Original Article

An Estimation of the Daily Intake of Di (2-ethlhexyl) Phthalate (DEHP) among Workers in Flavoring Factories*

LU Jie[1,^], ZHANG Jing[2,^], WANG Zhu Tian[2], and FAN Yong Xiang[2,#]

1. Key Laboratory of Food Safety Risk Assessment, Ministry of Health, China National Center For Food Safety Risk Assessment, Beijing 100022, China; 2. Division of Food Safety Standard, Ministry of Health, China National Center For food Safety Risk Assessment, Beijing 100022, China

Abstract

Objective To estimate the daily intake of DEHP among workers in flavoring factories.

Methods 71 workers in two flavoring manufacturers, 27 administrators in those factories and 31 laboratory technicians in a research institute were recruited and assigned to exposure group, control group 1 and control group 2 respectively. Their urinary DEHP metabolites, mono(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), were detected by isotope dilution-ultra performance liquid chromatography-tandem mass spectrometry(UPLC-MS/MS). The urinary metabolites concentrations were converted into DEHP intake levels using two pharmacokinetic models: the urine creatinine-excretion (UCE) one and the urine volume (UV) one.

Results No significant differences were found among the three groups. Based on the urinary concentrations of Σ_3MEHP, we got a median daily DEHP intake of 3.22 or 1.85 μg/kg body-weight/day applying the UV or UCE models respectively. Depending on the UV model, three subjects (2.34%) exceeded the RfD value given by US EPA and the P_{50} of estimate daily DEHP intakes accounted for 16.10% of the RfD value. No subjects exceeded the limitation depending on the UCE model.

Conclusion The workers in flavoring factories were not supposed to be the high DEHP exposure ones and their exposure level remained at a low risk.

Key words: Di (2-ethylhexyl) phthalate (DEHP); Estimate daily intake; Biomonitoring; Occupational exposure

Biomed Environ Sci, 2014; 27(6): 419-425 doi: 10.3967/bes2014.071 ISSN: 0895-3988

www.besjournal.com (full text) CN: 11-2816/Q *Copyright ©2014 by China CDC*

INTRODUCTION

Di(2-ethyhexyl) phthalate (DEHP), which may count for up to 40% of soft polyvinylchloride (PVC)[1], is commonly used as a plasticizer. Due to the widespread use of this material, DEHP has been found in numerous products such as toys, medical device, building material, food packaging and so on[2]. DEHP has been proved to be a reproductive and developmental toxicant inducing testicular atrophy and resulting in fewer sperm numbers and lower testosterone levels in laboratory animals[3-5]. DEHP could be toxic to humans. Studies have associated the DEHP exposure with reduced anogenital distance in human male infants[6-7]. Epidemiologic studies also suggested an association between phthalate exposure and the increased risk of asthma and allergies[8].

Great attentions have been paid to the risk assessment of DEHP considering its toxicity. Since

*This research was supported by the 12th five-year national science and technology support plan(2011BAK10B05-02).

#Correspondence should be addressed to FAN Yong Xiang, Tel: 86-10-52165410, E-mail: fanyongxiang@cfsa.net.cn

^LU Jie and ZHANG Jing contributed equally to this paper.

Biographical notes of the first authors: LU Jie, female, born in 1975, PhD, majoring in food hygiene; ZHANG Jing, female, born in 1987, master degree candidate, majoring in food hygiene.

Received: May 22, 2013; Accepted: July 29, 2013

the exposure of DEHP is affected by its ingestion, inhalation, and dermal exposure, DEHP biomonitoring, such as measuring the amount of DEHP metabolites in human body fluids, e.g. urine, blood, or tissues, possesses a remarkable advantage by integrating exposure across all possible sources[9]. Measuring urinary concentration of metabolites is a reliable and convenient way to determine DEHP exposure, in which the levels of monoesters, known as mono(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) are measured[10]. The concentrations of the urinary DEHP metabolite can be converted into its intake levels using simple pharmacokinetic models[10-12]. These intake levels are useful for DEHP risk assessment by comparing them to chronic oral reference doses (RfDs) established by the US Environmental Protection Agency (EPA)[13] and to tolerable daily intakes (TDIs) established by the European Food Safety Authority (EFSA)[14].

