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Exposure estimates of phthalates and DINCH from foods and personal care products in comparison with biomonitoring data in 24-hour urine from the Norwegian EuroMix biomonitoring study

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ABSTRACT

Phthalates are diesters of phthalic acid and have been widely used as plasticizers in polyvinyl chloride (PVC) plastics. Phthalates are also used as excipients in pharmaceuticals and personal care products (PCPs). Phthalates can migrate from the plastic into the air, water and food, and humans can be exposed via multiple pathways such as dermal, oral and inhalation. There is evidence that phthalates can induce reproductive and developmental toxicity not only in experimental animals but also in humans through disruption of estrogenic activity. The aim of this study was to collect concentration data on five phthalates in foods and PCPs from the scientific literature and combine these with food consumption data and PCP use frequency data from the EuroMix biomonitoring (BM) study in order to assess exposure. Probabilistic exposure assessments of phthalates were performed from foods and PCPs. Due to the very limited data available in the literature for DINCH, an exposure assessment was not carried out for this compound. The food groups with the highest contribution to phthalates exposure were: beverages, dairy, bread and meat products. The exposure estimates were compared with the measured phthalate metabolite levels from 24-hour urine samples. Regarding the oral route, measured phthalate exposure was between the lower bound (LB) and medium bound (MB) estimated exposure for all phthalates, except for DEP. The measured exposure from urine correlated with the estimated exposure from food for DEHP and DBP, while for BBP and DEP it correlated with the exposure estimates from PCPs. There were no significant differences between the BM data and the estimated exposure, except for DINP for males ($p = 0.01$). The LB and MB phthalate exposures estimated from foods and PCPs and the measured exposure from the urine were considerably lower than their respective tolerable daily intake (TDI) values established by the European Food Safety Authority (EFSA) and the World Health Organization (WHO). For the upper bound (UB), the exposure estimates are approximately double the TDI; however, this is regarded as a worst-case estimate and has low correlation with the measured exposure.

1. Introduction

Phthalates are a group of several diesters of phthalic acid and have been widely used as plasticizers giving flexibility and durability to PVC plastics. Their use commonly ranges from plasticizers in plastics, including food contact materials and toys, to emulsifying agents and

Abbreviations: ABS, dermal absorption factor; B&A, Bland-Altman; BBP, butyl-benzyl-phthalate; BM, biomonitoring; BW, body weight; cx-MiNP, mono-4-methyl-7-carboxyoctyl phthalate; DBP, di-n-butyl phthalate; DEHP, di (2-ethylhexyl) phthalate; DEP, diethyl phthalate; DiBP, Diisobutyl phthalate; DINCH, di(isononyl) cyclohexane-1,2-clicarboxylate; DINP, di-*iso*-nonyl phthalate; EFSA, European Food Safety Authority; HBGV, health-based guidance values; LB, lower bound; LOD, limit of detection; LOQ, limit of quantification; MB, medium bound; MBzP, monobenzyl 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; MMCHP, mono-2-carboxymethyl hexyl phthalate; oh-MINCH, 2-(((hydroxy-4-methyloctyl)oxy)carbonyl)-cyclohexanecarboxylic acid; oh-MiNP, mono-4-methyl-7-hydroxyoctyl phthalate; oh-MPHP, 6-hydroxy monopropylheptylphthalate; oxo-MINCH, 2-(((4-Methyl-7-oxyooctyl)oxy)carbonyl)-cyclohexanecarboxylic acid; oxo-MiNP, mono-4-methyl-7-oxooctyl phthalate; MnBP, mono-n-butyl phthalate; ND, non-detects; PCPs, personal care products; PVC, polyvinyl chloride; RPF, Relative Potency Factor; TDI, tolerable daily intake; TDS, total diet study; UB, upper bound; WHO, World Health Organization.

