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Influence of co-contaminant exposure on the absorption of arsenic, cadmium and lead

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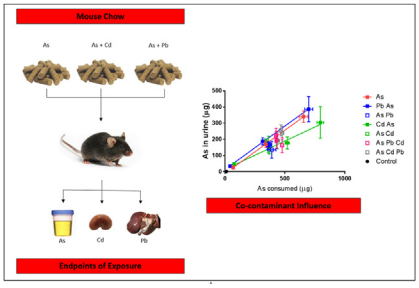
HIGHLIGHTS

- The influence of co-contaminant exposure was assessed using an in vivo mouse model.
- Cd co-exposure with As decreased the bioavailability of As.
- Cd co-exposure with Pb increased the accumulation of Pb in the liver.
- As and/or Pb co-exposure with Cd did not affect Cd accumulation in the kidney.

GRAPHICAL ABSTRACT



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ABSTRACT

Incidental ingestion of contaminated soil and dust is a major pathway for human exposure to many inorganic contaminants. To date, exposure research has focused on arsenic (As), cadmium (Cd) and lead (Pb), however, these studies have typically assessed metal(loid) bioavailability individually, even when multiple elements are present in the same matrix. As a consequence, it is unclear whether interactions between these elements occur within the gastro-intestinal tract, which may impact absorption and accumulation. In this study, the influence of contaminant co-exposure was assessed using a mouse bioassay and soluble forms of As, Cd and Pb supplied in mouse chow as individual, binary and tertiary elemental combinations. Arsenic urinary excretion and Pb-liver accumulation were unaffected by As-Pb co-exposure (1–10 mg As kg^{-1} and 3–30 mg Pb kg^{-1}) while Cd-kidney accumulation was unaffected by the presence of As and/or Pb. However, Cd co-exposure decreased As urinary excretion and increased Pb-liver accumulation. It was hypothesized that Cd influenced arsenate absorption as a consequence of the impairment of phosphate transporters. Although the reason for increasing Pb-liver accumulation following Cd co-exposure is unclear, enhanced Pb accumulation may occur as a result of transport protein overexpression or changes in divalent metal compartmentalization.

1. Introduction

Incidental ingestion of soil is often a major pathway for children's exposure to inorganic contaminants (e.g. arsenic [As], cadmium [Cd] and lead [Pb]) due to their tendency for hand-to-mouth contact (Rodriguez and Basta, 1999). Exposure to these ubiquitous

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environmental contaminants may result in a variety of health effects including skin lesions or cancer (As), bone fragility or kidney damage (Cd) and disruption to cognitive development for children (Pb) (ATSDR, 2007a, b; 2012). However, exposure is influenced by the propensity of the contaminant to be released from the soil matrix under gastrointestinal conditions and its subsequent absorption across intestinal epithelia into the systemic circulation (i.e. bioavailability). Although numerous studies have illustrated the influence of As, Cd and Pb speciation and soil physicochemical properties on contaminant relative bioavailability (Freeman et al., 1992, 1993; Ruby et al., 1992; Schilderman et al., 1997; Rodriguez and Basta, 1999; Schroder et al., 2003; Casteel et al., 2006; Drexler and Brattin, 2007; Juhasz et al., 2007, 2009a, 2009b, 2010; Bradham et al., 2011; Smith et al., 2011; Denys et al., 2012; Juhasz et al., 2014; Bradham et al., 2015; Li et al., 2016), these studies have typically assessed relative bioavailability for individual elements, when multiple elements are present in the same matrix.

Of the limited number of studies to assess the influence of co-exposure on contaminant bioavailability, Diacomanolis et al. (2013, 2014) determined that As bioavailability was reduced when rats were co-exposed to either Cd or Pb. The As elimination half-life was reduced to 13–22 days in the presence of Cd (3–6 mg kg^{-1} bw) and 27–30 days in the presence of Pb (0.5–20 mg kg^{-1} bw) compared to 67 days when As was administered individually (2.5 mg kg^{-1} bw). While the mechanisms for the reduction in As bioavailability were not elucidated, Diacomanolis et al. (2013, 2014) proposed that the formation of poorly soluble Cd arsenate and Pb arsenate in the gastrointestinal tract may account, in part, for the decreased bioavailability. Although the formation of these arsenate forms is not thermodynamically favoured (due to unfavourable pH conditions), other factors (e.g. transport effects) may influence absorption in the gastrointestinal, distribution within organs and therefore bioavailability.