In mid May 2011, two companies, Yu Shen Flavoring Co. and Pin Han Perfumery Co. were involved in a phthalate-contaminated food scandal in Taiwan, caused by illegally using DEHP as a substitute for palm oil in clouding agents as a way to keep cost down and improve profits. Thereafter, many flavoring companies began to check the level of DEHP in their products and found that food flavorings were extensively contaminated with DEHP. DEHP in micheliaalba flower concrete, Osmanthus concrete, Asian dementholized peppermint oil and orange essence reached up to 333 mg/kg, 318 mg/kg, 198 mg/kg, and 200 mg/kg, respectively, much higher than the present limit (total phthalates: 60 mg/kg, enforced by Ministry of Health of the People's Republic of China). Since human could be exposed to DEHP though ingestion, inhalation, and dermal absorption, the workers of flavoring factories are at higher risk and attracted our attention for DEHP risk assessment. Researches has been done on workers in PVC factories[15], but there is no report about DEHP exposure among workers in flavoring factories. In this study, we determined the levels of urine DEHP metabolites among workers in flavoring factories and estimated their daily intake of DEHP.

MATERIALS AND METHODS

Study Population

A total of 71 workers in two flavoring manufacturers were recruited and assigned to the exposure group. The subjects were involved in preparing raw materials, mixing, filling, and deploying the flavorings etc. Two control groups were designed in our study. For control group 1, we recruited totally 27 administrators who did not participated in the flavoring manufacturing in the above factories. For control group 2, we recruited 31 laboratory technicians in a research institute (National Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention), all of whom were not occupationally exposed to DEHP. A questionnaire was designed to collect data on each subject about basic information and DEHP exposure, including sex, age, bodyweight, occupation, smoking, and drinking habit, the use of plastic tableware and cup, the use of cosmetic and perfume, the application of gloves and mouth-muffles during work and the experience of home fitment. All participants provided their written informed consent.

Sample Collection and Analysis

Each participant collected about 100 mL end-shift urine sample during a single workshift, then the sample was distributed into two glass tubes and stored at -20 °C. Urine samples were analyzed for phthalate metabolites using a method involving solid-phase extraction, separation with ultra performance liquid chromatography, and detection by isotope dilution tandem mass spectrometry (SPE-UPLC-MS/MS) according to Silva et al.[16]. Briefly, the sample (1 mL) was deconjugated to release the glucuronidated phthalate metabolites. The pre-conditioned SPE cartridges (Varian Nexus) were loaded with the urine diluted with pH 2.0 phosphate buffer (1 mL) and rinsed with 0.1 mol/L formic acid (2 mL) and water (1 mL). Dry the SPE cartridges by passing air through the column. Then the analytes were eluted with acetonitrile (1 mL) followed by ethyl acetate (1 mL). The eluant was evaporated under nitrogen and the residue was reconstituted in acetonitrile (1 mL) for future analysis. The chromatographic separation was achieved by a column (ACQUITY UPLC BEH Phenyl 1.7 μm, 2.1x100 mm) on a UPLC (Waters Co.). The analytes were monitored in multiple reaction monitoring mode (MRM) and quantified by internal standards (D4-MEHP). Each analytical run also included calibration standards, reagent blanks and quality control samples. Analysts were blind to all participant information. We also analyzed each

sample for creatinine by using an automatic biochemistry analyzers (Hitachi Co.).

The Calculation of Estimated Daily Intake (EDI)

We evaluated the daily intake of the parent phthalate DEHP separately for each subject based on the measured urinary DEHP metabolite levels. There are two calculating models: one based on the urine creatinine excretion (UCE) and one based on the urine volume (UV).

