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ORIGINAL ARTICLE

Occupational exposure to diisononyl phthalate (DiNP) in polyvinyl chloride processing operations

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Abstract

Purpose Diisononyl phthalate (DiNP) is primarily used as a plasticizer in polyvinyl chloride (PVC) materials. While information is available on general population exposure to DiNP, occupational exposure data are lacking. We present DiNP metabolite urinary concentrations in PVC processing workers, estimate DiNP daily intake for these workers, and compare worker estimates to other populations.

Methods We assessed DiNP exposure in participants from two companies that manufactured PVC materials, a PVC film manufacturer ($n = 25$) and a PVC custom compounder ($n = 12$). A mid-shift and end-shift urine sample was collected from each participant and analyzed for the DiNP metabolite mono(carboxy-isooctyl) phthalate (MCiOP). Mixed models were used to assess the effect on MCiOP concentrations of a worker being assigned to (1) a task using DiNP and (2) a shift where DiNP was used. A simple pharmacokinetic model was used to estimate DiNP daily intake from the MCiOP concentrations.

Results Creatinine-adjusted MCiOP urinary concentrations ranged from 0.42–80 μg/g in PVC film and from 1.11–13.4 μg/g in PVC compounding. PVC film participants who worked on a task using DiNP ($n = 7$) had the highest MCiOP geometric mean (GM) end-shift concentration (25.2 μg/g), followed by participants who worked on a shift where DiNP was used ($n = 11$) (17.7 μg/g) as compared to participants with no task (2.92 μg/g) or shift (2.08 μg/g) exposure to DiNP. The GM end-shift MCiOP concentration in PVC compounding participants (4.80 μg/g) was comparable to PVC film participants with no task or shift exposure to DiNP. Because no PVC compounding participants were assigned to tasks using DINP on the day sampled, DiNP exposure in this company may be underestimated. The highest DiNP intake estimate was 26 μg/kg/day.

Conclusion Occupational exposure to DiNP associated with PVC film manufacturing tasks were substantially higher (sixfold to tenfold) than adult general population exposures; however, all daily intake estimates were less than 25% of current United States or European acceptable or tolerable daily intake estimates. Further characterization of DiNP occupational exposures in other industries is recommended.

Keywords Diisononyl phthalate · Occupational · Exposure assessment · Biological monitoring · Intake estimates · Polyvinyl chloride

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Introduction

Diisononyl phthalate (DiNP) (CAS Nos. 68575-48-0 and 28553-12-0) is a complex commercial mixture of mainly nine carbon branched-chain dialkyl phthalate isomers. It is used primarily as a plasticizer in polyvinyl chloride (PVC) products such as flooring, wire and cable coatings, coated fabrics, and gloves (Kavlock et al. 2002). DiNP is used as a replacement for di-(2-ethylhexyl) phthalate (DEHP) in some PVC products (TURI 2006). While human exposure to several phthalates is well documented (Koch and Calafat 2009), information on human exposure to DiNP is limited, especially in occupational settings where large quantities of DiNP are handled.

DiNP exposure can occur by ingestion, inhalation or dermal contact, with inhalation and dermal contact the most likely occupational exposure routes. Dermal absorption of DiNP in rats is slow, with 2–4% of a dermal dose absorbed within 7 days (McKee et al. 2002). Rat skin is generally more permeable to phthalates than human skin (Scott et al. 1987). Because DiNP is a mixture of isomers, its metabolites are also isomeric mixtures. DiNP is initially hydrolyzed in rodents and humans to its monoester, monoisononyl phthalate (MiNP). MiNP is further oxidized to several metabolites including mono(carboxy-isooctyl) phthalate (MCiOP), mono(hydroxy-isononyl) phthalate (MHiNP), and mono(oxo-isononyl) phthalate (MOiNP) (Silva et al. 2006a; Koch and Angerer 2007). DiNP metabolites are excreted as either glucuronide conjugates or free metabolites. MCiOP is excreted mainly in the free (unconjugated) form, MOiNP is mostly glucuronidated, while MHiNP is excreted with similar proportions of free and conjugate (Silva et al. 2006b).

