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An analysis of cumulative risks based on biomonitoring data for six phthalates using the Maximum Cumulative Ratio

Jeanette M. Reyes[a], Paul S. Price[b,*]

[a] Oak Ridge Institute for Science and Education (ORISE) Research Participation Program, hosted at U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, United States

[b] Office of Research and Development, National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, United States

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ABSTRACT

The Maximum Cumulative Ratio (MCR) quantifies the degree to which a single chemical drives the cumulative risk of an individual exposed to multiple chemicals. Phthalates are a class of chemicals with ubiquitous exposures in the general population that have the potential to cause adverse health effects in humans. This work used the MCR to evaluate coexposures to six phthalates as measured in biomonitoring data from the most recent cycle (2013–2014) of the National Health and Nutrition Examination Survey (NHANES). The values of MCR, Hazard Index (HI), and phthalate-specific Hazard Quotients (HQs) were determined for 2663 NHANES participants aged six years and older by using reverse dosimetry techniques to calculate steady-state doses consistent with concentrations of metabolites of six phthalates in urine and using Tolerable Daily Intake values. There were 21 participants (0.8% of the NHANES sample) with HI $>$ 1. Of those, 43% (9/21) would have been missed by chemical-by-chemical assessments (i.e. all HQs were less than one). The mean MCR value in the 21 participants was 2.1. HI and MCR values were negatively correlated ($p < 0.001$) indicating that most participants, especially those with elevated HI values, had their cumulative risks driven by relatively large doses of a single phthalate rather than doses of multiple phthalates. The dominate phthalate varied across participants. Children (aged 6–17 years) had a higher HI values ($p < 0.01$) than adults (18 + years). However, the probability of having HI $>$ 1 was not driven by age, gender, or ethnicity. The cumulative exposures of concern largely originated from a subset of three of the fifteen possible pairs of the six phthalates. These findings suggest that cumulative exposures were a potential concern for a small portion of the surveyed participants involving a subset of the phthalates explored. The largest risks tended to occur in individuals whose exposures were dominated by a single phthalate.

1. Introduction

Phthalates (esters of phthalic acid) are used as plasticizers in a wide range of consumer goods including vinyl flooring, food packaging, the outer coatings of pills, cosmetics, food containers, pipes and tubing, etc. (NRC, 2008). As plasticizers, phthalates can make nail polish less brittle, allow hair sprays to have more flexibility, and reduce volatility in fragrances. Phthalates are not strongly bound and leaching of the compounds can occur in many of these products (Sathyanarayana, 2008). Human exposure routes include dermal exposures, inhalation, intravenous injection and, most commonly, ingestion (Colacino et al., 2010). In 2008, the National Research Council concluded that phthalates met the conditions to warrant a cumulative risk approach. They stated that the general population is exposed to multiple phthalates which may contribute to a common adverse health outcome (NRC, 2008). Although the NRC report focused on effects related to disrupted male reproductive development known as the “phthalate syndrome”, there was evidence from both animal and human studies that phthalates impact a wide variety of health endpoints (Jurewicz and Hanke, 2011; Lyche et al., 2009; Martino-Andrade and Chahoud, 2009; Meeker and Ferguson, 2011; Pak et al., 2011).

The Hazard Index (HI) is a screening tool for estimating cumulative risks from exposures to multiple chemicals from a common mechanism group. This approach assumes dose addition (EPA, 1986, 2003, 2007; Teuschler and Hertzberg, 1995). The HI provides a straightforward method for quantifying risks by relating the intakes of substances to their Reference Values (RfVs) (NRC, 2008). This technique applied to individuals has been previously demonstrated in the literature (Kortenkamp and Faust, 2010; Søeborg et al., 2012). Examples of RfVs for oral exposures include the United States Environmental Protection

* Corresponding author.
E-mail address: price.pauls@epa.gov (P.S. Price).

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Agency's (USEPA's) Reference Dose (RfD) and the European Union's Tolerable Daily Intake (TDI). The Hazard Quotient (HQ) is calculated as the ratio of an individual's estimated exposure level to the RfV for that chemical. The chemical-specific HQs are then summed to give an individual's HI.

The Maximum Cumulative Ratio (MCR) is a measure of the contribution of the most dominant chemical to the risks posed by an individual's cumulative exposures to multiple chemicals (Kienzler et al., 2014; Price and Han, 2011; Vallotton and Price, 2016). The MCR along with measures of cumulative exposures can inform risk management decisions and help identify specific combinations of chemicals that result in elevated cumulative risks. The MCR approach has been applied to biomonitoring data on mixtures of dioxin-like chemicals (Han and Price, 2013), exposures to mixtures of chemicals in water (Han and Price, 2011; Price and Han, 2011; Silva and Cerejeira, 2015; Vallotton and Price, 2016), and mixtures in residential indoor air (De Brouwere et al., 2014).

The present study applied the MCR approach to a group of six phthalates from the National Health and Nutrition Examination Survey (NHANES) for the years 2013 and 2014. Reverse dosimetry techniques were used to reconstruct individuals' phthalate exposures from data using metabolite concentrations in their urine along with information about their physiologies and demographics (Christensen et al., 2014). Using hazard information from each phthalate, MCR values were constructed. The results are presented by age, gender, and ethnicity.

