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Development of biomonitoring equivalents for barium in urine and plasma for interpreting human biomonitoring data

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ABSTRACT

The objectives of the present work were: (1) to assemble population-level biomonitoring data to identify the concentrations of urinary and plasma barium across the general population; and (2) to derive biomonitoring equivalents (BEs) for barium in urine and plasma in order to facilitate the interpretation of barium concentrations in the biological matrices. In population level biomonitoring studies, barium has been measured in urine in the U.S. (NHANES study), but no such data on plasma barium levels were identified. The BE values for plasma and urine were derived from U.S. EPA's reference dose (RfD) of 0.2 mg/kg bw/d, based on a lower confidence limit on the benchmark dose ($BMDL_{05}$) of 63 mg/kg bw/d. The plasma BE (9 μg Ba/L) was derived by regression analysis of the near-steady-state plasma concentrations associated with the administered doses in animals exposed to barium chloride dihydrate in drinking water for 2-years in a NTP study. Using a human urinary excretion fraction of 0.023, a BE for urinary barium (0.19 mg/L or 0.25 mg/g creatinine) was derived for US EPA's RfD. The median and the 95th percentile barium urine concentrations of the general population in U.S. are below the BE determined in this study, indicating that the population exposure to inorganic barium is expected to be below the exposure guidance value of 0.2 mg/kg bw/d.

1. Introduction

Barium, the heaviest of the stable alkaline earth metals (Atomic number: 56, Atomic weight: 137.3, CAS: 7440-39-3) belonging to Group IIA of the periodic table, exists as divalent compounds such as barite ($BaSO_4$), witherite ($BaCO_3$), and barium chloride ($BaCl_2$) in the environment (US EPA, 2005; Oskarsson, 2015). Barium is not considered an essential element in human nutrition (Schroeder et al., 1972; Kravchenko et al., 2014). Of the 25 barium isotopes identified to-date, barium occurs as a mixture of seven stable isotopes with weights of 130, 132, 134, 135, 135, 137 and 138 and corresponding abundances (as %) of 0.101, 0.097, 2.42, 6.59, 7.81, 11.32 and 71.66, respectively (CCME, 2013).

Barium compounds are widely used in many industrial applications such as production of drilling muds, manufacturing of paints, bricks, plastics, steel, textile, glass, rubber, ceramics, paper, rodenticides, pharmaceuticals and cosmetics (Kravchenko et al., 2014). Its use in steel and semiconductor industries has also been reported (SCHER, 2012). Additionally, the medicinal use of barium as a contrasting agent in the gastrointestinal (GI) tract radiography has more than doubled during the last 40 years (Kravchenko et al., 2014).

While human exposure to barium may occur through oral, dermal and inhalation routes, non-occupational exposure in the general population is mainly through oral route by consumption of food and water (WHO, 2001; US EPA, 2005; Kravchenko et al., 2014; Oskarsson, 2015). The barium content in most foods is relatively low (<3 mg/100 g) except in Brazil nuts (150–300 mg/100 g), with bread being the largest source of dietary barium (about 20% of total intake) for the general population (US EPA, 2005). Several studies, including the Canadian Total Diet Studies, indicate that the average barium intakes in children and adults are in the range of 9–25 and 6–12 μg/kg bw/d, respectively (Health Canada, 2011; Rose et al., 2010; ANSES, 2011; CCME, 2013). The contribution of barium via drinking water is highly variable, depending upon the geographical area. The barium concentration in drinking water ranges from 1 to 20 μg/L in the U.S. (US EPA, 2005), to about 44 μg/L in France (ANSES, 2011) and to much higher levels in Bangladesh (Oskarsson,

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2015). The mean barium concentration in Canadian drinking water was determined to be 34.2 μg/L (SD = 68.6, n = 14144) based on data obtained from Ontario (1998–2007), Saskatchewan (2000–2009) and Newfoundland and Labrador (2000–2009) (CCME, 2013). The Canadian Council of Ministers of the Environment (CCME) estimated mean barium concentrations in human breast milk of 3.61 μg/L based on data from three studies (Krachler et al., 1998, 1999; Friel et al., 1999; CCME, 2013).

Barium compounds exhibit a range of water solubility, with the sulfate, carbonate, and sulfide being less soluble than acetate, cyanide, chloride, nitrates, oxides and hydroxide being highly soluble (Ramanathan, 2006). The acid-soluble barium compounds are more readily absorbed than the less soluble compounds (ICRP, 2012). Chronic human exposure to excess barium is associated with adverse outcomes including cardiac and/or renal failure, pulmonary edema, respiratory paralysis and gastric and respiratory hemorrhages (Kravchenko et al., 2014). While the kidney has been identified as the primary target organ for barium toxicity in rodents, cardiovascular effect such as hypertension is the primary effect in humans (WHO, 2015). NTP (1994) concluded that there was no evidence of carcinogenicity in chronic, oral exposure studies in both mice and rats. Barium is not considered mutagenic in bacteria mutagenicity assays and it does not damage DNA (WHO, 2015). There are only limited data on neurological, developmental and reproductive toxicity of barium in experimental animals or in humans (US EPA, 2005; Oskarsson and Reeves, 2007; WHO, 2015).

