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Biomonitoring of occupational exposure to phthalates: A systematic review

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ABSTRACT

Introduction: Phthalates, a group of ubiquitous industrial chemicals, have been widely used in occupational settings, mainly as plasticizers in a variety of applications. Occupational exposure to different phthalates has been studied in several occupational settings using human biomonitoring (HBM).

Aim: To provide a comprehensive review of the available literature on occupational exposure to phthalates assessed using HBM and to determine future data needs on the topic as part of the HBM4EU project.

Methods: A systematic search was carried out in the databases of Pubmed, Scopus, and Web of Science for articles published between 2000 and September 4, 2019 using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 22 studies on the occupational HBM of phthalates was considered suitable for review.

Results and discussion: Among the reviewed studies, 19 (86%) focused on DEHP, an old phthalate that is now subject to authorization and planned to be restricted in the EU. Concentrations of MEHHP, one of its metabolites, varied up to 13-fold between studies and across sectors when comparing extreme geometric means, ranging from 11.6 (similar to the general populations) to 151 μg/g creatinine. Only 2 studies focused on newer phthalates such as DiNP and DPHP. Concerning the geographical distribution, 10 studies were performed in Europe (including 6 in Slovakia), 8 in Asia, and 4 in North America, but this distribution is not a good reflection of phthalate production and usage levels worldwide. Most HBM studies were performed in the context of PVC product manufacturing. Future studies should focus on: i) a more uniform approach to sampling timing to facilitate comparisons between studies; ii) newer phthalates; and iii) old phthalates in waste management or recycling.

Conclusion: Our findings highlight the lack of recent occupational HBM studies on both old and new phthalate exposure in European countries and the need for a harmonized approach. Considering the important policy actions taken in Europe regarding phthalates, it seems relevant to evaluate the impact of these actions on exposure levels and health risks for workers.

1. Introduction

Phthalates (also known as phthalate esters or esters of phthalic acid) are a group of plasticizers with a worldwide production volume of around 5.5 million tons per year (OECD, 2018). This family of chemicals is widely used to soften plastics and has a strong performance in terms of durability and stability. Although regulatory restrictions have decreased exposure to old phthalates known as endocrine disruptors, workers in the plastics industry may still be exposed to newer phthalates and phthalate substitutes. In this review, the term "newer

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Table 1
Phthalates and their urinary metabolites together with 24-h molar excretion percentages of the metabolites.

Phthalates Systematic name	CAS No	Abbreviation/Acronym	Primary metabolite	Molar % excreted in 24 h	Secondary metabolite	Molar % excreted in 24 h	Ref
Low molecular weight (LMW) phthalates							
Dimethyl phthalate	131-11-3	DMP	MBP	n.a.	–	–	
Diethyl phthalate	84-66-2	DEP	MEP	n.a.[a]	–	–	
Di-n-butyl phthalate	84-74-2	DBP	MBP	69; 78; 84	–	–	3, 1, 2
					3OH–MBP	6.9	2
					MCPP[b]	0.5	2
Diisobutyl phthalate	84-69-5	DiBP	MiBP	70.3	–	–	2
					2OH-MiBP	19.3	2
					3OH-MiBP	0.7	2
Butyl benzyl phthalate	85-68-7	BBzP	MBzP	73	–	–	3
			MBP	6	–	–	3
High molecular weight (HMW) phthalates							
Di(2-ethylhexyl) phthalate	117-81-7	DEHP	MEHP	2.6; 6.2; 7.3	–	–	4,5,6
					MEHHP (or 5OH-MEHP)	13.3; 14.9; 24.1	4,5,6
					MEOHP (or 5oxo-MEHP)	10.9; 14.6; 15.0	5,6,4
					MECPP (or 5cx-MEPP)	13.2; 20.7	5, 7
Diisononyl phthalate	28553-12-0 68515-48-0	DiNP	MiNP	3	–	–	5
					OH-MiNP	11.4; 18.4	5, 8
					oxo-MiNP	6.3; 10.0	5, 8
					cx-MiNP	9.9; 9.1	5, 8
Diisodecyl phthalate	26761-40-0 68515-49-1	DiDP[c]	MiDP	n.a.	–	–	
					OH-MiDP	n.a.	
					oxo-MiDP	n.a.	
					cx-MiDP	n.a.	
Di(2-propylheptyl) phthalate	53306-54-0	DPHP	MPHP	<1[d]	–	–	9
					OH-MPHP	9.1	10
					oxo-MPHP	12.6	10
					cx-MPHxP	0.4	10

References: 1: Seckin et al. (2009); 2: Koch et al. 2012a; 3: Anderson et al. (2001); 4: Kessler et al. (2012); 5: Anderson et al. (2011); 6: Koch et al. (2004); 7: Koch et al. (2005); 8: Koch et al. (2017); 9: Wittassek and Angerer (2008); 10: Leng et al. (2014).
Other phthalates are not common in Europe: DOP, DPeP, DCHP, DiPP, DHNUP, DHP, DMEP.

[a] Sometimes set to be the same as that of DnBP (69%, Anderson et al., 2001).

[b] MCPP is also a metabolite of other phthalates (Calafat et al., 2006).

[c] Molar excretion percentages of DiDP metabolites are not available. Due to the similar molecular structure of DiDP and DPHP, it could be assumed that the molar excretion percentages of their metabolites are close to each other; CAS No 26761-40-0 is no longer produced in Europe (Leng et al., 2014).

[d] Determined 61 h after exposure.

phthalate" signifies phthalates that have substituted di(2-ethylhexyl) phthalate (DEHP). They are not necessarily "new," since many have been used for more than 10 years. With regard to occupational exposure, there are only limited data on the exposure of workers to different phthalates. Since phthalates usually have a low vapor pressure, inhalation is often not the dominant route of uptake; oral (e.g., hands-to-mouth transfer) and dermal routes can thus play an important role in the total exposure. Therefore, human biomonitoring (HBM) is the most relevant tool to estimate workers' total exposure to phthalates, regardless of the route of exposure.

An understanding of the various phthalates, their metabolism, distribution, and elimination kinetics is important for identifying valuable biomarkers of exposure. Phthalates such as DEHP, DiNP, DiDP, and DPHP (the definitions of abbreviations are provided in Table 1), which are made of alcohols with long alkyl chains and defined as high molecular weight (HMW) phthalates, are mainly used to make polyvinyl chloride (PVC) more flexible in various applications. The different phthalates are summarized in Table 1. Those with shorter chains (or aryl rings, low molecular weight (LMW) phthalates) such as DBP, DiBP, BBzP, DEP, and DMP are mainly used in non-PVC products such as personal care products and cosmetics (e.g., fragrances, skin lotions, nail polish, eye shadows), textiles, paints, pesticides, lubricants, and adhesives (Koch and Angerer, 2012). In the past, the most widely used phthalates were DEHP, BBzP, DMP, and DEP, whereas DEHP was the dominant plasticizer used globally in PVC (Wormuth et al., 2006) According to the available data, the time trend for the production volume of phthalates has declined worldwide (i.e., more than 8 million tons in 2011, between 6 and 8 million tons in 2015, and 5.5 million tons in 2018), thus highlighting the decrease in occupational exposure to these chemicals (Net et al., 2015; OECD, 2018; Wang et al., 2019).

Occupational exposure can take place by the dermal route (with low molecular weight phthalates such as DEP, DBP, and BBzP) (Cavallari et al., 2015), by inhalation (with more volatile phthalates like DEP and DMP), or to a less extent, by ingestion (especially with the high molecular weight DEHP and DINP). Human data on uptake after inhalation exposure, ingestion, or dermal contact are generally limited. Some studies suggest that phthalates are well absorbed from the gastrointestinal tract: for example, absorption of DEHP was shown to be more than 50% and that of DBP around 80% in humans (Anderson et al., 2011; Koch et al., 2005; Koch et al., 2012a; Seckin et al., 2009).

Following exposure and uptake, phthalates are rapidly metabolized, and both the conjugated and the free (non-conjugated) phthalate metabolites are excreted in urine and partly in feces (Silva et al., 2003). The relatively polar and short-chain phthalates such as DMP, DEP, DBP, and DiBP are rapidly hydrolyzed to monoesters and eliminated mainly as free monoesters and glucuronide conjugates. Long-chain phthalates such as DEHP, DiNP, and DPHP metabolize to their monoesters, which are extensively transformed to secondary oxidized metabolites.

Phthalates have short biological half-lives and are quickly excreted from the body. For long-chain phthalates, the elimination of oxidized metabolites is predominant, followed by monoesters. For shorter-chained phthalates (DEP, DBP, DiBP, BBzP), approximately 70–80% of

an oral dose is excreted as the simple monoester metabolite in urine compared to less than 10% and 3% of the long-chained phthalates DEHP and DiNP, respectively (Anderson et al., 2001; Johns et al., 2015; Koch and Angerer, 2007; Koch et al., 2003a, 2003b, 2012a, 2012b). The elimination of phthalate metabolites often follows a multi-phase pattern: for example, the elimination half-lives of OH-MiNP and oxo-MiNP are about 12 h in the second phase compared to 18 h for cx-MiNP. Indeed, after single oral doses of both DBP and DiBP in a human volunteer, the majority of the dose was excreted in the first 24 h, while less than 1% was excreted in urine on day 2. For MBP, the monoester of DBP, the final urinary elimination half-life was reported to be 2.6 h in one subject but slightly longer for oxidized metabolites (Koch and Angerer, 2012). Due to their kinetics, some phthalates such as DEHP, DiNP, and DiDP have the potential to accumulate during the working week in the case of daily exposure. For the occupational HBM of phthalates, the concentration of the degradation products (metabolites) is commonly analyzed in urine. The parent phthalates and their metabolites are presented in Table 1.

Due to their ubiquitous nature, phthalate diesters are not commonly measured in the biomonitoring of phthalate exposure (Koch et al. 2003b; Silva et al., 2007). Contamination by non-oxidized monoesters may also occur for two reasons: first, phthalate additives in PVC are not free of monoesters, and second, phthalates can hydrolyze to monoesters in the environment (general and occupational). In fact, contamination can occur during the collection, transportation, storage, and analytical processes, while plastics in laboratory equipment can also contain phthalates. Consequently, urinary metabolites (monoesters, and in the case of high molecular weight phthalates, preferably secondary oxidized metabolites) are usually used as biomarkers to assess phthalate exposure, because the type of matrix used in biomonitoring studies is urine, and in this type of sample, the result of the metabolism and not the original compounds will essentially be found (Latini, 2005; Townsend et al., 2013; Yoshida, 2017).

Many phthalates are shown to cause reproductive toxicity in animals. These effects are mediated by their anti-androgenic properties. Some of them (C3–C6 side chains) induce the so-called phthalate syndrome in rats, which covers different reproductive abnormalities in the male offspring of rats exposed during pregnancy. The most potent representative is DPeP, followed by DEHP, DBP, DiBP, BBzP, and DCHP with comparable potency (Gennings et al., 2014). DiNP has a somewhat lower potency as an anti-androgen, while there is no evidence of anti-androgenic activity in DiDP and DPHP (Bhat et al., 2014; Furr et al., 2014). In humans, some studies describe the association between adverse male reproductive effects (effects on anogenital distance, semen parameters, testosterone levels, time to pregnancy) and phthalates, especially DEHP and DBP (Radke et al., 2018). Mixtures of anti-androgenically active phthalates are likely to have dose additive effects, which was taken into account in recent risk assessments of these phthalates (ECHA, 2012, 2017/RAC opinion on phthalate restriction). Exposure to phthalates has been suggested to cause other effects such as immunotoxicity (increased risk of asthma and allergies), neurodevelopmental effects, and metabolic effects (obesity; Wang et al., 2019). Data on these associations are nevertheless weaker than those on reproductive effects and are not sufficient for the risk assessment of phthalates (ECHA, 2017).