In both orally dosed rodents and humans, the oxidative metabolites are detected in concentrations substantially higher than the monoester, with MCiOP the major metabolite in rats and MHiNP the major metabolite in a single exposed human volunteer (Koch and Angerer 2007; Silva et al. 2006a). A total of 43.6% of a single oral dose of deuterium-labeled DiNP administered to a male volunteer was recovered in the urine at 48 h as MiNP (2.15%), MCiOP (10.68%), MHiNP (20.18%), and MOiNP (10.6%), with 39.6% of the dose eliminated in the first 24 h (Koch and Angerer 2007). Metabolites were eliminated in at least two phases, with a first phase (8–24 h post-dosing) half-life of about 3 h for MiNP and 5 h for the oxidized metabolites, and a second phase (>24 h post-dosing) half-life of about 5 h for MiNP, 12 h MHiNP and MOiNP, and 18 h for MCiOP. The small fractional excretion of the monoester underscores the importance of measuring one or more oxidative metabolites when using urinary biological monitoring to assess DiNP exposure.

The chronic toxicity of DiNP has been studied in rodents and primates. In feeding studies, DiNP produces liver tumors in rats and mice, kidney tumors in rats, and mononuclear cell leukemia in rats (Kaufmann et al. 2002; Kavlock et al. 2002; Lington et al. 1997). The modes of action for the observed neoplastic effects in rodents may not be relevant to humans (Klaunig et al. 2003; Kavlock et al. 2002). For example, peroxisome proliferation, a likely mode of action for liver tumors in mice, was not observed when DiNP was administered by gavage to monkeys (Pugh et al. 2000; Hall et al. 1999). DiNP also caused skeletal and urinary system developmental toxicity in rats exposed prenatally to DiNP at maternally toxic doses (Hellwig et al. 1997; Waterman et al. 1999). Studies of fetal testicular testosterone production and other reproductive endpoints from prenatal DiNP exposure in rats have produced conflicting results, possibly due to experimental differences in the route, timing, and levels of dosing (Boberg et al. 2011; Adamsson et al. 2009; Borch et al. 2004; Masutomi et al. 2003; Waterman et al. 2000; Gray et al. 2000). Where reproductive effects have been observed, the potency of DiNP appeared to be about an order of magnitude less than DEHP (Gray et al. 2000).

An expert panel convened by the U.S. National Toxicology Program to review the reproductive and developmental toxicity of DiNP concluded that the potential health effects of DiNP exposure in unborn children could not be judged “due to the lack of toxicology data following inhalation exposures and the lack of occupational exposure information” (Kavlock et al. 2002). The National Institute for Occupational Safety and Health (NIOSH) conducted a pilot study in 2003–2005 to screen occupational populations for exposure to diethyl phthalate (DEP), dibutyl phthalate (DBP), and DEHP using urinary phthalate metabolites as exposure biomarkers (Hines et al. 2009). While DiNP was not an initial focus of the study, two companies that processed PVC also used DiNP, thus providing an opportunity to obtain information about DiNP exposure for these workers. Our objectives in this report are to describe worker urinary concentrations of the DiNP metabolite MCiOP, to evaluate the effect of task or shift use of DiNP on MCiOP concentrations, to estimate DiNP daily intake, and to compare these workers’ metabolite concentrations and intake estimates to those of other populations.

Methods

Population

Workers were recruited as part of a NIOSH study of occupational phthalate exposure (Hines et al. 2009, Hines et al. 2011). Two companies in the study used DiNP during the sampled period; one company manufactured PVC film ($n = 25$, recruited in 2004), and one company performed custom PVC compounding ($n = 12$, recruited in 2005). We identified participants who worked on shifts when DiNP was used in production (PVC film $n = 11$; PVC compounding $n = 4$), and participants who worked directly on tasks or processes that used DiNP (a subset of the former group) (PVC film $n = 7$, PVC compounding $n = 0$). Remaining workers in the two companies were used as internal comparison groups. Participation in the study was voluntary and informed consent was obtained. The NIOSH Human Subjects Review Board approved this study.

