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Using publicly available data, a physiologically-based pharmacokinetic model and Bayesian simulation to improve arsenic non-cancer dose-response

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ABSTRACT

Publicly available data can potentially examine the relationship between environmental exposure and public health, however, it has not yet been widely applied. Arsenic is of environmental concern, and previous studies mathematically parameterized exposure duration to create a link between duration of exposure and increase in risk. However, since the dose metric emerging from exposure duration is not a linear or explicit variable, it is difficult to address the effects of exposure duration simply by using mathematical functions. To relate cumulative dose metric to public health requires a lifetime physiologically-based pharmacokinetic (PBPK) model, yet this model is not available at a population level. In this study, the data from the U.S. total diet study (TDS, 2006–2011) was employed to assess exposure: daily dietary intakes for total arsenic (tAs) and inorganic arsenic (iAs) were estimated to be 0.15 and 0.028 μg/kg/day, respectively. Meanwhile, using National Health and Nutrition Examination Survey (NHANES, 2011–2012) data, the fraction of urinary As(III) levels (geometric mean: 0.31 μg/L) in tAs (geometric mean: 7.75 μg/L) was firstly reported to be approximately 4%. Together with Bayesian technique, the assessed exposure and urinary As(III) concentration were input to successfully optimize a lifetime population PBPK model. Finally, this optimized PBPK model was used to derive an oral reference dose (Rfd) of 0.8 μg/kg/day for iAs exposure. Our study also suggests the previous approach (by using mathematical functions to account for exposure duration) may result in a conservative Rfd estimation.

1. Introduction

Chronic exposure to elevated levels of arsenic (As) has resulted in many adverse effects appearing in humans (Maull et al., 2012; Naujokas et al., 2013). Epidemiological evidence provides opportunities to undertake a dose-response study, and furthermore to assist in assessment and management. For example, one study over a mean follow-up period of 9.7 years for 52,931 eligible participants suggested that the adjusted incidence rate ratios per 1 μg/L increment in arsenic levels in drinking water were 1.03 (95% confidence interval (CI): 1.01, 1.06) for all diabetes cases (Bräuner et al., 2014). Such epidemiological studies have convincingly linked the As exposure level and risk (Bräuner et al., 2014; U.S. EPA, 1988).

Excepting exposure level, previous research has also demonstrated the incidence of diseases increases with exposure duration (Liao et al., 2008; Mazumder et al., 1998; U.S. EPA, 1988). To quantify the exposure duration effects, mathematical functions (such as Weibull and Hill functions) have usually been employed, by parameterizing age factor to represent exposure duration effect (Liao et al., 2008; U.S. EPA, 1988). For long-term chronic exposure, since the dose metric emerging from exposure duration is not a linear or explicit variable, it is difficult to address these effects simply based on mathematical parameterization (Hodgson and Darnton, 2000; Philippe and Mansi, 1998). The case study on dioxin has successfully illustrated how to use toxicokinetic model to convert external exposure level and exposure duration into a cumulative dose metric, which was further applied in dose-response study (Becher et al., 1998; Crump et al., 2003). To understand the influence of exposure duration to public health requires a toxicokinetic model to appropriately quantify the impact of exposure duration on delivered dose and ultimately risk in a quantitative dose-response framework.

Several toxicokinetic models have been previously developed (El-Masri and Kenyon, 2008; Liao et al., 2008; Yu, 1999). Based on short-term oral exposures, Yu (1999) developed a seven-compartment physiologically-based pharmacokinetic (PBPK) model for inorganic As

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(iAs). More recently, El-Masri and Kenyon (2008) published an individual PBPK model that traced the relationships among iAs, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) for oral exposure. While these models offered an overview of the absorption, metabolism, distribution and excretion mechanisms in human systems, all such models were developed based on normal people at an individual level. To relate exposure to public health, a PBPK model needs to account for intrinsic heterogeneity at a population and lifetime scale.

Publicly available data have the potential to support the optimization of population PBPK models for use in quantitative risk assessment (Bernillon and Bois, 2000; Lyons et al., 2008), particularly in dose-response study. Specifically, the U.S. FDA has conducted a total diet study (TDS) program to monitor the levels of multiple elements, as well as As, in the country's food supply (Tao and Bolger, 1999). Also, the National Health and Nutrition Examination Survey (NHANES) program was initiated to assess the health and nutritional status of adults and children in the United States (Aylward et al., 2014). Fitting of PBPK models to available data using Bayesian methods such as Markov Chain Monte Carlo (MCMC), these publicly available data can be utilized to bridge As exposure and public health. To the best of our knowledge, this type of research has not previously been attempted and represents a novel interpretation of human health from existing data sets.

