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Urinary Phthalate Metabolite Concentrations among Workers in Selected Industries: A Pilot Biomonitoring Study

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Phthalates are used as plasticizers and solvents in industrial, medical and consumer products; however, occupational exposure information is limited. We sought to obtain preliminary information on occupational exposures to diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) by analyzing for their metabolites in urine samples collected from workers in a cross-section of industries. We also obtained data on metabolites of dimethyl phthalate (DMP), benzylbutyl phthalate (BzBP), di-isobutyl phthalate and di-isononyl phthalate. We recruited 156 workers in 2003–2005 from eight industry sectors. We assessed occupational contribution by comparing end-shift metabolite concentrations to the US general population. Evidence of occupational exposure to DEHP was strongest in polyvinyl chloride (PVC) film manufacturing, PVC compounding and rubber boot manufacturing where geometric mean (GM) end-shift concentrations of DEHP metabolites exceeded general population levels by 8-, 6- and 3-fold, respectively. Occupational exposure to DBP was most evident in rubber gasket, phthalate (raw material) and rubber hose manufacturing, with DBP metabolite concentrations exceeding general population levels by 26-, 25- and 10-fold, respectively, whereas DBP exposure in nail-only salons (manicurists) was only 2-fold higher than in the general population. Concentrations of DEP and DMP metabolites in phthalate manufacturing exceeded general population levels by 4- and >1000-fold, respectively. We also found instances where GM end-shift concentrations of some metabolites exceeded general population concentrations even when no workplace use was reported, e.g. BzBP in rubber hose and rubber boot manufacturing. In summary, using urinary metabolites, we successfully identified workplaces with likely occupational phthalate exposure. Additional work is needed to distinguish occupational from non-occupational sources in low-exposure workplaces.

Keywords: biological monitoring; BzBP; DBP; DEHP; DEP; DiBP; DMP; occupational exposure; phthalate

INTRODUCTION

Phthalates are used as plasticizers and solvents in industrial, medical and consumer products. Phthalates may be added to impart flexibility [e.g. in polyvinyl chloride (PVC) film], to act as a lubricant (e.g. in rubber) or to function as a fixative or carrier (e.g. in perfumes) (Stanley *et al.*, 2003; Wypych, 2004). In polymers, phthalates are not chemically bound and can migrate to the environment over time. Use of a specific phthalate depends on its physico-chemical properties, desired product performance characteristics, compatibility with other materials and cost. Multiple sources can contribute to human phthalate exposure, including the workplace, diet, off-the-job activities, personal care products and other home or environmental sources.

Phthalates have been evaluated as possible human reproductive and developmental toxicants and their

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toxicity has been extensively reviewed (Sharpe, 2001; Foster, 2005; Hauser and Calafat, 2005; Latini, 2005; Gray *et al.*, 2006; Heudorf *et al.*, 2007; Matsumoto *et al.*, 2008). Health effect assessments have largely been based on animals or non-occupationally exposed populations. No well-designed, large-scale epidemiologic studies have been conducted among phthalate-exposed workers. As a first step toward an epidemiologic study, the National Institute for Occupational Safety and Health (NIOSH) sought to identify industries and professions with likely occupational exposure to phthalates. Phthalates of primary interest were diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP). DBP and DEHP were selected based on their toxicity in animals; DEP had the highest phthalate monoester metabolite levels in the Third National Health and Nutrition Examination Survey (NHANES III) (Blount *et al.*, 2000).

Phthalates are initially hydrolyzed in the body to their corresponding hydrolytic monoesters (Table 1) (Albro *et al.*, 1982; Anderson *et al.*, 2001; Api, 2001). DEHP and other higher molecular weight phthalates are further metabolized to several oxidative metabolites which are the major metabolites of these phthalates (Table 1; Koch *et al.*, 2004, 2005; Silva *et al.*, 2006b,c; Koch and Angerer, 2007). Monoester and oxidative metabolites may be glucuronidated before excretion (Silva *et al.*, 2003; Kato *et al.*, 2004). Phthalate metabolite excretion into the urine is generally rapid. After oral dosing in humans, urinary excretion of DEHP metabolites is biphasic, with a first phase half-life of ~2 h for all metabolites and a second phase half-life of 5 h for mono(2-ethylhexyl) phthalate (MEHP), 10 h for mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and 12–15 h for mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) (Koch *et al.*, 2004, 2005). MEHP peaks at 2 h; MEHHP, MEOHP and MECPP peak at 4 h. At 24 h post-dosing, MEHHP is the most abundant (23%), followed by MECPP (18%), MEOHP (15%) and MEHP (6%). The oxidative metabolites account for almost 60% of the DEHP oral dose.

In humans, 69% of an oral DBP dose is excreted into the urine as monobutyl phthalate (MBP) within 24 h (Anderson *et al.*, 2001). In rats, 47% of an oral dose of DEP is excreted into the urine in 12 h and 82% in 24 h (Ioku *et al.*, 1976; Api, 2001).

These variations in excretion kinetics among phthalate metabolites, our interest in surveying a cross-section of industries and unknown exposure timing during the work shift posed challenges for optimizing sample collection for any given phthalate or workplace. Given ubiquitous non-occupational phthalate exposure (Clark *et al.*, 2003; Butte, 2004), it was also unclear how successfully phthalate metabolites could be used to detect occupational exposure. Thus, our goal was to evaluate the use of urinary metabolites to screen and identify workplaces with likely occupational phthalate exposure for possible future study. Our effort should be considered a pilot study. A more comprehensive and tailored biomonitoring approach should be adopted for specific phthalates and industries selected for further study.

In this article, we present worker phthalate metabolite concentrations measured in 2003–2005 in various industries, compare these concentrations to the US general population and comment on the likelihood of an occupational contribution to the observed concentrations. No occupational exposure limits have been established for phthalate metabolites in urine. The phthalate analytical method we used also captured concentrations of the metabolites of dimethyl phthalate (DMP), benzylbutyl phthalate (BzBP), di-*n*-octyl phthalate (DnOP) and di-isobutyl

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

Metabolite[a]	Phthalate diester	Parent phthalate use in participating sector companies							
		Phthalate manufacturing	PVC film[b]	Vehicle filters	PVC compounding[c]	Rubber hoses	Rubber boots	Rubber gaskets	Nail-only salons
MMP	DMP	X							
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		
MCPP and MOP (minor)	DnOP					X			

[a]LODs in $\mu g\ l^{-1}$: MMP = 1.0; MEP = 0.4, 0.09 and 1.0; MBP = 0.4, 1.1 and 1.6; MCPP = 0.2 and 1.0; MiBP = 0.3, 0.4 and 1.0; MBzP = 0.1, 0.3 and 1.0; MEHP = 0.9, 1.0 and 2.0; MEHHP = 0.3 and 1.0; MEOHP = 0.4 and 1.1; MECPP = 0.1 and 0.2 and MOP = not measured. LODs may vary by analytical batch but were constant within a sector.
[b]PVC film also used DiNP.
[c]PVC compounding also used DiNP and ditridecyl phthalate.
MOP = mono-*n*-octyl phthalate.

phthalate (DiBP), although the industries we surveyed did not always report using these phthalates.

METHODS

Recruitment

We recruited workers from manufacturing companies and nail-only salons that used at least one of the three target phthalates. To identify manufacturing companies, we used the US Environmental Protection Agency Toxic Release Inventory [2001 and 2002 for DEHP and DBP; 1994 (last available year) for DEP and US EPA, 2007] (57%), Dun and Bradstreet 2002 MarketPlace business records (Waltham, MA, USA) (21%), referrals (19%) and the 2002 Hazardous Substance Data Bank (3%; NLM, 2002). We contacted each company to ask about current phthalate use and to ascertain study interest. Of the 147 companies contacted, 19 (13%) reported current DEP use, 17 (12%) DBP use and 42 (29%) DEHP use. From the 147 current phthalate users, seven companies from seven manufacturing sectors (phthalate manufacturing, PVC film, vehicle filters, PVC compounding, rubber hoses, rubber gaskets and rubber boots) participated in the study. Among these seven companies, one used DEP, three used DBP and six used DEHP (Table 1). We identified workers scheduled to work on processes using DEP, DBP or DEHP and invited them to participate. A total of 130 workers in the seven manufacturing companies participated. The remaining 140 companies declined to participate, used the phthalate infrequently, had few workers or were solely chemical distributors or hazardous waste facilities.