Due to their classification as reproductive toxicants in category 1 B under Annex VI to the Classification Labelling and Packaging (CLP) regulation, DEHP, DBP, DiBP, and BBzP have been added to the list of substances of very high concern (Annex XIV EC, 1907/2006) in the EU and subjected to authorization under the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation. Furthermore, DPeP, DiPP, DHNUP, DHP, and DMEP are on the candidate list of substances of very high concern for authorization (i.e., SVHC candidates) due to the same toxicological properties. The most recent restriction of phthalates concerns articles containing DEHP, DBP, DiBP, and BBzP in a concentration greater than or equal to 0.1% (individually or in combination) on the market in the EU. This proposed restriction was supported by socioeconomic and risk assessment committees (SEAC and RAC) of the European Chemical Agency (ECHA) in 2017 and is currently waiting for adoption by the Commission. Under the EU occupational safety and health legislation, no EU-wide occupational guidance values have been set for phthalates, but the current recommendations of the Scientific Committee on Occupational Exposure Limits (SCOEL) with respect to DBP propose an occupational exposure limit of 0.58 mg/m^3 (0.05 ppm) as an 8-h time-weighted average. No biological limit value for occupational exposure is available at the European level. However, Germany and France have established their own biological limit values. Besides the German Research Foundation's (Deutsche Forschungsgemeinschaft, DFG) BAT value for DEHP (4 mg Σ(MEHP + 5OH-MEHP + 5oxo-MEHP + 5cx-MEPP)/g creatinine [cr]) (Rettenmeier et al., 2019), French biological limit values have been established for: i) DBP (urinary MBP of 70 µg/L or 50 µg/g cr), ii) BBzP (urinary MBzP of 40 µg/L or 30 µg/g cr), and iii) DEHP (urinary 5cx-MEPP of 200 µg/g cr regardless of smoking status) (ANSES website).

Biomonitoring equivalent values in urine, defined as the concentrations or range of concentrations of the metabolite in a biological matrix corresponding to an external health-based reference dose (RfD) or tolerable daily intake (TDI), have been derived for certain phthalate metabolites to be used as screening tools for the evaluation of general population biomonitoring data (Aylward et al., 2009a, 2009b; Hays et al., 2011). Also, the German Human Biomonitoring (HBM) Commission has provided some health-related guidance values for the general population (HBM assessment values – HBM values), mainly on the basis of internationally agreed TDI/RfD values for some phthalates: HBM I values (i.e., concentration of a substance in human biological material at or below which there is no risk of adverse health effects based on the current knowledge and assessment of the HBM Commission) for the sum of DPHP metabolites, oxo-MPHP, and OH-MPHP, as well as for the DEHTP metabolite 5cx-MEPTP in urine (Apel et al., 2017).

In the framework of the EU HBM initiative known as HBM4EU (www.hbm4eu.eu), a state-of-the-art review of occupational HBM data on phthalate exposure was performed. The aim of this review was to identify the industry fields/work tasks that may result in the highest exposure to phthalates. In addition, we provide an overview of available knowledge on occupational HBM of phthalate exposure, with particular attention given to the following: i) the specific biomarkers used (old and newer phthalates); ii) the (current) biomonitoring levels of workers in different occupational settings; iii) the observed links between biomarkers of exposure and health effects; and iv) the future needs in occupational HBM of phthalates in Europe.

2. Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic search was carried out in the databases of PubMed, Scopus, and Web of Science for articles published between 2000 and September 4, 2019. Initial search terms were developed to identify studies in occupational settings that use HBM of phthalates (metabolites) as well as HBM studies/surveillance programs that incorporate the monitoring of phthalate exposure. One search strategy was developed and adapted to each database (PubMed, Scopus, and Web of Science). In the databases, we used a combination of free text terms, and the search strategy was developed with low specificity to the advantage of high sensitivity: broad search terms included phthalate, workplace, worker, and occupation. No restrictions regarding language or publication type (articles or reviews) were applied in this phase. This search strategy led to 201 PubMed papers, 271 Scopus papers, and 256 Web of Science papers.

The titles and abstracts of all references were retrieved after removing duplicates. They were independently screened in parallel by 2 members of the project team with respect to the inclusion/exclusion

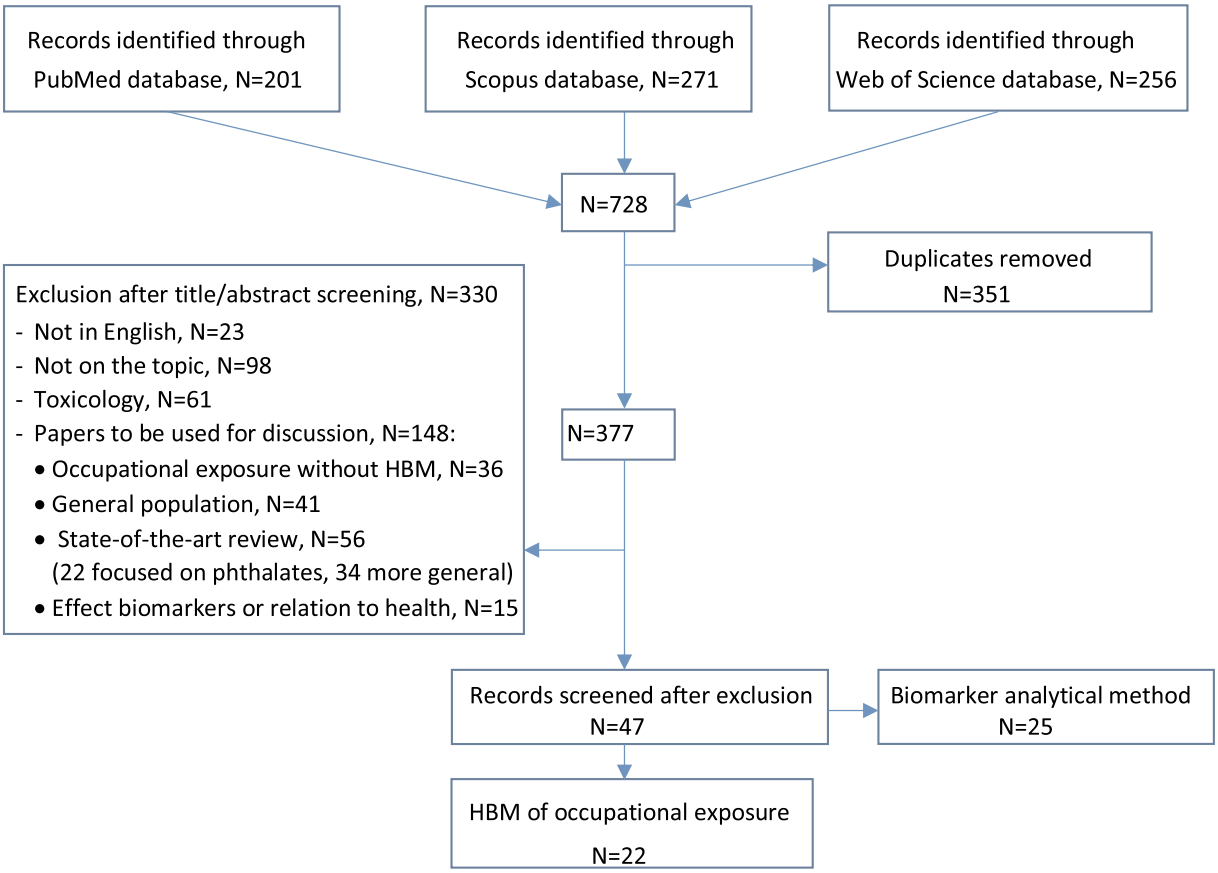

Fig. 1. Different phases of the selection process.

criteria. Articles that did not meet the inclusion criteria (see below) were excluded from further analysis, although a few are cited in the discussion. The 2 reviewers compared findings for consistency with the aim to highlight any discrepancies and define an agreed final set of papers to be analyzed. All the abstracts were reviewed and classified according to different categories (occupational HBM data on phthalate exposure, analytical methods, toxicological studies, not on the topic, not in English, occupational exposure study without HBM, HBM in the general population, review, HBM with effect biomarkers), and the final set of studies was decided (Fig. 1). Congress abstracts, studies on cellular and animal models, genotoxicity studies, and HBM studies focusing on the general population instead of occupational exposure were excluded except if occupational exposure was considered.

We included occupational HBM studies performed in different activity sectors, on old and new phthalates, and in different countries (Europe, Asia, and North America). Cross-sectional, longitudinal/cohort, and case-control studies were considered. There was no limit to the number of subjects included in the study; thus, the power of statistics was not used as criteria.

The sampling method could be random, convenience/intentional, or stratified, although intentional sampling is often the case in occupational HBM. The primary outcome was the reporting of occupational exposure measured as the mean/median concentration of phthalates in the different groups of exposure. Studies on analytical methods and new biomarkers were also included. Fig. 1 describes the different phases of the selection of papers.

Full papers were obtained for the 47 selected studies, and at the minimum, abstracts were available for the excluded papers that could be used for the discussion (see References); 22 occupational HBM studies on phthalate exposure and 25 on analytical methods were identified. A critical qualitative analysis of the available studies was performed to identify the strengths and limitations of the investigations. Relevant issues analyzed included: the study population (size of the target population, subgroups, inclusion criteria/sampling strategy, sample size); chemicals under investigation; studied biomarkers and matrix; sampling strategy (specificity and sensitivity of biomarkers, sampling timing); and applied analytical methods (quality assurance/limit of detection [LOD]-limit of quantification [LOQ], contamination, matrix adjustment, sampling strategies). These topics were adapted from the criteria commonly employed to assess the quality of non-persistent biomarker studies (e.g., LaKind score criteria, LaKind et al., 2014), although a quantitative quality assessment and tiering approach could not be applicable due to the complexity of the reviewed phthalate investigations (i.e., the large number of phthalates analyzed in each study). Moreover, we were unable to highlight the relationships between the available biomonitoring data and the operating conditions, as well as the risk management measures adopted in the studied sectors, as most of the studies lacked or did not provide sufficient details to understand their influence on the results.

Sixteen documents (gray literature) on phthalates were also identified from national agencies in Europe (European Plasticisers, 2018; ECHA, 2019) and North America, the International Agency for Research on Cancer (IARC, 2013), and the Scientific Committee on Occupational Exposure Limits in Europe (EC/SCOEL 2017), including 6 documents from France (3 from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES, 2011, 2013; ANSES et al., 2015), 1 from the National Research and Safety Institute (INRS, 2017), and 2 from the Public Health France (Dereumeaux et al., 2016; SpFrance, 2019)), 1 from Finland (Finnish Institute of Occupational Health; Porras et al., 2016), 1 from Sweden (Institutet för Kemisk Analys Norden; IFKAN, 2010), 2 from Germany (German Environment Agency (Rettenmeier et al., 2019) and Wuppertal Institut für Klima et al., 2015), 2 from the USA (Centers for Disease Control and Prevention; CDC 2013; 2019), and 1 from Canada (Health Canada, 2013). Seven of

Table 2
The most relevant occupational HBM studies on phthalate exposure (by chronological order).

