Journal of Exposure Science and Environmental Epidemiology (2011) 21, 133–141

www.nature.com/jes

Estimated daily intake of phthalates in occupationally exposed groups

CYNTHIA J. HINES[a], NANCY BN. HOPF[a], JAMES A. DEDDENS[a,b], MANORI J. SILVA[c] AND ANTONIA M. CALAFAT[c]

[a]*National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio, USA*
[b]*Department of Mathematical Sciences, University of Cincinnati, Cincinnati, Ohio, USA*
[c]*National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA*

Improved analytical methods for measuring urinary phthalate metabolites have resulted in biomarker-based estimates of phthalate daily intake for the general population, but not for occupationally exposed groups. In 2003–2005, we recruited 156 workers from eight industries where materials containing diethyl phthalate (DEP), dibutyl phthalate (DBP), and/or di(2-ethylhexyl) phthalate (DEHP) were used as part of the worker's regular job duties. Phthalate metabolite concentrations measured in the workers' end-shift urine samples were used in a simple pharmacokinetic model to estimate phthalate daily intake. DEHP intake estimates based on three DEHP metabolites combined were 0.6–850 μg/kg/day, with the two highest geometric mean (GM) intakes in polyvinyl chloride (PVC) film manufacturing (17 μg/kg/day) and PVC compounding (12 μg/kg/day). All industries, except phthalate manufacturing, had some workers whose DEHP exposure exceeded the U.S. reference dose (RfD) of 20 μg/kg/day. A few workers also exceeded the DEHP European tolerable daily intake (TDI) of 50 μg/kg/day. DEP intake estimates were 0.5–170 μg/kg/day, with the highest GM in phthalate manufacturing (27 μg/kg/day). DBP intake estimates were 0.1–76 μg/kg/day, with the highest GMs in rubber gasket and in phthalate manufacturing (17 μg/kg/day, each). No DEP or DBP intake estimates exceeded their respective RfDs. The DBP TDI (10 μg/kg/day) was exceeded in three rubber industries and in phthalate manufacturing. These intake estimates are subject to several uncertainties; however, an occupational contribution to phthalate daily intake is clearly indicated in some industries.
Journal of Exposure Science and Environmental Epidemiology (2011) **21,** 133–141; doi:10.1038/jes.2009.62; published online 16 December 2009

Keywords: *phthalates, biomonitoring, personal exposure.*

Introduction

Phthalates are used as plasticizers in polyvinyl chloride (PVC) plastics, as lubricants in certain rubbers (e.g. nitrile and neoprene), and as fixatives (or carriers) in perfumes and fragrances (Stanley et al., 2003; Wypych, 2004). Phthalates are not covalently bound to polymeric materials and can migrate to the environment over time resulting in human exposure. Sources of phthalate exposure include the workplace, diet, off-the-job activities, personal care products, and other home or environmental sources. Phthalates have been evaluated as possible reproductive and developmental toxicants in animals and humans (Hauser and Calafat, 2005; Latini, 2005; Heudorf et al., 2007; Matsumoto et al., 2008) and may also have a function in respiratory disease (Bornehag et al., 2004; Hoppin et al., 2004; Jaakkola and Knight, 2008; Kolarik et al., 2008).

Sensitive and specific analytical methods have been developed over the past decade to measure concentrations of phthalate metabolites in urine (Koch et al., 2003a; Itoh et al., 2005; Kato et al., 2005; Preuss et al., 2005; Silva et al., 2007, 2004). Phthalate urinary metabolite concentrations can be used in simple pharmacokinetic models to estimate daily intake (David, 2000; Kohn et al., 2000). These models assume steady state excretion of metabolites and a constant daily creatinine excretion (CE) rate, conditions that depend on the temporal variability of the phthalate exposure and the characteristics of the sampled individual. When multiple individuals are monitored in a given exposure setting, some of this temporal variability may be accounted for by averaging intake estimates across the group.

Intake estimates can be useful for risk assessment by comparing them to chronic oral reference doses (RfDs) established by the U.S. Environmental Protection Agency (EPA) (U.S. EPA, 2007a,b,c,d) and to tolerable daily intakes (TDIs) established by the European Food Safety Authority (EFSA). (EFSA (European Food Safety Authority), 2005a, b, c). The RfD (or TDI) is an estimate of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime.

Biomonitoring for phthalate exposure offers the advantages of integrating exposure across all routes (e.g.

1. Abbreviations: boot, rubber boot; cmpd, PVC compounding; film, PVC film; filt, vehicle filters; gask, rubber gasket; hose, rubber hose; manf, phthalate manufacturing; nail, nail-only salons

2. Address all correspondence to: Cynthia J. Hines, National Institute for Occupational Safety and Health, 4676 Columbia Pkwy, R-14, Cincinnati, 45230, USA. Tel.: 513 841 4453. Fax: 513 841 4486.
E-mail: cjh8@cdc.gov
Received 26 June 2009; accepted 4 November 2009; published online 16 December 2009

inhalation, dermal, ingestion). Moreover, as phthalates are ubiquitous in the environment, biomonitoring of metabolites largely avoids problems associated with the contamination of collection materials and analytical systems with parent compounds used in products. A recent study comparing different approaches for estimating human exposure to phthalates recommended using high quality measured concentrations in exposure media or back-calculation of intake from urinary metabolites (Franco et al., 2007).

Biomarker-based estimates of phthalate daily intake are available for adults and children in the United States, Germany, Korea, Japan, and Taiwan (David, 2000; Kohn et al., 2000; Koo et al., 2002; Clark et al., 2003; Itoh et al., 2005; Koo and Lee 2005; Itoh et al., 2007; Koch et al., 2007, 2006, 2003b; Wittassek et al., 2007; Chen et al., 2008; Wittassek and Angerer, 2008), for pregnant women (Marsee et al., 2006) and for infants in neonatal intensive care units (Calafat and McKee, 2006; Weuve et al., 2006); however, phthalate daily intake estimates for occupationally exposed groups are lacking. In 2003–2005, the National Institute for Occupational Safety and Health (NIOSH) conducted a preliminary study of phthalate exposures among 156 workers in eight industry sectors where materials containing diethyl phthalate (DEP), dibutyl phthalate (DBP), and di(2-ethylhexyl) phthalate (DEHP) were manufactured or used as part of the workers' regular job duties. Exposure was assessed by measuring urinary metabolite concentrations.