We identified 84 nail-only salons near Rockville, MD, USA, using the Maryland Board of Cosmetology 2003 roster of licensed nail-only salons. We contacted the salons by mail, phone and/or in person. We explained the study to 73 manicurists in 42 salons. A total of 26 manicurists (36%) in 13 salons participated.

We also collected information on participant's age, sex, race/ethnicity, height and weight. Participation in the study was voluntary and informed consent was obtained. The NIOSH Human Subjects Review Board approved this study.

Work processes at participating companies

During on-site visits, the seven participating manufacturing companies confirmed current phthalate use (Table 1) and identified phthalate-related processes. In phthalate manufacturing, DMP, DEP, DBP and DEHP were manufactured in batch or continuous processes by the addition of alcohols to phthalic anhydride in the presence of a catalyst. Operators could be exposed while taking or analyzing in-process samples or while performing maintenance.

The PVC compounding company produced custom-formulated PVC pellets using primarily DEHP and di-isononyl phthalate (DiNP) as plasticizers. Phthalate-related processes included mixing, extrusion and milling. The PVC film company also used DEHP and DiNP; phthalate-related processes included compounding, mixing, paste preparation, extrusion, milling and calendering. In the vehicle filter manufacturing company, exposure could occur while dispensing plastisol (a dispersion of resin and phthalate plasticizer) containing DEHP onto filter end caps and near convection ovens used for plastisol curing.

Companies manufacturing rubber products (rubber hoses, rubber boots and rubber gaskets for aerosol cans, inhalers and bottles) used phthalates only in neoprene or nitrile rubber. The hose company used DBP, DEHP and DnOP; the boot company DEHP and the gasket company DBP and DiBP. In rubber processing, phthalate exposure could occur during compounding, mixing, milling, calendering and curing (or vulcanizing). In rubber hose, exposure was also possible during compression molding, stripping and extrusion (conventional and microwave) and in rubber boot during extrusion, injection molding, buffing, boot making and stripping.

Various processes across the sectors involved the application of heat, including mixers, mills, calenders and extruders in rubber and PVC processing, curing ovens in rubber processing, presses in rubber boot making and reactors in phthalate manufacturing. Operating temperatures were <65 to >150°C for calenders and mills, generally >150°C for extruders, 65–150°C for mixers and >150°C for reactors. Milling and calendering also involved heated materials with large surface areas.

Manicure, pedicure and artificial nail services were provided at nail-only salons where DBP could be present in the polishes, topcoats and basecoats.

Sample collection and analysis

Each participant collected two urine samples, mid shift (half-way into the shift) and end shift, during a single work shift without regard to day of the week in 125-ml sterile polypropylene specimen cups prescreened for phthalates. On a scale of 0 (shift start) to 1 (shift end), participants collected the mid-shift sample, on average, at 0.498 (where 0.5 is mid shift), indicating good overall compliance with the sampling protocol. Samples were kept cold with refrigerant packs until aliquots were frozen on dry ice at the end of the shift, followed by storage at -80°C. As this was a screening study with limited funding, our goal was to maximize the number of workers screened given our resources. Thus, we focused on samples more likely to indicate exposure (e.g. end shift) than on samples less likely to indicate exposure (e.g. pre-shift). Initially, we planned to collect one end-shift sample per worker; however, if exposure occurred early in the shift only, certain metabolite concentrations might 'peak' before the end of the shift, depending on half-life. For this reason, we planned to analyze some mid-shift samples. When the number of participating companies was lower than anticipated, we were able to ultimately analyze a mid-shift sample on all participants. In a larger study, pre-shift and possibly several post-shift samples should be collected. We reimbursed participants \$10 per sample for their time and inconvenience.

We analyzed urine samples for 10 phthalate metabolites representing exposure to seven phthalate diesters (Table 1). The analytical approach involved 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.*, 2004b; Kato *et al.*, 2005). Each analytical run also included calibration standards, reagent blanks and quality control materials. Analysts were blind to all participant information. Limits of detection (LODs) are given in Table 1. For every fifth participant, we analyzed a blind duplicate of one sample. Mean relative standard deviations (SDs) for blind duplicates ranged from 4.1 to 9.8% for all metabolites, except MEHP (11%). We measured creatinine by a modified Jaffé kinetic rate method (Synchron CX® system, Beckman Coulter Inc., Fullerton, CA, USA). We measured specific gravity (SG) using a handheld refractometer (NSC Precision Cells Inc., Farmingdale, NY, USA) calibrated with distilled water. In each nail salon, we collected samples of the nail polish, basecoat and topcoat products that participants most commonly used on their sampled day. After extraction with acetone, these samples were analyzed by gas chromatography–mass spectrometry to qualitatively confirm the presence of DBP (unpublished method). DBP was confirmed in all basecoat (n = 15) and nail polish (n = 38) samples and in 14 of 16 topcoat samples.

Data analysis

Phthalate metabolite concentration distributions were skewed to the right and a natural log transformation was applied. Data below the LOD were handled using maximum likelihood estimation (MLE) procedures, except the LOD divided by two was imputed for Pearson correlation analyses. All statistical analyses were performed in SAS v. 9.1 (SAS Institute Inc., Cary, NC, USA) and run separately on unadjusted, creatinine-adjusted and SG-adjusted data. Statistical significance was set at $\alpha = 0.05$.

We tabulated participant's sex, age and race/ethnicity by sector. We estimated unadjusted, creatinine-adjusted and SG-adjusted mid- and end-shift geometric mean (GM) and geometric standard deviation (GSD) metabolite concentrations by sector. For left-censored data, we used MLE in the LIFEREG procedure to estimate the GM and GSD. Correlation between DEHP metabolites was evaluated using Pearson's correlation coefficient. To identify highly exposed jobs, we examined the top quartile of workers in the most highly exposed sectors.

To test for a significant change in phthalate metabolite concentration from mid- to end shift, we used mixed-effect models to account for correlation within person. For uncensored data, we used the MIXED procedure with restricted MLE, and for censored data, we used the NLMIXED procedure with MLE (Thiébauat *et al.*, 2006). Worker was treated as a random effect, shift time (mid/end) as a fixed effect and compound symmetric as the covariance structure.

To determine if the change (direction and magnitude) in metabolite concentrations from mid- to end shift depended on industry sector, we used a two-way analysis of variance with person as a random effect, the fixed effects of sector (four to eight levels) and shift time (two levels) and an interaction term of sector and shift time. We adjusted for age, sex and body mass in each interaction model. Race/ethnicity was confounded with sector (Table 2) and not included.

We compared our results to the unadjusted and creatinine-adjusted NHANES 2001–2002 phthalate metabolite results for adults 20 years and older (CDC, 2005) using a t-test (uncensored data) and MLE with a z-test (LIFEREG procedure, left-censored data). NHANES 2001–2002 is a representative sample of the US population (NCHS, 2008). Both NHANES and our study collected spot urine samples; however, NHANES collected samples between 08:30 and 20:00, whereas 28% of our samples fell outside these hours.

RESULTS

Most participants were male (73%) and either white (51%) or Hispanic/Latino (27%) (Table 2). Females clustered largely within vehicle filters (67%) and nail-only salons (65%). Mean (±SD) participant age was 38 (±12) years. Median shift length by sector ranged from 8.5 to 12 h. Unadjusted and creatinine-adjusted metabolite concentrations are presented by sector and shift time in Tables 3 and 4 and Figs 1 and 2. SG-adjusted concentrations are available as supplementary Table S1 (available at *Annals of Occupational Hygiene* online). Results discussed below are for creatinine-adjusted concentrations, with deviations for unadjusted and SG-adjusted concentrations noted.