The PVC film manufacturing company used DEHP and DiNP as plasticizers in the production of large, continuous sheets of film. Phthalate-related processes in PVC film manufacturing included compounding, mixing, paste preparation, extrusion, milling, and calendering. The PVC compounding company used DEHP and DiNP to produce custom-formulated PVC pellets. Phthalate-related processes in this company included mixing, extrusion, and milling.

Sample collection and analysis

Each participant collected two urine samples, one at mid-shift (half-way into the shift) and one at the end of shift, during a single work shift without regard to day of the week in 125-ml sterile polypropylene specimen cups. Samples were kept cold on refrigerant packs until aliquots were frozen on dry ice at the end of the shift, followed by storage at −80°C. Because this was a screening study, our goal was to maximize the number of workers screened given our resources. Thus, we focused on samples most likely to indicate exposure (i.e., mid-shift and end-shift) and less on samples less likely to indicate exposure (e.g., pre-shift). The term "exposure" is used in this article to indicate the body burden (internal exposure) of the measured analyte. We reimbursed participants $10 per sample for their time and inconvenience.

We analyzed urine samples from the two DiNP using companies for MCiOP. We used the "carboxy" metabolite (MCiOP) as the DiNP exposure biomarker. Under our experimental conditions, the isomeric MCiOP was not chromatographically resolved and eluted as a broad peak. Therefore, for quantification, we integrated the whole area under the cluster of peaks encompassing the various MCiOP isomers (Fig. 1). Specifically, we used calibration curves constructed with mono(2,6-dimethyl-6-carboxyhexyl) phthalate, a commercially available MCiOP isomer with a MS fragmentation pattern similar to that of other MCiOP isomers. We used D_4-mono(2,6-dimethyl-6-carboxyhexyl) phthalate as the internal standard (Silva et al.

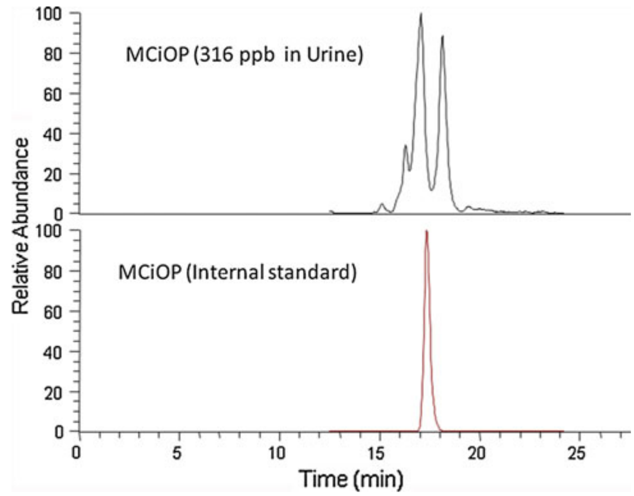

Fig. 1 Chromatogram from a person with a urinary MCiOP concentration of 316 ppb (μg/L) (*upper panel*). The chromatogram for the internal standard is shown in the *lower panel*

2007). The analytical approach involved enzymatic deconjugation of the metabolite from its glucuronidated form, automated solid-phase extraction, separation with high-performance liquid chromatography, and detection by isotope-dilution tandem mass spectrometry (Silva et al. 2007). Mono(2,6-dimethyl-6-carboxyhexyl) phthalate (>98%) and its D_4-labeled analog (>98%) were obtained from CanSyn (Ontario, Canada). The purity and supplier(s) information for other reagents and standards are provided in Silva et al. 2007. Each analytical run also included calibration standards, reagent blanks, and quality control materials. Procedures for preparing QC materials (i.e., urine specimens collected from multiple anonymous donors, pooled and spiked with the target analytes) can be found in Silva et al. 2007. The mean concentrations of the two pools used were 6.5 ng/mL, % coefficient of variation (CV) 8.6, and 29.1 ng/mL, %CV 2.6. Analysts were blind to all participant information. The limit of detection (LOD) for MCiOP was 0.7 μg/L. The relative standard deviation for blind duplicates averaged 5% (range 0–12%, $n = 6$). We measured creatinine by a modified Jaffé kinetic rate method (Synchron CX®system, Beckman Coulter Inc., Fullerton, CA, USA) and specific gravity (SG) using a handheld refractometer (NSC Precision Cells Inc., Farmingdale, NY, USA) calibrated with distilled water.