The UCE was calculated as the following equations[10-11,17]:

$$EDI = \frac{ME\ (\mu g/g) \times CE\ (mg/kg/d)}{F_{UE} \times 1\,000\ (mg/g)} \times \frac{MWd}{MWm} \quad (1)$$

$$EDI = \frac{Total_{ME}\ (mol/g) \times CE\ (mg/kg/d) \times MWd \times 1\,000\ (\mu g/mg)}{F_{UE}} \quad (2)$$

Equation 1 shows how to obtain the EDI of DEHP based on the concentration of MEHP, MEHHP, and MEOHP, respectively. ME is the urinary concentration of the metabolite adjusted for creatinine. CE is the creatinine excretion rate normalized by bodyweight. We set CE to 18 mg/kg/d for female and 23 mg/kg/d for male participants. F_{UE} is the molar fraction of the urinary excreted monoesters related to their parent compounds. F_{UE} values of MEHP, MEHHP, MEOHP are 0.059, 0.23, 0.15, respectively[18]. MWd and MWm are the molecular weights of the diesters and monoesters. Equation 2 shows how to get the EDI of DEHP based on the three DEHP metabolites. $Total_{ME}$ is the sum of molar concentration of MEHP, MEHHP, MEOHP (Σ_3MEHP) adjusted for creatinine. F_{UE} value of Σ_3MEHP is 0.442.

The urine volume-based calculation approach was performed by means of the following equations[12]:

$$EDI = UE\ (\mu g/L) \times V\ (L/d) \times \frac{MWd}{MWm} \times \frac{1}{F_{UE}} \times \frac{1}{W\ (kg)} \quad (3)$$

$$EDI = Total_{UE}\ (mol/L) \times V\ (L/d) \times MWd \times \frac{L}{F_{UE}} \times \frac{L}{W(kg)} \times 1\,000\,000\ (\mu g/g) \quad (4)$$

Equation 3 shows how to get the EDI of DEHP based on the concentration of MEHP, MEHHP, MEOHP respectively. UE is the urinary concentration of the phthalate metabolite. V is human daily excretion volume for urine. For V, we assumed a volume of 2.0 L for adults. W is body weight. Equation 4 shows the way to get the EDI of DEHP based on the three DEHP metabolites. $Total_{UE}$ is the sum of molar concentrations of MEHP, MEHHP, and MEOHP.

Statistical Analysis

Data were analyzed using the statistical software package SAS 9.2. (SAS Institute, Cary, NC, USA). All values below the detection limit were set half the detection limit for statistical analysis. To test for differences of urine metabolites concentrations among exposure group, control group 1 and control group 2, we performed a NPAR1WAY WILCOXON procedure. Statistical significance was set at $P<0.05$. Stepwise multiple Logistic regression analysis was performed to determine significant factors associated with DEHP exposure. The significance level for entry and inclusion in the model were $P<0.10$ and $P<0.15$, respectively.

RESULTS

Subject Demographics

Table 1 shows the age and sex information of the subjects. The sex ratiomale to female of exposure group, control group 1, and control group 2 were 48/23, 19/8, and 20/10, respectively. Their mean (±SD) age were 33.24 (±7.69), 35.44 (±8.73), and 29.47 (±5.95) years old, respectively.

Urinary DEHP Metabolite Concentrations of Exposure and Control Group

Table 2 shows the urinary concentrations of MEHP, MEHHP, MEOHP of different groups. DEHP metabolites were found in all urine samples. The P_{50} of MEHP among exposure group, control group 1, and control group 2 were 7.23, 9.65, and 7.73 μg/g creatinine, respectively. The P_{50} of MEHHP among above groups were 11.35, 11.64, 11.84 μg/g creatinine, and of MEOHP, 8.58, 7.47, 7.00 μg/g creatinine, respectively. No significant differences were

Table 1. The Age and Sex Distribution of Exposure Group, Control Group 1, and Control Group 2

Age (Years)	Exposure Group		Control Group 1		Control Group 2	
	Male	Female	Male	Female	Male	Female
<25	6	4	2	0	3	1
25-35	22	11	10	5	14	6
>35	20	8	7	3	3	3
Total	48	23	19	8	20	10

found among the three groups (P_1=0.42, P_2=0.73, P_3=0.58).