Study	Occupational setting/number of workers and controls	Analytical method/Biomarkers			Results	Main conclusions on exposure	Additional information
		Substances studied	Biomarker of exposure /Matrix/Sampling time	Method LOD and LOQ (ng/mL)	Creatinine-adjusted urinary phthalate concentration (μg/g creatinine)[a]		
Kolena et al. (2019) (Slovakia)	Hairdressing apprentices (n = 74: 66 females + 8 males)	DEP, DBP, DEHP	MEP, MBP, MEHP, MEHHP, MEOHP, sum DEHP (MEHP + MEHHP + MEOHP) /urine/pre-shift, end of the workweek	HPLC-MS/MS LOD: MEP (4.41), MBP (1.1), MEHP (0.81), MEHHP (0.54), MEOHP (0.64).	Mean (ng/mL – no creatinine-adjusted urinary concentration): MEP (330), MBP (130), MEHP (7.5), MEHHP (38), MEOHP (20), sum DEHP (65).	Significantly higher phthalate exposure in hairdressing activities when compared to controls. Biomonitoring of phthalates in this type of occupational environment is needed to minimize their potentially harmful effects on health.	See Table 4.
Huang et al. (2018) (Taiwan)	Salesclerks (n = 36: 23 cosmetics, 4 perfume, 9 clothing) No control group	DEP, DEHP, DBP, BBzP, DMP	MEP, MEHP, MBP, MBzP, MMP /urine/pre- and post-shift	LC-ESI-MS/MS LOD: MEP (1.0), MEHP (0.9), MBP (1.4), MBzP (1.4), MMP (1.4).	Median (pre-shift vs post-shift): Cosmetics: MEP (96.6 vs 91.4); MEHP (30.9 vs 53.3); MBP (215 vs 220.9); MBzP (11.9 vs 19.7); MMP (22.5 vs 34.4). Perfume: MEP (63.8 vs 93.2); MEHP (47.0 vs 47.0); MBP (145 vs 197); MBzP (8.5 vs 17.3); MMP (14.9 vs 26.6). Clothing: MEP (85.8 vs 29.9); MEHP (32.5 vs 35.5); MBP (107 vs 154); MBzP (11.8 vs 12.5); MMP (22.7 vs 33.4).	Cosmetics salesclerks: median MEHP and MMP levels significantly higher post-shift than pre-shift. Perfume salesclerks: MMP levels significantly higher post-shift than pre-shift. Clothing salesclerks: MEP levels significantly lower post-shift than pre-shift. Cosmetics and perfume salesclerks had higher levels of urinary MEP, MBP, and MEHP than clothing salesclerks. Risks derived from DBP, DEP, and DEHP inhalation and dermal exposure should be considered and investigated for cosmetics and perfume sales workers.	Environmental monitoring: higher median levels of air DEP in cosmetics (1.77 mg/m^3) and perfume (1.75 mg/m^3) groups and DEHP in perfume group (6.98 mg/m^3) compared to clothing group (DEP: 0.89 mg/m^3; DEHP: 2.16 mg/m^3). Non-parametric tests for comparison. Low sample size.
Wang et al. (2018) (China)	Waste plastic recycling site workers (n = 165) Controls: farmers (50 km from the site) (n = 152)	DMP, DEP, DBP, BBzP, DEHP, DOP	MMP, MEP, MBP, MBzP, BBzP, MEHP, MEHHP, MEOHP, MOP /urine/random	HPLC-MS/MS LOD: MMP (0.033), MEP (0.022), MBP (0.008), MBzP (0.008), MEHP (0.024), MEHHP (0.010), MEOHP (0.008), MOP (0.043).	Mean (exposed vs controls): MMP (24.80 vs 18.35); MEP (52.30 vs 33.23); MBP (94.84 vs 106.29); MBzP (1.88 vs 1.30); MEHP (16.58 vs 14.45); MEHHP (76.09 vs 44.63); MEOHP (12.53 vs 9.32); MOP (0.29 vs 0.13).	Higher urinary mean levels of phthalates in the exposed group vs controls for all phthalate metabolites except for MBP. Protective equipment decreased phthalate exposure.	See Table 4.
Kolena et al. (2017) (Slovakia)	Hairdressing apprentices (n = 68) Controls: university students and employees (n = 32)	DEP, DBP, DiBP, DEHP	MEP, MBP, MiBP, MEHP, MEHHP, MEOHP, sum DEHP (MEHP + MEHHP + MEOHP) /urine/pre-shift, end of the workweek	HPLC-MS/MS LOD: MEP (4.41), MBP (1.1), MiBP (1.1), MEHP (0.81), MEHHP (0.54), MEOHP (0.64).	Mean (exposed vs controls) (ng/mL) (no CR-adjusted urinary concentration): MEP (201.11 vs not measured), MBP (103.27 vs 83.52), MiBP (61.37 vs 43.67), MEHP (10.23 vs 5.63), MEHHP (53.37 vs 15.74), MEOHP (19.1 vs 10.79), sum DEHP (82.70 vs 32.16).	Significantly higher urinary levels of MiBP in hairdresser apprentices compared to control group.	See Table 4.

(*continued on next page*)

Table 2 (*continued*)

Study	Occupational setting/number of workers and controls	Analytical method/Biomarkers			Results Creatinine-adjusted urinary phthalate concentration (μg/g creatinine)[a]	Main conclusions on exposure	Additional information
		Substances studied	Biomarker of exposure /Matrix/Sampling time	Method LOD and LOQ (ng/mL)			
Petrovicova et al. (2016) (Slovakia)	Community service workers (n = 45) and plastic manufacturing workers (n = 35) Controls: general population (n = 49)	DEP, DBP, DiBP, DEHP	MEHP, MEHHP, MEOHP, sum DEHP (MEHP + MEHHP + MEOHP), MBP, MiBP /urine/during work shift	HPLC-MS/MS LOD: MEHP (0.69), MEHHP (0.74), MEOHP (0.45), MBP (1.89), MiBP (1.89).	Mean ± SD (μg/L) (no CR-adjusted urinary concentration) for community service workers vs plastic manufacturing workers vs controls: MEHP (7.13 ± 9.80 vs 13.42 ± 13.07 vs 3.99 ± 3.58), MEHHP (16.09 ± 16.60 vs 37.53 ± 34.40 vs 17.08 ± 13.57), MEOHP (12.53 ± 16.32 vs 22.20 ± 22.45 vs 8.81 ± 7.82), sum DEHP (35.74 ± 31.07 vs 73.15 ± 67.05 vs 29.89 ± 23.54), MiBP (24.10 ± 52.76 vs 87.17 ± 139.63 vs 30.59 ± 49.01), MBP (49.67 ± 56.40 vs 187.21 ± 240.56 vs 87.79 ± 116.71).	Significantly higher urinary concentration of MEHHP, MEOHP, MEHP, sum DEHP, MiBP, and MBP in plastic industry workers compared to controls and community service workers. No significant differences between community service workers and controls. Highest occupational exposure to DEHP in workers from plastic manufactory.	Non-parametric Kruskal-Wallis test used to compare urinary phthalate concentrations between study groups and consumer practices. Multivariate analysis of covariance (MANCOVA) used to estimate associations between urinary phthalate metabolite concentrations and anthropometric parameters adjusted to gender and occupational exposure. See Table 4
Cavallari et al. (2015) (USA)	Custodians (n = 68) working at 4 survey sites 2009–2010 NHANES population as comparison group (CDC, 2013)	DEP, DMP, DEHP, BBzP	MEP, MMP, MEHP, and MBzP /urine/first void, before shift, end of shift, before bedtime (68 workers provided a total of 269 urine samples)	LC-MS/MS LOQ: MEP (0.5), MMP (0.25), MEHP (1.00), MBzP (0.25).	Highest GM concentration of MEP and MMP were before shift (138) and before bedtime (3.2), respectively. Highest urinary concentrations of MEP (11 377) and MBzP (12 409) were pre-shift. N.s. differences across the 4 time periods for MEHP and MBzP. GM concentrations of MEP positively related to traditional cleaning chemical intensity (none: 87; medium: 95; high: 231); GM concentrations of MEHP positively related to the intensity of environmentally preferable products (none: 4.8; medium: 7.0; high: 11.3).	Elevated urinary phthalate levels among custodians compared to the 2009–2010 NHANES population samples (MEP: 107 vs 73.0; MMP: 2.69 vs 1.09; MEHP: 6.93 vs 1.65; MBzP: 8.79 vs 5.94). Significantly higher urinary MEP concentrations in custodians occupationally exposed to traditional cleaning chemicals. Identifying phthalates as ingredients in cleaning chemicals and consumer products may guide workers and consumers to avoid exposure.	Data on the distributions of urinary metabolite concentrations were $\log_{10}$, and correlations between the log-transformed metabolites were evaluated with Pearson correlation coefficients.
Fong et al. (2015) (Taiwan)	PVC production workers from 3 plants (n = 82) No control group	DEHP	MEHP, MEOHP, MEHHP /urine/pre- and post-shift, last day of the workweek	HPLC-ESI-MS/MS LOD: MEHP (0.06), MEOHP (0.10), MEHHP (0.13).	GM pre-shift vs post-shift: MEHP (15.40 vs 23.86); MEOHP (45.52 vs 66.87); MEHHP (55.27 vs 84.56).	Concentrations were significantly higher post-shift than pre-shift. Urinary DEHP metabolite concentrations were 2 or 3 times higher in exposed workers than in the general population. Task with highest exposure: PVC powder mixing with oily liquid DEHP.	Multivariate linear regression models with 6 covariates. See Table 4.

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Table 2 (*continued*)

Study	Occupational setting/number of workers and controls	Analytical method/Biomarkers			Results Creatinine-adjusted urinary phthalate concentration (μg/g creatinine)[a]	Main conclusions on exposure	Additional information
		Substances studied	Biomarker of exposure /Matrix/Sampling time	Method LOD and LOQ (ng/mL)			
Pilka et al. (2015) (Slovakia)	Employers working with plastic material (n = 85) divided into community service workers (n = 48) and plastic manufacturing workers (n = 37) Controls: university students and workers (n = 70)	DEHP, DBP, DiNP, DEP	MEHP, MBP, MiNP, MEP /urine/during work shift, in summer and winter	HPLC-MS/MS. LOD: MEHP (0.81), MBP (3.23), MiNP (8.12), MEP (5.02).	Median (μg/L) (no CR-adjusted urinary concentration) for general population vs community services workers vs plastic manufacture workers: MEHP (21.46 vs 5.94 vs 35.48); MBP (85.67 vs 90.04 vs 108.62); MiNP (13.82 vs 4.6 vs 13.65); MEP (78.5 vs 70.74 vs 93.79).	Higher urinary concentration of MEHP in occupationally exposed plastic manufacturers, compared to controls. Significantly higher urinary concentrations of all monitored phthalates during summer in the occupationally exposed group (higher urinary concentration of MEP and MBP in community service workers and MEHP and MiNP in plastic manufacturing workers).	Non-parametric Mann-Whitney U (Wilcoxon rank-sum) test was used for all comparisons. Positive associations between increasing indoor and outdoor temperatures and exposure to phthalates in specific types of working environments, an aspect to consider for human biomonitoring.
Kolena et al. (2014) (Slovakia)	Waste management workers (truck drivers and co-drivers, waste recycling; n = 30) No control group	DEHP, DBP, DEP, DiNP	MEHP, MBP, MEP, MiNP /urine/during work shift break	HPLC-MS/MS LOD: MEHP (0.81), MBP (3.23), MEP (5.02), MiNP (8.12).	Mean ± SD (ng/mL) (no CR-adjusted urinary concentration): MEHP (15.37 ± 20.09); MBP (71.42 ± 90.19); MEP (68.32 ± 43.74); MiNP (1.47 ± 4.47).	Higher concentration of MEHP in exposed workers compared to general population.	See Table 4.
Lu et al. (2014) (China)	Workers at 2 flavoring factories (n = 71) Controls: administrators at the same factories (n = 27), laboratory technicians in a research institute (n = 31)	DEHP	MEHP, MEHHP, MEOHP /urine/end-shift, during a single work shift	UPLC-MS/MS No information on LOD or LQQ.	Mean ± SD for exposed group vs administrators vs laboratory technicians: MEHP (9.63 ± 6.68 vs 12.47 ± 14.10 vs 9.26 ± 5.77); MEHHP (14.98 ± 13.79 vs 16.59 ± 24.98 vs 17.14 ± 14.15); MEOHP (10.18 ± 7.56 vs 12.21 ± 20.97 vs 9.71 ± 8.07).	N.s. differences between exposed group and controls. Workers in flavoring factories are not supposed to be a high DEHP exposure category.	DEHP exposure higher in women than in men. Questionable control group due to potential exposure.
Petrovicova et al. (2014) (Slovakia)	Workers in plastic manufacturing (films, composites, injection molding) (n = 37) Controls: university students and workers (n = 144)	DEHP, DBP, DEP, DiNP	MEHP, MnBP, MEP, MiNP /urine/during work shift	HPLC-MS/MS LOD: MEHP (0.81), MBP (3.23), MEP (5.02), MiNP (8.12).	Median (μg/L) (no CR-adjusted urinary concentration) for general population vs exposed group: MEHP (21.62 vs 35.48); MBP (88.99 vs 108.62); MEP (84.63 vs 93.79); MiNP (13.26 vs 13.65).	Significantly higher MEHP and marginally significantly higher MiNP urinary concentrations in occupationally exposed groups compared to controls. N.s. differences for MEP and MBP.	Means with SD, medians, and 5th to 95th percentiles of concentrations computed for each metabolite to describe the urinary phthalate metabolite levels. Non-parametric Mann-Whitney U (Wilcoxon rank-sum) test was used for comparisons.