For each metabolite, GM concentrations varied significantly across industry sectors ($P < 0.001$). Concentrations generally increased from mid- to end shift, although not always significantly (Tables

Table 2. Participant demographics by industry sector

	Phthalate manufacturing (n = 9) No. (%)	PVC film (n = 25) No. (%)	Vehicle filter (n = 18) No. (%)	PVC compounding (n = 12) No. (%)	Rubber hose (n = 25) No. (%)	Rubber boot (n = 21) No. (%)	Rubber gasket (n = 20) No. (%)	Nail-only salons (n = 26) No. (%)	Total (n = 156) No. (%)
Sex									
Male	9 (100)	19 (76)	6 (33)	10 (83)	24 (96)	17 (81)	20 (100)	9 (35)	114 (73)
Female	0	6 (24)	12 (67)	2 (17)	1 (4)	4 (19)	0	17 (65)	42 (27)
Age, years									
<30	0	12 (48)	9 (50)	1 (8)	8 (32)	4 (19)	2 (10)	7 (27)	43 (28)
30–49	6 (67)	9 (36)	8 (44)	11 (92)	14 (56)	12 (57)	14 (70)	15 (58)	89 (57)
50+	3 (33)	4 (16)	1 (6)	0	3 (12)	5 (24)	4 (20)	4 (15)	15 (15)
Mean (±SD)	46 (±10)	34 (±13)	31 (±10)	40 (±8)	37 (±11)	44 (±11)	41 (±11)	36 (±10)	38 (±12)
Range	33–62	18–56	19–56	24–50	19–61	20–60	22–63	22–58	18–63
Race/ethnicity									
Asian	0	0	0	1 (8)	0	0	3 (15)	23 (88)	27 (17)
Black[a]	0	0	0	1 (8)	0	2 (10)	4 (20)	1 (4)	8 (5)
Hispanic[b]	0	1 (4)	5 (28)	0	25 (100)	4 (19)	7 (35)	0	42 (27)
White	9 (100)	24 (96)	13 (72)	10 (83)	0	15 (71)	6 (30)	2 (8)	79 (51)
Shift length, h[c]									
Median	12	12	10.5	8.7	8.5	8.5	8.8	9.6	9.2

[a]Black or African-American.
[b]Hispanic or Latino.
[c]From start to end of participant's shift, including breaks.

Table 3. Unadjusted urinary phthalate metabolite concentrations at mid- and end shift by industry sector (μg l^{-1})

	Phthalate manufacturing		PVC film		Vehicle filter		PVC compounding		Rubber hose		Rubber boot		Rubber gasket		Nail-only salons	
n	9	9	25	25	18	18	12	12	25	25	21	21	20	20	25	26
Shift time	Mid	End	Mid	End	Mid	End	Mid	End	Mid	End	Mid	End	Mid	End	Mid	End
MMP																
% <LOD	0	0	48	20	89	78	100	100	16	16	95	100	35	20	20	19
GM	842	2300***	1.21	2.51	NE	NE			2.64	3.14	NE		1.36	1.88	4.39	5.01
GSD	2.97	3.92	4.97	2.91	NE	NE			2.56	2.33	NE		3.21	2.37	5.70	5.63
Median	856	2877	1.30	2.60	<LOD	<LOD			2.60	3.50	<LOD		1.05	1.75	3.70	3.55
Minimum	135	198	<LOD	<LOD	<LOD	<LOD			<LOD	<LOD	<LOD		<LOD	<LOD	<LOD	<LOD
Maximum	5140	20500	32.2	19.3	2.20	2.10			34.1	19.0	15.8		23.2	19.8	152	133
MEP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GM	556	1361***	162	113	235	130*	292	326	131	109	293	313	263	226	248	140*
GSD	2.57	3.40	4.66	3.31	5.46	3.95	5.00	4.50	2.81	2.65	3.74	3.43	3.57	3.74	4.46	4.61
Median	555	1270	104	131	298	145	373	405	108	97.3	290	302	246	189	116	196
Minimum	184	317	15.2	18.8	5.80	12.1	32.3	37.2	25.3	15.7	22.7	33.6	29.3	19.6	39.0	3.00
Maximum	2470	10900	2000	963	3340	1540	2480	2610	1470	775	6020	3870	2600	2230	3520	1100
MBP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	4
GM	306	766***	27.7	24.6	23.7	30.6	40.0	61.3	194	270	43.8	62.3	350	660***	23.3	26.0
GSD	2.59	3.26	1.69	2.41	2.70	2.75	2.48	2.19	2.31	2.25	2.59	2.39	2.11	2.16	3.41	3.63
Median	230	1010	25.9	26.1	18.2	30.8	38.0	63.0	211	257	38.5	56.8	334	643	29.3	38.0
Minimum	78.8	96.3	14.0	2.30	6.20	6.40	11.8	15.8	44.6	71.9	5.40	19.2	107	57.8	<LOD	<LOD
Maximum	1240	4680	152	116	202	360	196	169	1580	1790	326	321	1930	2010	114	147
MiBP																
% <LOD	0	0	0	0	11	11	0	0	0		0	0	0	5	4	15
GM	5.44	6.83	5.79	5.16	3.74	3.5	9.05	13.2	11.7	12.1	10.9	15.8*	10.1	11.6	4.51	4.33
GSD	1.60	2.24	1.47	1.92	2.54	2.21	2.46	2.03	3.71	3.76	2.22	2.76	2.17	2.25	2.33	3.12
Median	5.20	7.30	5.80	4.90	4.05	4.30	7.30	12.5	8.80	8.70	10.9	12.5	9.15	13.4	4.60	5.10
Minimum	2.40	2.30	2.40	1.10	<LOD	<LOD	2.20	3.40	1.40	1.80	2.00	3.60	2.60	<LOD	<LOD	<LOD
Maximum	10.3	25.0	13.2	16.1	13.4	10.1	39.9	35.4	586	850	36.4	236	83.0	54.1	26.5	22.9
MBzP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	44	31
GM	19.4	37.7	33.0	28.0	20.9	21.6	21.6	35.6*	14.7	16.1	42.7	69.2**	74.2	115***	1.78	3.45

Table 3. *Continued*

	Phthalate manufacturing		PVC film		Vehicle filter		PVC compounding		Rubber hose		Rubber boot		Rubber gasket		Nail-only salons	
GSD	1.99	6.15	2.18	2.49	1.83	2.46	2.29	2.39	2.18	1.96	2.80	2.97	4.03	4.13	8.37	5.98
Median	21.6	25	33.5	31.5	22.8	21.0	17.6	32.4	15.8	16.7	39.3	74.4	101	167	1.80	5.80
Minimum	7.10	5.00	6.90	3.10	5.10	4.10	6.90	12.0	2.90	4.60	3.80	5.30	5.20	11.5	<LOD	<LOD
Maximum	44.5	736	130	156	70.4	71.6	119	170	66.3	54.6	207	473	747	689	32.1	54.0
MCPP																
% <LOD	0	0	0	0	0	6	0	0	0	0	0	0	5	0	68	50
GM	9.50	12.1	4.60	4.73	6.74	5.65	10.8	15.3*	4.49	5.59	4.88	6.70	6.22	10.7**	NE	0.98
GSD	2.79	2.58	2.14	2.68	1.86	2.11	3.67	3.55	2.37	1.92	2.79	2.43	2.39	2.21	NE	4.42
Median	8.80	13.4	5.80	5.00	6.00	6.60	14.2	12.7	5.00	5.20	5.50	6.90	5.70	10.9	<LOD	<LOD
Minimum	3.60	2.50	0.50	0.30	2.30	<LOD	1.90	4.20	0.70	1.40	0.60	0.60	<LOD	1.40	<LOD	<LOD
Maximum	89.5	42.6	15.8	22.8	20.8	14.0	135	262	22.9	29.7	27.8	31.6	34.1	46.9	80.9	41.6
MEHP																
% <LOD	0	0	0	4	0	0	8	8	0	0	5	10	10	5	4	8
GM	7.71	7.14	24.7	31.4	11.1	13.0	13.0	24.0*	6.08	8.70*	4.98	9.21**	12.8	18.1	11.4	14.5
GSD	1.90	2.45	2.61	3.55	2.49	2.32	5.03	4.82	2.67	2.48	3.34	4.43	4.25	3.56	3.75	5.47
Median	6.10	7.6	26.7	37.3	10.1	11.1	22.6	29.2	5.30	7.60	5.40	12.5	14.2	22.3	10.2	23.0
Minimum	3.50	2.00	2.00	<LOD	3.30	2.90	<LOD	<LOD	1.20	1.30	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Maximum	21.7	27.9	186	257	196	66.7	112	220	151	107	36.3	117	131	161	266	1830
MEHHP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4
GM	45.5	48.4	220	283	35.0	44.0	103	203**	31.4	40.5	56.2	102**	55.5	78.6	16.2	25.0
GSD	2.20	2.63	2.30	3.22	2.45	2.53	4.76	3.36	2.58	2.63	3.57	3.46	4.69	4.31	3.19	7.15
Median	45.1	54.9	224	282	35.8	45.4	190	289	30.1	34.3	60.8	106	50.4	74.8	12.5	21.3
Minimum	11.4	9.90	45.8	11.8	6.50	11.4	8.50	16.2	7.40	6.30	6.40	9.10	1.60	1.20	3.30	<1od
Maximum	118	196	1230	3090	427	294	565	1040	899	891	1060	1640	1090	1820	338	10800
MEOHP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	5	8	12
GM	30.8	31.9	125	159	27.4	34.4	65.2	121**	19.3	24.8	36.1	63.2**	35.3	47.9	9.04	13.5
GSD	2.03	2.50	2.21	3.14	2.26	2.39	4.81	3.56	2.64	2.68	3.54	3.49	4.75	4.43	3.64	8.02
Median	34.2	36.8	111	148	28.1	36.6	131	200	18.4	22.1	37.5	70.0	31.3	42.4	8.10	12.2
Minimum	8.60	6.80	26.6	7.00	7.20	8.30	4.70	8.00	3.80	4.60	3.90	4.90	1.10	<LOD	<LOD	<LOD
Maximum	73.6	121	648	1490	224	179	327	675	571	552	701	1100	915	1130	205	6750