Comparisons between Our Study and Published Data on Urinary DEHP Metabolite Concentrations

Table 3 shows the concentrations of the Urinary DEHP metabolites among different researches. Workers in a factory manufacturing unfoamed polyvinyl chloride (PVC) flooring in Liaoning Province had urinary MEHP concentrations with a median of 565.7 μg/g creatinine[15]. Hines et al.[19] analyzed the urinary phthalate metabolites concentrations of workers in some high-exposure occupations, such as PVC film company, PVC compounding company, Rubber hoses, Rubber boots, Rubber gaskets producing company, and Nail-only salons. The concentrations of the urinary MEHP, MEHHP, MEOHP among workers in PVC compounding company were 12.6, 164, and 92 μg/g creatinine, respectively, higher than other companies mentioned above in the same research. In a studies of Chinese general people performed in 2011[12], the urinary DEHP metabolite levels were 1.8, 10.5, and 6.8 μg/g creatinine, respectively. Ying Guo et al.[20] studied urinary phthalates concentrations among people in seven Asian countries, China, India, Japan, Korea, Kuwait, Malaysia, and Vietnam. The concentrations among Japan people were 1.3, 5.3, and 3.0 μg/g creatinine, lower than other countries. The US Centers for Disease Control and Prevention (CDC) got their urinary phthalate metabolite concentrations by detecting the urine samples set of the National Health and Nutrition Examination Survey (NHANES) population. Their concentrations were 2.36, 19.30, and 11.00 μg/g creatinine. The data showed a lower MEHP level but higher MEHHP, MEOHP levels compared with our results[2].

Estimate Daily Intake of DEHP

Based on the urinary concentrations of MEHP, MEHHP, MEOHP, Σ_3MEHP as well as the steady-state exposure models, as shown in eq1 to eq4, the exposure levels of DEHP were estimated for the different groups in our study. Table 4 shows the results of the estimation. We obtained higher EDI values for the volume approach than for the creatinine-based approach, which was consistent with the research performed by Wittassek et al.[1]. No statistical differences of EDI were found among exposure group, control group 1, and control group 2. The EDI values calculated using MEHHP and MEOHP concentrations in urine were similar, but lower than the values gotten from MEHP, while the EDI value deduced from Σ_3MEHP lay between them.

Figure 1 illustrates the cumulative frequencies of estimated daily DEHP intakes calculated using Σ_3MEHP for all individuals in both evaluation models of different groups. The vertical dotted line marked the RfD of the US EPA (20 μg/kg body-weight/day). Depending on the Volume-Based evaluation model, three subjects (2.34%) exceeded the RfD value and the P50 of estimate daily DEHP intakes accounting for 16.10% of the RfD value. No subjects exceeded the TDI value of the EFSA. No subjects exceed the limitations depending on the creatinine-based evaluation model.

Table 2. The Urinary Concentrations of MEHP, MEHHP, MEOHP of Different Groups (μg/g creatinine)