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Table 2 (*continued*)

Study	Occupational setting/number of workers and controls	Analytical method/Biomarkers			Results Creatinine-adjusted urinary phthalate concentration (μg/g creatinine)[a]	Main conclusions on exposure	Additional information
		Substances studied	Biomarker of exposure /Matrix/Sampling time	Method LOD and LOQ (ng/mL)			
Fong et al. (2014) (Taiwan)	Workers from 3 PVC factories (n = 89, 66 production workers with high exposure and 23 administrative workers, with low exposure)	DEHP	MEHP, MEHHP, MEOHP /urine/pre- and post-shift, last day of the workweek	HPLC-ESI-MS/MS LOD: MEHP (0.06), MEHHP (0.13), MEOHP (0.10).	GM pre-shift for all workers vs low exposure vs high exposure: MEHP (15.8 vs 10.4 vs 18.2); MEHHP (56.3 vs 32.5 vs 68.1); MEOHP (46.2 vs 25.6 vs 56.7). GM post-shift for all workers vs low exposure vs high exposure: MEHP (22.5 vs 16.5 vs 25.1); MEHHP (84.6 vs 57.1 vs 97.1); MEOHP (66.4 vs 42.8 vs 77.4).	Post-shift levels of the 3 urinary metabolites significantly higher than pre-shift levels in all study participants. Post-shift MEOHP and MEHHP levels significantly higher in the high exposure group than in the low exposure group. Recommended local exhaust systems and personal protection equipment for PVC production workers. Task with highest exposure: PVC product manufacturing.	Personal air monitoring: DEHP levels significantly higher in the high vs low exposure group (Airborne DEHP GM [range]: 32.7 [1.26–1581.9] μg/m^3 vs 5.27 [0.10–236.8] μg/m^3), but SIP not significantly different. Significant association between airborne DEHP concentration and urinary DEHP metabolite levels in the high exposure group. Airborne exposure to DEHP for PVC production workers can contribute up to 46.7% of the daily intake dose for highly exposed workers. Non-parametric tests for comparison.
Huang et al. (2014) (Taiwan)	Workers from 2 PVC pellet manufacturing plants (n = 47), divided into high (n = 36) and low (n = 11) exposure groups Controls: graduate students (n = 15)	DEHP	MEHP, MEHHP, MEOHP Urine/post-shift	HPLC-ESI-MS/MS LOD: MEHP (0.04), MEHHP (0.09), MEOHP (0.05).	Mean ± SD for controls vs low exposure vs high exposure: MEHP (9.6 ± 8.0 vs 14.9 ± 7.2 vs 23.5 ± 15.1); MEHHP (21.6 ± 13.8 vs 50.0 ± 27.4 vs 91.4 ± 57.1); MEOHP (18.3 ± 12.3 vs 35.2 ± 19.2 vs 75.1 ± 46.7).	Urinary MEHP concentration significantly higher in the high exposure group compared to control group. Urinary MEHHP and MEOHP concentration significantly higher in the high exposure group compared to the low exposure and control groups. Average level of urinary MEHP, MEHHP, and MEOHP significantly higher in the high-DEHP-exposed group (DEHP ≥ 23.7 μg/m^3 in personal air) compared with the low-DEHP-exposed group (DEHP < 23.7 μg/m^3 in personal air) and controls.	Environmental monitoring of DEHP (data from Huang et al., 2011): workers divided into low- and high-DEHP-exposed groups in accordance with the median levels (23.7 μg/m3) of DEHP in ambient air. Age, smoking, alcohol consumption, and socioeconomic status of exposed and non-exposed groups differed significantly. Group size was appropriate for high exposure group, but small for control and low exposure groups.

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Table 2 (*continued*)

Study	Occupational setting/number of workers and controls	Analytical method/Biomarkers			Results	Main conclusions on exposure	Additional information
		Substances studied	Biomarker of exposure /Matrix/Sampling time	Method LOD and LOQ (ng/mL)	Creatinine-adjusted urinary phthalate concentration (µg/g creatinine)[a]		
Hines et al. (2012) (USA)	Workers from 2 PVC factories: film manufacturers (n = 25), custom compounders (n = 12) (with 15 working in shifts when DiNP was used in production, 7 working directly on tasks that used DiNP, and the remaining 15 used as a control group)	DiNP	MCiOP /urine/mid- and end-shift, during a single work shift	HPLC-MS/MS LOD: MCiOP (0.7).	MCiOP urinary concentrations ranged from 0.42 to 80 in PVC film and from 1.11 to 13.4 in PVC compounding. MCiOP GM end-shift; PVC film manufacturing workers on a task using DiNP (25.2; participants who worked on a shift where DiNP was used (17.7); participants with no task (2.92) or shift (2.08) exposure to DiNP. MCiOP GM end-shift in PVC compounding participants (4.80) was comparable to PVC film participants with no task or shift exposure to DiNP.	Higher occupational exposure to DiNP in PVC film manufacturing tasks compared to general population. Higher MCiOP urinary end-shift concentration in PVC film workers involved in a task using DiNP when compared to unexposed workers. End-shift MCiOP concentrations in PVC film workers were significantly higher than mid-shift concentrations. Performing tasks using DiNP without wearing rubber gloves caused the highest GM of any group, suggesting a possible protective effect from gloves.	Mixed models used to assess the effect of DiNP use (workers assigned to a task using DiNP or a shift where DiNP was used) () on MCiOP concentrations (difference between mid- and end-shift MCiOP concentrations).
Koch et al. (2012b) (Southern Germany)	Car manufacturing workers (n = 5) Controls: employers from the administration department of the same plant with no occupational exposure to phthalate (n = 10), general German population (n = 45)	DEHP, DiNP, DiDP/DPHP	21 phthalate metabolites MEHP, 5OH-MEHP, 5oxo-MEHP, 5cx-MEPP, OH-MiNP, oxo-MiNP, cx-MiNP, OH-MiDP, oxo-MiDP, cxMiDP, MBP, /urine/pre- (start of the workweek) and post-shift	LC-LC/MS-MS LOQ: MBP and MiBP (0.5), all other metabolites (0.25).	Median (pre-shift) for general German population vs plant unexposed comparison group vs plastisol exposed group: MEHP (2.4 vs 3.6 vs 3.9); 5OH-MEHP (15.1 vs 15.9 vs 30.4); 5oxo-MEHP (8.2 vs 10.0 vs 20.0); 5cx-MEPP (12.3 vs 15.6 vs 38.8); OH-MiNP (5.2 vs 4.8 vs 18.4); oxo-MiNP (1.6 vs 2.0 vs 8.0); cx-MiNP (5.2 vs 5.4 vs 15.5); OH-MiDP (1.2 vs 1.0 vs 1.4); oxo-MiDP (0.3 vs 0.4 vs 0.7); cx-MiDP (0.8 vs 0.7 vs 2.5). Median (post-shift) for plant unexposed comparison group vs plastisol exposed group: MEHP (5.8 vs 15.0); 5OH-MEHP (17.6 vs 41.4); 5oxo-MEHP (13.7 vs 27.1); 5cx-MEPP (21.2 vs 36.1); OH-MiNP (3.8 vs 117); oxo-MiNP (1.9 vs 44.4); cx-MiNP (4.5 vs 57.9); OH-MiDP (0.8 vs 17.0); oxo-MiDP (0.6 vs 5.2); cx-MiDP (0.7 vs 5.3).	DiNP and DiDP values in exposed workers were ~5–10 and ~20 times higher than the general population in pre-and post-shift assessments, respectively. No significant differences for DEHP exposure. Elevated post-shift urinary levels of DiNP metabolites in all workers in plastisol finishing (median: OH-MiNP: 117; oxo-MiNP: 44.4; carboxy-MiNP: 57.9) compared to the control group (median OH-MiNP: 3.8; oxo-MiNP: 1.9; cx-MiNP: 4.5). Pre-shift values of exposed workers were elevated (median OH-MiNP: 18.4; oxo-MiNP: 8.0; cx-MiNP: 15.5). High pre-shift values are required to better elucidate the elimination half-times depending on dermal route of exposure.	

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Table 2 (*continued*)

Study	Occupational setting/number of workers and controls	Analytical method/Biomarkers			Results Creatinine-adjusted urinary phthalate concentration (µg/g creatinine)[a]	Main conclusions on exposure	Additional information
		Substances studied	Biomarker of exposure /Matrix/Sampling time	Method LOD and LOQ (ng/mL)			
Gaudin et al. (2011) (France)	Workers from 6 flexible-PVC industries (n = 62) Controls: unexposed workers in these factories (n = 29)	DEHP	MEHP, 5cx-MEPP, 2EHA /urine/4 or 5 consecutive days, pre- and post-shift	HPLC-MS/MS LOQ: MEHP (0.5), 5cx-MEPP (1.0), 2-EHA (2.5).	Mean (range) for exposed workers (pre-shift vs post-shift): MEHP: 14.6 (0.3–111.0) vs 33.6 (0.6–942.0); 5cx-MEPP: 43.2 (1.7–277.0) vs 83.7 (0.7–924.0); 2-EHA: 25.8 (1.0–194.0) vs 79.7 (1.0–1021.0). Mean (range) for controls (pre-shift vs post-shift): MEHP: 7.3 (0.3–46.2) vs 6.8 (0.2–33.8); 5cx-MEPP: 23.6 (0.2–314.0) vs 18.6 (0.3–173.0); 2-EHA: 36.5 (0.4–342.0) vs 35.4 (0.7–502.0).	Significantly higher urinary concentrations for the 3 metabolites in exposed workers compared to controls. Significant increase in post-shift excretion in exposed workers vs pre-shift concentrations. Highest MEHP concentrations in compounding, plastisol application, and manufacture of wall coverings (use of plastisols). Automated DEHP manufacturing process limits the possibilities of DEHP contamination.	Non-parametric Mann-Whitney *U* test was used for all comparisons. Values of 250 and 500 µg/l (100 and 280 µ/g cr) for MEHP and 5cx-MEPP, respectively, were proposed as guidance values for DEHP. The proposed guideline values should prevent high exposures in the soft PVC industry, particularly in factories where DEHP compounds or plastisols are employed.
Park et al. (2010) (Korea)	Workers in dental laboratories (n = 25)	DEHP	MEHP, MEHHP, MEOHP /urine/post-shift and next morning pre-shift	HPLC-MS/MS LOQ: MEHP (2.5), MEHHP (2.3) MEOHP (1.5). LOD: MEHP (0.8), MEHHP (0.9), MEOHP (0.5).	GM pre-shift vs post-shift: MEHP (2.23 vs 3.10); MEHHP (3.54 vs 4.37); MEOHP (2.65 vs 3.40).	Post-shift urinary DEHP metabolite concentrations significantly higher than pre-shift. MEHP, MEHHP, and MEOHP levels significantly correlate with each other in the post- and pre-shift samples.	
Hines et al. (2009) (USA)	Workers from 7 companies from different sectors (n = 130): phthalate manufacturing, PVC film, vehicle filters, PVC compounding, rubber hoses, rubber gaskets, and rubber boots Manicurists from 13 nail-only salons (n = 26) Controls: US general population (NHANES, 2001–2002)	DEP, DBP, DEHP, DMP, BzBP, DiBP, DOP	MMP, MEP, MBP, MCPP, MiBP, MBzP, MBP, MEHP, MEHHP, MEOHP, MECPP, MCPP, MOP /urine/mid- and end-shift, during a single work shift	HPLC-MS/MS LOD: 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), MOP (not measured).	GM of DEHP metabolites in PVC film manufacturing vs PVC compounding vs rubber boot manufacturing: MEHP (31.4 vs 24.0 vs 9.1); MEHHP (283 vs 203 vs 102); MEOHP (159 vs 121 vs 63.2). GM of DBP metabolites in rubber gasket vs phthalate manufacturing vs rubber hose manufacturing: MBP (660 vs 766 vs 270); MCPP (10.7 vs 12.1 vs 5.59). US general population (NHANES, 2001–2002): MEHP 3.96; MEHHP 17.2; MEOHP 11.4; MBP 16.1; MCPP 2.24.	DEHP exposure in PVC film manufacturing, PVC compounding, and rubber boot manufacturing (GM end-shift concentrations of DEHP metabolites respectively 8, 6, and 3 times greater than NHANES, 2001–2002 and with a within-shift GM increase). DBP in rubber gasket, phthalate manufacturing, and rubber hose manufacturing (DBP metabolite concentrations respectively 26, 25, and 10 times greater than NHANES, 2001–2002). DHEP and DBP metabolites increased 2- to 3-fold compared to the general population in vehicle filters; PVC compounding; rubber hose, boot, gasket; nail-only salons.	Inhalation was a likely exposure route in most sectors. Evidence of occupational exposure to: DEP, DMP, and DBP in phthalate manufacturing; DBP in rubber gasket and hose manufacturing; DEHP in PVC film, PVC compounding, and rubber boot manufacturing. Some sectors also had metabolite concentrations above NHANES 2001–2002 even when parent phthalate use had not been reported (i.e., MzBP in rubber hose and rubber boot, MiBP in rubber boot, and MMP in nail-only salons). Factors likely influencing exposures included phthalate vapor pressure, heated processes, and heated materials with large surface areas.