Table 3. *Continued*

	Phthalate manufacturing	PVC film		Vehicle filter	PVC compounding		Rubber hose		Rubber boot		Rubber gasket	Nail-only salons
MECPP												
% <LOD	NM	0	0	NM	0	0	0	0	0	0	NM	NM
GM		235	298*		140	246**	48.2	58.1	71.2	119**		
GSD		2.31	2.93		4.39	3.46	2.14	2.23	3.78	3.55		
Median		222	283		286	391	47.7	51.4	75.4	132		
Minimum		47.9	23.0		12.8	22.4	11.5	15.1	10.3	13.8		
Maximum		1430	2030		998	1080	486	497	2840	3520		

NE = not estimated; >50% of the data less than the LOD. NM = not measured. Analysis for MECPP was only available part way through the study. End-of-shift GM significantly different than mid-shift GM: $*P < 0.05$, $**P < 0.01$ and $***P < 0.001$.

3 and 4). For monoethyl phthalate (MEP), we found a significant interaction between sector and shift time ($P < 0.001$); i.e. in phthalate manufacturing, the GM concentration increased from mid- to end shift, but decreased from mid- to end shift in the other seven sectors. We also observed a significant interaction of sector and shift time for MBP ($P < 0.01$), monobenzyl phthalate (MBzP) ($P < 0.01$), mono(3-carboxypropyl) phthalate (MCPP) ($P < 0.05$) and MECPP ($P < 0.05$). For these metabolites, the GM concentration changed in the same direction (i.e. increased from mid- to end shift), but the magnitude of the change depended on the sector. For example, the MBP GM concentration increased from mid- to end shift by 215 μg g^{-1} in phthalate manufacturing, 190 μg g^{-1} in rubber gasket, 28 μg g^{-1} in rubber hose and by only 8.2 μg g^{-1} in nail-only salons. Interaction results were similar for unadjusted and SG-adjusted concentrations.

DEHP

Concentrations of DEHP metabolites were highly correlated, especially among oxidative metabolites (MEHHP versus MEOHP $r = 0.98$; MECPP versus MEHHP and MECPP versus MEOHP $r = 0.96$ each, all $P < 0.001$). MEHP correlated less strongly with the oxidative metabolites, with coefficients highest for MECPP ($r = 0.77$), followed by MEHHP ($r = 0.70$) and MEOHP ($r = 0.68$). MEHP's weaker correlation with oxidative metabolites has been previously reported (Barr *et al.*, 2003; Koch *et al.*, 2003; Kato *et al.*, 2004; Silva *et al.*, 2006a).

MEHHP and MEOHP end-shift GM concentrations were highest in PVC film (151 and 84.6 μg g^{-1}, respectively), followed by PVC compounding (102 and 60.8 μg g^{-1}, respectively), rubber boot (59.5 and 36.9 μg g^{-1}, respectively) and rubber gasket (54.6 and 33.4 μg g^{-1}, respectively) (Table 4). End-shift GM concentrations of MEHP were generally 2–10 times lower than MEHHP, MEOHP and MECPP, with MECPP having the highest GM concentrations. Nail-only salons had the highest MEHP end-shift GM concentration (19 μg g^{-1}). Of the six sectors using DEHP, concentrations of one or more DEHP metabolites increased significantly from mid- to end-shift in PVC film (by 40%), in PVC compounding (by 40–60%) and in rubber boot (by 30–40%) (Table 4). A significant within-shift increase in MEHHP and MEOHP was also observed in rubber gasket (by 50%), although the sector did not report using DEHP.

In PVC film, the seven highest DEHP-exposed workers operated or worked in the mix mill area, operated the calender or worked in the mixing department either dispensing DEHP or compounding PVC resin with DEHP. In PVC compounding, the three highest DEHP-exposed workers worked in the mixing department. In rubber boot, the six highest

Table 4. Creatinine-adjusted urinary phthalate metabolite concentrations[a] at mid- and end shift by industry sector (μg g^{-1})

	Phthalate manufacturing		PVC film		Vehicle filter		PVC compounding		Rubber hose		Rubber boot		Rubber gasket		Nail-only salons	
n	9	9	25	25	18	18	12	12	25	25	21	21	20	19	25	25
Shift time	Mid	End	Mid	End	Mid	End	Mid	End	Mid	End	Mid	End	Mid	End	Mid	End
MMP																
% <LOD	0	0	48	20	89	78	100	100	16	16	95	100	35	16	20	20
GM	512	1210**	0.54	1.29*	NE	NE			1.89	1.94	NE		0.83	1.12	4.96	6.19
GSD	2.73	2.72	5.66	2.81	NE	NE			2.34	2.31	NE		4.10	2.49	4.76	4.39
Median	484	1267	0.82	0.99					1.82	2.54			0.91	1.14	4.57	4.83
Minimum	117	228	<LOD	<LOD	<LOD	<LOD			<LOD	<LOD	<LOD		<LOD	<LOD	<LOD	<LOD
Maximum	2680	7650	14.2	12.1	1.61	1.43			14.3	12.1	8.02		13.7	7.69	78.7	88.9
MEP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GM	338	716*	77.7	60.2	198	102***	181	164	94.6	68**	221	183	171	143	275	199
GSD	2.67	3.92	4.06	2.78	4.11	3.29	4.38	4.50	2.83	2.37	3.81	2.91	3.63	3.44	4.86	3.32
Median	317	429	58.6	57.3	149	110	216	205	80.6	68.1	201	195	212	120	176	183
Minimum	70.9	140	8.59	12.6	18.7	16.7	25.2	22.3	20.9	20.8	14.3	22.0	15.0	16.8	23.7	17.6
Maximum	1380	4520	924	606	1450	968	1550	1980	1110	469	3810	1300	2000	1330	15300	1580
MBP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	4
GM	187	402*	13.3	13.1	20.0	24.1	24.8	30.9	140	168	33.0	36.4	228	418***	26.0	34.2
GSD	2.44	2.27	1.60	2.12	1.97	2.08	2.52	2.08	2.23	2.16	2.74	2.30	2.00	1.76	2.10	1.94
Median	121	363	12.9	14.7	16.4	21.2	23.6	28.8	130	135	26.4	32.1	269	403	29.9	38.3
Minimum	65.5	157	6.01	2.35	6.56	6.28	7.48	10.3	26.4	46.4	3.40	11.8	65.6	137	<LOD	<LOD
Maximum	647	1750	38.8	85.9	101	163	105	92.4	1370	1810	592	313	623	1320	77.2	119
MiBP																
% <LOD	0	0	0	0	11	11	0	0	0	0	0	0	0	0	4	12
GM	3.31	3.59	2.77	2.74	3.16	2.80	5.60	6.63	8.44	7.52	8.22	9.26	6.56	7.42	5.00	6.26**
GSD	1.74	2.21	1.45	1.58	1.79	1.54	2.35	1.79	3.58	3.57	2.26	2.37	1.93	1.76	2.04	1.85
Median	3.14	3.11	2.93	2.53	3.30	2.99	5.75	7.65	5.80	4.87	8.31	8.98	6.82	7.66	5.70	6.42
Minimum	1.34	1.06	1.32	1.12	<LOD	<LOD	1.72	2.22	1.73	1.96	1.26	2.35	2.28	2.66	<LOD	<LOD
Maximum	5.98	10.0	5.36	8.28	7.84	4.57	20.2	15.1	915	766	58.3	125	18.2	19.7	27.0	26.6
MBzP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	44	32
GM	11.8	19.8	15.8	14.9	17.6	17.0	13.4	17.9	10.6	10.0	32.2	40.4*	48.2	70.1***	2.24	4.59*

