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A new method for generating distributions of biomonitoring equivalents to support exposure assessment and prioritization

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ABSTRACT

Biomonitoring data are now available for hundreds of chemicals through state and national health surveys. Exposure guidance values also exist for many of these chemicals. Several methods are frequently used to evaluate biomarker data with respect to a guidance value. The "biomonitoring equivalent" (BE) approach estimates a single biomarker concentration (called the BE) that corresponds to a guidance value (e.g., Maximum Contaminant Level, Reference Dose, etc.), which can then be compared with measured biomarker data. The resulting "hazard quotient" estimates (HQ = biomarker concentration/BE) can then be used to prioritize chemicals for follow-up examinations. This approach is used exclusively for population-level assessments, and works best when the central tendency of measurement data is considered. Complementary approaches are therefore needed for assessing individual biomarker levels, particularly those that fall within the upper percentiles of measurement distributions. In this case study, probabilistic models were first used to generate distributions of BEs for perchlorate based on the point-of-departure (POD) of 7 μg/kg/day. These distributions reflect possible biomarker concentrations in a hypothetical population where all individuals are exposed at the POD. A statistical analysis was then performed to evaluate urinary perchlorate measurements from adults in the 2001 to 2002 National Health and Nutrition Examination Survey (NHANES). Each NHANES adult was assumed to have experienced repeated exposure at the POD, and their biomarker concentration was interpreted probabilistically with respect to a BE distribution. The HQ based on the geometric mean (GM) urinary perchlorate concentration was estimated to be much lower than unity (HQ ≈ 0.07). This result suggests that the *average* NHANES adult was exposed to perchlorate at a level well below the POD. Regarding individuals, at least a 99.8% probability was calculated for all but two NHANES adults that a higher biomarker concentration would have been observed compared to what was actually measured if the daily dietary exposure had been at the POD. This is strong evidence that *individual* perchlorate exposures in the 2001–2002 NHANES adult population were likely well below the POD. This case study demonstrates that the "stochastic BE approach" provides useful quantitative metrics, in addition to HQ estimates, for comparison across chemicals. This methodology should be considered when evaluating biomarker measurements against exposure guidance values, and when examining chemicals that have been identified as needing follow-up investigation based on existing HQ estimates.

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Abbreviations: ADME, absorption, distribution, metabolism, elimination; ATUS, American Time Use Survey; BE, biomonitoring equivalent; BE_{POD}, biomonitoring equivalent corresponding to the point of departure; BW, body weight; CDC, Centers for Disease Control and Prevention; GM, geometric mean; GSD, geometric standard deviation; HQ, hazard quotient; HQ_{GM}, hazard quotient corresponding to the geometric mean; HQ_{95}, hazard quotient corresponding to the 95th percentile; mpd, meals per day; NHANES, National Health and Nutrition Examination Survey; NOAEL, no observed adverse effect level; NSC, normalized sensitivity coefficient; PBPK, physiologically-based pharmacokinetic; POD, point of departure; UO, urine output (L/h).

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1. Introduction

Humans are exposed to thousands of distinct chemicals every day from both natural and man-made sources (USEPA, 2013c). Understanding the impacts of these exposures on human health requires accurate and precise exposure estimation. Conventional methods for exposure estimation integrate environmental measurements, records of human time/location activities, and other exposure factors (e.g., hand-to-mouth frequency) (USEPA, 1992). Alternative strategies now utilize chemical biomarker measurements (USNRC, 2006). Biomarkers of exposure are generally parent chemicals or their metabolite(s) measured in biological media (Fields and Horstman, 1979). These measurements provide direct evidence of human exposure to a chemical. Given the availability of these data in nationwide exposure and health surveys (e.g., the Centers for Disease Control and Prevention's [CDC] National Health and Nutrition Examination Survey [NHANES]), there is a move to make use of biomarker measurements to support exposure and risk assessments.

Several approaches exist for evaluating exposures and/or health risks using biomarker data. The "biomonitoring equivalent" (BE) approach, developed by Hays and colleagues, is a popular screening method for comparing biomarker data to exposure guidance values (Hays et al., 2007). This approach uses pharmacokinetic (PK) models or analytical expressions to predict a steady state or average biomarker concentration given exposure at an existing guidance value. The predicted biomarker concentration (i.e., the BE) is then compared to biomarker measurements from a population of interest to estimate a hazard quotient (HQ), where HQ = [biomarker concentration]/BE. These HQs can be compared across chemicals to identify those that are of higher concern with respect to human health risk.