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solvents in cosmetics, and excipients in the pharmaceutical industry (US EPA, 2012; Kelley et al., 2012). Their widespread usage leads to ubiquitous, constant and potentially inevitable exposure in humans. The Organisation for Economic Co-operation and Development (OECD) reported in 2018 that global production volumes of phthalate plasticisers could reach approximately 5.5 million metric tonnes per year. The biggest market is the People's Republic of China, accounting for 45% of all use, followed by Europe and the United States of America with a combined use of 25% (OECD, 2018). There is substantial evidence that phthalates can induce disruption in estrogenic activity, and cause reproductive, developmental and liver toxicity in experimental animals and in humans (Gray et al., 2000; Heudorf et al., 2007; Lyche et al., 2009; Chen et al., 2014). Di-2-ethylhexyl phthalate (DEHP), one of the most widely used phthalates, has been linked with liver carcinogenicity in rodents and was also initially classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic in humans (Category 2B), but, in a more recent evaluation, DEHP was in the unclassified group of compounds (Category 3) (IARC, 2013). Phthalates were authorised for use as food contact materials in the EU market in 2011 (EC 10/2011). Due to their toxicological potential in humans, uses of DBP (di-n-butyl phthalate), DEHP and DiBP (diisobutyl phthalate) were regulated so as not to exceed concentrations equal or greater than 0.1% by weight of plasticised material, individually or in combination in the EU market after July 2020 (EU 2018/2005). Thus, various phthalate substitutes have emerged such as di(isononyl)cyclohexane-1,2-clicarboxylate (DINCH), tributyl O-acetylcitrate, triethyl 2-acetylcitrate, and trihexyl O-acetylcitrate (Schutze et al., 2012; Kim et al., 2019). Phthalates can migrate into the air, water and food, and humans can be exposed via multiple pathways such as dermal, oral and inhalation. In order to evaluate the likely human exposure to phthalates, an exposure assessment can be performed. In exposure assessments, the magnitude, frequency and duration of human exposure to an agent is measured and the different exposure pathways, including inhalation, ingestion of water or food and dermal contact are considered (Giovanoulis et al., 2018). Exposure is a crucial aspect in risk assessment as it informs the transition of an identified hazard to a risk or a non-risk. In order to estimate human exposure to a chemical, concentration data in food and PCPs are needed, in addition to data on consumption, and use frequency.

After obtaining data on the concentrations of the chemical agents in food and drinks and on dietary consumption, the dietary exposure assessment is conducted using a deterministic (using point estimates) or a probabilistic analytical approach. Probabilistic analyses include more complicated modelling approaches than deterministic ones, and rely on distributions of data as input instead of single values. The outcome of a probabilistic analysis is a distribution of possible exposure estimates, rather than a point estimate derived by the deterministic approach, and assists in characterising variability and uncertainty within the population. Additionally, by using a distribution of exposure estimates rather than point estimates, there is less likelihood of generating biased results. The use of statistical methods such as Monte Carlo simulations also provides greater credibility in comparison with deterministic approaches and/or expert judgment, which may be influenced by subjectivity. Even though probabilistic methods can provide a more reliable exposure estimate, it should be mentioned that availability of consumption and concentration data is paramount and limited concentration data can lead to high uncertainty in the final exposure estimate. The aim of this work is to assess exposure to phthalates and DINCH from diet and PCPs in the Norwegian population from the EuroMix BM study and compare these with the phthalate and DINCH metabolites quantified in urine. The phthalates were the following; DEHP, DINP (di-*iso*-nonyl phthalate), DEP (diethyl phthalate), DBP, BBP (butyl-benzyl-phthalate) and the phthalate substitute DINCH. Finally, risk characterisation was performed on each phthalate individually and for the phthalate mixture.

2. Materials and methods

2.1. Biomonitoring study and dietary intake assessment

A biomonitoring (BM) study was performed in Norway between September 2016 and November 2017 as part of the EuroMix project, financed by the H2020 programme. The study included 144 participants, comprising 44 males with a mean age of 43.4 ± 11.7 years and 100 females aged of 42.2 ± 12.3 years, on the first study day and of whom 140 (43 males and 97 females) completed the second study day. There were 2–3 weeks between the sampling and, for the two study days, the participants recorded all food and drink consumed (weight records) and recorded PCP usage in two separate diaries. All urine was collected for both study days, and blood samples were taken at the end of each 24-hour period. Consumption time and urinary data measured were divided into three consumption and urinary pools respectively: consumption and urine collected from 06:00–12:00 (pool 1), from 12:00–18:00 (pool 2) and from 18:00–06:00 the next day (pool 3). In the different time pools, the exposure was estimated and plotted against the phthalate metabolite levels measured in the urine of the respective time pools. A detailed description of the EuroMix BM study can be found in the paper published by Husøy et al. (2019).

