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Physiologically-based pharmacokinetic and toxicokinetic models for estimating human exposure to five toxic elements through oral ingestion

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ABSTRACT

Biological monitoring and physiologically-based pharmacokinetic (PBPK) modelling are useful complementary tools in quantifying human exposure to elements in the environment. In this work, we used PBPK models to determine the optimal time for collecting biological samples in a longitudinal study to determine if participants who consumed allotment produce had been exposed to arsenic, cadmium, chromium, nickel or lead. There are a number of PBPK models for these elements published in the literature, which vary in size, complexity and application, given the differences in physiochemical properties of the elements, organs involved in metabolism and exposure pathways affected. We selected PBPK models from the literature to simulate the oral ingestion pathway from consumption of allotment produce. Some models required modification by reducing or removing selected compartments whilst still maintaining their original predictability. The performance of the modified models was evaluated by comparing the predicted urinary and blood elemental levels with experimental data and other model simulations published in the literature. Overall, the model predictions were consistent with literature data ($r > 0.7$, $p < 0.05$), and were influential in predicting when samples should be collected. Our results demonstrate the use of mathematical modelling in informing and optimising the design of longitudinal studies.

1. Introduction

Arsenic (As), cadmium (Cd), chromium (Cr), nickel (Ni) and lead (Pb) are known to occur in urban horticultural sites (allotments) and gardens, as a result of pollution from traffic, general urban activities, industrial emissions and the actions of allotment tenants (Bechet et al., 2016; Kelly et al., 1996; Alloway, 2004). Fruits and vegetables grown in contaminated soil may lead to humans ingesting these elements through the consumption of home grown produce. According to the Environment Agency (2009), the consumption rates for allotment produce by adults in the United Kingdom (UK) range from 0.22 to 2.97 (g^{-1} fresh weight (fw) kg^{-1} body weight (bw) day^{-1}), depending on the produce categories used in the Contaminated Land Exposure Assessment (CLEA) model. The CLEA model, a tool used in the UK to assess human exposure to soil contaminants, groups allotment produce into six categories (green, root, tuber, herbaceous, shrub and tree) (Environment Agency, 2009). The toxicological effects of these elements are well documented and As, Cd, Cr and Ni are Group 1 inorganic human carcinogens (IARC, 2012). Oral exposure to Pb can cause toxic effects on various body organs and tissues including kidney dysfunction, cardiovascular effects (e.g., increase in blood pressure), gastrointestinal effects (e.g., colic), haematological effects (e.g., anaemia), and brain damage (ATSDR, 2007).

Biological monitoring (biomonitoring) and physiologically-based pharmacokinetic (PBPK) modelling are useful tools in quantifying human exposure to elements in the environment; they are complementary in exposure studies (Clewell et al., 2008; Lyons et al., 2008). Human biomonitoring is the assessment of an individual's exposure to an element or compound through the measurement of a biomarker (e.g., blood, urine) which results from exposure to that

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element (Coelho et al., 2014). Meanwhile, physiologically-based pharmacokinetic (PBPK) modelling involves predicting the fate of elements in the body (Schmitt and Willmann, 2005), using physiological and biochemical information to describe and quantify the pharmacokinetic processes affecting the absorption, distribution, methylation (biotransformation) and excretion of an element (Wen et al., 1999). PBPK models are based on compartments (e.g., body organs, tissues) and the interconnections among them. The level of model detail relates to the compartments and elements (including associated chemical forms such as metabolites) that are tracked within the model (Krishnan et al., 2010). PBPK models provide a scientific basis for quantitatively estimating risk to human health (Yu, 1999).

In this paper, our aim is to use PBPK models to determine the optimal time for collecting biological samples to determine if participants who consumed allotment produce during a longitudinal biomonitoring study had been exposed to As, Cd, Cr, Ni or Pb. To do this, we sought to obtain applicable published PBPK and physiologically-based toxicokinetic (PBTK) models for these elements from the literature. Some of these models are quite complex in terms of their structure and formulation because of the differences in physiochemical properties of the elements, organs involved in metabolism and exposure pathways simulated by the authors. For example, PBPK models for As published by the El-Masri and Kenyon (2008), Liao et al. (2008), Yu (1999) and Mann et al. (1996) indicate that As undergoes biotransformation into different species within the body, with kidney and liver being the key organs for As methylation. The Cr models published by Finley et al. (1997), O'Flaherty et al. (2001) and Kirman et al. (2013) indicate that Cr species undergo oxidation and reduction in the body. No biological transformations are shown to occur in the models for Cd (Kjellstrom and Nordberg, 1978), Ni (Sunderman et al., 1989) and Pb (Fleming et al., 1999; White et al., 1998; O'Flaherty, 1993). Due to the structural complexity of some of the models, to construct models suitable for our purpose, some of the published models required modification by reducing or removing some compartments whilst maintaining their predictive ability.