To date, the BE approach has been used to interpret biomonitoring data for approximately 100 chemicals in a wide range of classes, such as dioxins (Aylward et al., 2008), phthalates (Aylward et al., 2009), and heavy metals (Hays et al., 2010). In a recent article by Aylward et al. (2013), HQs were calculated based on geometric mean (HQ_{GM}) and 95th percentile (HQ_{95}) estimates for a subset of analytes measured as part of the NHANES. These calculated HQs were used to prioritize chemicals; a small number had HQ_{GM} near unity. The number of chemicals with HQ_{95} near unity increased, but the importance of HQ_{95} is difficult to interpret.

There is general agreement that the central tendency of a distribution of biomarker measurements reflects longer-term average exposures in the sample population (Aylward et al., 2012; Pleil and Sobus, 2013). Thus, HQ estimates based on GM levels provide insight into these longer-term average exposures, where estimates near unity suggest that population-wide exposure is likely to be near the guidance level. However, HQ estimates based on distribution tails are much more difficult to interpret. For distributions of short-lived biomarkers, it is difficult and sometimes impossible to tell whether very high levels reflect elevated acute exposures, chronic exposures, or a combination of factors that are independent of exposure magnitude (e.g., the timing of exposure with respect to sample collection). This limitation has important implications for interpreting biomarker measurements within a risk context since regulatory agencies establish tolerable limits based on chronic exposure. Thus, new strategies are needed for interpreting biomarker distribution tails with respect to BEs and other biomarker-based screening values.

The current study presents a stochastic approach for estimating a distribution of BEs that takes into accounts both exposure and PK variability. A statistical methodology is also presented for interpreting tails of a measured biomarker distribution with respect to the estimated BE distribution. These techniques are illustrated using perchlorate as a case study. Perchlorate was chosen because of the abundance of relevant exposure and biomarker data, as well as the existence of a physiologically-based pharmacokinetic (PBPK) model that describes the dose–biomarker relationship. The stochastic approach presented in this article may be used to supplement existing HQ estimates and to facilitate the quantitative interpretation of human biomonitoring data.

2. Methods

2.1. Stochastic BE approach

The new stochastic BE approach is based on the original BE approach developed by Hays et al. (2007). Similarities and key differences between approaches are illustrated in Fig. 1 and are discussed in detail in the following subsections. Throughout the article, perchlorate is used as a case study chemical to demonstrate the stochastic approach. Perchlorate is a well-studied chemical that is used in rocket fuel, explosives, and fireworks (Motzer, 2001). It also originates from natural sources, and is a byproduct of some water disinfection processes (Rao et al., 2012). Dietary ingestion is considered the major route of environmental exposure to perchlorate (Huber et al., 2011; Mendez et al., 2010; Murray et al., 2008), and is therefore the only exposure route considered in this analysis.

2.1.1. Exposure guidance value

Generally an existing exposure guidance value is considered the starting point for BE derivation (Aylward et al., 2009). In some cases, the starting point is a point of departure (POD), which is the dose–response point that marks the beginning of a low-dose extrapolation (USEPA, 2014). An example of a POD is a no observed adverse effect level (NOAEL), which is the highest dose tested that does not produce an adverse effect (USEPA, 2013a; USNRC, 2005). When a POD is based on studies of laboratory animals, an uncertainty factor (e.g., 10×) is used to adjust for interspecies differences prior to the derivation of a BE. For our case study of perchlorate, the POD is a NOAEL of 7 μg/kg/day (USNRC, 2005) that was determined from human studies (Greer et al., 2002). Therefore, no interspecies uncertainty factor is required, and the human POD was chosen to be the starting point of our case study.

2.1.2. Exposure model

Once a guidance value is selected as a starting point, it is incorporated into the BE calculation as the exposure concentration. As shown in Fig. 1, the original approach uses a simplified scenario of continuous steady state exposure, whereas the stochastic approach uses a probabilistic exposure model to simulate real-life scenarios. In this study, multiple perchlorate dietary exposure scenarios (one or three meals per day [mpd] at different meal times) were simulated. One mpd exposures were simulated with the total daily dose (7 μg/kg/day) given at 7:00 am, noon, or a randomized time based on a distribution of meal times gathered from the American Time Use Survey (Fig. S2). Three mpd simulations were simulated based on a fraction of the total daily dose (7 μg/kg/day) given at 7:00 am, noon, and 5 pm, or at three randomized times based on the ATUS. For these 3 mpd cases with randomized meal times, simulated days were first segmented into breakfast (midnight – 10:30 am), lunch (10:30 am–3:00 pm), and dinner (3:00 pm – midnight) time frames. Each meal time was then randomized using the ATUS by choosing one meal from within each time frame with no meal being allowed to take place less than one hour after the previous meal. The daily dose was split across the three meals in one of the two ways: (1) each meal was one

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