In this study, the aim is to illustrate how to integrate publicly available data, PBPK model and Bayesian simulation to refine human health risk assessment, using arsenic as a case study. In particular, the objectives include: 1) assessment of As exposure from U.S. TDS; 2) reporting As biomonitoring information based on the latest U.S. NHANES data (2011—2012); 3) optimizing an As population lifetime PBPK model; and 4) improving As non-cancer dose-response study. The newly proposed dose-response study has the potential to protect human health from arsenic exposure.

2. Materials and methods

2.1. Procedure for establishing arsenic dose response

As shown in Fig. 1, the procedure for establishing As dose response consisted of three steps. In step 1, a national As exposure assessment was conducted based on TDS data. Then, the urinary As data was retrieved from NHANES database. The As exposure information and urinary As concentration were set as PBPK model input and output, respectively. Therefore a population, lifetime PBPK model was optimized by using Bayesian simulation (step 2). Finally, the optimized PBPK model assisted in As dose-response study (step 3).

2.2. Exposure assessment

The U.S. FDA has released analytical results for samples (all the samples in the TDS study were table-ready prior to analysis) collected during 2006–2011 for toxic and nutritional elements (U.S. FDA, 2014). The total As concentrations (tAs) in 272 types of foods were also measured. The foods were collected based on the food list representing the major components of American people's diet. In the meantime the U.S. FDA compiled food consumption data from 9 age subgroups (U.S. FDA, 2009). Therefore, the daily tAs exposure (E_{As}) was estimated by multiplying arsenic concentration (C_{As}) and the age-specific consumption amount (A_{As}) for each TDS food:

$$E_{As} = C_{As} \times A_{As}. \quad (1)$$

In this study, all 272 types of food were classified into seven categories: seafood (exclude fish), rice/bread/wheat, fish, vegetables, meat, wine and others.

Only tAs was available in the current TDS study. Lynch et al. (2014) have evaluated the iAs fraction of tAs in food based on >6500 data points. To our knowledge, their research is the most comprehensive available analysis on arsenic forms in food. Thus, the fractions of iAs in different food categories were summarized in this study (Supplementary material (SM) Table S1), and were used to estimate daily exposure for different forms of As in each food category.

Excepting diet exposure, drinking water was also deemed to be an important pathway for iAs exposure. Xue et al. (2010) have estimated that the daily iAs exposure from drinking water was 0.025 ± 0.104 μg/kg bw/day (median: 0.002 μg/kg bw/day) for the U.S. population. Consequently this median value was considered to be geometric

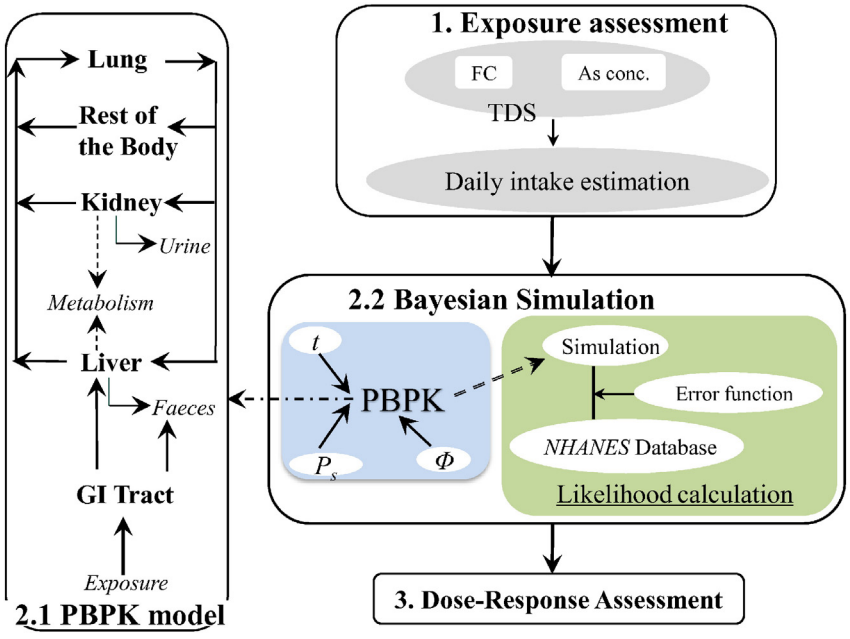

Fig. 1. Framework for establishing arsenic dose response. Abbreviations. FC: food consumption; con.: concentration; TDS: total diet study; GI: gastrointestinal; PBPK: physiologically-based pharmacokinetic model; t: time; P_s: sensitive parameters; ϕ: other parameters; NHANES: National Health and Nutrition Examination Survey.