Table 4. *Continued*

	Phthalate manufacturing		PVC film		Vehicle filter		PVC compounding		Rubber hose		Rubber boot		Rubber gasket		Nail-only salons	
GSD	1.55	5.27	1.92	1.90	1.79	1.94	2.19	2.14	1.95	1.99	2.00	2.09	4.53	4.42	5.16	3.78
Median	9.10	12.6	14.0	15.8	15.8	17.3	15.0	21.8	10.0	10.6	33.6	32.2	107	139	2.78	4.61
Minimum	7.71	2.20	4.21	3.16	8.92	5.81	5.38	6.96	2.82	2.37	5.85	10.2	4.03	5.11	<LOD	<LOD
Maximum	21.2	386	50.8	68.8	87.1	49.8	51.9	61.1	37.2	32.7	127	125	272	438	29.4	90.0
MCPP																
% <LOD	0	0	0	0	0	6	0	0	0	0	0	0	5	0	68	48
GM	5.78	6.35	2.20	2.51	5.69	4.45	6.7	7.72	3.25	3.48	3.68	3.92	3.98	6.62***	NE	1.33
GSD	2.34	1.92	1.75	2.06	1.70	1.95	3.31	3.11	2.22	1.85	2.29	1.98	2.24	2.00	NE	3.58
Median	5.03	5.70	2.21	2.89	4.91	4.76	7.15	6.66	2.73	3.3	3.82	4.51	4.1	6.24	0.77	1.80
Minimum	2.25	2.20	0.81	0.81	2.84	<LOD	1.15	1.77	0.76	1.38	0.64	0.50	<LOD	2.08	<LOD	<LOD
Maximum	37.6	17.9	7.28	10.0	20.0	11.1	61.2	69.3	19.7	30.0	17.6	12.7	31.0	34.4	42.8	27.7
MEHP																
% <LOD	0	0	0	4	0	0	8	8	0	0	5	10	10	0	4	8
GM	4.69	3.75	11.8	16.7**	9.33	10.2	8.09	12.1	4.40	5.41	3.67	5.37*	8.10	12.1	12.7	19.0
GSD	1.74	1.92	2.37	3.08	2.24	2.13	4.51	4.4	2.80	2.36	2.75	3.54	3.59	2.77	3.44	4.02
Median	5.16	3.98	12.0	20.0	10.0	9.00	12.1	12.6	3.60	4.14	3.42	8.93	5.87	13.9	13.0	18.6
Minimum	1.96	1.10	1.77	<LOD	3.63	3.58	<LOD	<LOD	0.71	1.84	<LOD	<LOD	<LOD	1.73	<LOD	<LOD
Maximum	11.3	10.4	74.6	83.3	130	60.6	95.0	85.0	62.4	54.4	19.7	21.2	248	96.0	681	1480
MEHHP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4
GM	27.7	25.4	105	151**	29.6	34.6	63.8	102*	22.7	25.2	42.4	59.5*	36.1	54.6*	18.0	34.4
GSD	2.21	1.89	1.85	2.31	2.33	2.29	4.24	3.05	2.53	2.45	2.63	2.47	3.85	2.98	3.16	5.90
Median	35.2	22.1	93.4	138	27.4	32.4	121	164	21.7	21.2	40.0	69.9	24.1	40.2	13.6	21.9
Minimum	6.37	10.1	40.5	12.0	7.50	11.4	6.64	10.6	6.29	7.77	10.6	8.10	6.59	15.7	5.70	<LOD
Maximum	61.0	73.0	456	703	283	267	407	366	372	455	756	553	1380	1090	791	8690
MEOHP																
% <LOD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	12
GM	18.8	16.8	60.0	84.6**	23.1	27.1	40.4	60.8*	14.0	15.5	27.2	36.9*	22.9	33.4*	9.96	17.9
GSD	2.05	1.79	1.78	2.21	2.00	2.12	4.27	3.27	2.50	2.48	2.61	2.50	3.89	3.20	3.50	6.70
Median	20.4	14.8	54.8	74.0	23.5	27.8	82.5	92.0	12.6	13.5	23.7	41.3	15.2	26.9	7.44	11.1
Minimum	4.80	7.44	24.9	7.14	6.80	9.38	3.67	5.23	3.64	4.82	7.13	4.05	4.96	8.95	<LOD	<LOD
Maximum	41.7	45.1	212	348	148	163	261	233	236	282	501	369	705	673	525	5440

Table 4. *Continued*

	Phthalate manufacturing		PVC film		Vehicle filter		PVC compounding		Rubber hose		Rubber boot		Rubber gasket		Nail-only salons	
MECPP																
% <LOD	NM		0	0	NM		0	0	0	0	0	0	NM		NM	
GM			112	158***			86.8	124**	34.9	36.2	53.7	69.3*				
GSD			1.93	2.09			3.86	3.18	2.02	2.09	3.06	2.71				
Median			102	142			150	200	29.4	31.0	50.5	69.7				
Minimum			34.0	23.5			10.0	14.6	10.5	10.9	9.44	11.3				
Maximum			574	625			598	444	201	53.0	2030	1180				

NE = Not estimated; >50% of the data less than the LOD. NM = not measured. Analysis for MECPP was only available part way through the study. End-of-shift GM significantly different than mid-shift GM: *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$.

[a]Creatinine-adjusted concentration (μg g^{-1}) = (metabolite concentration, μg l^{-1})/(creatinine concentration, g l^{-1}).

DEHP-exposed workers operated buffers or presses, vulcanizing autoclaves and rubber mills. In rubber gasket, the four highest DEHP-exposed workers worked in the calender and compounding areas. In rubber hose, the seven highest DEHP-exposed workers were either mixer operators or worked in the calender area. In vehicle filters, four of the five highest DEHP-exposed workers dispensed DEHP-containing plastisol.

No obvious job differences explained the highest DEHP-exposed workers in nail-only salons. Because nail-only salons, on average, had MEHP concentrations higher than all other sectors, we considered possible MEHP sample contamination by abiotic hydrolysis of DEHP; however, nail technicians with high MEHP concentrations also had high oxidative metabolite concentrations, suggesting either an unknown DEHP source or perhaps metabolic differences among the predominately Asian workers.

