.6%, respectively) (WHO, 2004). Inorganic tin distributes