Due to the lack of knowledge of the influence of co-contaminants on As, Cd and Pb exposure, it is unclear whether interactions between these elements occur within the gastrointestinal tract which impacts absorption and bioavailability. This is important to elucidate as factors influencing contaminant bioavailability will impact exposure estimates which in turn will affect risk calculations. As a consequence, the aim of this study was to assess the influence of co-contaminant exposure on the absorption of As, Cd and Pb using a C57BL/6 mouse bioassay. Soluble forms of these elements, which have been used in toxicological reference value studies, were added to AIN93G mouse chow in order to provide a consistent exposure medium where As, Cd or Pb concentration was the only adjusted variable. The influence of co-contaminant exposure on As, Cd and Pb absorption was assessed in single, binary and tertiary combinations through the quantification of elements in key biomarkers of exposure (urine, kidney, liver). It was hypothesised that absorption of the oxyanion would not be influenced by the presence of divalent cations, however, co-administration of Cd and Pb may influence divalent cation absorption as a result of competitive transport processes.

2. Materials and methods

2.1. Test materials

Sodium arsenate (Na_2HAsO_4), cadmium chloride ($CdCl_2$) and lead acetate ($Pb[CH_3COO]_2$) were utilised to assess the influence of co-contaminants on the bioavailability of As, Cd and Pb exposure. These soluble salts were chosen as they are reference compounds that have been used to determine toxicological reference values (TRVs) for each individual element (Juhasz et al., 2010; Denys et al., 2012; NEPM, 2013). Sodium arsenate, Cd chloride, Pb acetate and binary or tertiary combinations of these elements were dissolved in MilliQ water at the desired concentration and combined thoroughly with oven dried (70 °C) AIN93G mouse chow to achieve a smooth paste (i.e. 80% water holding capacity). Mouse chow pastes were dried overnight at 70 °C then processed (crushed and blended) to produce a crumb which was utilised in exposure studies. Reference compounds were added to AIN93G mouse chow to achieve concentrations of 1, 5, 10 mg As kg^{-1}, 0.2, 1, 2 mg Cd kg^{-1}, and 3, 15, 30 mg Pb kg^{-1}. These values were chosen as they represent diet concentrations equivalent to, five-fold and ten-fold the National Environmental Protection Measure for the Assessment of Site Contamination (NEPM, 2013) health investigation (HIL A) value ((NEPM), 2013) if impacted soil was amended to mouse chow at a 1% (w/w soil:diet) loading. To confirm the concentration of As, Cd and Pb in amended AIN93G mouse chow, triplicate diets were digested using USEPA method 3051 in a Mars6 microwave (CEM) (USEPA, 1998) with elemental concentrations determined using inductively-coupled plasma-mass spectrometry (ICP-MS). Initially, experiments were conducted with each element supplied individually, while subsequent studies utilised binary and tertiary elemental combinations as detailed in the Supporting Information (Table S1).

2.2. In vivo assessment of As, Cd and Pb exposure

Female C57 BL/6 mice, aged between 4 and 6 weeks, were utilised for exposure experiments. Experimental protocols were approved by the SA Pathology/South Australian Health and Medical Research Institute Animal Ethics Committees (application number SAM73). Animal care was compliant with the Standard Operating Procedures of the South Australian Health and Medical Research Institute, and the Guidelines for the Care and Use of Laboratory Animals (NRC, 1996). Initially, animals were acclimated for a period of 7 days to animal house conditions (12/12-hr photocycle) during which mice had unlimited access to unamended AIN93G mouse chow and water. Following the acclimation period, mice were transferred to metabolic cages (3 per cage; 12 per treatment) and supplied As, Cd and/or Pb amended AIN93G mouse chow for a period of 9 days. A negative control group was also included which consumed unamended AIN93G mouse chow. During the exposure period, food consumption was monitored by determining the difference between the weight of the food hopper after filling and before replenishment on the following day while cumulative food consumption was the sum of the daily food consumption. Supply of amended mouse chow did not significantly influence food consumption or mouse weight gain compared to unamended feed, nor was the clinical condition of the mice affected at the concentrations tested. At the end of the 9 day exposure period, mice were maintained for an additional 24 h on unamended AIN93G mouse chow after which they were humanely euthanized and targeted tissues collected (liver, kidney). Urine and faeces were collected from each metabolic cage every 2 days and pooled to produce single cumulative urine and faecal samples. The following endpoints were used to assess contaminant exposure; urine (As; (Bradham et al., 2013)), kidneys (Cd; (Liu et al., 2000; Juhasz et al., 2010)) and liver (Pb; (Marschner et al., 2006)). Kidney, liver and faecal samples were frozen at −20 °C prior to freeze drying using a Modulyod Freeze Dryer. Following freeze drying, the aforementioned samples and urines were digested using concentrated nitric acid (HNO_3). Whole kidney and liver samples were digested whereas urine samples were divided into duplicates. Samples were digested using 70% HNO_3 (10 ml; Univar analytical reagent), using a block digester ramped to a maximum temperature of 140 °C (A.I. Scientific AIM500). Once the volume was reduced to 1–2 ml, samples were

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