Environment International 98 (2017) 137–142

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

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

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ARTICLE INFO

Article history:
Received 23 August 2016
Received in revised form 26 October 2016
Accepted 27 October 2016
Available online 3 November 2016

Keywords:
Over-the-counter medicine
Phthalate esters
Di-n-butyl phthalate
Human exposure
Chinese population

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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http://dx.doi.org/10.1016/j.envint.2016.10.025
0160-4120/

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

examine the extraction efficiency, 12 of extracted samples were randomly selected for re-extraction. Six of the 12 samples were spiked with the target analytes at 100 ng/g before re-extraction and the remaining six samples were re-extracted directly. The recoveries of the target analytes ranged from 81 to 120% in five spiked samples and 105–1500% in one, which was obviously due to the extremely high concentrations of DEHP and DBP in the original medicine. At the same time, concentrations of the target analytes in the other six re-extracted samples were <20% of their reported concentrations, indicting good extraction efficiency. Concentrations below the LOQ were set as zero for statistical analysis. Data analysis was conducted with SPSS Statistics version 17.0. Comparison among different sample types was conducted using non-parametric tests (Kruskal-Wallis H and Mann-Whitney U). Statistical significance was set at $p < 0.05$.

3. Results and discussion

3.1. Levels and composition profiles of phthalates

All medicines contained at least one phthalate. The frequently found phthalates were DBP (detection frequency: 99%), DIBP (77%) and DEHP (85%), followed by DMP (64%), DEP (54%) and BzBP (44%), and DNHP, DCHP and DNOP were rarely detected (9–21%). The detection frequency was not significantly different between CHPM and western medicines for all target analytes except for DEP, which was found in 48% of CHPM and 72% of western medicines, respectively. All medicines were grouped into three categories based on the type of packing materials used, i.e., plastic bag/capsule, aluminum plastic and glass. It was found that fewer phthalates were detected in medicines packed with glass materials than in those packed with plastic and aluminum plastic materials.

The occurrence of the target phthalates in the medicines are shown in Table 1. The mean concentrations ranged from 0.001 μg/g (DCHP) to 5.85 μg/g (DEP), indicating large variability in analyte concentrations among the samples. Generally, the analyte concentrations followed the sequence of DBP, DEHP, BzBP, DIBP and DMP, with the greatest value (978 μg/g) for DEHP detected in a CHPM packed in plastic bag (Fig. 1). The levels of DEP varied widely with samples. In addition, western medicine samples contained significantly higher concentrations of DMP and DEP and lower concentrations of BzBP than CHPM ($p < 0.05$), but the concentrations of other phthalates were not significantly different between them ($p > 0.05$). For CHPM, there was no significant difference in the concentrations of DMP, DEP and BzBP among the four medicine types, but significantly higher levels of DBP, DIBP and DEHP were found in pills or capsules than in granules or oral liquid. For western medicines, the levels of BzBP were lower in capsules than in pills, and the concentrations of other target phthalates were not significantly different. Furthermore, no difference in the concentrations of all target phthalates was observed among different packing materials.

Among the detected phthalates, DBP was the most dominant, accounting for >65% of the total amount in all samples (Fig. 2), followed by DEHP and DEP. Although DMP, DIBP and BzBP were detected frequently, their relative abundances were quite low (<4%). Compared to CHPM, western medicines had higher abundance of DEP but lower abundance of DMP (Fig. 2). A study conducted in 2003, which investigated phthalates in selected liquid medicines and intravenous injection solutions from Japan, also found that DBP was detected (7–60 ng/mL) in most intravenous injection solutions in plastic containers, but not in glass bottles (Mitani et al., 2003). Similar to our study, DBP was also the most dominant congener.

3.2. Potential sources of phthalates in medicines

The occurrence of the target phthalates in the medicines as discussed above may be explained by various potential input routes. First, phthalates are insoluble in acidic solution but soluble in neutral and alkaline media. They are commonly used as plasticizing agents in gastroresistant film coatings for tablets, capsules, beads and granules,

Table 1
Phthalate concentrations in over-the-counter medicines from China (μg/g).