The toxicity of barium is mediated by the free cation through substitution for calcium, in addition to being a physiological antagonist for potassium channels (SCHER, 2012; CCME, 2013). Consequently, the principal physiological effect of barium is the stimulation of smooth muscles of the gastrointestinal tract, the cardiac muscle, and the voluntary muscles (UNEP, 2005). Since the solubility of barium compounds is a key aspect of the mode of action, compounds that are water soluble (e.g. barium acetate, barium chloride, barium nitrate, barium hydroxide) or soluble in physiological fluids (e.g. barium carbonate) exhibit greater potential for absorption and toxicity. In comparison, the relatively insoluble compounds such as barium chromate, barium fluoride, and barium oxalate exhibit low bioavailability (CCME, 2013).

Barium concentrations in biological matrices (usually in urine) have been measured in population-level and some smaller scale biomonitoring studies (Goullé et al., 2005; Heitland and Köster, 2006a,b; Cesbron et al., 2013; CDC, 2015). These biomonitoring data are representative of exposure to barium by general population through all routes of exposure by all sources and to all bioavailable forms in the environment. The biomonitoring data constitute a useful base for investigating the levels of population exposure of environmental chemicals (NRC, 2006; Angerer et al., 2011; Gurusankar et al., 2017). While biomonitoring studies provide barium concentrations in biological matrices (e.g., mg/L urine), the exposure guidance values for toxicity, such the reference doses (RfD) are reported as oral intake values (in mg Ba/kg bw/d). In order to interpret the barium levels measured in the biomonitoring surveys, the exposure guidance values and biomonitoring data need to be converted to the same measures and units. In this regard, tools such as Biomonitoring Equivalents (BE) have been developed to facilitate the interpretation of available biomonitoring data. BEs are estimates of the concentration of a chemical or its metabolites in blood or urine that are consistent with risk assessment-derived exposure guidance values such as RfDs (Hays et al., 2007, 2008; Angerer et al., 2011). The BE value is useful in interpretation of human biomonitoring data in relation to the exposure guidance value (Aylward et al., 2013; St-Amand et al., 2014) but such BE values are not available for barium. Therefore, the objectives of the current study were twofold: (1) to assemble population-level biomonitoring data to identify the concentrations of barium in biological matrices across the general population; and (2) to derive BE values for barium in order to facilitate the interpretation of the barium concentrations in the biological matrices reported in the general population.

2. Data sources and approaches

2.1. Biomonitoring data

Urine is the most common matrix used to measure barium levels in biomonitoring studies. Barium concentrations in urine have been measured in NHANES III (1988–94) and seven consecutive cycles of CDC-NHANES up to 2012 (Paschal et al., 1998; CDC, 2015). NHANES, designed to evaluate the nutritional status of adults and children, offers the most comprehensive data on urinary barium concentrations based on a representative sample of the US population of all ages (n = 2502 in sampling years 2011–2012). The NHANES survey reports population weighted median and 95th percentile estimates of the urinary barium concentrations. In addition to urinary matrix, the plasma and whole blood concentrations have also been reported in several other small scale biomonitoring studies conducted in Germany and France (Goullé et al., 2005; Heitland and Köster, 2006a,b; Cesbron et al., 2013).

2.2. Exposure guidance value

Risk assessment-based exposure guidance values for barium have been derived by various organizations (Health Canada, 1990; WHO, 2004, 2011; US EPA, 2005, 2013; ATSDR, 2007; NHMRC/NRMMC, 2011; SCHER, 2012).

The US EPA (2005), the ATSDR (2007) and the SCHER (2012) have developed a reference dose (RfD), a chronic minimal risk level (MRL) and a tolerable daily intake level (TDI), respectively for barium. When deriving the guidance values, all three organizations have used the same point of departure (POD) from the NTP (1994) study and uncertainty factors (UF) to achieve exposure guidance value (RfD, MRL and TDI) of 0.2 mg Ba/kg bw/d. NHMRC/NRMMC (2011) has used the same POD to derive a drinking water guideline of 6 mg/L. However, WHO (2004) and Health Canada (1990) established a drinking water guideline of 0.7 mg/L based on the mean barium concentration of 7.3 mg/L (range: 2–10 mg/L) reported in an epidemiology study. In this study, the participants did not show significant differences in blood pressure or the prevalence of cardiovascular disease compared to control population ingesting drinking water containing 0.1 mg/L barium (Brenniman and Levy, 1985). A summary of the exposure guidance values are presented in Table 1. The BE derivation is based on oral exposure guidance values (mg/kg bw/d) and not on media-specific guidelines (Hays et al., 2007, 2008). Since all existing oral exposure guidance values for barium are based on the same POD identified in US EPA's RfD assessment (NTP, 1994), the present study derived BEs using US EPA (2005) rather than Health Canada (1990) or WHO (2004). The U.S. EPA's RfD for barium was based on the benchmark dose modeling of the nephropathy incidence in B6C3F$_1$ mice (n = 60 animals per group) exposed to drinking-water containing 0, 500, 1250, or 2500 mg barium chloride dihydrate/litre for 2 years (corresponding to estimated daily doses of 0, 30, 75, or 160 mg Ba/kg bw/d in male mice and 0, 40, 90, or 200 mg Ba/kg bw/d in female mice) (NTP, 1994). The multistage model was reported to provide the best fit of the dose-response data in male mice, and the corresponding benchmark dose for a 5% extra risk of barium-induced nephropathy was 63 mg/kg bw/d (NTP, 1994; U.S. EPA, 2005; ATSDR, 2007; SCHER, 2012). In this assessment, a cumulative uncertainty factor of 300 was applied including a factor of 10 for mice