2.2. Systematic literature search

A systematic literature search was performed (November 2019) for the collection of phthalate concentration in foods and PCPs. The search included DBP, BBP, DEHP, DEP, DINP and DINCH for the period 2008 to 2019, using multiple databases such as: Embase, Cochrane, Medline and Web of Science. A PRISMA flow chart summarising the outcome of the literature search is presented in Figure S1. A detailed description of the search strategy used can be found in the Supplementary Materials (Tables S1-S4). The retrieved papers were organised in an EndNote 9 file to ensure traceability, and duplicates were excluded. The phthalate concentrations and food item/category were extracted to an Excel table (2267 data points), where information on the country of origin, type of analytical method, number of samples and the type of descriptive data (median, mean, minimum, maximum) were also collected.

2.3. Exposure modelling

After filtering the collected papers, 102 studies containing phthalate concentrations in foods and PCPs were identified. Of the 88 studies with food concentrations, 32 were conducted in the EU and 56 contained data originating from countries around the world. We selected studies reporting minimum, maximum and median values of concentrations in foods, purchased in the EU market for foods, while including studies also from USA and Canada for PCPs (n = 14 studies for food and n = 8 studies for PCP), as an appropriate estimate for the Norwegian population. Three different exposure estimates were calculated for each phthalate (except for DINP), based on the concentration in food, reported as lower, medium and upper bound by taking account of minimum, median and maximum values, respectively. In respect of DINP, there was insufficient data for minimum and maximum values, and only medium bound was estimated (Table S5). It should be noted that, in the literature, no concentration data were reported for DINCH, either dietary or from PCPs. Additionally, for DINP, no PCP concentration data were found.

The dietary concentration data were treated in three scenarios (LB, MB and UB) (Table S5). In the LB, the non-detects (NDs) were replaced by 0, while in the MB, NDs were replaced by half of the limit of detection (LOD) or half of the limit of quantification (LOQ) (if LOD was unavailable) and for the UB, NDs were replaced by their respective LOD/LOQ (Claeys et al., 2008; Sakhi et al., 2014). However, due to the very limited descriptive concentration data found on PCPs, only the MB scenario was included for the exposure modelling. The ND values were treated in the same way as for the dietary data (described above).

The LB, MB and UB phthalate concentrations were calculated using R (3.6.4 version). Data were summarized by 50th (P50), 5th (P5), 95th (P95) percentiles, mean, standard deviation, minimum, maximum and, when possible, the geometric mean and geometric standard deviation, for LB, MB and UB for each phthalate. P5, P50 and P95 were used for the probabilistic exposure estimates.

For the estimated exposure of the five phthalates, the consumption data from the EuroMix study were combined with the concentration data from the literature, using the following equation (1).

$$Diet\ Exposure = \sum \frac{x \times C}{BW} \left[\frac{ng}{kg\ bw\ day}\right] \quad (1)$$

where C is the concentration of phthalates in foods (ng/g); x is the individual grams of food eaten (g/day) as reported in the weighed food diary and aggregated into the broader food categories shown in Table 1, and BW is the individual body weight (kg).

Regarding PCP exposure estimates of the five phthalates, the following equation (2) was used.

$$Dermal\ \ exposure = \sum \frac{C \times PCP_{fr} \times PCP_{a} \times ABS \times R_{f}}{BW} \left[\frac{\mu g}{kg\ bw\ day}\right] \quad (2)$$

where C is the concentration of phthalates in PCPs (μg/g) (Table S6); PCPfr is the frequency of application (application/day); PCPα is the amount per application (g/application) (Karrer, 2020); ABS is the dermal absorption factor (non-dimensional) (Table S7); Rf is the retention factor for rinse-off products (non-dimensional) as taken from SCCS (2018), and BW is the individual body weight (kg).

The individual estimated exposure for each phthalate was modelled using 1000 Monte Carlo iterations using the triangular type of distribution based on P5, P50 and P95 as parameter values. Triangular distributions were used due to the limited availability of concentration data in foods. The triangular distribution is a continuous probability shaped as a triangle and can be used when minimum, maximum and the mode are available (Borek et al., 2014; Martínez et al., 2017). A detailed description of the Monte Carlo parameters for the LB, MB and UB exposure to phthalates from different food categories, including the respective data points, can be found in Table 1. The estimated exposure was calculated in R version 3.6.4.