In the human body, phthalates are rapidly metabolized and excreted into the urine (Hauser and Calafat, 2005). Phthalates are initially hydrolyzed to their corresponding monoesters. Some monoesters are further metabolized to several oxidative metabolites. Monoester and oxidative metabolites may be glucuronidated before excretion. We used the monoester metabolites, monoethyl phthalate (MEP), and monobutyl phthalate (MBP), respectively, as markers of DEP and DBP exposure. Exposure to DEHP was monitored using its hydrolytic monoester, mono(2-ethylhexyl) phthalate (MEHP), and three oxidative metabolites, mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP). Although we were primarily interested in DEP, DBP, and DEHP exposure, the analytical method we used also captured metabolites of diisobutyl phthalate (DiBP) and benzylbutyl phthalate (BzBP).

We previously reported urinary phthalate metabolite concentration data for workers in the surveyed industries manufacturing or using the target phthalates as part of their regular job duties and evaluated the likelihood of an occupational contribution to these concentrations (Hines et al., 2009). In this article, we use these data to generate worker daily intake estimates by industry sector, compare estimates to U.S. and European reference values, and discuss methodological limitations.

Methods

Study Population

We recruited 156 participants in 2003–2005 from eight phthalate-using sectors as described earlier (Hines et al., 2009). These sectors included one company from each of seven manufacturing sectors: phthalate manufacturing, PVC film, PVC compounding, vehicle filters, rubber hoses, rubber gaskets, and rubber boots, and 13 companies from one service sector: nail-only salons. Recruited participants worked in jobs or on processes where DEP, DBP, and/or DEHP were manufactured or used (Table 1). Participation was voluntary and informed consent was obtained. This study was approved by the NIOSH Human Subjects Review Board.

The sectors have been described earlier (Hines et al., 2009). In brief, dimethyl phthalate, DEP, DBP, and DEHP were produced as raw materials in phthalate manufacturing by the addition of alcohols to phthalic anhydride in the presence of a catalyst. The PVC film sector produced sheets of PVC film using either DEHP or diisononyl phthalate (DiNP) as plasticizers. In PVC compounding, custom-formulated PVC pellets were produced using DEHP, DiNP, or ditridecyl phthalate as plasticizers. In the production of vehicle filters, a plastisol (a dispersion of resin and plasticizer) containing DEHP was dispensed onto filter end-caps, followed by convection oven curing. Three sectors manufactured neoprene and nitrile rubber products containing phthalates (rubber hose: DBP, DEHP, and di-*n*-octyl phthalate; rubber gasket: DBP and DiBP; rubber boot: DEHP). Nail-only salons provided manicure, pedicure, and artificial nail services using nail care products containing DBP.

Sample Collection and Analysis

Each participant collected an end-shift urine sample during a single work shift without regard to day of the week in 125 ml sterile polypropylene specimen cups prescreened for phthalates. We analyzed samples for phthalate metabolites using an analytical approach involving enzymatic deconjugation of the metabolites from their glucuronidated form, automated solid-phase extraction, separation with high performance liquid chromatography, and detection by isotope-dilution tandem mass spectrometry (Silva et al., 2004; Kato et al., 2005). Each analytical run also included calibration standards, reagent blanks, and quality control materials. Analysts were blind to all participant information. We also analyzed each sample for creatinine (Hines et al., 2009).

Daily Intake Estimates

We used end-shift creatinine-adjusted concentrations and the method of David (2000) (Eq. 1) to estimate each participant's daily intake of DEP, DBP, DEHP, BzBP, and DiBP.

Table 1. Phthalate diesters, their urinary metabolites, and use in participating sector companies.

Phthalate metabolite	Phthalate diester	Diester use in participating sector companies							
		Phthalate manufacturing	PVC film[a]	Vehicle filters	PVC compounding[b]	Rubber hoses	Rubber boots	Rubber gaskets	Nail-only salons
MEP	DEP	X							
MBP and MCPP (minor)	DBP	X				X		X	X
MiBP	DiBP							X	
MBzP and MBP (minor)	BzBP								
MEHP, MEHHP, MEOHP and MECPP	DEHP	X	X	X	X	X	X		

Abbreviations: Phthalate diesters: DEP, diethyl phthalate; DBP, di-*n*-butyl phthalate; DiBP, diisobutyl phthalate; BzBP, benzylbutyl phthalate; DEHP, di(2-ethylhexyl) phthalate. Metabolites: MEP, monoethyl phthalate; MBP, monobutyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate.
[a]PVC film also used diisononyl phthalate (DiNP).
[b]PVC compounding also used DiNP and ditridecyl phthalate (DTDP).

The David (2000) method is a variation of a linear two-compartment model initially used by Kohn et al. (2000). Equation 1 assumes steady-state excretion. Marsee et al. (2006) found close agreement between the David (2000) and Kohn et al. (2000) models.

$$\frac{DI\ (\mu g/kg/day) = UE\ (\mu g/g) \times CE\ (mg/kg/day)}{F_{UE} \times 1000\ (mg/g)} \times \frac{MW_d}{MW_m} \quad (1)$$

UE (urinary excretion) is the urinary concentration of the metabolite adjusted for creatinine, CE is the daily creatinine excretion rate normalized by body weight and is set at 23 mg/kg/day and 18 mg/kg/day for men and women, respectively (Harper et al., 1977; Kohn et al., 2000; Wallach, 2000), F_{UE} (fractional urinary excretion) is the molar fraction of excreted metabolite relative to total intake at 24-h post-dosing, and MW_d/MW_m is the molecular weight ratio of diester to metabolite. F_{UE} values for MBP (0.69) and monobenzyl phthalate (MBzP, 0.73) were taken from published human data (Anderson et al., 2001). F_{UE} values for MEP and monoisobutyl phthalate (MiBP) were set to that of MBP (Kohn et al., 2000; Koch et al., 2003b).