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Table 2 (*continued*)

Study	Occupational setting/number of workers and controls	Analytical method/Biomarkers			Results Creatinine-adjusted urinary phthalate concentration (μg/g creatinine)[a]	Main conclusions on exposure	Additional information
		Substances studied	Biomarker of exposure /Matrix/Sampling time	Method LOD and LOQ (ng/mL)			
Kwapniewski et al. (2008) (USA)	Manicurists (n = 37)	DBP	MBP, MiBP, MCPP /urine/pre- and post-shift, on a single workday	HPLC-MS/MS LOD: all metabolites (1 or less).	Medians (SG-adjusted) pre-shift vs post-shift: MBP (58.5 vs 87.2); MiBP (10.7 vs 10.5); MCPP (4.3 vs 4.5) MBP medians (SG-adjusted) pre-shift vs post-shift without gloves: 42.6 vs 87.2. MBP medians (SG-adjusted) pre-shift vs post-shift with gloves: 91.6 vs 69.9.	Statistically significant cross-shift increase in SG-adjusted MBP concentrations. Glove use associated with a significant cross-shift reduction in urinary MBP concentrations preventing dermal absorption that may occur among manicurists.	
Gaudin et al. (2008) (France)	Workers from a factory using PVC plastisols (n = 25) Controls: unexposed workers (n = 19)	DEHP	MEHP, MECPP, 2-EHA /urine/pre- and post-shift for 5 successive days	HPLC–MS/MS LOD: MEHP (0.5), MCEPP (1.0), 2-EHA (2.5).	Mean (range) for exposed workers (pre-shift vs post-shift): MEHP: 12.7 (0.6–46.6) vs 51.1 (2.1–187.6); MCEPP: 36.0 (4.1–276.7) vs 98.4 (11.1–533.0); 2-EHA: 22.6 (6.8–78.0) vs 46.7 (0.5–89.4). Mean (range) for controls (pre-shift vs post-shift): MEHP: 11.0 (4.7–33.9) vs 11.9 (2.3–33.3); MCEPP: 33.1 (1.2–77.2) vs 24.6 (1.1–165.0); 2-EHA: 54.6 (16–341.5) vs 41.3 (6.9–127.0).	Significantly higher urinary concentrations for each of the 3 metabolites in the exposed workers compared to controls. Significant increase in post-shift excretion in the exposed workers vs unexposed controls and in post-shift vs pre-shift concentrations only in the exposed workers.	Non-parametric Mann-Whitney *U* test was used for all comparisons.
Pan et al. (2006) (China)	Workers at a factory producing unfoamed PVC flooring (n = 74) Controls: workers from a construction company (n = 63)	DBP, DEHP	MBP, MEHP /urine/pre-shift (not on the first day of the workweek or after a night shift)	LC-ESI-MS/MS LOD: MBP (0.5), MEHP (0.6). LOQ: 5.	GM unexposed vs exposed: MBP (129.6 vs 644.3); MEHP (5.7 vs 565.7).	Significantly higher levels of MBP and MEHP in the exposed group compared to unexposed workers.	

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Table 2 (*continued*)

Study	Occupational setting/number of workers and controls	Analytical method/Biomarkers			Results	Main conclusions on exposure	Additional information
		Substances studied	Biomarker of exposure /Matrix/Sampling time	Method LOD and LOQ (ng/mL)	Creatinine-adjusted urinary phthalate concentration (µg/g creatinine)[a]		
Vermeulen et al. (2005) (Netherlands)	Rubber workers employed in 9 different factories (n = 101) No control group	Total phthalates	PA /urine/post-shift on Sunday, Tuesday, Wednesday, and Thursday	LC-MS/MS LOD: 5.	GM PA (µg//l) (no CR-adjusted urinary concentration): Sunday (83); Tuesday (148); Wednesday (152); Thursday (164).	Significantly increased (~70 µg//l) PA levels during the working week compared to Sunday levels. N.s. differences in PA levels between the different days of the workweek. Increases seemed to be restricted to molding and curing departments (identified as requiring additional attention/follow-up biomonitoring).	Non-parametric tests were used for comparison. Correlations between biomarker levels by day of urine collection calculated using the Pearson correlation. Unspecific biomarker. Individual background levels may lead to overestimating the occupational contribution to total phthalate exposure.

2-EHA: 2-ethylhexanoic acid; 5cx-MEPP: mono(2-ethyl-5-carboxypentyl) phthalate; 5OH-MEHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; 5oxo-MEHP: mono(2- ethyl-5-oxohexyl) phthalate; BzBP: benzylbutyl phthalate; DBP: dibutyl phthalate; cx-MiDP: mono(carboxy-iso-decyl) phthalate; cx-MiNP: mono(carboxy-iso-nonyl) phthalate; DEHP: di(2-ethylhexyl) phthalate; DEP: diethyl phthalate; DiBP: di-iso-butyl phthalate; DiDP: di-iso-decyl phthalate; DiNP: di-iso-nonyl phthalate; DMP: dimethyl phthalate; DOP: di-*n*-octyl phthalate; DBP: di-*n*-butyl phthalate; MBP: monobutyl phthalate; MBzP: monobenzyl phthalate; MCiOP: mono(carboxy-isooctyl) phthalate; MCPP: mono(3-carboxy-propyl) phthalate; MECPP: mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEOHP: mono(2- ethyl-5-oxohexyl) phthalate; MEP: monoethyl phthalate; MiBP: mono-iso-butyl phthalate; MiDP: mono-iso-decyl phthalate; MiNP: mono-iso-nonyl phthalate; MMP: monomethyl phthalate; MnBP: mono-*n*-butyl phthalate; MOP: mono-*n*-octyl phthalate; OH-MiDP: mono(hydroxy-iso-decyl) phthalate; OH-MiNP: mono(hydroxy-iso-nonyl) phthalate; oxo-MiDP: mono(oxo-iso-decyl) phthalate; oxo-MiNP: mono(oxo-iso-nonyl) phthalate; PA: phthalic acid.
CR: creatinine; GM: geometric mean; HPLC-ESI-MS/MS: high-performance liquid chromatography electrospray ionisation-tandem mass spectrometry; HPLC-MS/MS: high-performance liquid chromatography-tandem mass spectrometry; LC-ESI-MS/MS: liquid chromatography electrospray ionisation-tandem mass spectrometry; LC-LC/MS-MS: two-dimensional high-performance liquid chromatography-tandem mass spectrometry; LC-MS/MS: liquid chromatography-tandem mass spectrometry; LOD: limit of detection; LOQ: limit of quantitation; NHANES: National Health and Nutrition Examination Survey; N.s.: not significant; PVC: polyvinyl chloride; SD: standard deviation; SIP: semi-quantified summary index for plastic materials contact (an index used to determine potential DEHP exposure in the daily diet); SG: specific gravity; UPLC-MS/MS: ultra-performance liquid chromatography-tandem mass spectrometry.

[a] When results were not adjusted to creatinine values, the unit of measurement is reported in the table.

them were in English, while the remainder were in French, German, and Finnish. Seven focused on occupational exposure, while the others related to the general population.

3. Results

Several topics are addressed in this review of occupational HBM studies on phthalate exposure: i) the availability of HBM data on old and new phthalates and their levels; ii) the analytical methods employed to determine phthalate metabolite concentrations; iii) the countries involved in HBM studies; iv) the strengths and limitations of the reviewed HBM studies according to the countries in which they were performed; v) biomonitoring levels; vi) the occupational settings under investigation; vii) sex-related characteristics; and viii) any associations observed with health effects.

3.1. Studied phthalates in HBM studies on occupational exposure

Table 2 presents the HBM studies on occupational phthalate exposure. Most of the studies present urinary data on "old" phthalates, which are no longer used in Europe or remain in limited use. DEHP was analyzed in 19 out of 22 studies (86%), of which only 7 deal only with DEHP exposure. Other old phthalates studied were DMP (4 studies), DEP (10), DBP (11), DiBP (3), BBzP (4), and DOP (2). Occupational exposure to "newer" phthalates such as DiNP, DiDP, and DPHP was investigated much less frequently. Five studies were identified in which DiNP exposure was evaluated (Hines et al., 2012; Koch et al., 2012; Kolena et al., 2014; Petrovicova et al., 2014; Pilka et al., 2015), and in one of them, workers were also co-exposed to DiDP or DPHP (Koch et al. 2012b). No other occupational DiDP/DPHP studies were published in international journals. Further, no occupational biomonitoring studies exist for the other phthalates cited in Table 1 (DPeP, DCHP, DiPP, DHP, DMEP), but as stated, they have either no use or a very limited use in Europe. In the oldest phthalate study considered in this review, Vermeulen et al. (2005) analyzed phthalic acid as a common metabolite for several phthalates. The authors did not specify the phthalates to which the rubber manufacturing workers who participated in the study were exposed. However, they stated that the most common phthalates used at the time by the rubber industry were DBP and diisooctyl phthalate (DiOP), while DEHP, DiBP, and diallyl phthalate (DAP) were also employed.

3.2. Analytical methods used

Typically, total phthalate metabolite concentrations (free + conjugated) are measured. Thus, in sample pretreatment, glucuronyl-conjugated phthalate metabolites are transferred to their free forms after enzymatic hydrolysis. Offline or online solid-phase extraction are the most common extraction methods but liquid-liquid extraction is also used. Liquid chromatography (LC) is the dominant separation method in phthalate analytics, and occupational studies are no exception (Table 2). However, gas chromatography (GC) can be used to separate phthalate metabolites, although a derivatization step is needed, which makes it slightly more time-consuming than LC analytics. The GC method nevertheless offers some advantages over LC, especially in the separation of secondary metabolites of high molecular weight phthalates (Gries et al., 2012; Kumar and Sivaperumal, 2016). For example, Gries et al. (2012) presented a GC-high-resolution mass spectrometry (MS) method, which allows the specific determination of DPHP metabolites in the presence of DiDP metabolites. Due to the lower separation power, this is not possible with LC-MS/MS methods.

Typically, the LOD of the reported analytical methods ranges from sub-μg/L to <5 μg/L for the different metabolites in human urine samples (Kumar and Sivaperumal, 2016). This is also the case with most of the occupational biomonitoring studies (Table 2).

3.3. Countries

Regarding the countries in which the investigations were performed, from the 22 HBM studies considered in this review (Table 2), 8 were performed in Asia (3 in China: Lu et al., 2014; Pan et al., 2006, Wang et al., 2018; 4 in Taiwan: Fong et al., 2014, 2015; Huang et al., 2014, 2018; and 1 in Korea: Park et al., 2010; among the most recent), 4 in North America (Cavallari et al., 2015; Hines et al., 2009, 2012; Kwapniewski et al., 2008) and 10 (45.5%) in Europe. The distribution of occupational HBM studies in Europe was as follows: 6 studies in Slovakia (Petrovicova et al., 2014, 2016; Pilka et al., 2015; Kolena et al., 2014, 2017, 2019), 2 in France (Gaudin et al., 2008, 2011), 1 in Germany (Koch et al. 2012b) and 1 in the Netherlands (Vermeulen et al., 2005). The German study, however, was limited in size, while the Dutch study used unspecific biomarkers for exposure assessment.