2.4. Phthalate and DINCH findings in urinary samples

Eleven different phthalate metabolites (monoethyl phthalate (MEP), mono-*iso*-butyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-2-ethyl 5-carboxypentyl phthalate (MECPP), mono-2-carboxymethyl hexyl phthalate (MMCHP), mono-4-methyl-7-hydroxyoctyl phthalate (oh-MiNP), mono-4-methyl-7-oxooctyl phthalate (oxo-MiNP), mono-4-methyl-7-carboxyoctyl phthalate (cx-MiNP), 6-hydroxy monopropylheptylphthalate (oh-MPHP)) and two metabolites of DINCH (2-(((hydroxy-4-methyloctyl) oxy)carbonyl)-cyclohexanecarboxylic acid (oh-MINCH), 2-(((4-methyl-7-oxyooctyl)oxy)carbonyl)-cyclohexanecarboxylic acid (oxo-MINCH)) were determined in the three urine time pools (1 = 06:00–12:00, 2 = 12:00–18:00, 3 = 18:00–06:00) and a 24-hour concentration of each metabolite was estimated by adding the amounts of the three time pools of urine from study days 1 and 2, respectively.

On-line column switching liquid chromatography coupled to tandem mass spectrometry was used in order to determine the phthalate metabolites. Additionally, labelled internal standard solution and enzyme solution to deconjugate glucoronidates (betaglucuronidase in ammonium acetate buffer, pH 6.5) were added to the urine sample (300 μL). The samples were incubated for 1.5 h at 37 °C, after an addition of 20% formic acid. The samples were centrifuged, and the supernatant was injected into the system. The LODs were between 0.07 and 0.7 ng/ml. The accuracy of the method ranged from 70% to 120%. In-house pooled urine samples and standard reference material from the National Institute of Standards and Technology (NIST) were simultaneously analysed with the samples and the precision for the phthalate metabolites was below 20%. For both sexes, the phthalate metabolites recovered at the highest amounts in the urine were the sums of DEHP and DINP, followed by MEP, MnBP, MiBP, MBzP (Fig. 1). Additionally, the urinary analysis identified sumDINCH and oh-MPHP at lower levels in both sexes (Fig. 1). The phthalate metabolites in the urinary samples from day 2 were measured as well and they are presented in the supplementary materials (Figure S2), since their levels did not differ significantly from the ones measured on day 1.

2.5. Measured vs estimated phthalate exposure

In order to compare the exposure estimates with the phthalate levels found in the urine, the individually measured phthalate metabolite concentrations in the urine were back-calculated (μg/kg bw) to external exposure (equation (3)) of their respective parent compounds by taking into account toxicokinetic parameters such as oral/dermal absorption and percentage of the phthalate metabolites excreted in the urine (Table S7).

$$Parent\ \ concentration(x) = \frac{\left(\frac{y}{ap}\right)}{de} \quad (3)$$

where y is the total amount of phthalate metabolites in urine (ng/kg bw); ap is the percentage (%) of absorption for each respective phthalate and de is the (%) of the oral dose excreted as phthalate metabolites determined in urine, in order to correct for metabolites not analysed in this study.

In Table S7, important toxicokinetic parameters such as absorption (oral, dermal), elimination half-life and % of dose excreted are summarised from the literature for the five phthalates of interest for this study (INSERM (institute national de la santé et de la recherche medicale), 2011; Wang et al., 2019; Koch et al., 2006; Kawano, 1980).

2.6. Statistical analysis

Further statistical analysis was performed by calculating the linear regression between middle bound and urine for males and females on both days. Repeated measures ANOVA tests were used to test for differences between the sexes and the two days with the levels of phthalates found in the BM study. For all calculations, R version 3.6.4 was used.

2.7. Phthalates grouping for risk characterisation

In order to calculate the phthalate exposure as a mixture, it was first necessary to group the five substances. According to EFSA (2019b), a method for grouping substances in a mixture is by calculating the Relative Potency Factor (RPF). After choosing reproductive toxicity as toxicological endpoint, the most data-rich compound DEHP was selected as the index compound (RPF = 1). By considering the health-based guidance values (HBGV) for each phthalate as established by EFSA and WHO (summary in Table S8) and their respective difference from the HBGV of DEHP (50 μg/kg bw per day), the RPFs were defined as: 0.01, 5, 0.1 and 0.3 for DEP, DBP, BBP, DINP, respectively.