DEHP daily intake was estimated using three or four DEHP metabolites combined and F_{UE} values based on human data ($F_{UE} = 0.442$ for MEHP + MEHHP + MEOHP (MEHP3); $F_{UE} = 0.627$ for MEHP + MEHHP + MEOHP + MECPP (MEHP4)) (Eq. 2) (Koch et al., 2005a). We converted creatinine-adjusted metabolite concentrations to moles per gram before summing. We had MEHP, MEHHP, and MEOHP concentration data in all eight sectors, but MECPP concentrations in only four, as the capability to analyze for MECPP was not available until midway through the study.

$$DI\ (\mu g/kg/day) = \frac{\text{Total DEHP metabolites (moles/g)} \times \text{CE (mg/kg/day)} \times MW_{DEHP} \times 1000\ (\mu g/mg)}{F_{UE}} \quad (2)$$

We estimated DBP daily intake separately using MBP alone or MBP and MiBP combined. Current RfDs and TDIs for DBP do not distinguish between the two isomers (Marsee et al., 2006). We estimated BzBP and DiBP daily intake using their respective monoesters only. Only 6% of ingested BzBP is excreted as MBP (Anderson et al., 2001); therefore, MBzP was considered the principal BzBP metabolite.

Data Analysis

The distribution of the phthalate daily intake estimates was skewed to the right (suggesting log-normality) and therefore a natural log transformation was applied to the estimates. Analyses were performed in SAS *vs* 9.1 (SAS Institute, Cary, NC, USA). We estimated the geometric mean (GM) and geometric standard deviation (GSD) of the daily intake estimates for each sector. Left censoring at the limit of detection (LOD) was generally low (i.e. $<12\%$) for all metabolites, except for MzBP in nail-only salons (32% $<$LOD). For left-censored data, we used maximum likelihood estimation (MLE) in the LIFEREG procedure to estimate the GM and GSD. Where use of MLE was not feasible (i.e. where metabolites were summed (MEHP3 and MEHP4) and in Figure 1), we imputed one-half of the LOD. To test for differences in intake estimates across sectors (sector effect), we performed a one-way analysis of variance using the NLMIXED procedure and Bonferroni's adjustment for multiple comparisons. We also computed the proportion of DEP, DBP, BzBP, and DEHP daily intake estimates greater than their respective RfDs and TDIs by sector. Statistical significance was set at $\alpha = 0.05$.

Results

Participants included 114 (73%) men and 42 (27%) women. Demographics have been described earlier (Hines et al.,

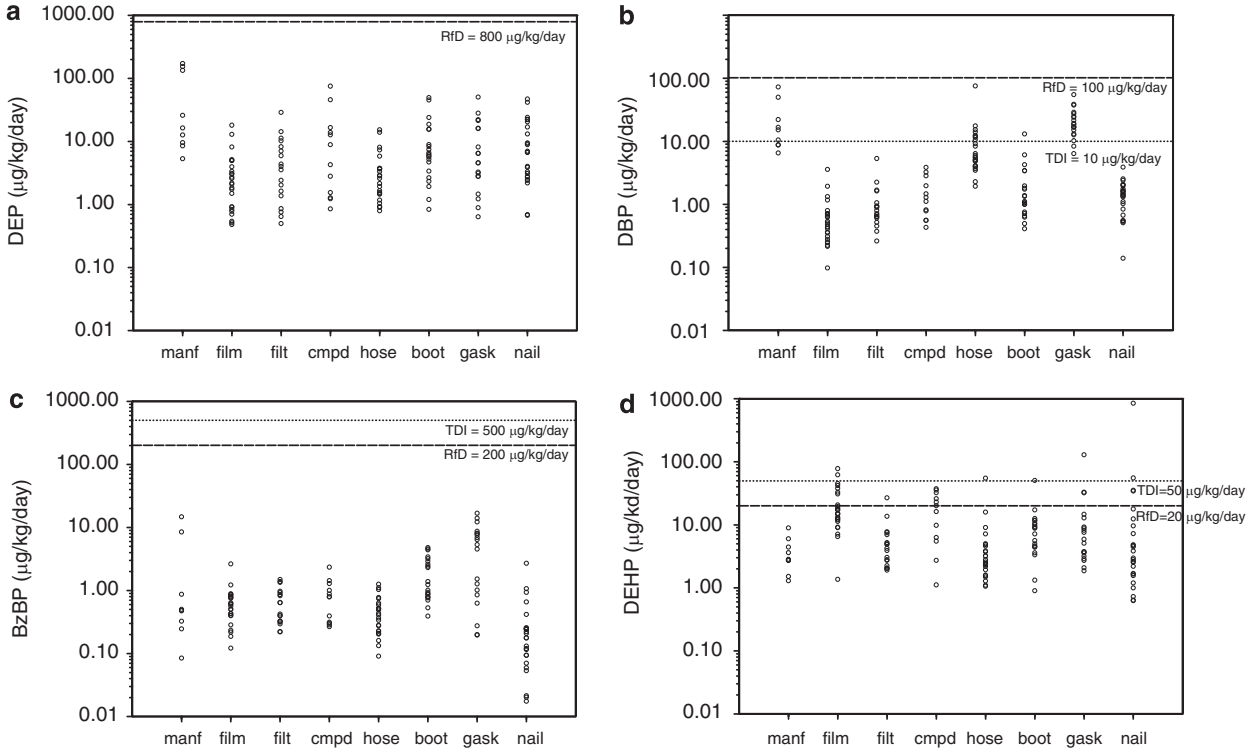

Figure 1. Estimated daily intake (μg/kg/day) of (a) diethyl phthalate (DEP), (b) dibutyl phthalate (DBP), (c) benzylbutyl phthalate (BzBP), and (d) di(2-ethylhexyl) phthalate (DEHP) by industry sector using end-shift urinary phthalate metabolite concentrations based on monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), and mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) combined (MEHP3). The dashed horizontal line is the U.S. EPA reference dose (RfD). The dotted horizontal line is the EFSA tolerable daily intake (TDI). In these plots, the LOD divided by two was used for observations below the LOD. Sector abbreviations: manf, phthalate manufacturing; film, PVC film, filt, vechicle filters; cmpd, PVC compounding; hose, rubber hose; boot, rubber boot; gask, rubber gasket; nail, nail-only salons.

2009). Briefly, most participants were white (51%) or Hispanic (27%). Mean ($\pm$SD) participant age was 38 ($\pm$12) years. Estimated daily intakes for DEP, DBP, DiBP, BzBP, and DEHP are summarized by sector in Table 2 and in Figure 1.