Groups	Urinary DEHP Metabolites	Min	P_5	P_{25}	P_{50}	P_{75}	P_{95}	Max	Geometric Mean	Mean±SD
Exposure Group	MEHP	1.98	2.70	5.31	7.23	11.70	21.64	40.89	7.90	9.63±6.68
	MEHHP	3.63	4.65	6.80	11.35	19.46	34.66	102.58	11.59	14.98±13.79
	MEOHP	2.26	3.62	5.17	8.58	12.23	24.67	52.48	8.40	10.18±7.56
Control Group 1	MEHP	1.44	3.14	6.81	9.65	12.31	23.26	78.61	9.32	12.47±14.10
	MEHHP	1.32	5.21	7.08	11.64	14.80	38.66	136.30	11.19	16.59±24.98
	MEOHP	0.94	2.16	4.61	7.47	11.02	22.04	114.55	7.64	12.21±20.97
Control Group 2	MEHP	1.41	2.72	5.28	7.73	11.40	24.47	24.75	7.77	9.26±5.77
	MEHHP	1.49	2.22	7.74	11.84	26.64	47.83	59.97	12.46	17.14±14.15
	MEOHP	1.53	2.24	4.74	7.00	11.46	26.24	37.11	7.45	9.71±8.07
All Subjects	MEHP	1.41	2.72	5.44	8.08	11.62	23.26	78.61	8.16	10.14±8.62
	MEHHP	1.32	4.38	7.18	11.58	17.09	38.66	136.30	11.78	11.83±16.71
	MEOHP	0.94	2.96	4.98	7.86	11.62	24.67	114.55	8.00	10.50±11.72

Note. Abbreviations: Max, maximum; Min, minimum.

Influencing Factor of DEHP Exposure

Based on the results from Logistic regression analysis, among the selected factors, sex is the only one significantly associated with high DEHP exposure (P=0.01). The OR value of male versus female was 0.2431.

DISCUSSION

To our knowledge, this study firstly profiled urinary DEHP metabolites among workers in flavoring factories. The results suggested that there was no statistical difference between DEHP exposure levels of those workers and general people. This may

Table 3. The Urinary MEHP, MEHHP, MEOHP Concentrations In Different Researches (μg/g creatinine)

Country	Description of Subjects	Median			Reference	Time
		MEHP	MEHHP	MEOHP		
China	Flavoring factories (n: 40)	7.23	11.35	8.58	This study	2012
	Control group 1 (n: 27)	9.65	11.64	7.47		
	Control group 2 (n: 30)	7.73	11.84	7.00		
China	PVC flooring factory (n: 74)	565.7	–	–	[15]	2006
	construction factory (n: 63)	5.7	–	–		
China	General population selected from 3 cities (n: 183)				[12]	2010
	Guangzhou: 110; Shanghai: 24; Qiqihaer: 49	1.8	10.5	6.8		
China	General population (n: 40); male/female: 21/19	1.9	7.1	4.7	[20]	2010
America	PVC film (n: 25); male/female:19/6	20	138	74	[19]	2008
	Vehicle filter (n: 18); male/female: 6/12	9	32.4	27.8		
	PVC compounding (n: 12); male/female: 10/2	12.6	164	92		
	Rubber Hose (n: 25); male/female: 24/1	4.14	21.2	13.5		
	Rubber boot (n: 21); male/female: 17/4	8.93	69.9	41.3		
	Rubber gasket (n: 20); male/female: 20/0	13.9	40.2	26.9		
	Nail-only salons (n: 26); male/female: 9/17	18.6	21.9	11.1		
America	General population (n: 2604); male/female: 1294/1310	2.36	19.30	11.00	[2]	2007-2008
India	General population (n: 22); male/female: 15/7	1.6	16.1	11.2	[20]	2010
Japan	General population (n: 35); male/female: 8/27	1.3	5.3	3		
Korea	General population (n: 60)	1.2	7	4.9		
Kuwait	General population (n: 46); male/female: 22/24	4.1	18.1	12.5		
Malaysia	General population (n: 29); male/female: 19/10	2.5	10.3	5.5		
Vietnam	General population (n: 30); male/female: 16/14	1.7	6.7	4.1		

Table 4. The Median(P_{95}) of Estimated Daily Intake Values (μg/kg body-weight/d) of the Participants Based on Different Exposure Models