		DMP	DEP	DBP	DIBP	DNHP	BzBP	DCHP	DEHP	DNOP
Chinese patented medicine										
Total ($n = 71$)	Mean	0.024	6.62	3.45	0.049	0.003	0.439	0.001	14.5	0.001
	Median	0.002	ND[a]	0.611	0.006	ND	ND	ND	0.072	ND
	Max	0.549	467	48.6	1.73	0.185	29.4	0.028	978	0.019
Pills ($n = 30$)	Mean	0.019	15.1	4.47	0.039	0.007	0.995	0.002	32.1	0.001
	Median	0.002	0.003	1.62	0.010	ND	ND	ND	0.192	ND
	Max	0.143	467	40.4	0.443	0.185	29.4	0.028	978	0.019
Capsules ($n = 9$)	Mean	0.043	0.046	4.99	0.039	0.003	0.004	ND	0.375	ND
	Median	0.002	0.012	1.51	0.008	ND	ND	ND	0.157	ND
	Max	0.368	0.244	34.1	0.263	0.018	0.015	0.004	1.85	ND
Granules ($n = 26$)	Mean	0.006	0.033	0.317	0.005	ND	0.001	ND	0.088	0.001
	Median	0.002	ND	0.197	0.001	ND	ND	ND	0.028	ND
	Max	0.067	0.666	1.50	0.037	0.004	0.009	0.001	1.26	0.009
Oral liquid ($n = 6$)	Mean	0.093	0.017	8.90	0.296	0.002	0.041	ND	4.99	ND
	Median	0.002	0.003	0.030	ND	0.001	ND	ND	ND	ND
	Max	0.549	0.087	48.6	1.73	0.008	0.238	ND	29.8	ND
Western medicine										
Total ($n = 25$)	Mean	0.056	3.65	3.35	0.056	0.003	0.030	0.001	1.09	0.004
	Median	0.007	0.017	0.687	0.008	ND	0.006	ND	0.115	ND
	Max	0.549	43.8	37.1	0.589	0.049	0.313	0.022	23.2	0.081
Pills ($n = 15$)	Mean	0.055	3.35	2.38	0.087	0.004	0.047	ND	1.73	0.007
	Median	0.015	0.016	0.779	0.016	ND	0.018	ND	0.115	ND
	Max	0.549	43.8	8.40	0.589	0.049	0.313	ND	23.2	0.081
Capsules ($n = 10$)	Mean	0.056	4.13	4.81	0.009	0.001	0.003	0.002	0.132	ND
	Median	0.003	0.058	0.684	0.005	ND	ND	ND	0.095	ND
	Max	0.494	31.0	37.1	0.030	0.010	0.013	0.022	0.346	ND
Total medicine ($n = 96$)										
	Mean	0.032	5.85	3.42	0.051	0.003	0.332	0.001	11.0	0.002
	Median	0.003	0.002	0.668	0.007	ND	ND	ND	0.080	ND
	Max	0.549	467	48.6	1.73	0.185	29.4	0.028	978	0.081

[a] ND = not detectable.

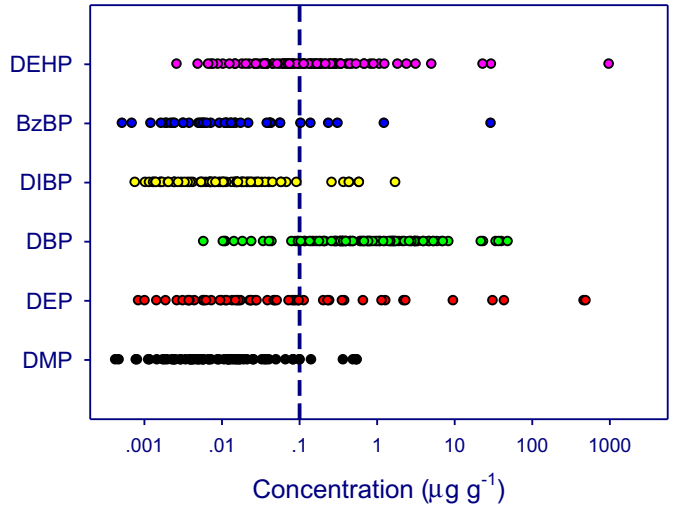

Fig. 1. Distribution of phthalate concentrations in over-the-counter medicines made in China.