Estimation of DINP Daily Intake

We used end-shift creatinine-adjusted (CR-adjusted) MCiOP concentrations and the method of David (2000) as previously described in Hines et al. (2011) to estimate each participant's daily intake of DiNP (Eq. 1). Equation 1 assumes steady-state excretion. UE (urinary excretion) is the MCiOP urinary concentration 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 (DiNP) to metabolite (MCiOP). An F_{UE} of 0.0907 at 24 h based on a human dosing study was used (Koch and Angerer, 2007). The U.S. Environmental Protection Agency does not have a reference dose (RfD) for DiNP. The U.S. Consumer Product Safety Commission (CPSC) has recommended an acceptable daily intake of 120 µg/kg/day for DiNP (CPSC (Consumer Product Safety Commission) 2001). The European Food Safety Authority (EFSA 2005) has established a tolerable daily intake (TDI) for DiNP of 150 µg/kg/day.

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

Data analysis

Concentrations of MCiOP unadjusted, adjusted for creatinine, and adjusted for specific gravity, were skewed to the right and a natural log transformation was applied. MCiOP concentrations in all samples were above the LOD. All statistical analyses were performed in SAS v. 9.1 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $\alpha = 0.05$.

Due to within-person correlation between the mid-shift and end-shift samples, mixed-effects models were developed for the PVC film manufacturing and PVC compounding workers (separately) to test for two fixed effects, shift time (i.e., difference between mid-shift and end-shift MCiOP concentrations) and DiNP use. In PVC film manufacturing, models were run separately for two DiNP use conditions a) use of DiNP on the worker's assigned task (yes/no) and b) use of DiNP on the worker's assigned shift (yes/no), but not necessarily on their assigned task. In PVC compounding, no participants worked directly on tasks with DiNP use, therefore, the PVC compounding model included only DiNP use on the worker's shift. Models were constructed using the MIXED procedure with worker treated as a random effect, two fixed effects (shift time and DiNP use), and an interaction term for shift time and DiNP use (shift time*DiNP use). Because of the small sample size in PVC compounding ($n = 12$), the interaction term was not included in PVC compounding models in order to avoid over parameterization. A compound symmetric covariance structure and restricted maximum likelihood estimation were used. Models were run separately on the unadjusted, CR-adjusted, and SG-adjusted MCiOP concentrations.

In PVC film manufacturing, we computed the geometric mean (GM) and geometric standard deviation (GSD) for mid-shift and end-shift MCiOP concentrations stratified by DiNP use on task, then on shift. Because DiNP use on the worker's shift was not significant in PVC compounding, GMs and GSDs for MCiOP concentration in these participants were computed separately for mid-shift and end-shift samples across all shifts.

Results

Participants in the PVC film ($n = 25$) and PVC compounding ($n = 12$) companies were predominately male ($n = 19$ and $n = 10$, respectively). All participants, except one in PVC compounding, were white. The mean age (± SD) was 46 ± 10 years (range, 18–56) in PVC film and 40 ± 8 years (range, 24–50) in PVC compounding. Median shift length was 12 h in PVC film and 8.7 h in PVC compounding.