Group	Creatinine-based Evaluation				Volume-based Evaluation			
	MEHP	MEHHP	MEOHP	Σ_3MEHP	MEHP	MEHHP	MEOHP	Σ_3MEHP
Exposed Group	3.85 (10.95)	1.35 (3.68)	1.60 (4.01)	1.86 (4.18)	6.47 (20.54)	2.47 (7.29)	2.33 (7.89)	3.43 (8.97)
Control Group 1	5.09 (11.47)	1.40 (4.02)	1.51 (3.54)	1.82 (4.63)	5.09 (17.51)	2.19 (6.84)	2.49 (7.20)	2.97 (8.15)
Control Group 2	4.13 (10.50)	1.51 (6.24)	1.39 (5.39)	1.84 (5.24)	5.75 (24.76)	2.69 (14.4)	2.25 (8.77)	3.27 (13.53)
All Subjects	4.13 (10.62)	1.41 (4.30)	1.53 (4.06)	1.85 (4.63)	6.32 (20.53)	2.44 (11.22)	2.33 (7.98)	3.22 (9.85)

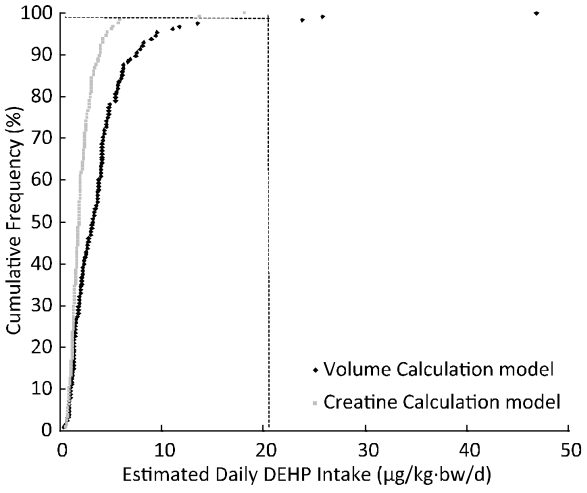

Figure 1. Cumulative frequencies of estimate daily DEHP intakes (μg/kg body-weigh/d) calculated using Σ_3MEHP for all individuals.

be because the managers in those factories have strengthen their management over DEHP after the Taiwan food scandal, for instance, choosing the raw materials and solvents free of DEHP, replacing the plastic component parts to avoid DEHP contamination. Other reasons may be the good occupational protection such as well-ventilated working circumstances.

The urinary DEHP metabolite levels among workers in PVC flooring factory far exceeded the levels detected in workers recruited in our study[15]. Urinary DEHP metabolite concentrations among workers in rubber hoses, rubber boots, rubber gaskets producing company and Nail-only salons were much lower than workers in PVC flooring factory mentioned above but higher than the exposure group in our study[19], indicating that workers in flavoring factories may be not under high DEHP exposure. The DEHP exposure among PVC factories including DEHP manufacturing companies should be paid more attention. The results in our study showed that our people had higher urinary MEHP, MEHHP, MEOHP concentration values than people in other Asian countries such as Japan, Korea and Vietnam, which was in line with previously studies researched on Chinese people[12,20]. The US CDC has monitored the phthalate exposure by detecting the urine samples collected from the National Health and Nutrition Examination Survey (NHANES) population. We could get the more representative and accurate DEHP exposure data of Chinese people the same way as US CDC has done.

In this study, we used both the Creatinine-based one and Volume-based one to evaluate the EDI of DEHP. Neither of them is preferable at the present level of knowledge; both approaches must be regarded as equiprobable[1]. Taking all the DEHP metabolites we detected into account, we compared the EDI calculated using Σ_3MEHP to RfD and TDI values. Only three subjects exceeded the RfD value, the P_{50} of DEHP EDI only accounting for 16.10% of the RfD value. No subjects exceeded the TDI value of the EFSA. This suggests that the exposure of DEHP remains at a low risk, indicating the management measures taken at present, such as the GB9685 standards[21], 551 and 773 documents published by Ministry of Health of the People's Republic of China (MOH), are effective. The results of our study also showed that the risk of DEHP exposure of women was higher than that of men, which needs further investigation. The study was subject to several limitations. On the one hand, more subjects are needed to draw the representative conclusion about the DEHP exposure among flavoring workers, on the other hand, other phthalates metabolites such as mono-n-butyl phthalate (MBP), monomethyl phthalate (MMP), monoethyl phthalate (MEP), mono (2-isobutyl phthalate) (MIBP) etc. should be detected to get more phthalate exposure information. Future studies may investigate on above aspects.