3.4. Strengths and limitations of the reviewed studies

3.4.1. Asian studies

The most recent Asian HBM studies used for this review were performed in China and Taiwan (Huang et al., 2018; Wang et al., 2018). Most of the 8 Asian papers (Lu et al., 2014; Pan et al., 2006; Wang et al., 2018 in China; Fong et al., 2014, 2015; Huang et al., 2014, 2018 in Taiwan) included more than 40 workers. A control group was not systematically included (Fong et al., 2015; Huang et al., 2018; Park et al., 2010 in Korea). When included, however, controls were farmers (Wang et al., 2018) or students (Huang et al., 2014), but in most cases, they were workers from the same plant (such as administrative workers: Huang et al., 2014; Lu et al., 2014). The possible occupational phthalate exposure of control workers could not be excluded in all cases (e.g., laboratory workers, as phthalates are widely used in labs, Lu et al., 2014; construction workers, Pan et al., 2006). In one study, no difference in phthalate metabolite levels was observed between exposed workers and controls (Lu et al., 2014), whereas in other studies, the median concentration of phthalates among workers was usually up to 5 times higher than in controls. Analytical measurements were performed by LC/MS-MS, and biomarkers were adjusted for creatinine. LODs were given except in Lu et al. (2014). All measured phthalates were old phthalates (DEHP, DEP, DBP, BBzP, DMP), and the measured biomarkers were generally specific to the studied phthalates (e.g., MEHHP, MEOHP). An exception was the study of Pan et al. (2006), which only measured MBP and MEHP; MBP is not only a major metabolite of DBP but also a minor metabolite of BBzP (6% of the dose; Anderson et al., 2001). Further, MEHP is not a recommended biomarker, since DEHP can be hydrolyzed outside the body (abiotically) to MEHP, and external contamination can thus confound the results (as discussed by Hines et al., 2012 and Koch et al. 2012b). Nevertheless, there is a lack of data on the importance of this process. Another reason why MEHP is perhaps an inappropriate biomarker is that it occurs at lower levels and is rapidly transformed to secondary metabolites. In all these studies, spot urine samples were collected both pre- and post-shift, except in Huang et al. (2014) and Lu et al. (2014) where samples were collected only post-shift.

3.4.2. European studies

From the 10 European HBM studies on phthalates, the most recent were from Slovakia (2014–2019). The sample sizes in the Slovakian studies ranged from 30 to 82, which is a common sample size for an occupational HBM study (Petrovicova et al., 2014, 2016; Pilka et al., 2015; Kolena et al., 2014, 2017, 2019). In some cases, the timing of the sampling was not appropriate for the studied biomarkers. For example, in the studies of Kolena et al. (2017, 2019), the analyses were performed in the first spot urine samples, collected the morning after a workday (at the end of the workweek, i.e., Friday), which may not correctly represent occupational exposure, because phthalates have short half-lives, meaning that the morning phthalate levels may be less elevated than those from the evening workday samples. No pre-shift

Table 3
Occupational biomonitoring studies with urinary MEHHP (or 5OH-MEHP: main metabolite of DEHP; in μg/g creatinine (μg/L)) according to the work tasks.

Reference	Country	Work task	n	GM	GSD	Min	Median	Max	Statistical comparison
Hines et al. (2009)	USA	Phthalate manufacturing	9	25.4 (48.4)	1.89 (2.63)	10.1 (9.9)	22.1 (54.9)	73.0 (196)	–[a]
Hines et al. (2009)	USA	PVC film manufacturing	25	151 (283)	2.31 (3.22)	12.0 (11.8)	138 (282)	703 (3090)	$p < 0.01$[b] (–[a])
Hines et al. (2009)	USA	Vehicle filter manufacturing	18	34.6 (44.0)	2.29 (2.53)	32.7 (11.4)	32.4 (45.4)	267 (294)	–[a]
Hines et al. (2009)	USA	PVC compounding	12	102 (203)	3.05 (3.36)	10.6 (16.2)	164 (289)	366 (1040)	$p < 0.05$[b] ($p < 0.01$[b])
Hines et al. (2009)	USA	Manufacturing rubber hoses	25	25.2 (40.5)	2.45 (2.63)	7.77 (6.3)	21.2 (34.3)	455 (891)	–[a]
Hines et al. (2009)	USA	Manufacturing rubber boots	21	59.5 (102)	2.47 (3.46)	8.10 (9.1)	69.9 (106)	553 (1640)	$p < 0.05$[b] ($p < 0.01$[b])
Park et al. (2010)	Korea	Dental technicians	25	4.37 (3.81[c])	0.66 (0.69)	20.9 (15.1)	86.17 (43.35)	215.19 (276)	$p < 0.0001$[d] (–)
Koch et al. (2012b)	Germany	PVC plastisol workers	5	–	–	5.5 (13.6)	41.4 (35.2)	120 (119)	–
Lu et al. (2014)	China	Workers in flavoring factories	71	11.59	–	3.63	11.35	102.58	–[e]
Fong et al. (2014)	Taiwan	Administrative staff, PVC production	23	57.1	–	23.8	–	481.1	$p < 0.05$[f]
Fong et al. (2014)	Taiwan	Raw material processing, PVC production	66	97.1	–	10.8[g]	–	677.5	$p < 0.01$[f]
Huang et al. (2014)	Taiwan	PVC production (direct contact with PVC)	36	75.9 (90.9)	1.9 (2.6)	–	78.8 (107.2)	–	$p < 0.05$[h] ($p < 0.05$[h])
Huang et al. (2014)	Taiwan	PVC production (administrative, sales, guards)	11	44.3 (34.6)	1.6 (2.8)	–	44.7 (35.9)	–	–[e]
Fong et al. (2015)	Taiwan	PVC production workers	82	84.6	2.3	–	78.8		$p < 0.01$[f]
Petrovicova et al. (2016)	Slovakia	Community service workers	45	–	–	(0.52)	(12.93)	(78.25)	(-[i])
Petrovicova et al. (2016)	Slovakia	Plastic manufacturing workers	35	–	–	(3.18)	(27.48)	(143.21)	($p = 0.005$[i])
Kolena et al. (2017)	Slovakia	Hairdressers	68	–	–	(2.88)	(16.8)	(654.14)	(–[k])
Wang et al. (2018)	China	Waste plastic recycling workers	165	36.84	–	0.28	38.84	2403.5	$p < 0.05$[h]
Kolena et al. (2019)	Slovakia	Hairdressers	74	–	–	(5.4)	(27[l])	(173.47)	(–)

GM, geometric mean; GSD, geometric standard deviation.
[a] End-shift mean is not significantly different from mid-shift mean.
[b] End-shift mean is significantly different from mid-shift mean.
[c] Note: both GMs are smaller than the respective minimum concentrations, which cannot be correct.
[d] Post-shift mean is significantly different from next-morning pre-shift mean.
[e] Post-shift median is not significantly different from control group median.
[f] Post-shift mean is significantly different from pre-shift mean.
[g] Note: in the original paper, the numerical value is marked as "10.8.3".
[h] Post-shift median is significantly different from control group median.
[i] Median of samples collected during the shift is not significantly different from control group median.
[j] Median of samples collected during the shift is significantly different from control group median.
[k] Median of first morning void urine samples (at the end of the workweek) is not significantly different from control group median.
[l] Median of first morning void urine samples (at the end of the workweek).

Table 4
Occupational HBM studies on the effects of phthalates on health or effect markers.

Study	Occupational setting/numbers of workers	Exposure	Outcome	Parameters investigated/Matrix/ Sampling time	Results	Main conclusions
Kolena et al. (2019) (Slovakia)	Hairdressing apprentices (n = 74)	DEP, DBP, DEHP	Relationship between urinary phthalate metabolites and spirometric values	FEV1, FVC, FEV1/FVC, PEF, VC	✓ In females (n = 66), a decrease in FVC% of predicted value was detected for MEOHP and sum DEHP; a decrease in VC% of predicted value was detected for MEHHP, MEOHP, and sum DEHP. ✓ In males (n = 8), negative associations were detected between MBP and waist circumference (WC), hip circumference (HC), and WHtR and between MEP and FVC% of predicted value.	The authors hypothesize that occupational exposure to phthalates causes changes in body constitution, which can secondarily affect pulmonary function.
Wang et al. (2018) (China)	Waste plastic recycling site workers (n = 165) Controls: farmers (50 km from the site) (n = 152)	DEP, DEHP, DBP, BBP, DMP	Relationship between urinary phthalate metabolites and thyroid function parameters	TSH, total T3, total T4 /peripheral venous blood/not given	✓ Workers have higher levels of T3 (1.04 vs 0.92 ng/mL) and T3/T4 ratio (1.44 vs 1.09) compared to controls. ✓ Phthalate metabolites positively associated with total T3 or T3/T4 ratio among all participants. ✓ Non-monotonic dose-response associations between urinary MMP and serum total T3 or T3/T4 ratio, and between urinary MEP and T3/T4 ratio in exposed workers.	Further studies are needed to investigate the relationship between phthalate exposure and thyroid function disruption.
Kolena et al. (2017) (Slovakia)	Hairdressing apprentices (n = 68) Controls: university students and employees (n = 32)	DEP, DBP, DiBP, DEHP	Relationship between urinary phthalate metabolites and spirometric values	FEV1, FVC, FEV1/FVC, PEF, VC	✓ In exposed subjects, negative associations were found between MEHP, MEOHP, MEHHP, sum of DEHP, and vital capacity (VC) and also between MEHP and FVC as percentages of predicted value. ✓ In controls, only negative associations between MEHHP, sum DEHP, and FEV1/FVC were observed in females.	Phthalate exposure can result in negative outcomes in the breathing mechanism and influence body composition.
Petrovicova et al. (2016) (Slovakia)	Community service workers (n = 45) and plastic manufacturing workers (n = 35) Controls: general population (n = 49)	DEP, DBP, DiBP, DEHP, DiNP	Relationship between urinary phthalate metabolites and anthropometric parameters	BMI, FMI, FFMI, HC, WC, WHR, WHtR	✓ Significant inverse associations between MEHP and BMI, WC, WHR, WHtR, and HC in females, whereas a positive association was detected for FFMI. ✓ No association between phthalate metabolites and anthropometric parameters in males.	The antiandrogenic effect of MEHP along with age-dependent lower estrogen levels in women may affect the estrogen/androgen ratio, which may be responsible for the inverse association between WC and MEHP.
Fong et al. (2015) (China)	PVC production workers from 3 plants (n = 82) No control group	DEHP	Relationship between urinary DEHP metabolites and reproductive hormones	SHBG, inhibin B, T, E_2, FSH, LH /peripheral venous blood/last day of the workweek	✓ Serum E_2 levels and E_2:T ratios significantly associated with increased concentrations of urinary DEHP metabolites in multiple regression models adjusted for potential confounders and in quartile analysis. ✓ No significant relationships between urinary DEHP metabolites and other measured hormones.	Long-term exposure to DEHP in the workplace may cause disruptions to the circulation of reproductive hormones.
Kolena et al. (2014) (Slovakia)	Waste management workers (truck drivers and co-drivers, waste recycling; n = 30) No control group	DEHP, DBP, DEP, DiNP	Relationship between urinary phthalate metabolites and spirometric values	FEV1, FVC, FEV1/FVC, PEF	✓ Urinary concentration of MEHP was positively associated with FEV1/FVC. ✓ Urinary MEHP and MINP were positively associated with pulmonary function	Occupational exposure to phthalates estimated from urinary metabolites (MEHP, MiNP) can modify pulmonary function.