In PVC film workers, MCiOP urinary concentrations varied 100 to 200-fold across all workers (unadjusted: 0.9–184 µg/L, CR-adjusted: 0.42–80 µg/g, and SG-adjusted: 1.6–164 µg/L, Table 1). In PVC compounding workers, MCiOP urinary concentrations had a narrower range and a lower maximum value (unadjusted: 1.20–21.9 µg/L; CR-adjusted: 1.11–13.4 µg/g; SG-adjusted: 1.80–21.0 µg/L, Table 1) than in PVC film.

End-shift MCiOP concentrations in PVC film workers were significantly higher than mid-shift concentrations for CR-adjusted ($p = 0.010$) and SG-adjusted concentrations ($p = 0.016$). Participants who worked directly on tasks where DiNP was used ($n = 7$) had GM MCiOP concentrations significantly higher (approximately 6–8 fold) for both the mid-shift and end-shift samples ($p < 0.0001$) as compared to those who did not work on tasks with DiNP ($n = 18$, Table 1). These DiNP tasks included operating mix mills and winders, calenders, and working in the mixing department. No interaction terms were significant in models with DINP use on task; however, the interaction of DiNP use on shift and shift time was significant for all three metrics (unadjusted: $p = 0.009$; CR-adjusted: $p = 0.0032$; SG-adjusted: $p = 0.0038$), indicating that the magnitude of the change in MCiOP concentration from mid-shift to end-shift depended on the DiNP shift use condition. In other words, the mid-shift and end-shift GM MCiOP concentrations were not significantly different for persons who worked on shifts where DiNP was *not used* (e.g., 1.90 µg/g for mid vs. 2.08 µg/g), but for participants who worked on a shift where DINP *was used*, the GM

Table 1 Concentrations of MCiOP at mid-shift and end-shift in PVC film manufacturing and PVC compounding. MCiOP concentrations in PVC film manufacturing are shown for two conditions, (1) DiNP used on the worker's assigned task and (2) DiNP used on the worker's shift, but not necessarily on the assigned task

	Sample	*n*	Unadjusted, μg/L		CR-adjusted, μg/g		SG-adjusted, μg/L	
			GM (GSD)	Range	GM (GSD)	Range	GM (GSD)	Range
PVC Film Manufacturing								
DiNP used on worker's TASK[a]	Mid-shift							
	Yes	7	34.4* (2.0)	15.1–77.4	14.7* (2.3)	4.45–38.9	33.6* (2.2)	11.7–78.6
	No (ref)	18	4.92 (2.2)	0.9–26.8	2.46 (2.2)	0.78–13.4	5.10 (2.0)	1.99–26.8
	End-shift							
	Yes	7	51.0* (2.4)	12.5–184	25.2* (2.1)	9.19–80.0	50.5* (2.3)	15.0–164
	No (ref.)	18	5.34 (2.8)	0.90–27.9	2.92 (2.6)	0.42–16.0	5.86 (2.3)	1.60–24.4
DiNP used on worker's SHIFT	Mid-shift							
	Yes	11	22.8* (2.2)	9.1–77.4	10.7* (2.2)	4.45–38.9	21.9* (2.4)	8.09–78.6
	No (ref.)	14	3.90 (2.1)	0.9–26.8	1.90 (1.9)	0.78–13.4	4.17 (1.8)	1.99–26.8
	End-shift							
	Yes	11	34.9* (2.4)	11.7–184	17.7* (2.2)	5.49–80.0	34.1* (2.4)	12.2–164
	No (ref.)	14	3.78 (2.4)	0.9–27.9	2.08 (2.1)	0.42–9.72	4.32 (1.9)	1.60–22.3
PVC Compounding								
DiNP used at facility[b]	Mid-shift	12	6.64 (2.4)	1.20–21.9	4.11 (2.0)	1.41–13.4	7.03 (2.1)	1.80–21.0
	End-shift	12	9.53** (2.3)	1.70–21.7	4.80 (2.1)	1.11–13.3	9.05** (2.1)	1.86–19.8

All samples had MCiOP concentrations above the LOD

CR creatinine; *SG* specific gravity

[a] The same 25 individuals were used to create the "TASK" groups (yes/no) and the "Shift" groups (yes/no)