REFERENCES

1. Wittassek M, Heger W, Koch HM, et al. Daily intake of di(2-ethylhexyl)phthalate (DEHP) by German children-A comparison of two estimation models based on urinary DEHP metabolite levels. Int J Hyg Environ Health, 2007; 210, 35-42.
2. US CDC. Fourth National Report on Human Exposure to Environmental Chemicals. http://www.cdc.gov/ exposurereport
3. Blystone CR, Kissling GE, Bishop JB, et al. Determination of the di-(2-ethylhexyl) phthalate NOAEL for reproductive development in the rat: importance of the retention of extra animals to adulthood. Toxicol Sci, 2010; 116, 640-6.
4. Crinnion WJ. Toxic effects of the easily avoidable phthalates and parabens. Altern Med Rev, 2010; 15, 190-6.
5. Kavlock R, Barr D, Boekelheide K, et al. NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of di(2-ethylhexyl) phthalate. Reprod Toxicol, 2006; 22, 291-399.
6. Marsee K, Woodruff TJ, Axelrad DA, et al. Estimated daily phthalate exposures in a population of mothers of male infants exhibiting reduced anogenital distance. Environ Health Perspect, 2006; 114, 805-9.
7. Swan SH, Main KM, Liu F, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect, 2005; 113, 1056-61.
8. Jaakkola JJ and Knight TL. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. Environ Health Perspect, 2008; 116, 845-53.
9. Calafat AM and McKee RH. Integrating biomonitoring exposure

data into the risk assessment process: phthalates [diethyl phthalate and di(2-ethylhexyl) phthalate] as a case study. Environ Health Perspect, 2006; 114, 1783-9.
10. David RM. Exposure to phthalate esters. Environ Health Perspect, 2000; 108, A440.
11. Kohn MC, Parham F, Masten SA, et al. Human exposure estimates for phthalates. Environ Health Perspect, 2000; 108, A440-2.
12. Guo Y, Wu Q, and Kannan K. Phthalate metabolites in urine from China, and implications for human exposures. Environ Int, 2011; 37, 893-8.
13. EPA. Di (2-ethylhexyl)phthalate (DEHP) Quickview. http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance _nmbr=0014#reforal. In
14. European Food Safety Authority. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC)on a request from the Commission related to Bis(2-ethylhexyl)phthalate (DEHP) for use in food contact materials [EB/OL]. [2005] http://www.efsa.europa.eu/en/efsa journal/doc/243.pdf
15. Pan G, Hanaoka T, Yoshimura M, et al. Decreased serum free testosterone in workers exposed to high levels of di-n-butyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP): a cross-sectional study in China. Environ Health Perspect, 2006; 114, 1643-8.
16. Silva MJ, Slakman AR, Reidy JA, et al. Analysis of human urine for fifteen phthalate metabolites. J Chromatogr B Analyt Technol Biomed Life Sci, 2004; 805, 161-7.
17. Hines CJ, Hopf NB, Deddens JA, et al. Estimated daily intake of phthalates in occupationally exposed groups. J Expo Sci Environ Epidemiol, 2011; 21, 133-41.
18. Koch HM, Bolt HM, Preuss R, et al. New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. Arch Toxicol, 2005; 79, 367-76.
19. Hines CJ, Nilsen Hopf NB, Deddens JA, et al. Urinary phthalate metabolite concentrations among workers in selected industries: a pilot biomonitoring study. Ann Occup Hyg, 2009; 53, 1-17.
20. Guo Y, Alomirah H, Cho HS, et al. Occurrence of Phthalate Metabolites in Human Urine from Several Asian Countries. Environ Sci Technol, 2011; 45, 3138-44.
21. MOH. GB9685 Hygienic standards for uses of additives in food containers and packaging materials. 2008.