DEP

DEP daily intake estimates ranged from 0.5 to 170 μg/kg/day (Table 2). DEP GM intake estimates varied significantly by sector ($P<0.0001$). Phthalate manufacturing, which produced DEP, had the highest sector GM estimate (27 μg/kg/day). In all other sectors, DEP GM intake estimates (2.2–6.7 μg/kg/day) were several-fold lower than in phthalate manufacturing. None of the DEP daily intake estimates exceeded the RfD (800 μg/kg/day), and most intake estimates were $<25\%$ of the RfD. A TDI has not been established for DEP.

DBP

DBP daily intake estimates ranged from 0.1 to 76 μg/kg/day (Table 2). GM DBP intake estimates differed significantly by sector ($P<0.0001$) and were highest in rubber gasket (17 μg/kg/day), phthalate manufacturing (17 μg/kg/day), and rubber hose (6.9 μg/kg/day). All other sectors had GM intake estimates <2 μg/kg/day. When MiBP was combined with MBP, the increase in the GM DBP intake estimate for all sectors was <1 μg/kg/day, with most increases <0.5 μg/kg/day.

None of the DBP intake estimates exceeded the DBP RfD (100 μg/kg/day). Most DBP intake estimates were $<25\%$ of the RfD; the highest estimate (in rubber hose) was 76% of the RfD. Four sectors had sampled workers whose DBP intake estimates (based on MBP alone) exceeded the TDI (10 μg/kg/day): phthalate manufacturing (67%); rubber hose (32%), rubber boot (5%), and rubber gasket (80%). Phthalate manufacturing produced DBP, and rubber gasket, and rubber hose each produced neoprene and nitrile rubber products containing DBP; however, we are not aware of a DBP source in rubber boot.

DiBP

DiBP daily intake estimates ranged over several orders of magnitude (0.02–32 μg/kg/day) (Table 2). GM DiBP estimates were significantly different by sector ($P<0.0001$ each) and were highest in the rubber sectors: rubber boot (0.37 μg/kg/day); rubber hose (0.31 μg/kg/day), and rubber gasket

Table 2. Estimated daily intake of DEP, DBP, DiBP, BzBP, and DEHP (μg/kg/day) by the David (2000) method using end-shift creatinine-adjusted urinary concentrations of MBP, MEP, MBzP, MiBP, MEHP3, and MEHP4, respectively.

Parent (metabolite)	n (% <LOD)	GM (GSD)	Range	% >RfD[a]	% >TDI[b]
DEP (MEP)					
Phthalate manufacturing	9 (0)	27 (3.9)	5.3–170	0	[c]
PVC film	25 (0)	2.2 (2.7)	0.5–18	0	
Vehicle filter	18 (0)	3.3 (3.2)	0.5–29	0	
PVC compounding	12 (0)	6.0 (4.4)	0.8–75	0	
Rubber hose	25 (0)	2.6 (2.3)	0.8–15	0	
Rubber boot	21 (0)	6.7 (3.0)	0.8–50	0	
Rubber gasket	19 (0)	5.5 (3.4)	0.6–51	0	
Nail-only salons	25 (0)	6.5 (3.1)	0.7–47	0	
DBP (MBP)					
Phthalate manufacturing	9 (0)	17 (2.3)	6.5–73	0	67
PVC film	25 (0)	0.52 (2.1)	0.1–3.6	0	0
Vehicle filter	18 (0)	0.86 (2.0)	0.3–5.3	0	0
PVC Compounding	12 (0)	1.2 (2.1)	0.4–3.9	0	0
Rubber hose	25 (0)	6.9 (2.1)	1.9–76	0	32
Rubber boot	21 (0)	1.5 (2.4)	0.4–13	0	5
Rubber gasket	19 (0)	17 (1.8)	5.7–55	0	80
Nail-only salons	25 (4)	1.2 (1.9)	0.1–3.9	0	0
DiBP (MiBP)					
Phthalate manufacturing	9 (0)	0.15 (2.2)	0.04–0.4	[d]	[c]
PVC film	25 (0)	0.11 (1.6)	0.05–0.3		
Vehicle filter	18 (11)	0.10 (1.6)	0.02–0.2		
PVC compounding	12 (0)	0.27 (1.8)	0.09–0.6		
Rubber hose	25 (0)	0.31 (3.6)	0.08–32		
Rubber boot	21 (0)	0.37 (2.4)	0.1–5.2		
Rubber gasket	19 (0)	0.31 (1.8)	0.1–0.8		
Nail-only salons	25 (12)	0.22 (1.8)	0.1–0.9		
DBP (MBP+MiBP)					
Phthalate manufacturing	9[e]	17 (2.3)	6.7–73	0	67
PVC film	25	0.63 (2.0)	0.1–3.8	0	0
Vehicle filter	18	1.0 (1.9)	0.3–5.5	0	0
PVC compounding	12	1.6 (1.9)	0.5–4.2	0	0
Rubber hose	25	7.8 (2.2)	2.2–76	0	32
Rubber boot	21	1.9 (2.3)	0.6–14	0	9.5
Rubber gasket	19	18 (1.8)	5.8–56	0	84
Nail-only salons	25	1.5 (1.8)	0.3–4.3	0	0
BzBP (MBzP)					
Phthalate manufacturing	9 (0)	0.76 (5.3)	0.1–15	0	0
PVC film	25 (0)	0.54 (1.9)	0.1–2.6	0	0
Vehicle filter	18 (0)	0.55 (1.9)	0.2–1.5	0	0
PVC compounding	12 (0)	0.66 (2.1)	0.3–2.3	0	0
Rubber hose	25 (0)	0.38 (2.0)	0.1–1.3	0	0
Rubber boot	21 (0)	1.5 (2.2)	0.4–4.8	0	0
Rubber gasket	19 (0)	2.7 (4.4)	0.2–17	0	0
Nail-only salons	25 (32)	0.15 (3.7)	0.02–2.7	0	0
DEHP (MEHP3)					
Phthalate manufacturing	9[e]	3.2 (1.8)	1.3–8.9	0	0
PVC film	25	17 (2.3)	1.4–78	32	8
Vehicle filter	18	4.3 (2.1)	1.9–27	5.6	0
PVC compounding	12	12 (3.1)	1.1–37	50	0
Rubber hose	25	3.2 (2.4)	1.1–55	4	4
Rubber boot	21	6.9 (2.4)	0.9–51	4.8	4.8
Rubber gasket	19	7.2 (3.0)	1.9–130	15	5.3
Nail-only salons	25	4.7 (5.2)	0.6–850	15	8
DEHP (MEHP4)					
PVC film	25[e]	19 (2.2)	2.0–75	40	8
PVC compounding	12	14 (3.0)	1.5–42	50	0
Rubber hose	25	4.0 (2.2)	1.2–51	4	4
Rubber boot	21	8.0 (2.4)	1.2–79	9.5	4.8

Abbreviations: BzBP, benzylbutyl phthalate; DBP, di-*n*-butyl phthalate; DEP, diethyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DiBP, diisobutyl phthalate; GM, geometric mean; GSD, geometric standard deviation; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MEHP3, MEHP + MEHHP + MEOHP; MEHP4, MEHP + MEHHP + MEOHP + MECPP; MIBP, monoisobutyl phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; PVC, polyvinyl chloride.