2. Methods and materials

2.1. NHANES data set

Phthalate biomarker data came from the 2013–2014 cycle of NHANES (CDC, 2016a). NHANES is a nationwide survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and is representative of the general non-institutionalized, civilian population in the United States. This survey has a complex multistage, stratified, random sampling design based on the sampling of counties, households, and household members. NHANES gathers information through interviews, physical examinations, and laboratory tests. Samples of urine are collected from participants six years and older and samples of blood are collected from participants aged one year and older (CDC, 2016b). Urine samples from a subset of participants were analyzed for metabolites of phthalates. Of the 2777 participants sampled for phthalate analysis, 82 participants were missing a necessary metabolite concentration, and an additional 32 were missing either height or weight information. Thus, there were data from a total of 2663 participants from the 2013–2014 NHANES cycle used in this analysis.

The six phthalates and associated metabolites included in this analysis were di-n-butyl phthalate (DBP; with metabolite MBP), diisobutyl phthalate (DIBP; with metabolite MIBP), butyl benzyl phthalate (BBP; with metabolite MBZP), di(2-ethylhexyl) phthalate (DEHP; with metabolites MECPP, MEOHP, MEHHP, and MEHP), diisononyl phthalate (DINP; with metabolites MINP and MCOP), and diisodecyl phthalate (DIDP; with metabolite MCNP; Table 1). At the time of this writing, the 2013–2014 NHANES cycle constitutes the most recent publically available NHANES biomonitoring data for these compounds. This combination of phthalates has been explored in previous works (Qian et al., 2015) and is a slight expansion on the five phthalates investigated by Christensen et al. (2014). The set of phthalates selected are due to their wide and varied use in consumer products (Qian et al., 2015).

2.2. Daily intake dose

Internal Daily Intake (DI) doses of phthalates for NHANES participants were calculated using the methodology presented in Christensen et al. (2014). In brief, the DI was calculated through adjusting metabolite concentrations of phthalates by creatinine concentrations while incorporating other variables such as daily creatinine excretion rates, the molar fraction of a given metabolite that was excreted, and information about the molecular weights of the metabolites and their parent phthalates. Under the assumption of steady state exposures, the DI for each participant i and metabolite k originating from parent phthalate j was calculated using the following equation:

$$DI_{i,j,k} = ([100*(Met_{i,k}/Cr_i)*CE_i]/[F_{UE,i,k}*1000\,]) \times (MW_{i,j}/MW_{i,j,k}) \quad (1)$$

where $DI_{i,\,j,\,k}$ (μg/kg/d) in urine is the daily intake dose for metabolite k, 100 is a unit conversion factor, $Met_{i,\,k}$ (ng/mL) is the metabolite concentration as given in the NHANES data set, Cr_i (mg/dL) is the creatinine concentration in urine as given in the NHANES data set, CE_i (mg/kg/d) is the creatinine excretion per day as calculated by Mage et al. (2008) using information about a participant's age, ethnicity, gender, weight, and height, $F_{UE,\,i,\,k}$ (unitless) is the molar fraction of the metabolite excreted, 1000 is a unit conversion factor, $MW_{i,\,j}$ (mg/mol) is the molecular weight of the parent phthalate, and $MW_{i,\,j,\,k}$ (mg/mol) is the molecular weight of the metabolite (Table S1). Among the phthalates that have multiple metabolites (i.e. DEHP and DINP), within an individual i, the value of $DI_{i,\,j}$ was calculated by taking a weighted mean of the values of $DI_{i,\,j,\,k}$ estimated from each metabolite k using $F_{UE,\,i,\,k}$ (Christensen et al., 2014; Qian et al., 2015). The weighted mean was determined using the following equation:

$$DI_{i,j} = \sum_{k=1}^{n_k} \left(DI_{i,j,k} \times \frac{F_{UE,i,k}}{\sum_{l=1}^{n_k} F_{UE,i,l}} \right) \quad (2)$$

where $DI_{i,\,j}$ is the daily intake dose for phthalate j and n_k is the number of metabolites for a given parent phthalate. In this work, $n_k \in \{1, 2, 4\}$.

We used the NHANES convention of setting metabolite concentrations below the Limit of Detection (LOD) to $LOD/\sqrt{2}$. Table 1 gives the LOD for each metabolite and the number (and percentage) of participants with metabolites below the LODs. Table 1 indicates the majority of the metabolites were detectable in > 97% of the surveyed participants. The predictions of $DI_{i,\,j}$ for each participant, the measurements of metabolite concentrations obtained from NHANES, and the physiological and demographic information used to determine $DI_{i,\,j}$ values are provided in the Supplementary Data.

2.3. Maximum cumulative ratio

The following equations were used to determine the values of HQ and HI for participant i and phthalate j for N phthalates:

$$HQ_{i,j} = DI_{i,j}/TDI_j \quad (3)$$

$$HQ_{M,i} = \max_{j \in \{1,\ldots,N\}} HQ_{i,j} \quad (4)$$

$$HI_i = \sum_{j=1}^{N} HQ_{i,j} \quad (5)$$

There were six phthalates used in this analysis (i.e. $N = 6$) and HQ_M quantifies the maximum HQ among the six phthalates for participant i. The TDIs used in this study and their references are given in Table 1. Five of the six were taken from several sources (EFSA, 2005a, 2005b, 2005c, 2005d; Saillenfait et al., 2008) with DIDP taken from an additional source (CPSC, 2010). Because many Lowest Observed Adverse Effect Level (LOAEL) and No Observed Adverse Effect Level (NOAEL) are based on findings in animal studies, a series of Uncertainty Factors (UFs) are applied to these measures to make them applicable to humans (NRC, 2008). Different toxicological studies have led to different UFs (Table 1).

The MCR is a function of the doses that reach an exposed individual. As a result, values of MCR will vary across individuals in an exposed population ranging from one to N (i.e. $MCR_i \in [1, N]$), where N is the number of chemicals considered in the assessment. A value close to one