[b] No statistically significant difference ($p > 0.05$) was found between those who did ($n = 4$) and did not ($n = 8$) work on shifts, where DiNP was used in PVC compounding; therefore, results are presented for all shifts combined. Sample size was insufficient to stratify by task

* Significantly different from referent condition. $p < 0.0001$

** End-shift significantly different than mid-shift, $p = 0.2$ unadjusted; $p = 0.03$ SG-adjusted

MCiOP concentration was approximately 1.7-fold higher for the end-shift sample than for the mid-shift sample (17.7 μg/g vs. 10.7 μg/g, Table 1). Also, PVC film workers who worked directly on a task where DiNP was used ($n = 7$) had GM MCiOP concentrations approximately 40% higher than workers on shifts were DiNP was used.

In PVC compounding, GM MCiOP concentrations for participants who worked on shifts with and without DiNP use were not statistically significant ($p > 0.05$); however, a significant increase in the GM MCiOP concentration from mid-shift to end-shift was found for the unadjusted concentrations ($p = 0.020$ and the SG-adjusted concentrations ($p = 0.03$), but not for the CR-adjusted concentrations ($p = 0.1$). The change in the MCiOP GM from mid-shift to end-shift in PVC compounding was small, approximately 2 μg/L.

Only one sampled worker in PVC film wore a respirator during the shift (a dust mask); none in PVC compounding. Nine workers in PVC film wore rubber gloves at sometime during the shift; none in PVC compounding. The number of PVC film participants was insufficient to formally evaluate the effect of gloves in the presence of both shift time and DINP use effects; however, persons who worked on a task where DiNP was used and did not wear rubber gloves had the highest GM of any group, suggesting a possible protective effect from wearing gloves (Table 2). Interestingly, among those who did not use DiNP on either their task or shift, a small increase in the GM was seen for those who wore gloves. A possible explanation for this finding is internal glove contamination (Rawson et al. 2005; Garrod et al., 2001, Hines et al. 2001).

GM DiNP intake estimates in PVC film workers who did and did not work on shifts where DiNP was used were 5.6 μg/kg/day (range, 1.8–26 μg/kg/day) and 0.6 μg/kg/day (range, 0.1–3.2 μg/kg/day), respectively (~9-fold difference) (Table 3). The GM intake estimates in PVC film workers who did and did not work on a task with DiNP in PVC film were 8.0 μg/kg/day (range, 2.4–26 μg/kg/day) and 0.9 μg/kg/day (0.1–5.3 μg/kg/day), respectively (~9-fold difference) (Table 3). The GM DiNP intake estimate in PVC compounding workers was 1.5 μg/kg/day (range, 0.4–4.4 μg/kg/day) (Table 3).

Table 2 Geometric means and geometric standard deviations for use of rubber gloves stratified by DiNP use on the worker's assigned task and DiNP use during the worker's shift

DiNP Used on worker's TASK	Wore rubber gloves during shift	N	K	Unadjusted, μg/L		CR-adjusted, μg/g		SG-adjusted, μg/L	
				GM	GSD	GM	GSD	GM	GSD
No	Yes	14	7	6.53	2.6	3.42	2.4	6.52	2.33
No	No	22	11	4.40	2.4	2.29	2.2	4.89	1.9
Yes	Yes	4	2	16.6	1.3	8.14	1.5	15.3	1.23
Yes	No	10	5	60.7	1.8	27.2	1.9	61.3	1.8
DINP used during worker's SHIFT									
No	Yes	12	6	5.73	2.6	2.80	2.2	5.74	2.3
No	No	16	8	2.84	1.7	1.54	1.6	3.38	1.2
Yes	Yes	6	3	15.8	1.4	9.10	1.5	14.9	1.5
Yes	No	16	8	35.1	2.4	16.0	2.42	34.4	2.5