thus enabling targeted delivery of active ingredients to the alkaline environment (Jamieson and McCully, 2015). According to the medicine regulations in China, Europe and the United States, DMP, DEP and DBP are still allowed to be added to pharmaceutical accessories with supervision. For example, the threshold of DMP content in medicines is 0.41 mg/dose (U.S. Food and Drug Administration). A recent review on the occurrence of phthalates in United Kingdom licensed medications found that 27 medicines contained DBP or DEP at concentrations ranging from 0.14 to 8.0 mg/tablet or capsule (Jamieson and McCully, 2015). Upon administration of phthalates-containing medicine by patients, the levels of phthalates in patients' bodies may increase significantly (Hauser et al., 2004). An extremely high urinary DBP concentration (16,900 ng/mL) was reported by the United States Center for Disease Control in a man who took Asacol for treating ulcerative colitis for three months. This concentration was more than two orders of magnitude greater than the 95th percentile of the concentrations in males reported in the 1999–2000 National Health and Nutrition Examination Survey (Hauser et al., 2004). However, the concentrations of urinary DEP, BzBP and DEHP in the man's body were not significantly different from other males, implicating Asacol as a potential source of DBP. In addition, concentrations of DBP in 88% of the medicines in the present study were >0.1 μg/g (Fig. 1), significantly greater than those of other phthalates, which may reflect the large amount of DBP used in pharmaceutical accessories or medical devices (Mitani et al., 2003).

Second, the medicines under investigation were packed with different types of materials, but none of them was actually free of plastics. Even glass bottle, one of the packing materials, was sealed with plastic caps. The widespread usage of plastics in packing materials led to the detection of phthalates in all medicines analyzed. It also explained the large variability in the concentrations of the target phthalates among the samples, as phthalates in these medicines may have been derived largely from leaching of packing materials.

Third, CHPM are produced from herbal plants, which may contain phthalates sorbed from cultivation soils. For example, DIBP, DEHP, and DBP were found in some Chinese rural herbal plants, which are materials for manufacturing CHPM, such as pueraria, Chinses angelica or radix raeoniae alba, and the phthalate concentrations in their extracted oils were from 0.1%–2.5% (Sun and Cui, 2014). In addition, a study of herbal medicines from China indicated that the concentrations and profiles of pesticides in root parts were closer to those in soils, as compared to the above ground parts (Zhang et al., 2012). Two previous studies reported widespread occurrence of phthalates in agricultural soils of China, and the phthalate contaminations in these soils were mainly from wastewater sludge and/or plastic film (Meng et al., 2014; Wang et al., 2015). Apparently, contaminated soil has become an unique source of phthalates in CHPM as compared to western medicines.

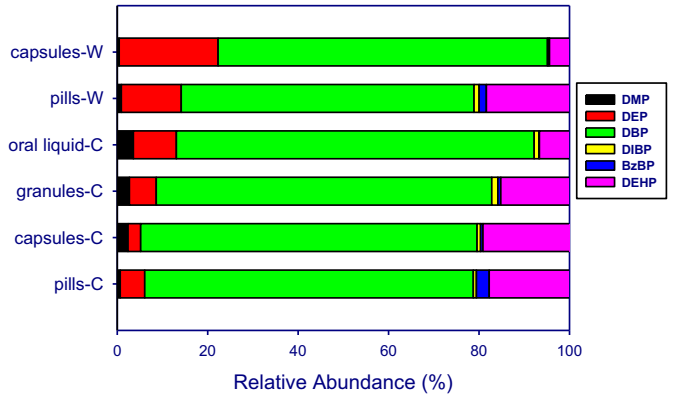

Fig. 2. Phthalate profiles in over-the-counter medicines made in China.

3.3. Human exposure to phthalates by medicines

Daily exposure doses of phthalates were estimated by the suggested amounts of medicines administrated per day, the measured phthalate concentrations in the medicines, and the absorption factors of medicines (phthalates) in human body (assumed as 100%) (Table 2). The mean doses of DEP were 16.1 and 20.5 μg day^{-1} for CHPM and western medicines, respectively. Except for DEP, the exposure doses of phthalates from CHPM were more than those from western medicines, especially for DBP and DEHP, which is apparently because the daily consumption amount of CHPM is generally larger than that of western medicines (Table S1). The suggested administrated dose is usually three times or more daily and five pills or more each time for CHPM, as compared to twice a day and 2 pills each time for western medicines. In addition, the concentrations of the target phthalates in children medicines (all were CHPM) were also used for estimating daily exposure doses for children separately. The mean exposure doses for children were 1.95, 5.18 and 0.59 μg day^{-1} for DEP, DBP and DEHP, respectively, several times less than those of CHPM, but similar to those of western medicines for adult (Table 2). The result indicated low levels of phthalates in children medicines as compared to other CHPM.