(*continued on next page*)

Table 4 (*continued*)

Study	Occupational setting/numbers of workers	Exposure	Outcome	Parameters investigated/Matrix/ Sampling time	Results	Main conclusions
					expressed as PEF% of predicted value and FEV1/FVC.	
Huang et al. (2014) (Taiwan)	Workers from 2 PVC pellet manufacturing plants (n = 47); divided into high (n = 36) and low (n = 11) exposure groups Controls: graduate students (n = 15)	DEHP	Relationship of DEHP exposure to semen quality, sperm ROS generation, and sperm apoptosis	Semen volume, semen quality (concentration, motility, percentage with normal morphology), sperm apoptotis, sperm ROS (H_2O_2 and O_2^-) generation /semen/after 72 h of sexual abstinence	✓ No significant differences for semen volume, concentration, percent of normal morphology, and apoptosis among the 3 groups. ✓ Sperm concentration was significantly lower in PVC workers (in both groups) compared to controls. ✓ Sperm motility was significantly reduced in the high exposure group compared to controls. ✓ Significant increases were found in the percentage and intensity of sperm H_2O_2 generation in PVC workers compared to controls. ✓ Significantly higher sperm O_2 percentage and intensity in highly exposed workers compared to controls.	Urinary DEHP metabolites may be accurate and sensitive biomarkers for reflecting the relationships between DEHP exposure and semen quality.
Park et al. (2010) (Korea)	Workers in dental laboratories (n = 25)	DEHP	Relationship between urinary DEHP metabolites and steroid hormones	T, E_2, FSH, LH /peripheral venous blood/between 8 and 10 a.m., after a 12-h overnight fast	✓ No correlation between concentrations of urinary DEPH metabolites and sex hormone levels.	Further studies on the reproductive effects of DEHP exposure are needed to confirm or refute its anti-androgenic effect.
Pan et al. (2006) (China)	Workers at a factory producing unfoamed PVC flooring (n = 74) Controls: workers from a construction company (n = 63)	DBP, DEHP	Relationship between occupational exposure to high levels of phthalate esters on gonadotropin and gonadal hormones	LH, FSH, E_2, fT /peripheral venous blood/between 8 and 10 a.m., not on the first day of the workweek or the day after a night shift	✓ fT was significantly lower (8.4 vs 9.7 μg/g CR) in exposed workers than in unexposed workers. ✓ fT negatively correlated to urinary MBP and MEHP in the exposed worker group. ✓ No significant difference between exposed and unexposed workers for FSH, LH, or E_2.	Modest and significant reductions occurred in serum fT in workers with higher levels of DBP and DEHP metabolites compared with unexposed workers. In future studies, an analysis of the effects of phthalate exposure on gonadotropin and steroid hormone levels should form part of an overall risk assessment for phthalate ester exposure.

BMI: body mass index; cr: creatinine; E_2: estradiol; FEV1: forced expiratory volume in 1s; FMI: fat mass index; FFMI: free fat mass index; FSH: follicle-stimulating hormone; fT: free testosterone; FVC: forced vital capacity; HC: hip circumference; LH: luteinizing hormone; PEF: peak expiratory flow; ROS: reactive oxygen species; SHBG: sex hormone-binding globulin; T: testosterone; TSH: thyroid-stimulating hormone; T3: triiodothyronine; T4: thyroxine; VC: vital capacity; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height rate; for the abbreviations for the phthalates, see Table 1 or 2.

samples were collected. In the studies of Petrovicova et al. (2014, 2016), Pilka et al. (2015), and Kolena et al. (2014), the biological sampling was a single spot urinary sample collected during a work shift break (between the start and the end of the workday) for exposed workers; in this case, however, metabolite concentration peaks associated with occupational exposure could occur later. Biomonitoring results in exposed subjects were compared to a control group recruited from students and general workers, except in the studies of Kolena et al. (2014, 2019), which did not include a control group. Though carried out in 2 different regions of Slovakia, the studies of Kolena et al. performed in 2017 and 2019 were very similar. In all studies, the analytical techniques using high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS) had a high sensitivity, and LODs were reported for all metabolites. Some of the measured biomarkers corresponded to currently used phthalates (DiNP), but most were for old phthalates (DEHP, DBP, DEP). No adjustments to creatinine or specific gravity were made. Most of the measured biomarkers can be considered specific for the studied phthalates, except MBP (also a minor metabolite of BBzP; studied in all the Slovakian studies). As discussed above, MEHP and MiNP assessed in these studies were perhaps not the best choice for biomarkers, while the oxidized metabolites of DEHP and DiNP were not studied. The sum of the different biomarkers was also presented. The aim to detect associations between urinary phthalate metabolite concentrations and i) occupation, ii) consumer practices, and iii) body composition was somewhat ambitious in view of the sample size of participants (lack of statistical power to study all the parameters; Petrovicova et al., 2016, 80 workers and 49 controls).

Concerning the 2 French studies (Gaudin et al., 2008, 2011), they only assessed DEHP exposure. The biomarkers used included 3 urinary metabolites of DEHP, MEHP, and MECPP, and 2-ethylhexanoic acid (2-EHA), a degradation product of DEHP. In both studies, the analytical performance seemed appropriate: HPLC-MS/MS, LODs reported for all metabolites, creatinine-adjusted biomarkers, an external quality control, and biological sampling based on pre- and post-shift urinary spot samples collected over 5 days. The first study of Gaudin et al. (2008) aimed to test the biomarker measurement (very small sample size of only 5 workers), while the second study (Gaudin et al., 2011) applied this method to 6 PVC factories, with simple group comparisons (62 workers and 29 controls).

The German study was rather an analytical approach to measure exposure to DEHP, DiNP, and DiDP/DPHP and their metabolites (Koch et al. 2012b), since it was performed on only 5 workers and 10 controls from the same plant. Single pre-shift (at the start of the workweek) and post-shift urine samples were collected. The analytical method was performed using HPLC-MS/MS, reported LODs, and creatinine-adjusted biomarkers.

The oldest European study reported in this review was conducted in the Netherlands (Vermeulen et al., 2005). It assessed total phthalates through a non-specific biomarker (urinary phthalic acid) in around 100 workers without a control group. It used LC-MS, and spot urine samples were collected on Sunday, Tuesday, Wednesday, and Thursday at approximately the same time of the day.

3.4.3. North American studies

In the 4 North American HBM papers (Cavallari et al., 2015; Hines et al., 2009, 2012; Kwapniewski et al., 2008), most of the studied biomarkers corresponded to old phthalates (DEP, DBP, DEHP, DiBP, BBzP), except for the study of Hines et al. (2012) (DiNP). In the earlier study of Hines et al. (2009), the sample size exceeded 100 individuals, which provides a good overview of the exposure in different sectors of the studied manufacturing companies. No control group was included in these studies, although the results were compared to the data from the general US population. Hines et al. (2009, 2012) collected mid- and end-shift urine samples in a single work shift on any day of the working week. Kwapniewski et al. (2008) and Cavallari et al. (2015) collected pre- and post-shift samples, and in the latter study, 4 samples per worker were collected at different moments during the day (first void, before shift, end of shift, before bedtime). The analyses were performed using HPLC-MS/MS; the studies reported LODs (most biomarker concentrations were above the LODs), and biomarker concentrations were adjusted for creatinine. Most of the measured biomarkers were specific, except MBP in Hines et al. (2009) and Kwapniewski et al. (2008), and MEHP in Cavallari et al. (2015). In addition, DiNP exposure assessment by analyzing cx-MiNP can lead to some uncertainty, because cx-MiNP is not a single compound but rather a mixture of several structural isomers (see Hines et al., 2012).

3.5. Biomonitoring levels

Although various biomarkers of phthalates were studied in the reviewed papers, to compare results across studies, Table 3 presents the data on MEHHP (or 5OH-MEHP), which is the main secondary metabolite of DEHP. A variation in concentration levels up to about 13-fold could be observed when comparing the lowest and highest geometric means (GMs) in the different studies (GM of MEEHP: from 11.6 μg/g cr in workers from flavoring factories in China to 151 μg/g cr in a PVC film manufacture in the USA); most GMs of MEHHP were under 50 μg/g cr. We noted that for some workers, the exposure could reach very high values (max around 700 μg/g cr for MEHHP).

3.6. Occupational settings

Most HBM studies were performed in relation to the manufacturing of PVC plastic products (12 papers); other sectors included waste management (3), beauty (5, manicurists, hairdressers, and cosmetics sales), cleaning (1), dental laboratory (1), and flavoring factory (1) (Table 2). From the studies on MEHHP in Table 3, 18 work tasks can be differentiated, most of which concern PVC plastics. There are limited data on the use of newer phthalates in the manufacturing of different plastic products and on exposure in the construction sector (e.g., installation/removal of PVC floorings). In addition, there are no data from the use of phthalates in the cosmetics industry.

3.7. Sex-related characteristics

It was not possible to directly compare the exposure of male and female workers, since they were involved in different job tasks in the available occupational studies. Since the majority of studies focused on the plastics sector (industrial sector), it is not surprising that most data relate to male workers. Nevertheless, 4 studies (Hines et al., 2009; Kolena et al., 2017, 2019; Kwapniewski et al., 2008) focused on activities usually performed by women (hairdressers and manicurists). In hairdressing apprentices (Kolena et al., 2017), the median phthalate metabolite levels were significantly higher than in controls for MiBP: median MiBP: 40.33 vs 24.20 μg/L, $p \leq 0.05$; median for sum of DEHP metabolites (MEHP, MEHHP, and MEOHP): 31.37 vs 26.94 μg/L; median MBP: 81.17 vs 73.85 μg/L in controls. Yet these concentrations were significantly lower than those observed in the 2019 study of Kolena et al., which was also performed in hairdressing apprentices but in another Slovakian region (median MEHHP in Western (Kolena et al., 2017) vs Central Slovakia (Kolena et al., 2019): 16.8 vs 27 μg/L, $p \leq 0.005$; median MEOHP: 10.3 vs 14 μg/L, $p \leq 0.005$; median sum of DEHP: 31.4 vs 45 μg/L, $p \leq 0.05$). However, since the samples were collected from the first morning voids on the day after the workday, no far-reaching conclusions can be drawn from these studies regarding occupational exposure (due to the short half-life of phthalates). In the study of Kwapniewski et al. (2008), manicurists showed significant cross-shift (post-pre) increases of 17.4 μg/L for MBP (median of 90 μg/L MBP post-shift) and 0.3 μg/L for mono-(3-carboxypropyl) phthalate (MCPP), a minor metabolite of DBP (also a metabolite of other phthalates; Calafat et al., 2006). In another American study, the exposure in manicurists was relatively low but similar to those observed in workers from PVC film or vehicle filter manufacturing companies (median MBP around 30 μg/L) and lower than those seen in workers in phthalate manufacturing in the rubber industry (MBP at mid-exposure 230 μg/L and end-exposure around 1000 μg/L; Hines et al., 2009).

3.8. Health effects in occupationally exposed subjects

Available HBM studies give insight into the major health effects of phthalates but also open avenues for further investigation. Table 4 presents the HBM studies on occupational phthalate exposure in relation to the effect biomarkers and health indicators.

3.8.1. Hormones

Few biomonitoring studies evaluate the association between phthalate levels and hormonal disturbances in workers. Workers at a factory producing unfoamed PVC flooring had significantly higher concentrations of MBP and MEHP as well as significantly lower levels of free testosterone than unexposed workers (Pan et al., 2006). In this study, the difference in phthalate levels between control and exposed workers was very clear: on average, MEHP levels were approximately 100 times higher in exposed workers than in controls (MBP: 644.3 vs 129.6 μg/g cr; MEHP: 565.7 vs 5.7 μg/g cr). In PVC production workers, a statistically significant positive association was observed between urinary concentrations of DEHP metabolites and estradiol, and the ratio of estradiol to testosterone (Fong et al., 2015). No unexposed control group was included in this study. Park et al. (2010) studied the association between sex hormone levels and phthalate exposure in 25 workers from dental labs, but no association was observed. On average, post-shift phthalate concentrations in urine were less than twice their pre-shift levels, although the differences were statistically significant (post-vs pre-shift GMs: 3.10 vs 2.23 μg/g cr for MEHP; 4.37 vs 3.54 μg/g cr for MEHHP and 3.40 vs 2.65 μg/g cr for MEOHP) (Park et al., 2010). In China, workers engaged in waste plastic recycling had significantly higher urinary concentrations of phthalate metabolites (MBzP, MOP, MEHHP, MEP) and total triiodothyronine (T3) or T3/T4 (thyroxine) ratio than controls. However, positive correlations between phthalate metabolites and total T3 or T3/T4 ratio were observed among all participants, not only exposed workers, except for urinary MBzP; in the exposed group, only urinary MBzP was positively correlated with serum total T3 (Wang et al., 2018).

3.8.2. Sperm quality

In a group of occupationally exposed PVC workers with elevated DEHP metabolite levels (MEHP, MEHHP, MEOHP), Huang et al. (2014) reported lower sperm concentration, reduced sperm motility, and increased sperm reactive oxygen species (ROS) generation compared to controls. However, the age and smoking status of exposed and control groups significantly differed, as well as their alcohol consumption, particularly in the high exposure group, which may have affected the results. In addition, the number of persons in both control and low exposure groups was very low. Therefore, it is not possible to draw reliable conclusions based on this study.