[a]Reference dose (RfD): DEP = 800 μg/kg/day (U.S. EPA, 2007c), DBP = 100 μg/kg/day (U.S. EPA, 2007b), BzBP = 200 μg/kg/day (U.S. EPA, 2007d), DEHP = 20 μg/kg/day (U.S. EPA, 2007a).

[b]Tolerable daily intake (TDI): DBP = 10 μg/kg/day (EFSA, 2005b), BzBP = 500 μg/kg/day (EFSA, 2005c), DEHP = 50 μg/kg/day (EFSA, 2005a).

[c]TDIs have not been established for DEP and DiBP.

[d]RfD not established for DIBP.

[e]See Hines et al., 2009.

(0.31 μg/kg/day). Neither an RfD nor a TDI has been established for DiBP. The highest individual worker estimate (32 μg/kg/day) was in rubber hose, although DiBP use was not reported at the facility.

BzBP

BzBP daily intake estimates varied by 2–3 orders of magnitude (0.02–17 μg/kg/day) (Table 2). BzBP GM estimates were <3 μg/kg/day in all sectors. Rubber gasket had the highest individual BzBP estimate (17 μg/kg/day); this intake was <10% of the RfD (200 μg/kg/day) and <5% of the TDI (500 μg/kg/day). No company reported using BzBP, therefore, these estimates may reflect only background BzBP exposure.

DEHP

DEHP daily intake estimates varied >1000-fold (MEHP3: 0.6–850 μg/kg/day) (Table 2). Variability was generally less within- than across-sectors. GM DEHP intake estimates varied by approximately four-fold across sectors (MEHP3:

4.3–17 μg/kg/day), and differed significantly by sector ($P<0.0001$). PVC film and PVC compounding, two PVC sectors that used DEHP, had the highest GM DEHP intake estimates based on MEHP3 (17 and 12 μg/kg/day, respectively).

All sectors, except phthalate manufacturing, had some fraction of sampled workers whose intake estimates (based on MEHP3) exceeded the RfD (Table 2; Figure 1). The exceedance fractions were highest for PVC compounding (50%) and PVC film (32%), and <15% in the remaining sectors, a figure that may be within the uncertainty of the estimation method. Generally, fewer workers in each sector exceeded the DEHP TDI (50 μg/kg/day), which is 2.5 times higher than the RfD (Table 2).

Discussion

Heretofore, biologically based estimates of phthalate daily intake have been limited to non-occupationally exposed populations. Our earlier report (Hines et al., 2009) of urinary phthalate metabolite concentrations in eight workplace sectors was a first step toward understanding workers' risk from phthalate exposure. Additional steps include estimating daily intake, comparing estimates to reference values, and ultimately evaluating exposure–response relationships in human populations. In this article, we report daily intake estimates for DEP, DBP, DiBP, BzBP, and DEHP among workers in eight sectors where DEP, DBP, and/or DEHP were manufactured or used as part of the workers' regular job duties.

Not surprisingly, use of a specific phthalate in a sector often, but not always, coincided with an increased intake estimate as compared with sectors not using the phthalate. For example, use of DEP and DBP in a sector (with the exception of the nail technicians) corresponded well with elevated DBP intake estimates. Nail technicians handle small quantities of DBP in lacquer-type materials at room temperature. DBP is unlikely to vaporize from these nail products, thus reducing the opportunity for inhalation exposure. Also, nail products are not typically applied to the technician's skin. The correspondence of DEHP use in a sector with DEHP intake estimates is more likely influenced by heated processes, large open heated surface areas, and large quantities of DEHP used. The two PVC sectors with the highest DEHP intake estimates had some or all of these conditions. The other DEHP-using sectors may have had a few workers on jobs with these process characteristics, but the majority of persons worked with DEHP under either more controlled conditions or conditions less likely to release DEHP.

Our phthalate daily intake estimates for workers can be compared with published estimates for non-occupationally exposed populations where the David (2000) method was used. DEP intake estimates for workers in phthalate manufacturing (GM = 27 μg/kg/day) that produced DEP were 4–5-fold higher than U.S. pregnant women (Marsee et al., 2006) (median = 6.64 μg/kg/day) and a subset of U.S. adults and children in the National Health and Nutrition Examination Survey (NHANES) 1999 (Clark et al., 2003) (GM = 5.42 μg/kg/day); DEP intake estimates for workers in the remaining sectors were similar to these two groups.

DBP daily intake estimates for workers in our two highest DBP-exposed sectors, phthalate manufacturing, and rubber gasket (GM = 17 μg/kg/day, each), were 4- to 20-fold higher than estimates for a subset of U.S. adults and children in NHANES 99 (GM = 0.90 μg/kg/day) (Clark et al., 2003), U.S. pregnant women (median = 0.84 μg/kg/day) (Marsee et al., 2006), German children (median = 4.07 μg/kg/day) (Koch et al., 2007) and German adults and children (median = 2.1 μg/kg/day) (Wittassek and Angerer, 2008); however, our highest individual DBP intake estimate (76 μg/kg/day) was lower than for some people using medications with coatings containing DBP (Hernández-Diaz et al., 2009)

DEHP daily intake has been estimated using different DEHP metabolites (Calafat and McKee, 2006; Koch et al., 2006, 2005b; Weuve et al., 2006; Wittassek and Angerer, 2008). DEHP intake estimates (based on MEOHP only) reported for infants in a neonatal intensive care unit (Weuve et al., 2006) (median = 325 μg/kg/day) and for premature neonates (Calafat and McKee, 2006) (GM = 1256 μg/kg/day) were 1–2 orders of magnitude higher than for workers in our most highly exposed sector (PVC film, GM = 16 μg/kg/day, based on MEOHP only, data not shown). In PVC film and PVC compounding, DEHP intake estimates (based on MEHP3) were ~2–6-fold higher than in German adults and children (Koch et al., 2006; Wittassek and Angerer, 2008), but approximately half that of platelet donors highly exposed to DEHP leaching from PVC materials used during apheresis (Koch et al., 2005b).