DBP

MBP end-shift GM concentrations varied 30-fold across sectors and were highest in rubber gasket (418 μg g^{-1}), phthalate manufacturing (402 μg g^{-1}) and rubber hose (168 μg g^{-1}), all sectors using DBP (Table 4). The MBP end-shift GM concentration in the remaining DBP-using sector, nail-only salons (34.2 μg g^{-1}), was 12-fold lower than in rubber gasket. The four non-DBP-using sectors had MBP end-shift GM concentrations 10- to 30-fold lower than in rubber gasket. MBP increased significantly (2-fold) from mid- to end shift in phthalate manufacturing and in rubber gasket (Table 4). Although sampled workers in rubber hose only reported working with DEHP on sampled days, their exposure to DBP (which the facility also uses) ranked third of all sectors. In phthalate manufacturing, the three highest DBP-exposed workers worked shifts when DBP reactors were operating; in rubber gasket, the five highest DBP-exposed workers worked on calenders and in rubber hose, the seven highest DBP-exposed workers worked on or near Banbury mixers, calenders and in the molding department.

DEP and DMP

Phthalate manufacturing, which produced DEP and DMP, had the highest MEP and monomethyl phthalate (MMP) end-shift GM concentrations (716 and 1210 μg g^{-1}, respectively; Table 4). MEP and MMP end-shift GM concentrations in phthalate manufacturing were 4- to 12-fold higher and 200- to 1000-fold higher, respectively, than in all other sectors, none of which used DEP or DMP. MEP and MMP in phthalate manufacturing increased significantly (2-fold) from mid- to end shift (Table 4). MEP end-shift GM concentrations in all other sectors were lower than at mid shift, but only significantly in vehicle filters and in rubber hose. The three highest

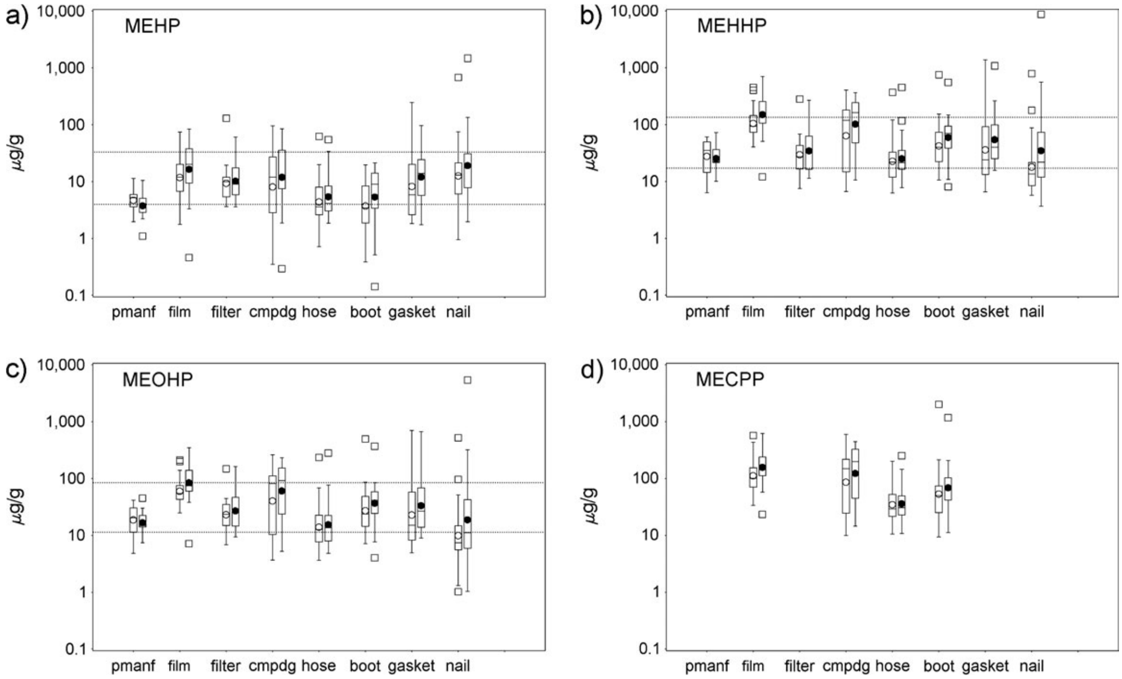

Fig. 1. Box plots of creatinine-adjusted DEHP metabolite concentrations (μg g^{-1}) at mid- and end shift by industry sector for (a) MEHP, (b) MEHHP, (c) MEOHP and (d) MECPP. Open circles indicate mid shift; closed circles indicate end shift. The lower dashed horizontal line is the NHANES 2001–2002 creatinine-adjusted GM; the upper dashed horizontal line is the NHANES 2001–2002 95th percentile. NHANES 2001–2002 data were not available for MECPP. pmanf = phthalate manufacturing; film = PVC film; filter = vehicle filters; cmpdg = PVC compounding; hose = rubber hose; boot = rubber boot; gasket = rubber gasket and nail = nail-only salons.

DEP-exposed workers in phthalate manufacturing worked in shifts when DEP reactors operated; two of the three highest DMP-exposed workers worked in shifts when DMP reactors operated.

DiBP, BzBP and DnOP

Mono-isobutyl phthalate (MiBP) end-shift GM concentrations were highest in three rubber sectors: rubber boot (9.26 μg g^{-1}), rubber hose (7.52 μg g^{-1}) and rubber gasket (7.42 μg g^{-1}) (Table 4); only rubber gasket reported using DiBP. Nail-only salons had a significant within-shift increase in MiBP. MBzP end-shift GM concentrations were highest in two rubber sectors, rubber gasket (70.1 μg g^{-1}) and rubber boot (40.4 μg g^{-1}) (Table 4). MBzP increased significantly from mid- to end shift in both these sectors and also in nail-only salons, although none of these sectors reported using BzBP. End-shift GM concentrations of MCPP, a metabolite of DnOP and a minor metabolite of DBP, ranged from 7.72 μg g^{-1} (PVC compounding) to 1.33 μg g^{-1} (nail-only salons). No sector used DnOP during sampling, although DiNP was sometimes used in rubber hose.

Tests for mid- to end-shift differences were similar for creatinine- and SG-adjusted concentrations; however, using the unadjusted data, 20% of the results changed from either significant to non-significant (12%) or non-significant to significant (8%). Creatinine- and SG-adjusted results likely agreed because each adjusted for urine dilution.

NHANES 2001–2002 comparisons

Across sectors, most phthalate metabolite end-shift GM concentrations (71%) were significantly higher than in NHANES 2001–2002 (Table 5, Figs 1 and 2). One or more DEHP metabolites in all sectors, except phthalate manufacturing, were significantly higher than in NHANES 2001–2002. In all sectors, except PVC film and vehicle filters, MBP significantly exceeded NHANES 2001–2002. Compared to NHANES 2001–2002, MEP was significantly higher in phthalate manufacturing and significantly lower in PVC film and rubber hose. Non-target phthalates (MiBP, MMP, MBzP and MCPP) were significantly elevated in many sectors compared to NHANES 2001–2002.

DISCUSSION

Human exposure to phthalates can arise from both occupational and non-occupational sources. We sought to identify groups with work-related phthalate exposure using urinary metabolites as biomarkers of exposure. Evidence of phthalate occupational exposure was most strongly indicated by a metabolite end-shift GM concentration significantly greater than