N number of samples, *K* number of workers

Table 3 DiNP intake estimates (μg/kg/day) based on end-shift concentrations of MCiOP for PVC film manufacturing and PVC compounding

	n	GM (GSD)	Range
PVC film manufacturing			
DiNP used on worker's TASK			
Yes	7	8.0* (2.2)	2.4–26
No (ref.)	18	0.9 (2.6)	0.1–5.3
DiNP used on worker's SHIFT			
Yes	11	5.6* (2.4)	1.8–26
No (ref.)	14	0.6 (2.1)	0.1–3.2
PVC Compounding			
DiNP used at facility	12	1.5 (2.1)	0.4–4.4

* Significantly different from referent condition. $p < 0.0001$

Discussion

Initial efforts to assess DiNP exposure in the United States measured only the monoester in participants from four U.S. National Health and Nutrition Examination Surveys, (NHANES) III (1988–1994) (Blount et al. 2000) and NHANES 1999–2000, 2001–2002, and 2003–2004 (CDC 2009). MiNP was infrequently detected in these samples, suggesting that the monoester may not be a sensitive biomarker of DiNP exposure. After metabolism studies in rats and humans indicated that the oxidative metabolites of DiNP were much more abundant than the monoester (Koch and Angerer 2007; Silva et al. 2006a), human biological monitoring studies began including one or more oxidative urinary metabolites (Latini et al. 2009; Becker et al. 2009; Ye et al. 2008; Wittassek et al. 2007; Koch et al. 2007; Fromme et al. 2007; Silva et al. 2006b), all of which are highly correlated with each other because they derive from the same parent metabolite (Silva et al. 2006b). Subsequent analysis of 2,548 urine samples from NHANES 2005–2006 found that MCiOP was detected much more frequently (95.2% vs. 12.9%) and at higher concentration ranges than MiNP, confirming that MCiOP is a more sensitive biomarker of DiNP exposure than MiNP (Calafat et al. 2010).

Using MCiOP as a urinary biomarker, PVC film manufacturing participants who worked on a task using DiNP ($n = 7$) had GM end-shift concentrations of 25.2 μg/g (CR-adjusted) and 51.0 μg/L (unadjusted). These concentrations were 5- to 10-times as high as those in a representative sample of 1,040 U.S. adults ages 20–59 years from NHANES 2005–2006 (GM = 4.98 μg/g, CR-adjusted; GM = 5.19 μg/L, unadjusted) (Calafat et al. 2010). The GM end-shift unadjusted MCiOP concentration (51.0 μg/L) in the task-exposed PVC film participants was also approximately 10-times as high as that in a random sample of the German population (median = 5.0 μg/L, $n = 25$) (Koch et al. 2007), and approximately 3-times as high as that in German children (GM = 13.8 μg/L, $n = 599$) (Becker et al. 2009).

Our highest DiNP intake estimate, 26 μg/kg/day in a PVC film manufacturing worker, was 17% of the EFSA TDI (150 μg/kg/day) and 22% of the CPSC ADI (120 μg/kg/day) for DINP (EFSA 2005; CPSC 2001). Intake estimates in PVC film manufacturing workers with shift or task exposure to DINP averaged approximately 4–5% of the TDI and 5–7% of the ADI, while intake estimates for PVC film workers with no shift or task exposure to DiNP averaged less than 1% of both the TDI and ADI. In PVC compounding workers, all DiNP intake estimates were less than 3% of the TDI and less than 4% of the ADI.