After taking into consideration the HBGV and the estimation of the RPFs, the equation used to translate the other compounds to DEHP was modified from EFSA (2019a), as:

DEHP Equivalents (μg/kg food) = DEHP*1 + DEP*0.01 + DBP*5 + BBP*0.1 + DINP*0.3 (4)

Table 1
Monte Carlo parameters for the phthalate exposure from food.

Parameter	Symbol	Units	Type	P50 conc. (P5-P95)LB {data points}	P50 conc. (P5-P95) MB {data points}	P50 conc. (P5-P95) UB {data points}	References
DEHP conc. in	C	–					
Bread		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {387}	71(46–71) {414}	2264(2264–2264) {377}	Sakhi et al., 2014; Van Holderbeke et al., 2014; Biedermann et al., 2013; Škrbić et al., 2017; Fierens et al., 2012a, 2012b, 2013; Guerranti et al., 2016; Dugo et al., 2011; Vavrouš et al., 2019; Lo Turco et al., 2016; Amiridou and Voutsa, 2011; Chatonnet et al., 2014; Del Carlo et al., 2008)
Cereals		μg/kg	T	$1e^{-5}$($1e^{-5}$-386) {129}	40(5–130) {240}	1073(276.5–1628) {129}	
Cakes		μg/kg	T	32(32–32) {11}	61(56–85) {122}	165(165–165) {11}	
Fruits and vegetables		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {69}	5(0.1–33) {143}	1413(361–1413) {69}	
Meat and meat products		μg/kg	T	10(10–10) {209}	37(5–117) {579}	850(433–850) {209}	
Fish and fish products		μg/kg	T	$1e^{-5}$($1e^{-5}$-17.7) {41}	12.5(5–86) {212}	5932(2596–5932) {41}	
Dairy		μg/kg	T	$1e^{-5}$($1e^{-5}$-312) {158}	24.5(9.3–463) {195}	260(19–743) {158}	
Cheese		μg/kg	T	31(31–360) {43}	173(124–265) {152}	2385(2286.3–2385) {41}	
Butter and different oils		μg/kg	T	$1e^{-5}$($1e^{-5}$-182) {253}	120(42.1–520) {170}	1827(1200–10110) {288}	
Sweets		μg/kg	T	$1e^{-5}$($1e^{-5}$-32) {90}	9.5(5.6–191.3) {127}	243(243–483.1) {90}	
Beverages		μg/kg	T	$1e^{-5}$($1e^{-5}$-0.1) {361}	0.7(0.005–353) {521}	133(0.09–1131.7) {361}	
Snacks		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {29}	35(35–35) {29}	308(308–308) {29}	
BBP conc. in							
Bread		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {387}	0.8(0.8–1.3) {424}	8.1(8.1–8.1) {387}	
Cereals		μg/kg	T	$1e^{-5}$($1e^{-5}$-0.8) {129}	1.25(0.2–3.7) {240}	14(5.8–70) {129}	
Cakes		μg/kg	T	0.2(0.2–0.2) {11}	3.75(1.25–3.75) {122}	14(14–14) {11}	
Fruits and vegetables		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {69}	0.25(0.05–0.25) {126}	26(9–58) {69}	
Meat and meat products		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {209}	2.5(0.25–78) {542}	12(12–18) {209}	
Fish and fish products		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {41}	2.5(0.25–32) {226}	8(3–8) {41}	
Dairy		μg/kg	T	$1e^{-5}$($1e^{-5}$-1.9) {158}	1.5(0.25–2.5) {195}	5(1.7–13) {158}	
Cheese		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {43}	3.75(2.5–3.75) {152}	48(46.1–48) {41}	
Butter and different oils		μg/kg	T	7.8($1e^{-5}$-99) {227}	10(1.65–29) {170}	1040(3.63–1210) {288}	
Sweets		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {90}	0.2(0.2–0.25) {88}	23(23–23) {51}	
Beverages		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {361}	2(0.005–9) {361}	96(0.1–269) {361}	

(*continued on next page*)

Table 1 (*continued*)