The objectives of this part of our research were: (i) to review published PBPK and PBTK models for these elements and select models for use in our study; (ii) to make the necessary modifications to the models to fit our purpose (i.e., to use the models to determine the optimal time for collecting biological samples); (iii) to evaluate their predictive performance by comparing the reduced model predictions with data published in the literature; and (iv) to use the modified models to predict optimal times (following oral exposure to the elements) for collecting biological samples during our biomonitoring study, in order to maximise the detection of the elements in urine and blood samples.

Based on the consumption of allotment produce, we set out to investigate human exposure to As, Cd, Cr, Ni and Pb from soil with low levels of these elements. We identified 30 allotment sites across central Scotland, UK with varying levels of toxic element contamination. Allotment users (36 adults) were recruited to participate in the study. Informed consent was obtained from each participant and ethical approval was granted by the University of Reading Research Ethics Committee (UREC), approval reference UREC 15/21.

2. Methods

2.1. Model selection

We reviewed previously published PBPK/PBTK models for As, Cd, Cr, Ni and Pb in humans, and selected suitable ones based on whether the model was reproducible, relevant to adult humans, included a description of the oral ingestion pathway, and the most recent/most used model. The mathematical equations for each modified model are given in the Supplementary material along with the schematic details of the original models obtained from the literature (Figs. S1–S5). The physiological and chemical-specific parameters were obtained from the literature and are detailed in Tables S1 to S5 of the Supplementary material. In the following sections, we detail the models selected for each toxic element and the modifications made to the original published models.

2.2. Arsenic

We identified a number of human PBPK models for inorganic As published in the literature (Mann et al., 1996; El-Masri and Kenyon, 2008; Liao et al., 2008; Yu, 1999). These models are largely similar in structure, and they account for oxidation of trivalent inorganic As (As (III)) to its pentavalent form (As(V)), reduction of As(V) to As(III), and methylation of As(III) to monomethylarsenic acid (MMA) and dimethylarsinic acid (DMA) in the body. The model by Mann et al. (1996) included both oral and inhalation exposure pathways, whereas other models only included the ingestion pathway. Ingestion is the primary route of exposure studied, because exposure to As from allotment land use occurs mainly through oral intake (CL:AIRE, 2014). In addition, a pilot study we carried out identified air As concentrations at the allotments were not significantly elevated enough above background air concentrations to warrant inclusion in our model. The model proposed by Liao et al. (2008) for children was not evaluated using experimental data, whereas the predictive performance of the other models were tested using data from human studies included in the same publications. We adopted the model published by El-Masri and Kenyon (2008) because it is the most recent model (hence the most informed parameter wise) out of those considered. The El-Masri & Kenyon model comprises 9 compartments: gastrointestinal (GI) tract, liver, kidney, blood, muscles, brain, skin, heart and lung. The lung compartment was included in the model because it receives total blood flow, thus mathematically accounting for As reduction that may occur in other body tissues (El-Masri and Kenyon, 2008). We made the following modifications to the model: (i) we considered oxidation and reduction in the lung, liver and kidney only, and assumed that oxidation and reduction occurs in all perfused tissues as previously reported by Mann et al. (1996) and Yu (1999); (ii) we ignored the oxidation and reduction reactions between MMA(III) and MMA(V), DMA(III) and DMA(V) and treated MMA and DMA as single species because in our laboratory analysis we tested for total inorganic As (sum of inorganic As species); and (iii) included biliary excretion of As from the liver as reported by Yu (1999) and Liao et al. (2008). Fig. 1 shows the schematic representation of our resulting modified PBPK model for As.

2.3. Cadmium

There are a number of PBTK models for Cd published in the literature (Nordberg and Kjellstrom, 1979; Choudhury et al., 2001; Amzal et al., 2009; Ju et al., 2012; Fransson et al., 2014) based on the original PBTK model for Cd published by Kjellstrom and Nordberg (1978) (KN model). The KN model consists of eight compartments, describing Cd uptake from the GI tract and the lungs, distribution of absorbed Cd to three blood compartments, liver, kidney and 'other tissues', and Cd elimination through urine and faeces. The KN model was tested using data from studies involving Cd exposure through inhalation (Nordberg and Kjellstrom, 1979). The model has been used in other studies (Ruiz et al., 2010; Ju et al., 2012; Fransson et al., 2014) to simulate Cd exposure through oral ingestion. It was modified by Ruiz et al. (2010) and used to accurately predict urinary Cd concentrations following oral ingestion using data from the National Health and Nutrition Examination Survey (NHANES). A study by Choudhury et al. (2001) also used a modified version of the KN model to predict urinary Cd concentrations consistent with the NHANES data.

We adopted the KN model in this study because it is the most used model and it is also the basis for other published Cd PBTK models.