Limited data are available on DiNP intakes estimates for other populations. Wittassek et al. (2007) estimated DiNP daily intake based on urinary concentrations of MOiHP and MHiNP DINP metabolites in German students (aged 20–29 years) for 9 years between 1988 and 2003 and reported a range of intake estimates over all years of 0.02–20.2 μg/kg/day, a maximum 95th percentile of 7.8 μg/kg/day in 1998, and 50th percentile that gradually increased from 0.20 μg/kg/day in 1988 to 0.40 μg/kg/day in 2003. Our PVC film participants who worked on tasks with DiNP had GM intake estimates 20–40-fold higher than the 50th percentile of these young German adults; however, the 50th percentile intake estimates for the young adults were comparable to our workers with no shift or task exposure to DiNP. Although Wittassek et al. (2007) used different DiNP metabolites than we did to estimate intake, theoretically this difference should not bias comparisons as the procedure takes into account the molar fraction of the specific metabolite(s) used to estimate the intake. Our workers without shift or task exposure to DiNP also had GM daily intake estimates comparable to a group of 289 individuals (aged 20–60 years) from NHANES III whose GM DiNP intake estimate (0.21 μg/kg/day) was based on the monoester MiNP (David, 2000), a metabolite now considered potentially less reliable as a biomarker based on its low abundance and susceptibility to contamination by abiotic processes.

While the aforementioned studies derived daily intake estimates using urinary metabolite concentrations, Wormuth et al. (2006) estimated DiNP daily intake for different European age groups based on scenarios that considered sources and mechanisms of oral, dermal, and inhalation exposure. For men and women, the mean estimated DiNP intake was less than 0.01 μg/kg/day, about two orders of magnitude below other non-occupationally exposed estimates (Wittassek et al. 2007; David 2000) including non-exposed participants in our study, illustrating the challenges of estimating intake accurately in the absence of human exposure data.

Because companies in the screening study were not selected based on DiNP use, we were able to compare MCiOP concentrations in PVC film participants who worked on shifts where DiNP was used (but not necessarily on the person's specific tasks during the shift) to participants who did not work on either a task or shift where DiNP was used (internal comparison group). As might be expected, DiNP task exposure was greater than DiNP shift exposure which was greater than no task or shift exposure. The lack of a difference in MCiOP concentrations in PVC compounding between persons who did and did not work on a shift where DiNP was used may not hold for all workers handling DiNP in PVC compounding. We had limited statistical power and the four persons who volunteered on shifts where DiNP was used were in jobs with more limited or incidental exposure to DiNP, such as process engineer, manager, and maintenance.

Although the vapor pressure of DiNP is considered low ($<6.7 \times 10^{-5}$ Pa, Staples et al. 1997), DiNP was used in several heated (i.e., >65°C) processes in PVC film (mixing, milling, extruding, and calendering) and in PVC compounding (mixing, milling, and extruding) with temperatures exceeding 150°C for calendering, some milling, and some extruding processes.

Although the results presented here are limited to two companies, and as such are not representative of all companies in their respective industries, they are some of the first biological monitoring data for persons occupationally exposed to DiNP. Because these data were collected as part of a larger screening study of phthalate occupational exposures with limited sampling, future studies of DiNP occupational exposure should include additional samples (e.g., pre-shift, over multiple shifts and across seasons) to further characterize exposures and temporal variability. We also did not have information on non-occupational DiNP exposure, such as diet, off-the-job activities, and at home. Although the method we used to estimate DiNP daily intake from urinary metabolite concentrations has been commonly used, the method has certain limitations, including temporal variability in metabolite concentrations, source variability, variability in model input parameters (F_{UE} and CE), and within- and between-person variability in metabolism (discussed more fully in Hines et al. 2011); thus, our DiNP intake estimates should be interpreted with caution. No occupational exposure standards have been established for DiNP metabolites in urine; hence, we compared our estimated DiNP daily intake to intake limits recommended by the U.S. CPSC and the European FSA. These intake limits were established for the general population and may not necessarily be appropriate for workers who are generally considered "healthier" than the general population, although workers may include sensitive subgroups such as pregnant and nursing women.

Conclusion

In this preliminary study, exposure to DiNP associated with PVC film manufacturing tasks was substantially higher (fivefold to tenfold) than U.S. and German adult general population exposures; however, daily intake estimates derived from these exposures were all less than 25% of current U.S. or European acceptable or tolerable intake values. Further characterization of DiNP exposures in other industries is recommended.

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Conflict of interest The authors declare that they have no conflict of interest.

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