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Occurrence of phthalate esters in over-the-counter medicines from China and its implications for human exposure

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ABSTRACT

Food, air, personal care products and indoor dust have been recognized as the main routes of exposure to phthalates in Chinese population, but other sources may have been overlooked, e.g., medicines. To fill the knowledge gap, phthalate esters were measured in 96 over-the-counter medicines made in China, including selected 71 Chinese patented medicines and 25 western medicines. It was found that none of the medicines was free of phthalates. The mean concentrations of individual phthalates ranged from 0.001 μg/g (dicyclohexyl phthalate) to 5.85 μg/g (diethyl phthalate). Among 9 targeted phthalates, di-n-butyl phthalate was the dominant congener, accounting for >65% of the total phthalates in all medicine samples, followed by di-(2-ethylhexyl) phthalate and diethyl phthalate. Phthalates in medicines appeared to derive from gastroresistant film coatings, plastic packing materials or phthalate contaminated rural herbal plants (especially for Chinese patented medicines). Daily human exposure to phthalates was estimated for local patients for one treatment cycle (e.g., one week) based on suggested consumption dosage and phthalate concentrations. Almost all exposure levels were below the guidelines suggested by the United States Environmental Protection Agency or European Food Safety Authority, indicating low health risk with phthalates from consumption of the medicines. In addition, concentration levels of phthalates in patients would increase upon administration but are expected to decrease to the same values as those in patients before they took medicines in several days. Because the number of medicine samples was limited and the concentrations of phthalates varied in a large range, further investigations are needed to acquire more data for better assessment of human health effects for Chinese population.

Capsule: Distribution of phthalate esters in over-the-counter medicines and related exposure for Chinese population are examined

1. Introduction

Phthalates are used to impart flexibility and durability of polyvinyl chloride and other plastics, and also occur in personal care products, detergents, pesticides and food wrap (Latini, 2005). Over 470 million pounds of phthalates are produced globally every year (United States Environmental Protection Agency, 2009). Commercially available phthalates are dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DBP), di-iso-butyl phthalate (DIBP), benzyl butyl phthalate (BzBP), di-(2-ethylhexyl) phthalate (DEHP) and di-*n*-octyl phthalate (DNOP), with DEHP accounting for 50% of the total phthalate production (Strutt, 1997). In 2006, the production of DEHP was 0.045 to 0.023 million tons and 3.0 to 3.4 million tons in the United States and in China, respectively, and DEHP accounted for 80% of phthalate production in China (Zolfaghari et al., 2014). Phthalates are recognized as environmental endocrine disrupters because of their ability to interfere with the endocrine system, especially for male, although the toxicity of phthalates varies with their chemical structures (Matsumoto et al., 2008; Witorsch and Thomas, 2010). In 2009, several phthalates were classified by the United States Environmental Protection Agency (USEPA) as "chemicals of concern" (United States Environmental Protection Agency, 2009).

Several biomonitoring studies indicated that people are widely exposed to phthalates (Becker et al., 2009; Berman et al., 2009; Guo et al., 2011a; Itoh et al., 2009; Latini et al., 2009; Silva et al., 2004). Levels

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of urinary metabolites of DEP and BzBP were an order of magnitude lower in the populations of China, Korea, Japan, Malaysia and Vietnam than in those of India and North America (Guo et al., 2011a). The contribution of urinary metabolites of DBP and DIBP to total phthalate metabolites in Chinese population (~50%) was twice as much as that in Koreans and Vietnamese (~25%), but the trend was reversed for urinary metabolite of DEHP (Guo et al., 2011a). These exposure patterns may have reflected the different exposure routes or usage patterns of phthalates in different countries. For instance, DMP was frequently detected in food samples (>80%) from China (Guo et al., 2012), but rarely found in foods from the United States (~37%) (Schecter et al., 2013).

Our previous studies conducted during 2010 to 2014 (Guo and Kannan, 2011; Guo et al., 2011b; Guo et al., 2012; Guo et al., 2014) estimated human exposure to phthalates for Chinese population. The total daily exposure doses of phthalates were back calculated by urinary biomonitoring data (Koch et al., 2003; Koch et al., 2004; Koch et al., 2005), and were also estimated by summing doses from various potential uptake sources, such as indoor dusts, food stuffs and personal care products (PCPs) (Wormuth et al., 2006). The total exposure doses of phthalates estimated by the two methods were on the same order of magnitude for several phthalates, e.g., DEHP and DEP. Diet and PCPs were the dominant sources of DEHP and DEP, respectively, for Chinese population. However, the exposure doses of DBP, DIBP, BzBP and DMP estimated by the two methods were quite different, probably suggesting that other potential sources may have been overlooked and therefore merit further investigations.

