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Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment

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ABSTRACT

Exposures to multiple chemicals may contribute to increased risk of similar adverse effects. Cumulative risk may be estimated using a hazard index (HI), the sum of individual hazard quotients (HQ, ratio of exposure to the reference value). We demonstrate the HI approach for five phthalates: di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), diisobutyl phthalate (DiBP), diisononyl phthalate (DiNP), and butyl benzyl phthalate (BBP). Phthalate exposure for the US general population is estimated using urine metabolite levels from NHANES, extrapolating to ingested 'dose' using the creatinine correction approach. We used two sets of reference values: European Union Tolerable Daily Intakes and Denmark Environmental Protection Agency Derived No Effect Levels. We also investigated the use of an alternate reference value for DEHP, derived from a recent study on male reproductive system development. HQs and HIs were calculated for the total population ages 6 years and older, as well as for men and women of approximate reproductive age (18–39 years), and children (6–11 years). Median HQs ranged from <0.01 for BBP, to ~0.1 (using established values) or ~2 (using an alternate value) for DEHP. Median HIs were <0.30 (95th percentiles just >1.0), and were driven by DEHP and DBP exposures.

1. Introduction

In 2008, the National Research Council published a report titled 'Phthalates and Cumulative Risk Assessment: the Task Ahead' (NRC, 2008). In this report, the panel concluded that phthalates met the conditions necessary to warrant a cumulative risk approach—the general population is exposed to multiple different phthalates, and these phthalates may contribute to common adverse outcomes. Although the report focused on effects related to the 'phthalate syndrome' of disrupted male reproductive development, there is evidence from both animal and human studies that phthalates impact a wide variety of health endpoints (see recent reviews including: (Jurewicz and Hanke, 2011; Lyche et al., 2009; Martino-Andrade and Chahoud, 2010; Meeker et al., 2009; Pak et al., 2011)).

One approach to estimating cumulative risk for non-cancer outcomes, from multiple exposures to toxicologically similar chemicals, is the hazard index (HI) approach which assumes dose addition (EPA, 2003, 2007; Teuschler and Hertzberg, 1995). As outlined in the NRC report, the HI provides a straightforward method to relate intake of a group of substances to their reference values (RfVs) (NRC, 2008) and this approach has been previously demonstrated in the literature (Kortenkamp and Faust, 2010; Soeborg et al., 2012). Example RfVs for oral exposure include the US Environmental Protection Agency (EPA) Reference Dose, RfD, and the European Union (EU) Tolerable Daily Intake, TDI. For each exposure a hazard quotient (HQ) is calculated as the ratio of the estimated exposure level to the RfV for that chemical. The chemical-specific HQs are then summed to estimate the overall summary HI. Guidance documents for conducting cumulative risk assessments emphasize that a final step is the interpretation of results (EPA, 2003, 2007). In this paper, we focus on the generation of the

Abbreviations: AGD, anogenital distance; BBP, butyl benzyl phthalate; CE, creatinine excretion; DBP, di-n-butyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DI, daily intake; DNEL, Derived No Effect Level; DiBP, diisobutyl phthalate; DiNP, diisononyl phthalate; EPA, Environmental Protection Agency; EU, European Union; FUE, fraction excreted in urine; HI, hazard index; HQ, hazard quotient; LOAEL, lowest observed adverse effect level; MBP, mono-n-butyl phthalate; MBZP, mono-benzyl phthalate; MCOP, mono-(carboxyoctyl) phthalate; MEP, monoethyl phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MIBP, monoisobutyl phthalate; MINP, monoisononyl phthalate; MW, molecular weight; NHANES, National Health and Nutritional Evaluation Survey; NCHS, National Center for Health Statistics; NOAEL, no observed adverse effect level; POD, point of departure; RfD, Reference Dose; RfV, reference value; TDI, Tolerable Daily Intake; US, United States.

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quantities that go into the cumulative risk assessment – phthalate-specific intake estimates, HQs, and HIs. Regarding the interpretation, both the HQ and HI have practical interpretations and uses within a public health and regulatory context. These interpretations and uses derive from the careful wording of the definitions of these RfVs. For example, the EU defines the TDI as follows: "*A TDI is an estimate of the amount of a substance in air, food or drinking water that can be taken in daily over a lifetime without appreciable health risk. TDIs are calculated on the basis of laboratory toxicity data to which uncertainty factors are applied*" (EU, 2014). Therefore, if an individual's daily exposure is less than the TDI (i.e., the HQ is less than one), it is often concluded that this level of exposure is not likely to cause harmful effects during a lifetime. Similarly, if the HQ is found to be less than one for all individuals within a defined population, one might conclude that this exposure would not be of concern over their lifetimes. However, if the exposure is greater than the TDI (i.e., the HQ exceeds one), this does not imply that a health effect will occur. Several additional considerations include, among other things, whether the exposure is ongoing; whether the health effect used in developing the TDI is relevant for the exposed individual; and what uncertainty factors were used in developing the TDI. Similarly, an HI at or above one for a group of contaminants may indicate the need for further investigation, such as to take into account the degree of toxicological similarity, the appropriateness of dose additivity, and other issues.