Workplace air sampling data have also been used to estimate worker phthalate daily intake. Using published air sampling data, and assuming 10 m^3 of air inhaled during a work shift, a body weight of 70 kg, and a 5-day work week, Huber et al. (1996) estimated mean DEHP daily intake in PVC processing at 12–26 μg/kg/day (data from Dirven et al. (1993)) and <2–30 μg/kg/day (data from Vainotalo and Pfäffli (1990)), pipe coating with DEHP-based plastisol at 10 μg/kg/day (data from NIOSH (1979)), and phthalate manufacturing at 7.1 μg/kg/day (data from Liss et al. (1985)). GM daily intake estimates in our PVC-processing operations, PVC film (17 μg/kg/day) and PVC compounding (12 μg/kg/day), were comparable to the air sample-based estimates. The GM daily intake estimate in vehicle filter (6.9 μg/kg/day), which used a DEHP plastisol, was ~30% lower than the air sample-based estimate for pipe-coating. Our estimate of DEHP daily intake in phthalate manufacturing was approximately half of the air sample-based estimate.

Estimating phthalate daily intake based on biological monitoring data and the relatively simple pharmacokinetic

model we used entails a number of uncertainties, including temporal variability in metabolite concentrations, source variability (e.g. changes in work processes and emission rates), variability in certain model input parameters (i.e. F_{UE} and CE), within- and between-person metabolic variability, and variability due to exposure route. Our daily intake estimates were based on end-shift urine samples; however, phthalate exposure can fluctuate within the work day (Hines et al., 2009), between work- and non-work periods within-a-day, and from day-to-day. Moreover, depending on the timing and intensity of phthalate exposure during work, workers could excrete metabolites for some time after leaving work. Nonetheless, with 9–25 workers per sector, some of this temporal variability was likely averaged across workers. Temporal variability in metabolite concentrations is further heightened by the metabolites' relatively short half-lives and rapid elimination in the urine (Anderson et al., 2001; Api, 2001; Koch et al., 2005a, 2004). Within-person variability in urinary phthalate metabolite concentrations has been shown to depend on the population, phthalate metabolite, and time frame of interest (Hoppin et al., 2002; Hauser et al., 2004; Fromme et al., 2007; Teitelbaum et al., 2008). The degree of temporal variability has implications for using a single urine sample to predict phthalate exposures over a specified time. A 24-h urine sample may be preferable when within-day variability is high. The above factors illustrate the importance of population-specific studies to assess temporal variability of phthalate urinary biomarkers over relevant exposure periods.

The effects of exposure route, individual differences in metabolism, and dose-dependent differences in metabolism on F_{UE} values are largely unknown. Our workers were most likely exposed to phthalates by inhalation or dermal contact. Koch et al. (2005a) found no dose dependency in DEHP metabolism and excretion (dose range: 4.7 to 650 μg/kg). Although one of our workers had a DEHP daily intake estimate $>800\,\mu$g/kg/day, 95% of our workers had DEHP estimates that were $<70\,\mu$g/kg/day.

CE is also subject to uncertainty. CE is reported to range from 19 to 26 mg/kg/day in men and from 14 to 21 mg/kg/day in women, an accuracy of $\sim$10–20% (Wallach, 2000). Empirically based regression equations for adults using height, body weight, and gender have also been used for estimating CE (Kawasaki et al., 1991; Itoh et al., 2005, 2007). The values we applied, 23 mg/kg/day (men) and 18 mg/kg/day (women), have been commonly used in the David (2000) model (Koo and Lee, 2005; Koch et al., 2006; Marsee et al., 2006; Chen et al., 2008).

Racial/ethnic differences in CE are also possible. Creatinine concentrations in spot urine samples from NHANES III were significantly higher among non-Hispanic blacks as compared with other racial/ethnic groups (Barr et al., 2005); however, race/ethnicity was confounded within sector in our study (Hines et al., 2009). Demographic characteristics such as education, family income, and place of residence have also been associated with concentrations of certain urinary phthalate metabolites in a subset of NHANES III participants (Koo et al., 2002).

In the absence of occupational exposure standards, we compared our phthalate intake estimates to U.S. EPA RfDs and European TDI's. These reference values may not be entirely appropriate for workers who are usually considered to be "healthier" than the general population; however, workers may include pregnant women, a sensitive subgroup. Workers may also be exposed over shorter, more intense time periods (i.e. 40–60 h/week, 4–6 days/week) than is presumed for the general population. Sectors with $\geq$25% of sampled workers exceeding the RfD for DEHP and the TDI for DBP used these phthalates in heated processes or in heated materials with large surface areas (Hines et al., 2009).

Certain other study limitations should be noted. We recruited a convenience sample of likely phthalate exposed workers from interested companies. Therefore, our results were not intended to be representative of all workers in each company, of all companies in each sector, nor of all work sectors using the target phthalates. We also had no information on off-the-job activities, use of personal care products, materials in the home environment, diet, medical procedures or medications. Phthalate exposures from these other sources could have contributed to the observed urinary concentrations.

In summary, all sectors except phthalate manufacturing had workers whose DEHP daily intake estimates exceeded the DEHP RfD, with exceedance fractions highest in PVC film and PVC compounding. No sampled workers in any sector had daily intake estimates that exceeded the RfD for DEP, DBP, or BzBP; however, some workers in rubber gasket, phthalate manufacturing, rubber hose, and rubber boot (to a lesser extent) had DBP estimates greater than the 10-fold lower TDI. These results should be considered preliminary and are subject to a number of uncertainties. Additional occupational exposure monitoring studies with multiple, timed urine collections over several days pre-, during-, and post-exposure are needed to develop more sophisticated pharmacokinetic models for workers than the model used here. Nonetheless, our study offers the first biologically based intake estimates for workers, thus enabling us to better understand where workers fall in the human phthalate exposure continuum.