Our previous studies estimated the daily intake doses of phthalates from indoor dust, food and PCPs for Chinese population (Guo and Kannan, 2011; Guo et al., 2012; Guo et al., 2014), which were used to estimate the contribution of each potential sources to total phthalate exposures (back-calculated from the urinary phthalate metabolite concentrations). Similar, we added medicine as one of potential sources in the present study (Table 3). As shown, the contribution of medicines (median values) to total exposure doses of phthalates was low. For DMP and DBP, the contribution of the medicines was similar to those of

Table 2
Daily exposure dose by taking over-the-counter medicines from China (μg/day).

	DMP	DEP	DBP	DIBP	BzBP	DEHP
Chinese patent medicine						
Mean	0.11	16.1	22.2	0.13	2.39	27.7
Median	0.02	-[a]	4.93	0.03	–	0.68
Max	1.37	1112	767	2.30	153	1760
Western medicine						
Mean	0.05	20.5	4.30	0.07	0.03	1.48
Median	0.01	0.03	1.07	0.01	–	0.10
Max	1.01	493	75.7	0.88	0.41	34.9
CHPM for children						
Mean	0.15	1.95	5.18	0.09	0.02	0.59
Median	0.03	0.07	3.12	0.03	–	0.44
Max	1.33	20.0	22.5	0.38	0.10	2.00

[a] "-" = not available.

Table 3
Daily exposure dose from potential sources (median, μg/day) and their contribution to total phthalate exposure (100%) for Chinese population.

	Total Exposure[a]	Dust[b]	Diet[c]	PCPs	Over the counter medicine[e]	
					CHPM	WM
DMP	36	0.01 (0.03%)	0.96 (2.67%)	-[d] –	0.02/0.11 (0.06%/0.31%)	0.01/0.05 (0.03%/0.14%)
DEP	66	0.01 (0.02%)	2.52 (3.82%)	44.4 (67.3%)	−/16.1 (−/24.4%)	0.03/20.5 (0.05%/31.1%)
DBP	510	1.82 (0.36%)	41.8 (8.20%)	0.60 (0.12%)	4.96/22.3 (0.97%/4.37%)	1.08/4.37 (0.21%/0.86%)
DEHP	132	9.56 (7.24%)	76.8 (58.2%)	0.50 (0.38%)	0.68/27.7 (0.52%/21.0%)	0.10/1.48 (0.08%/1.12%)

[a] Values for DMP, DEP, DBP (sum of DBP and DIBP) and DEHP were median values of Chinese population (Guo et al., 2011b).
[b] Values were estimated from ingestion (daily intake of dust is 0.03 g/day), not included dermal absorption from dusts because of its relative low contribution compared with ingestion (Guo and Kannan, 2011).
[c] Values are total exposures from various foodstuffs (Guo et al., 2012).
[d] "-" = not available.
[e] CHPM = Chinese patented medicine, WM = Western medicine; median/mean value.

indoor dust and PCPs (<0.1%), lower than that from diet (~5%). For DEP, the contribution of the medicines was similar to that of indoor dust (<0.1%), lower than those from diet (~5%) and PCPs (~60%). The contribution of the medicines for DEHP was similar to that of PCPs (<0.5%), lower than those of dust (~5%) and diet (~60%). In addition, the daily exposure doses of the target phthalates from the medicines were much higher if calculated with mean phthalate concentrations. Therefore, over-the-counter medicines appeared to be a viable route for Chinese population to expose to phthalates, and their contributions to total exposure vary with individual phthalates. Obviously, consumption of medicines does not constitute a main source of total exposure to the target phthalates by Chinese population, and other sources may exist.