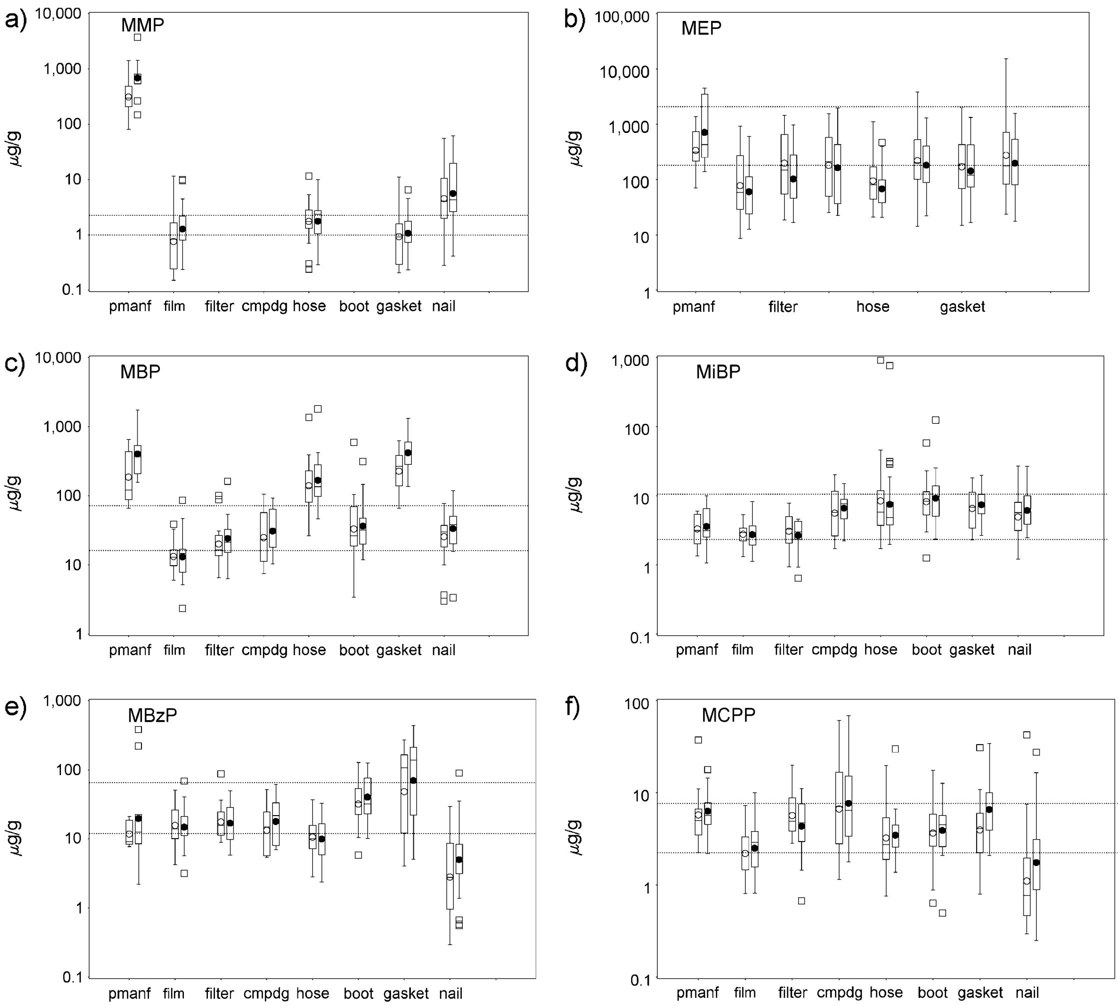

Fig. 2. Box plots of creatinine-adjusted concentrations (μg g^{-1}) at mid- and end shift by industry sector for (a) MMP, (b) MEP, (c) MBP, (d) MiBP, (e) MBzP and (f) MCPP. Open circles indicate mid shift; closed circles indicate end shift. The lower dashed horizontal line is the NHANES 2001–2002 creatinine-adjusted GM; the upper dashed horizontal line is the NHANES 2001–2002 95th percentile. pmanf = phthalate manufacturing; film = PVC film; filter = vehicle filters; cmpdg = PVC compounding; hose = rubber hose; boot = rubber boot; gasket = rubber gasket and nail = nail-only salons.

NHANES 2001–2002 (Tables 5 and 6). A within-shift increase in the GM concentration was an additional evidence of phthalate exposure during work. As this was a pilot study, these results should be considered preliminary evidence of occupational exposure.

Our strongest evidence of occupational exposure for DEHP was in PVC film, PVC compounding and rubber boot. These three sectors used DEHP, had GM concentrations of DEHP metabolites ∼3- to 8-fold greater than NHANES 2001–2002 and showed a within-shift GM increase. Four other sectors also had DEHP exposures greater than NHANES 2001–2002 (vehicle filters, rubber hose, rubber gasket and nail-only salons); however, increases were smaller (generally 2- to 3-fold), and only vehicle filter and rubber boot reported DEHP use.

Evidence of DBP exposure was strongest in phthalate manufacturing and rubber gasket (both used DBP), with each having a 25-fold increase in MBP end-shift GM concentrations compared to NHANES 2001–2002 (Table 6). In five other sectors (vehicle filters, PVC compounding, rubber hose, rubber boot and nail-only salons), MBP end-shift GM concentrations also significantly exceeded NHANES 2001–2002, but the factor difference was small, ∼2-fold, except for rubber hose (10-fold). DBP use was reported in two of these five sectors (rubber hose and nail-only salons). DBP exposure among manicurists has been of general interest (Kwapniewski *et al.*, 2008); however, the MBP end-shift GM concentration in nail-only salons exceeded NHANES 2001–2002 by <2-fold. Other potential sources of MBP include *in vivo* hydrolysis of BzBP (∼6%) (Anderson *et al.*, 2001) and medications with DBP (Hauser *et al.*, 2004); however, we had no information on participant medication use.

Table 5. Ratio of creatinine-adjusted end-shift GM phthalate metabolite concentrations (μg g^{-1}) by sector to NHANES 2001–2002 adults 20 years and older[a]

	GM Ratios: Sector to NHANES 2001–2002							
	Phthalate manufacturing	PVC film	Vehicle filters	PVC compounding	Rubber hose	Rubber boot	Rubber gasket	Nail-only salons
MMP	1210***	1.3	NE	NE	1.9***	NE	1.1	6.2***
MEP	4.0*	0.33***	0.56[b]	0.91	0.38***	1.0	0.79	1.1
MBP	25***	0.81	1.5*	1.9*	10***	2.3***	26***	2.1***
MiBP	1.6	1.2	1.2	2.9***	3.3***	4.0***	3.2***	2.71***
MBzP	1.6	1.2	1.4*[c]	1.5	0.83	3.4***	5.8***	0.38***
MCPP	2.8**	1.1	2.0***	3.4**	1.6**	1.8**	3.0***	0.59
MEHP	0.9	4.2***	2.6***	3.1**	1.4	1.4	3.1***	4.8***
MEHHP	1.5	8.8***	2.0**	5.9***	1.5*[d]	3.5***	3.2***	2.0
MEOHP	1.5	7.4***	2.2***	5.6***	1.4	3.4***	1.9***	1.6

NE = not estimated; >50% of sector data below the LOD. Sector and NHANES 2001–2002 GMs significantly different.
*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$.
[a]NHANES 2001–2002 GM reference values for adults 20 years and older: MMP = 1.0 μg g^{-1}; MEP = 181 μg g^{-1}; MBP = 16.1 μg g^{-1}; MiBP = 2.31 μg g^{-1}; MBzP = 12.0 μg g^{-1}; MCPP = 2.24 μg g^{-1}; MEHP = 3.96 μg g^{-1}; MEHHP = 17.2 μg g^{-1}; MEOHP = 11.4 μg g^{-1}.
[b]For unadjusted values, $P = 0.04$; for creatinine-adjusted values, $P = 0.06$.
[c]For unadjusted values, $P = 0.08$; for creatinine-adjusted values, $P = 0.04$.
[d]For unadjusted values, $P = 0.08$; for creatinine-adjusted values, $P = 0.04$.

Strong evidence of occupational exposure to DEP and DMP was found only in phthalate manufacturing where MEP and MMP end-shift GM concentrations exceeded NHANES 2001–2002 by 4- and >1000-fold, respectively (Table 6). Use of personal care products with fragrances containing DEP (Koo and Lee, 2004; Duty *et al.*, 2005; Hubinger and Havery, 2006) in the hours immediately before work with little or no DEP re-exposure during work may explain MEP within-shift decreases in the other sectors. In NHANES 1999–2000, MEP was also higher at midday than in the evening (Silva *et al.*, 2004a).

We observed some unexpected findings among non-target phthalates. MBzP end-shift GM concentrations significantly exceeded NHANES 2001–2002 in three sectors (rubber gasket, 5.8-fold; rubber boot, 3.4-fold and vehicle filters, 1.4-fold) (Table 5), although none of these sectors reported using BzBP. The source of BzBP exposure among these workers is unknown; however, the two sectors with the highest MBzP increase relative to NHANES 2001–2002 manufactured rubber products. In contrast, the MBzP end-shift GM concentration in nail-only salons was significantly (60%) lower than NHANES 2001–2002.