Conflict of interest

The authors declare no conflict of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of

the Centers for Disease Control and Prevention (CDC). Mention of any company or product does not constitute endorsement by the CDC.

References

Anderson W.A.C., Castle L., Scotter M.J., Massey R.C., and Springall C. A biomarker approach to measuring human dietary exposure to certain phthalate diesters. *Food Addit Contam* 2001: 18: 1068–1074.

Api A.M. Toxicological profile of diethyl phthalate: a vehicle for fragrance and cosmetic ingredients. *Food Chem Toxicol* 2001: 39: 97–108.

Barr D.B., Wilder L.C., Caudill S.P., Gonzalez A.J., Needham L.L., and Pirkle J.L. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. *Environ Health Perspect* 2005: 113: 192–200.

Bornehag C.G., Sundell J., Weschler C., Sigsgaad T., Lundgren B., and Hasselgren M., *et al.* The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. *Environ Health Perspect* 2004: 112: 1393–1397.

Calafat A.M., and McKee R.H. 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: 1783–1789.

Chen M-L., Chen J-S., Tang C-L., and Mao I-F. The internal exposure of Taiwanese to phthalate—an evidence of intensive use of plastic materials. *Environ Int* 2008: 34: 79–85.

Clark K., Cousins I.T., and MacKay D. Assessment of critical exposure pathways. In: Staples C. (Ed.). *The Handbook of Environmental Chemistry. 3Q Phthalate Esters*. Springer, New York, 2003. pp 227–262.

David R.M. Exposure to phthalate esters [Letter]. *Environ Health Perspect* 2000: 108: A440.

Dirven H.A.A.M., van den Broek P.H.H., Arends A.M.M., Nordkamp H.H., de Lepper A.J.G.M., and Henderson P.T., *et al.* Metabolites of the plasticizer di(2-ethylhexyl)phthalate in urine samples of workers in polyvinyl-chloride processing industries. *Int Arch Occup Environ Health* 1993: 64: 549–554.

EFSA (European Food Safety Authority). Bis(2-ethylhexyl)phthalate (DEHP) for use in food contact materials. *EFSA J* 2005a: 243: 1–20.

EFSA (European Food Safety Authority). Di-butylphthalate (DBP) for use in food contact materials. *EFSA J* 2005b: 242: 1–17.

EFSA (European Food Safety Authority). Butylbenzylphthalate (BBP) for use in food contact materials. *EFSA J* 2005c: 241: 1–14.

Franco A., Prevedouros K., Alli R., and Cousins I.T. Comparison and analysis of different approaches for estimating the human exposure to phthalate esters. *Environ Int* 2007: 33: 283–291.

Fromme H., Bolte G., Koch H.M., Angerer J., Boehmer S., and Drexler H., *et al.* Occurrence and daily variation of phthalate metabolites in the urine of an adult population. *Int J Hyg Environ Health* 2007: 210: 21–33.

Harper H.A., Rodwell W.V., and Mayes P.A. *Review of Physiological Chemistry*. 16th edn Lange Medical Publications, Los Altos, CA, 1977. p 625.

Hauser R., and Calafat A.M. Phthalates and human health. *Occup Environ Med* 2005: 62: 806–818.

Hauser R., Meeker J.D., Park S., Silva M.J., and Calafat A.M. Temporal variability of urinary phthalate metabolite levels in men of reproductive age. *Environ Health Perspect* 2004: 112: 1734–1740.

Hernández-Diaz S., Mitchell A.A., Kelley K.E., Calafat A.M., and Hauser R. Medications as a potential source of exposure to phthalates in the U.S. population. *Environ Health Perspect* 2009: 117: 185–189.

Heudorf U., Mersch-Sunderman V., and Angerer J. Phthalates: toxicology and exposure. *Int J Hyg Environ Health* 2007: 210: 623–634.

Hines C.J., Hopf N.B.N., Deddens J.A., Calafat A.M., Silva M.J., Grote A.A., and Sammons D.L. Urinary phthalate metabolite concentrations among workers in selected industries: a pilot biomonitoring study. *Ann Occup Hyg* 2009: 53: 1–17.

Hoppin J.A., Brock J.W., Davis B.J., and Baird D.D. Reproducibility of urinary phthalate metabolites in first morning urine samples. *Environ Health Perspect* 2002: 110: 515–518.

Hoppin J.A., Ulmer R., and London S.J. Phthalate exposure and pulmonary function. *Environ Health Perspect* 2004: 112: 571–574.

Huber W.W., Grasl-Kraupp B., and Schulte-Hermann R. Hepatocarcinogenic potential of di(2-ethylhexyl)phthalate in rodents and its implications on human risk. *Critical Rev Toxicol* 1996: 26: 365–481.

Itoh H., Yoshida K., and Masunaga S. Evaluation of the effect of governmental control of human exposure to two phthalates in Japan using a urinary biomarker approach. *Int J Hyg Environ Health* 2005: 208: 237–245..

Itoh H., Yoshida K., and Masunaga S. Quantitative identification of unknown exposure pathways of phthalates based on measuring their metabolites in human urine. *Environ Sci Technol* 2007: 41: 4542–4547.

Jaakkola J.K., and Knight T.L. 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: 845–853.

Kato K., Silva M.J., Needham L.L., and Calafat A.M. Determination of 16 phthalate metabolites in urine using automated sample preparation and on-line preconcentration/high performance liquid chromatography/tandem mass spectrometry. *Anal Chem* 2005: 77: 2985–2991.

Kawasaki T., Uezono K., Itoh K., and Ueno M. Prediction of 24-hour urinary creatinine excretion from age, body weight and height of an individual and its application. *in Japanese] Nippon Koshu Eisei Zasshi* 1991: 38: 567–574.

Koch H.M., Angerer J., Drexler H., Eckstein R., and Weisbach V. Di(2-ethylhexyl)phthalate (DEHP) exposure of voluntary plasma and platelet donors. *Int J Hyg Environ Health* 2005b: 208: 489–498.