Medical devices or medicine may have been the missing sources. Previous studies mainly focused on phthalates, especially DEHP, in medical devices. For example, the occurrence of DEHP in human tissues and organs of recipients with blood transfusion first reported in 1970 was attributed to leaching of DEHP from blood bags (Jaeger and Rubin, 1970). Similarly, high exposure level of DEHP in patients of neonatal intensive care units were also ascribed to association of phthalates with medical devices (Fischer et al., 2013). On the other hand, investigations into the occurrence of phthalates in oral medicine have been scarce. Phthalates may enter into medicines from packing materials. One study reported that surfactants-containing drugs, including cyclosporine, miconazole and teniposide and vehicles used in formulating taxotere, received large amounts of phthalates from PVC bays after being packaged within 24 h (Pearson and Trissel, 1993). Previous epidemiological studies also found that urinary concentrations of DEP or DBP in persons who took medicines were much higher than those who did not (Hauser et al., 2004; Hernandez-Diaz et al., 2009; Hernandez-Diaz et al., 2013). These findings pointed to the likelihood for medicines as a potential source of human exposure to phthalates.

The present study was conducted to examine whether medicines would be another important source of human exposure to phthalates, through determination of the concentrations and composition profiles of phthalates in 96 over-the-counter medicines made in China and estimation of their potential exposure doses. The aims of the present study were to 1) examine the occurrence of phthalates in these over-the-counter medicines; 2) determine the input sources of the phthalates and 3) estimate the potential human health risk due to consumption of the medicines.

2. Materials and methods

2.1. Materials

Analytical standards of nine phthalates, DMP, DEP, DBP, DIBP, BzBP, DEHP, di-*n*-hexyl phthalate (DNHP), dicyclohexyl phthalate (DCHP) and DNOP, and their deuterated counterparts used as internal standards were purchased from AccuStandard (New Haven, CT, USA) and/or C/D/N Isotopes (Pointe-Claire, Quebec, Canada), with a purity of >99%. Methyl tertiary-butyl ether of analytical grade was purchased from Macron Chemicals (Nashville, TN, USA), and hexane and HPLC grade water were purchased from J.T. Baker (Pillipsburgh, NJ, USA).

2.2. Sample collection and preparation

In June 2014, a total of 96 over-the-counter medicines made in China, including 13 for children and 83 for adults, were collected from eight Chinese families residing in Albany, New York, USA. They are the most popular medicines used in mainland China for alleviating common cold, fever and dyspepsia, or others, and all of them were oral medicines. None of the medicines were exactly the same, but included some medicines with the similar name made by different medicine manufacturers (Table S1 of the Supporting information). According to their ingredients, these samples contained 71 Chinese patented medicines (CHPM), including 30 pills, 9 capsules, 26 granules and 6 oral liquids, and 25 western medicines, including 15 pills and 10 capsules.

Each sample was weighed in a 12-mL glass tube with a polytetrafluoroethylene cap (a whole pill/capsule, 1.0 g granules or 5 g oral liquid) and spiked with deuterated phthalates as internal standards. Four milliliters of HPLC grade water and 1.0 mL of ethyl acetate (except for oral liquid) were added to the glass tube, which was then placed in the dark at room temperature for at least three days until the medicine was nearly melted. The mixture was extracted with 3 mL of hexane and 2 mL of methyl tertiary-butyl ether on a mechanical shaker (Eberbach, Ann Arbor, MI, USA) at 250 oscillations/min for 30 min. After centrifugation at 4500 $\times g$ for 15 min, the organic solvent layer was transferred into a clean glass tube. The residue was extracted two more times and the organic solvent extracts were combined, concentrated to almost dryness under a gentle stream of nitrogen and redissolved into hexane to 0.5 mL prior to instrumental analysis.

2.3. Instrumental analysis

Concentrations of nine phthalates were determined with an Agilent 6890 gas chromatograph coupled with an Agilent 5973 mass spectrometer operated in the selected ion monitoring mode. A fused-silica capillary column (DB-5; 30 m × 0.25 mm i.d.; 0.25 μm film thickness) was used for separation. The responses of individual deuterated internal standards and the corresponding phthalate esters were used for quantification. The instrumental conditions and column oven temperature program were similar to those described previously (Guo and Kannan, 2011). Briefly, the oven temperature was programmed from 80 °C (held for 1 min), raised to 180 °C at 12 °C/min (held for 1 min), increased to 230 °C at 6 °C/min, elevated to 270 °C at 8 °C/min (held for 2 min), and finally ramped to 300 °C at 30 °C/min (held for 12 min). The limits of quantification (LOQ) were calculated from the lowest concentrations of the calibration curves and a nominal sample weight of 1.0 g. The LOQ was 10 ng/g for DNOP and DEHP and 2 ng/g for other phthalates. If any of the analyte concentrations exceeded the calibration ranges the sample was diluted 50 times with hexane containing internal standards and re-analyzed.

2.4. Quality assurance and quality control

To minimize cross contamination, all glassware was baked at 450 °C overnight and maintained at 120 °C in furnace. Water of HPLC grade for melting medicine was extracted with hexane. All solvents were concentrated and analyzed in the same manner as the samples to obtain background levels of the target phthalates, and solvents with the lowest background levels were used throughout the study.

For every batch of 30 samples, three procedural blanks were also processed. Trace levels of DEP, DBP, BzBP and DEHP were detected, and the highest concentrations of individual phthalates in these blanks (12.0, 60.0, 5.0 and 18.0 ng/mL for DEP, DBP, BzBP and DEHP, respectively) were subtracted from reported data. The average recoveries of the internal standards ranged from 82% to 132% in all medicines. To further

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