MiBP is a metabolite of DiBP. MiBP end-shift GM concentrations in five sectors significantly exceeded NHANES 2001–2002 by ~3- to 4-fold (Table 5). One of these sectors, rubber gasket, used both DiBP and DBP; two other sectors, rubber hose and nail-only salons, used only DBP.

Our ability to detect within-shift increases may have been limited by collecting a mid shift rather than a pre-shift sample, individual metabolite kinetics, exposure timing and small sector sample sizes. Although phthalate metabolites are excreted rather rapidly into the urine, high exposures the day prior to urine collection, especially for metabolites with longer elimination half-lives, might contribute to urine concentrations the next day.

Our observations of work practices and processes suggested that inhalation was a likely exposure route in most sectors. Workers with the highest DEP, DBP and DEHP exposures all worked on or near processes with either applied heat or heated materials with large surface areas. Air sampling results in PVC-processing industries (Nielsen *et al.*, 1985; Vainiotalo and Pfäffli, 1990; Dirven *et al.*, 1993) and in phthalate manufacturing (Liss *et al.*, 1985) have shown elevated process temperatures and large surface areas associated with the most exposed workers. We observed few opportunities for dermal contact, mainly when liquid phthalate or plastisol was handled. Urinary biomarkers integrate exposure from all routes and cannot be used to distinguish exposure routes or sources.

Differing phthalate volatilities likely affected exposure levels. Phthalate vapor pressure is inversely related to alkyl chain length (Staples *et al.*, 1997). The influence of vapor pressure may be best illustrated in phthalate manufacturing where DMP, DEP, DBP and DEHP were produced. Given urinary molar excretion fractions (F_{UE}) of 0.69 for MBP, 0.69 for MEP and MMP by analogy to MBP and 0.44 for MEHP + MEHHP + MEOHP, F_{UE}-adjusted end-shift GM concentrations for MMP (1750 μg g^{-1}) and MEP (1040 μg g^{-1}) were two to three times higher than MBP (583 μg g^{-1}) and 10–16 times higher than total DEHP metabolites (105 μg g^{-1}).

Personal protective equipment use possibly affected some individual exposures. We used a simple

Table 6. Summary of urinary phthalate metabolite findings

Metabolite	Phthalate manufacturing	PVC film	Vehicle filter	PVC compounding	Rubber hose	Rubber boot	Rubber gasket	Nail-only salons
DEHP metabolites[a]								
Known use of DEHP[b]	Y	Y	Y	Y	Y	Y		
Mid- to end-shift increase[c]		Y		Y		Y	Y	
End shift > NHANES 2001–2002[d]		Y	Y	Y	Y	Y	Y	Y
MBP								
Known use of DBP	Y				Y		Y	Y
Mid- to end-shift increase	Y						Y	
End shift > NHANES 2001–2002	Y		Y	Y	Y	Y	Y	Y
MEP								
Known use of DEP	Y							
Mid- to end-shift increase	Y							
End shift > NHANES 2001–2002	Y							
MBzP								
Known use of BzBP								
Mid- to end-shift increase						Y	Y	Y
End shift > NHANES 2001–2002			Y			Y	Y	
MiBP								
Known use of DiBP or DBP	Y				Y		Y	Y
Mid- to end-shift increase								Y
End shift > NHANES 2001–2002				Y	Y	Y	Y	Y
MMP								
Known use of DMP	Y							
Mid- to end-shift increase	Y	Y						
End shift > NHANES 2001–2002	Y				Y			Y
MCPP								
Known use of DnOP or DBP	Y				Y		Y	Y
Mid- to end-shift increase							Y	
End shift > NHANES 2001–2002	Y		Y	Y	Y	Y	Y	

[a]One or more of the DEHP metabolites, MEHP, MEHHP, MEOHP and MECPP.
[b]In workplace.
[c]Significant increase in the GM from mid-shift to end shift.
[d]End-shift GM significantly greater than NHANES 2001–2002 GM.

t-test to examine the effect of respirator (yes/no) and glove use (yes/no) on log-transformed end-shift creatinine-adjusted metabolite concentrations. Respirators were used mainly in rubber hose (36%). Nail technicians (85%) wore medical masks not approved as respirators. No respirator effect was found in either sector. Chemical-resistant gloves were used primarily in phthalate manufacturing (89%), PVC film (36%) and rubber gasket (45%), with 'surgical' gloves used in nail-only salons (35%). In PVC film, we saw no glove effect for all DEHP metabolites; however, compared to non-users, glove users in rubber gasket had a 40% reduction in MBP concentrations (546 versus 311 μg g^{-1}, $P = 0.02$), and glove users in nail-only salons had a 50% reduction in MBP concentrations (44.7 versus 20.1 μg g^{-1}, $P = 0.03$). Glove use among manicurists has been reported previously to be associated with decreased MBP urinary concentrations (Kwapniewski *et al.*, 2008). Due to small sample sizes, our results should be considered exploratory.

Urinary biomarkers have been used in a limited number of studies to assess phthalate occupational exposure. These biomarkers include total phthalates measured as either phthalic acid (Vermeulen *et al.*, 2005) or as the methyl diester of phthalic acid (Liss *et al.*, 1985; Nielsen *et al.*, 1985) and, as in our study, monoester or oxidative metabolites (Dirven *et al.*, 1993; Martens and Martens, 2002; Gaudin *et al.*, 2008). MBzP concentrations in workers preparing PVC plastisols containing BzBP (Martens and Martens, 2002) were comparable to our rubber gasket workers, even though BzBP use was not reported in rubber gasket. Dirven *et al.* (1993) measured MEHP, MEHHP and MEOHP in a PVC boot factory and a PVC cable factory. MEHP concentrations in our sectors were 4- to 30-fold lower than both factories; however, MEHHP and MEOHP concentrations in PVC film and PVC compounding were 2- to 3-fold higher than in the cable factory and 20–50% higher than in the boot factory. Gaudin *et al.* (2008) measured MEHP and MECPP among workers preparing and using DEHP-containing plastisols in a glass coating factory. The post-shift MECPP to MEHP ratio (creatinine-adjusted medians) in their study was 1.5 as compared to 7- to 16-fold in our study. Their lower ratio may be related to post-sector median MEHP levels 2-fold higher than in our highest exposed sector. The reason for this ratio reversal is not clear; however, MEHP can arise from exogenous DEHP sources, and MEHP may be a less reliable biomarker of DEHP exposure than oxidative metabolites.

Our study has some limitations. This study was a preliminary screening of phthalate exposures in selected industries; therefore, study companies may not be representative of all companies in their sector and selected sectors may not include all industries that use phthalates. The sampling time points may not have been optimal for capturing each metabolite's peak elimination. Additional samples (i.e. pre-shift, within a day and across seasons) are needed to better characterize exposures. We did not collect information on non-occupational phthalate exposures. Assessing non-occupational phthalate exposures by interview may introduce misclassification as participants may not know reliably which products in their diet or environment contain specific phthalates. Moreover, non-occupational phthalate exposures would have to be elevated in sector participants, as a group, in order for such exposures to explain GM concentrations above NHANES 2001–2002. Despite these limitations, this study provides much needed information on phthalate occupational exposures for identifying populations for future health and exposure studies.

In summary, using urinary biomarkers, we found strong evidence of occupational exposure to DEP and DMP in phthalate manufacturing, to DBP in phthalate manufacturing, rubber gasket and rubber hose and to DEHP in PVC film, PVC compounding and rubber boot. We also found some evidence of occupational exposure to BzBP, DiBP and DnOP in certain sectors. Some sectors also had metabolite concentrations above NHANES 2001–2002 even when parent phthalate use had not been reported, most notably MzBP in rubber hose and rubber boot, MiBP in rubber boot and MMP in the nail-only salons. Factors likely influencing exposures included phthalate vapor pressure, heated processes and heated materials with large surface areas. In future analyses, we hope to identify key exposure determinants (e.g. heat, surface area, ventilation, enclosures, protective equipment, etc.) by classifying workers across sectors on these work characteristics.

SUPPLEMENTARY MATERIAL

Supplementary Table S1 can be found at http://annhyg.oxfordjournals.org/

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