It should be noted that medicines are different from indoor dusts or food in that they are taken only by patients when needed. Patients are exposed to phthalates by taking over-the-counter medicines during a short period of time, e.g., one week, as suggested by most prescriptions. The USEPA's reference doses (RfDs) are 100, 200, 800 and 20 μg/kg bw/day for DBP, BzBP, DEP and DEHP, respectively (Aylward et al., 2009; Marsee et al., 2006). The tolerable daily intakes suggested by the European Food Safety Authority for DBP, BzBP and DEHP are 10, 500 and 50 μg/kg bw/day, respectively. The proposed permitted daily exposure in the European Medicines Agency's guidance is <0.7 mg for DBP and 280 mg for DEP for an individual with a body weight of 70 kg (Jamieson and McCully, 2015). As shown in Table 3, the median daily exposure doses of phthalates from medicines are much lower than all the safety guidelines suggested by these agencies, implicating low health risk from consumption of over-the-counter medicines manufactured in China. However, if the highest daily exposure doses of the target phthalates (769, 153, 1110, and 1760 μg day^{-1} for DBP, BzBP, DEP and DEHP, respectively) are considered, there is potential health risk from exposure to DBP or DEHP for patients taking over-the-counter medicines during one treatment cycle.

The total exposure doses of DBP and DEHP were 8.5 and 2.2 μg/kg bw/day for the Chinese general population as estimated previously (Guo et al., 2011b). The half-life of DEHP was approximately 12 h in human body (Koch et al., 2004). If a patient continuously consumes 1760 μg day^{-1} of DEHP (the highest exposure dose from medicine) for 7 days, the effect of DEHP in medicine will almost be eliminated in 60 h after one treatment cycle. For DBP, approximately 90% of oral dose may be excreted from human body in the first 24 h (Koch et al., 2012) with an elimination rate faster than that of DEHP. These conservative assessments suggested that the health risk for patients exposed to DBP and DEHP through administration of the over-the-counter medicines under investigation was low. However, patients may take over-the-counter medicines on a daily base, such as hypertension medications or multivitamins, and the affection of phthalates in these medicines to them will last for a long time.

On the other hand, several studies indicated that even brief exposure to phthalates or their metabolites introduced health effects in rats (Hu et al., 2013; Planello et al., 2011; Shono and Taguchi, 2014). For example, exposure to mono-n-butyl phthalate (MBP), one major metabolite of DBP, for 3 days induced oxidative DNA damage in rat testes (Shono and Taguchi, 2014). Therefore, brief exposure to phthalates through administration of over-the-counter medicines may potentially trigger adverse human health effects.

3.4. Impact of chemical contaminants in Chinese patented medicines on human health

The data from the National Bureau of Statistics of the People's Republic of China showed that the gross production of CHPM industry amounted to 516 billion RMB in 2012, accounting for 31.2% of the total pharmaceutical industry output (National Bureau of Statistics of the People's Republic of China, 2014). The gross amount of total imports and exports was $3.4 billions in 2012, posting a 11% annual growth rate (National Bureau of Statistics of the People's Republic of China, 2014). Although there are few reports on the occurrence of phthalates in CHPM, residual pesticides or other organic pollutants and heavy metals have been frequently detected in CHPM or rural herbal medicines (Harris et al., 2011; Zhang et al., 2012). Harris et al. (2011) analyzed 334 commonly prescribed raw Chinese herbal medicines for five heavy metals (total arsenic, cadmium, chromium, lead and mercury) and 162 pesticides, and detected at least one metal in all samples, all target metals in 115 samples and 42 pesticides in 108 samples. The potential health risk of exposure to pesticides and heavy metals from consuming these herbal medicines was negligible (Harris et al., 2011; Zhang et al., 2012). To sum up, Chinese population may expose to chemical contaminants by consuming CHPM, which is low anyway based on the present study.

4. Conclusions

The present study indicated that phthalates were frequently detected in over-the-counter medicines made in China; none of the medicines examined was free of phthalates. Patient exposure doses of phthalates from consuming CHPM were more than those from western medicines, but were still much lower than the health guidelines suggested by various agencies. The health risk of phthalates through consumption of the medicines was low, but further investigations are warranted to obtain additional data because the number of medicine samples analyzed was limited and the concentrations of phthalates varied in a large range in the present study. Because over-the-counter medicines are easy to acquire and readily available to everyone, their rigid regulation seems urgently needed.

Supplementary data to this article can be found online at doi:10.1016/j.envint.2016.10.025.

Acknowledgements

This study was financially supported by the National Natural Science Foundation of China (Nos. 21577050, 21447002 and 41390240).

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