In order to estimate the HQ and HI, it is necessary to know the exposure level in the population of interest. There are two general approaches used to estimate phthalate exposure. The 'forward' approach combines information on the concentration of phthalates in exposure media (including food, water, air, etc.) with exposure media contact rates (see for example, (Clark et al., in press; Wormuth et al., 2006)). This approach requires that both the exposure sources and the concentrations of phthalates for each source are known. This information is often not available or is not of sufficient quality. Concentrations may be widely varied according to factors such as geographic region, distribution and use of products containing phthalates, and other issues. Further, laboratory equipment and reagents may themselves contain phthalates, which could lead to sample contamination (Guo and Kannan, 2012). This may bring into question the validity of exposure media measurements of phthalates, particularly phthalates in food. The 'backward' approach uses human biomonitoring data in combination with human metabolism information to extrapolate backward to the 'dose' which would have resulted in the observed biomarker level. For phthalates, the biomarkers used are generally phthalate metabolites present in urine. By measuring metabolites rather than parent compounds, this approach circumvents the contamination issue (Koch and Calafat, 2009). Additionally, the measurement of phthalate metabolites in urine provides an integrated measure of phthalate exposure from all sources (known and unknown), and incorporates individual variability in exposure profiles.

In the US, the majority of general population exposure comes from six specific phthalates: diethyl phthalate, DEP; di (2-ethylhexyl) phthalate, DEHP; di-n-butyl phthalate, DBP; diisobutyl phthalate, DiBP; diisononyl phthalate, DiNP; and butyl benzyl phthalate, BBP. In the nationally representative National Health and Evaluation Survey (NHANES), the metabolites of these phthalates show the highest levels among the phthalate metabolites measured (CDC, 2013b), and a recent study of estimated dietary exposure also identified these six as having the highest potential for exposure (Schecter et al., 2013). In this paper, we estimate daily intakes for five of these phthalates for the US population using the 'backward' approach applied to measurements in the NHANES, then estimate individual and population HQs and HIs for these phthalates; DEP is not included because in toxicology studies, it has not been shown to cause effects within the phthalate syndrome, a constellation of male developmental reproductive effects (NRC, 2008). We also look at the results for different population groups, including all adults (>18 years), women of approximate reproductive age (18–39 years), and children (6–11 years). We used two sources for health RfVs, EU TDIs and Denmark EPA Derived No Effect Levels (DNELs). Our rationale for selecting these two sources includes these considerations: (1) the RfVs were derived within the past 10 years, (2) the RfVs were developed based on effects within the "phthalate syndrome", (3) although the RfVs from these two sources are not derived by exactly the same methodology, they were consistently derived by each governing body. We selected two sources of RfVs for comparison to highlight potential differences in approach to deriving RfVs and subsequent variability in the resulting HQ/HI estimates. The available US EPA's RfDS were not used for this analysis, because they were not all developed based on the phthalate syndrome. For example, the EPA RfD for DEHP was developed based on increased relative liver weight in guinea pigs (Carpenter et al., 1953; EPA). Finally, we explore the impact of selecting an alternative RfV for one of the phthalates, DEHP, on estimated hazard. This phthalate was selected for the impact analysis because it was found to drive the cumulative exposures and risk, as discussed below.

2. Materials and methods

Total exposure to phthalates has been studied primarily with the measurement of phthalate metabolites in urine. The phthalate metabolites, rather than the parent compound, are measured in urine because the parent compound is metabolized very quickly, before being excreted, and also due to issues of contamination from phthalates present in plastic laboratory equipment. One complexity is that these metabolites are not entirely specific—that is, more than one parent compound may degrade to a common metabolite. However, this is more the exception than the rule, and for each phthalate in our assessment, specific metabolites are identified which correspond to only the single parent. This section describes the method used to infer daily intakes from spot samples of phthalate metabolites, and applies that method to the NHANES database. The NHANES is a nationally representative complex sample survey of the civilian, non-institutionalized US population, and is maintained by the National Center for Health Statistics (CDC, 2013a). The current NHANES is a continuous cycle of surveys conducted every 2 years. Starting with the 1999–2000 survey, phthalates have been measured via spot urine sample in a one-third random sample of NHANES participants aged 6 years and older. Implications of the use of these data are discussed in Section 4. For this analysis, the cycles from 2005–2006 and 2007–2008 were used—earlier surveys were not included because measurements of the metabolites of DiNP were not available until 2005. In order to generate nationally representative estimates of daily phthalate intake, statistical survey procedures are used to account for sampling-associated variability, using the sampling strata and primary sampling unit information, and sampling weights provided by the National Center for Health Statistics (NCHS). All analyses were performed using the SAS statistical software package.

The primary method to back calculate estimated phthalate intake corresponding to a given measurement of phthalate metabolite in urine is known as the 'creatinine correction' approach (David, 2000; Kohn et al., 2000). The key assumption behind this approach is that phthalate intakes and eliminations are at steady state, such that the daily intake is equal to the daily elimination (with proper correction for elimination of metabolite versus intake of parent compound). Much data exist to support this assumption, including data on phthalates in exposure media, near 100% occurrence frequency of phthalate metabolites in urine, and evidence

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