Koch H.M., Becker K., Wittassek M., Seiwert M., Angerer J., and Kolossa-Gehring M. Di-n-butylphthalate and butylbenzylphthalate—urinary metabolite levels and estimated daily intakes: pilot study for the German Environmental Survey on children. *J Exp Sci Environ Epi* 2007: 17: 378–387.

Koch H.M., Bolt H.M., and Angerer J. Di(2-ethylhexyl)phthalate (DEHP) metabolites in human urine and serum after a single oral dose of deuterium-labelled DEHP. *Arch Toxicol* 2004: 78: 123–130.

Koch H.M., Bolt H.M., Preuss R., and Angerer J. New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. *Arch Toxicol* 2005a: 79: 367–376.

Koch H.M., Drexler H., and Angerer J. An estimation of the daily intake of di(2-ethylhexyl)phthalate (DEHP) and other phthalates in the general population. *Int J Hyg Environ Health* 2003b: 206: 77–83.

Koch H.M., Gonzalez-Reche L.M., and Angerer J. On-line clean-up by multidimensional liquid chromatography-electrospray ionization tandem mass spectrometry for high throughput quantification of primary and secondary phthalate metabolites in human urine. *J Chromatog B* 2003a: 784: 169–182.

Koch H.M., Preuss R., and Angerer J. Di(2-ethylhexyl)phthalate (DEHP): human metabolism and internal exposure-an update and latest results. *Int J Androl* 2006: 29: 155–165.

Kohn M.C., Parham F., Masten S.A., Portier C.J., Shelby M.D., and Brock J.W., *et al.* Human exposure estimates for phthalates [Letter]. *Environ Health Perspect* 2000: 108: A440–A442.

Kolarik B., Naydenov K., Larsson M., Bornehag C.-G., and Sundell J. The association between phthalates in dust and allergic diseases among Bulgarian children. *Environ Health Perspect* 2008: 116: 98–103.

Koo H.J., and Lee B.M. Human monitoring of phthalates and risk assessment. *J Toxciol Environ Health, Part A* 2005: 68: 1379–1392.

Koo J-W., Parham F., Kohn M.C., Master S.A., Brock J.W., and Needham L.L., *et al.* The association between biomarker-based exposure estimates for phthalates and demographic factors in a human reference population. *Environ Health Perspect* 2002: 110: 405–410.

Latini G. Monitoring phthalate exposure in humans. *Clinica Chimica Acta* 2005: 361: 20–29.

Liss G.M., Albro P.W., Hartle R.W., and Stringer W.T. Urine phthalate determinations as an index of occupational exposure to phthalic anhydride and di(2-ethylhexyl)phthalate. *Scan J Work Environ Health* 1985: 11: 381–387.

Marsee K., Woodruff T.J., Axelrad D.A., Calafat A.M., and Swan S.H. Estimated daily phthalate exposures in a population of mothers of male infants exhibiting reduced anogenital distance. *Eviron Health Perspect* 2006: 114: 805–808.

Matsumoto M., Hirata-Koizumi M., and Ema M. Potential adverse effects of phthalic acid esters on human health: a review of recent studies on reproduction. *Reg Toxicol Pharmacol* 2008: 50: 37–49.

NIOSH. *Health hazard evaluation determination report: Dresser Industries, Inc., Bradford, PA, HETA-78–91–621*. U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH, 1979.

Preuss R., Koch H.M., and Angerer J. Biological monitoring of the five major metabolites of di-(2-ethylhexyl)phthalate (DEHP) in human urine using column-switching liquid chromatography-tandem mass spectrometry. *J Chromatog B* 2005: 816: 269–280.

Silva M.J., Samandar E., Preau J.L., Reidy J.A., Needham L.L., and Calafat A.M. Quantification of 22 phthalate metabolites in human urine. *J Chromatog B* 2007: 860: 106–112.

Silva M.J., Slakman A.R., Reidy J.A., Preau J.L., Herbert A.R., and Samandar E., *et al.* Analysis of human urine for fifteen phthalate metabolites using automated solid-phase extraction. *J Chromatogr B* 2004: 805: 161–167.

Stanley M.K., Robillard K.A., and Staples C.A. Introduction. In: Staples C.A. (Ed.). *Phthalate Esters*. Springer-Verlag, Berlin, 2003. pp 1–7.

Teitelbaum S.L., Britton J.A., Calafat A.M., Ye X., Silva M.J., and Reidy J.A., *et al.* Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens, and phenols among minority children in the United States. *Environ Res* 2008: 106: 257–269.

U.S. EPA. *Integrated Risk Information System: Di(2-ethylhexyl)phthalate*. Washington DC:US Environmental Protection Agency, 2007a. Available: http://www.epa.gov/iris/subst/0014.htm [accessed 13 February 2009].

U.S. EPA. *Integrated Risk Information System: Dibutyl Phthalate*. Washington DC: US Environmental Protection Agency, 2007b. Available: http://www.epa.gov/iris/subst/0038.htm [accessed 13 February 2009].

U.S. EPA. *Integrated Risk Information System: Diethyl Phthalate*. Washington DC:US Environmental Protection Agency, 2007c. Available: http://www.epa.gov/iris/subst/0226.htm[accessed 13 February 2009].

U.S. EPA. *Integrated Risk Information System: Butyl Benzyl Phthalate*. Washington DC: US Environmental Protection Agency, 2007d. Available: http://www.epa.gov/iris/subst/0293.htm [accessed 13 February 2009].

Vainotalo S., and Pfäffli P. Air impurities in the PVC plastics processing industry. *Ann Occup Hyg* 1990: 34: 585–590.

Wallach J. *Interpretation of Diagnostic Tests*, 7th edn. Lippincott Williams & Wilkins, Philadelphia, PA, 2000. p 87.

Weuve J., Sánchez B.N., Calafat A.M., Schettler T., Green R.A., and Hu H., *et al.* Exposure to phthalates in neonatal intensive care unit infants: urinary concentrations of monoester and oxidative metabolites. *Environ Health Perspect* 2006: 114: 1424–1431.

Wittassek M., and Angerer J. Phthalates: metabolism and exposure. *Int J Androl* 2008: 31: 131–138.

Wittassek M., Heger W., Koch H.M., Becker K., Angerer J., and Kolossa-Gehring M. 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.

Wypych G. Introduction. In: Wypych G. (Ed.). *Handbook of Plasticizers*. ChemTec Publishing, Toronto, 2004. pp 1–6.