3.8.3. Other health effects

Petrovicova et al. (2016) found an inverse correlation between urinary MEHP levels and anthropometric parameters (waist-to-height ratio, body mass index, waist-to-hip ratio, hip circumference, and waist circumference) in female but not in male workers. The study included a control group as well as workers from the plastic waste management and community service sectors, with the highest exposures observed in plastic sectors.

In waste management workers, there was an association between occupational urinary phthalate metabolites (MEHP, MiNP) and alterations in pulmonary function parameters (Kolena et al., 2014), but it may be speculated that other agents present in the working environment, which were not part of the study's analysis, could also contribute to such a result. Among hairdressing apprentices, relationships between urinary phthalate metabolites and spirometry values were observed; negative associations were found between urinary MEHP, MEOHP, MEHHP, sum of DEHP, and vital capacity, and also between MEHP or MEOHP and forced vital capacity (Kolena et al., 2017, 2019). Also, in this case, it should be noted that hairdressers are exposed to many other substances that affect their respiratory health.

4. Discussion

Some critical issues emerging from the analysis of the HBM studies on occupational phthalate exposure need to be considered for a suitable interpretation of the results as well as for future investigations on the topic. Overall, most of the reviewed occupational studies focused on the biological monitoring of exposures to older phthalates whose use is limited in Europe, although they are still expected in waste management and recycling activities. The majority of investigations were performed in Europe and Asia and were predominantly focused on male employees involved in PVC plastic production. Although exposed workers could demonstrate greater levels of biomarkers of exposure compared to control groups, when included, non-definite and homogeneous conclusions could be obtained from all the revised studies in this regard. Interestingly, some studies also addressed some possible biomarkers of effect related to occupational exposure to phthalates. These aspects will be discussed in greater detail in the following paragraphs.

Most of the occupational HBM studies were on “old” phthalates, with the majority of the reviewed data coming from the plastics sector. However, one of the obvious data gaps relates to the shortage of occupational exposure studies on the phthalates currently used in the industry (e.g., DiNP, DiDP, DPHP). Few studies assess DiNP exposure, and only 2 of them analyze the secondary metabolites of DiNP (Hines et al., 2012; Koch et al. 2012b). The other investigations only dealt with the primary metabolite MiNP, which is known to be an inappropriate marker of DINP exposure (Hines et al., 2012). Regarding the other phthalates currently in use, only one study evaluated occupational DiDP/DPHP exposure using a method that could not differentiate the two phthalates (Koch et al. 2012b). It should be noted that in this study, the workers in a car manufacturing plant in Germany were exposed to DiNP-based plastisol, which may also contain other high molecular weight phthalates like DiDP and DPHP. To our knowledge, no single occupational study on workers directly exposed to DiDP or DPHP has been published in international journals. However, at least one national report on small-scale occupational DPHP exposure was identified (Porras et al., 2016).

Nevertheless, it is still useful to monitor old phthalates in some sectors. The use of older phthalates (restricted under REACH) may still be authorized in special applications falling under different regulatory frameworks. Even if the EU published regulations in 2018 to expand the number of restricted phthalates from 3 (DEHP, DBP, and BBP) to 4 (DEHP, DBP, BBP, and DIBP), the new legislation exempts certain categories of articles from this restriction. Thus, specific uses of these phthalates such as exclusively industrial, agricultural, or open air applications in which there is no direct contact, or their usage in specific articles for motor vehicle/aircraft repair or maintenance may be still permitted despite their restriction at the EU level. The same applies to food contact materials and medical packaging as well as uses for medical or measuring devices covered by other legislation. However, because most DEHP and other older phthalates have been replaced by newer ones, occupational exposure to them is nowadays expected to occur through waste management and recycling. In this respect, there is also a data gap, because only a single study from China includes urinary MEHHP and MEOHP concentrations of waste plastic recycling workers (Wang et al., 2018) (Table 3). In another investigation analyzing MEHP, waste management workers in Slovakia were studied (Kolena et al., 2014). Urinary MEHP has a significant contamination risk, and thus, HBM data based on MEHP should be taken into account with caution. In this study, waste management workers were exposed to a range of phthalates, and when comparing workers with the general population, a higher concentration of MEHP was observed in workers’ urine (median 5.94 μg/L; 95th percentile 60.71 μg/L; Kolena et al., 2014). However, as plastic waste is also used as construction material, there is still an open question as to whether old phthalates may once again be present in working environments. For the use of phthalates included in Annex XIV of REACH for recycled plastics, authorization is needed. Currently, there is one (transient) authorization granted for the use of DEHP in recycled plastics for specific purposes (ECHA, 2019). Thus,

it would seem that in the waste management setting, it is still relevant to collect more data due to the increasing reuse of plastic materials boosted by the circular economy.

There is a large variability in phthalate concentrations between studies and across sectors, up to 13-fold when comparing extreme GMs of MEHHP, a metabolite of DEHP and one of the most widespread phthalate plasticizers (Table 3). This can be mostly explained by differences in the processes, operating conditions, and risk management methods resulting in variable occupational exposures, although some variations may also be caused by worker variability, short biomarker half-lives, and differences in sampling strategies and analytical techniques. In addition, the comparison of these results (GM of MEHHP generally 25–50 μg/g cr, but observed up to 151 μg/g cr) with those observed in the general population shows that workers are more highly exposed overall (GM of MEHHP in adults: 12.2 μg/g cr in France in 2014–2016, SpFrance, 2019; 13.1 μg/g cr in 2010, 6.1 μg/g cr in 2014, and 5.4 in 2016 in the USA, CDC, 2019; about 12 μg/g cr in Canada in 2009–2011, Health Canada, 2013). Given the various time trends in phthalate usage in the different countries and thus the varying background exposure of the general population, one must be cautious when occupational exposure data are compared to those of the general population. In occupational exposure studies, it is advisable to have a separate control group of non-occupationally exposed workers from the same area (or at least from the same country), and the sample collection should be done in the same manner as that of workers. If this is not possible, general population data could be used by matching the sample collection location and date as closely as possible to those of occupationally exposed workers.

Another issue to be considered is the origin of the phthalate studies. Taking DEHP as an example, 47% were from Europe, with the others originating from China, Korea, and the USA. If we consider only MEHHP studies, 5 were from Europe (1 from Germany and 4 from Slovakia), but they dealt with 4 different work tasks (Table 3). In addition, these studies included limitations in terms of sample size (German study) or sampling time (Slovakian studies). Taking this into account, together with the almost complete lack of data for newer phthalates, it is evident that the insufficient data available in European countries prevents us from drawing any far-reaching conclusions about the level and regional clustering of phthalate exposure in Europe.

The occupational exposure studies frequently report data for more than one phthalate, suggesting that in many cases, there may be occupational exposure to phthalate mixtures. However, this depends on the industrial sector and their use of many different phthalates (e.g., in plastics manufacturing), or only 1 or 2. This occupational exposure adds to the body burden from the living environment, consumer products, and food (Serrano et al., 2014). This is why combining environmental and occupational exposures is useful when estimating associated health risks, especially in the case of endocrine disruptors, which may express biological effects at low doses.

Additionally, only a few studies included a non-occupationally exposed control group in the experimental design, but in some cases, possible workplace exposure could not be excluded for such reference groups, thus preventing the extrapolation of definite conclusions about their occupational contact (Lu et al., 2014; Pan et al., 2006). Concerning the timing of biological monitoring sampling, in some cases, it was not always appropriate for the studied biomarkers: for example, when performed the morning after a workday or as a spot sample collection during the shift (Kolena et al., 2014, 2017; 2019; Petrovicova et al., 2014, 2016; Pilka et al., 2015). In some studies, no pre-shift samples were collected (Huang et al., 2014; Lu et al., 2014). This may suggest the need for a standardized approach to biological sampling in order to extrapolate more suitable data for comparison.

This review shows that there are only a few occupational HBM studies available on the potential endocrine-disrupting effects of phthalates. They report associations between phthalate metabolite levels and hormone levels or sperm quality in occupational populations (Fong et al., 2015; Huang et al., 2014; Pan et al., 2006; Wang et al., 2018). However, occupational data on these effects are currently very limited and include different confounders. Therefore, further studies are needed to explore these associations in occupational populations that are possibly exposed to high phthalate levels. There is a concern about the potential transgenerational effect of phthalates. In an environmental exposure study, it was shown that the fetus is transplacentally exposed to higher levels of MBP than the mother (Kolatorova et al., 2018). Also, effects on fetal steroidogenesis have been proposed. It was further suggested that transplacental exposure to phthalates is associated with methylation changes in several genes involved in the control of spermatogenesis, testes development, inflammatory response, and even cancer and infertility (Solomon et al., 2017). Concerning occupational exposure, there is a lack of published reports dealing with exposure to phthalates and transplacental effects. The other health effects of phthalates have been studied among workers, such as alterations in pulmonary function parameters or anthropometric parameters, but these studies are very limited. The scientific literature on toxicology and general population studies is much more abundant and offers a broader overview of the potential health effects of phthalates (Lymperi and Giwercman, 2018).

Based on this review, it is easy to appreciate that the available data do not report the occupational settings susceptible to phthalate exposure such as the exposures to newer phthalates in the production of different products (e.g., waterproof gloves, tablecloths, shower curtains, floor tiles, toys, blood bags, beer bottle caps), where DEHP was commonly used in the past (Alexander and Baxter, 2014; Van Tongeren et al., 2002). Moreover, occupational settings such as waste management and recycling are of relevance for future research (Muenhor et al., 2018), as well as the construction sector in which exposure to phthalates may occur through floorings, for example (Fucic et al., 2018).

Combining biomonitoring data with relevant contextual information (work tasks, operational conditions, risk management measures in place, etc.) allows us to understand the most important exposure route and workplace conditions that influence exposure and, consequently, identify the type of interventions that are still needed to prevent exposure. Unfortunately, contextual information is missing in most of the studies reviewed here; it should therefore be collected in future studies. The use of validated, sensitive, and accurate analytical methods to measure trace concentrations of phthalate metabolites in humans is also essential for assessing exposure to phthalates. The analysis of phthalate metabolites follows a typical procedure for organic contaminants, namely sample pretreatment, extraction and cleanup, concentration and re-constitution in a suitable solvent, separation by chromatography, and detection by mass spectrometry (Kumar and Sivaperumal, 2016). The LOD (and LOQ) of phthalate metabolites used in the occupational HBM studies should be low enough to compare results across different population subgroups and countries and between occupational HBM studies and national HBM studies in the general population (SpFrance, 2019; CDC, 2019; Koch et al., 2017; Health Canada, 2013).

5. Conclusion

Overall, our findings indicate that there is a lack of recent occupational HBM studies in European countries, and considering the important policy actions taken in Europe, it seems relevant to evaluate the impact of these actions on workers' exposure. To compare such data, a harmonized approach for sample collection and analysis is needed. Furthermore, most of the studies are still dedicated to "old" phthalates (already with regulatory/policy actions in place in the EU) as opposed to the currently used "newer" phthalates that have substituted them. Future occupational HBM studies should therefore include exposure to newer phthalates in the production of various plastic products, but also the waste management, recycling, and construction sectors. Combining biomonitoring data with the description of work tasks, operational conditions, and workplace characteristics would further support future interventions to reduce exposures.

New biomonitoring studies should focus on occupational settings where exposure is expected to include a large number of workers, and

in addition to the old phthalates (for comparative purposes), newer phthalates should also be included in the biomonitoring studies. This new biomonitoring data will result in evidence that can be used to prioritize actions and measures for policymaking, evaluate the effectiveness of the policy measures already taken, and promote more comprehensive health impact assessments of policy options (Ganzleben et al., 2017).

Additionally, depending on the selection of target populations and their exposure, the inclusion of appropriate effect biomarkers such as hormone levels (e.g., estrogen, testosterone, thyroid hormones), sperm quality, or information on infertility and transplacental effect of phthalates could be considered and interpreted while paying attention to participants' age groups and sex as well as other potential confounders.

Since reliable biomonitoring methods exist for many commonly used phthalates, the biomonitoring of phthalates should be considered in workplaces given the potential phthalate exposure and be recognized not only as an important health surveillance tool but also as a relevant exposure assessment resource to be used in risk assessment and management. With the HBM4EU project (www.hbm4eu.eu), EU-wide reference values and biomonitoring guidance values will be developed to be used in the interpretation of biomonitoring results.

Declaration of competing interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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