Parameter	Symbol	Units	Type	P50 conc. (P5-P95)LB {data points}	P50 conc. (P5-P95) MB {data points}	P50 conc. (P5-P95) UB {data points}	References
Snacks		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {29}	0.6(0.6–0.6) {29}	14(14–14) {29}	
DBP conc. in							
Bread		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {387}	3.8(2.8–3.8) {424}	106(106–106) {388}	
Cereals		μg/kg	T	$1e^{-5}$($1e^{-5}$-80) {129}	4.6(1.3–16) {240}	61(17–133) {133}	
Cakes		μg/kg	T	1.3(1.3–1.3) {11}	5.1(2.5–7.1) {122}	65(65–302.5) {12}	
Fruits and vegetables		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {69}	1.2(0.25–1.7) {143}	17(5.6–480) {69}	
Meat and meat products		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {209}	1.5(0.25–6) {579}	25(15–25) {209}	
Fish and fish products		μg/kg	T	$1e^{-5}$($1e^{-5}$-0.21) {41}	2.5(0.75–12) {226}	12.5(12–13) {41}	
Dairy		μg/kg	T	$1e^{-5}$($1e^{-5}$-15) {158}	1.9(0.25–15) {195}	6.5(0.8–54) {158}	
Cheese		μg/kg	T	$1e^{-5}$($1e^{-5}$-15) {43}	4.6(2.5–31) {152}	54(52–54) {41}	
Butter and different oils		μg/kg	T	$1e^{-5}$($1e^{-5}$-101) {253}	6(2.5–26) {170}	203(16–309) {288}	
Sweets		μg/kg	T	$1e^{-5}$($1e^{-5}$-23.5) {90}	1.9(0.92–39.4) {127}	41(41–58.4) {90}	
Beverages		μg/kg	T	$1e^{-5}$($1e^{-5}$-0.1) {381}	0.46(0.044–104) {498}	125(0.2–2212) {381}	
Snacks		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {29}	3.2(3.2–3.2) {29}	65(65–65) {29}	
DEP conc. in							
Bread		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {387}	1.6(0.75–1.6) {414}	23(23–23) {377}	
Cereals		μg/kg	T	$1e^{-5}$($1e^{-5}$-4.7) {129}	0.75(0.3–1.5) {240}	558(5.37–558) {129}	
Cakes		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {11}	1.5(1.5–2.1) {122}	5.3(5.3–5.3) {11}	
Fruits and vegetables		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {69}	0.75(0.25–1.8) {143}	2.8(2–26) {69}	
Meat and meat products		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {209}	1.7(0.75–4) {579}	11(1.4–11) {209}	
Fish and fish products		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {41}	0.75(0.6–1.5) {189}	5(2.7–9.3) {41}	
Dairy		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {158}	2.5(2.5–5) {147}	11(1–11) {147}	
Cheese		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {39}	2.5(1.5–9.3) {150}	11(11–11) {39}	
Butter and different oils		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {253}	4(2.5–6.3) {166}	198(4–230) {284}	
Sweets		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {90}	0.75(0.25–5.8) {127}	2.4(2.4–25.2) {90}	
Beverages		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {231}	0.067(0.005–7.5) {391}	0.3(0.01–15) {231}	
Snacks		μg/kg	T	$1e^{-5}$($1e^{-5}$-$1e^{-5}$) {29}	0.1(0.1–0.1) {29}	5.3(5.3–5.3) {29}	
DINP conc. in							
Bread		μg/kg	T	N/A	74(74–74) {38}	N/A	
Cereals		μg/kg	T	N/A	3.9(0.5–7.1) {112}	N/A	
Cakes		μg/kg	T	N/A	362(88–734) {112}	N/A	
Fruits and vegetables		μg/kg	T	N/A	6.15(2.9–9.4) {75}	N/A	
Meat and meat products		μg/kg	T	N/A	43(0.5–275) {371}	N/A	
Fish and fish products		μg/kg	T	N/A	38(2–55) {186}	N/A	
Dairy		μg/kg	T	N/A	17(17–17) {38}	N/A	
Cheese		μg/kg	T	N/A	81(6.8–166) {112}	N/A	
Butter and different oils		μg/kg	T	N/A	15(4–360) {110}	N/A	
Sweets		μg/kg	T	N/A	4(4–4) {38}	N/A	
Beverages			T	N/A		N/A	

(*continued on next page*)

Table 1 (*continued*)

Parameter	Symbol	Units	Type	P50 conc. (P5-P95)LB {data points}	P50 conc. (P5-P95) MB {data points}	P50 conc. (P5-P95) UB {data points}	References
		µg/kg			0.4(0.4–3.2) {112}		
Snacks		µg/kg	T	N/A	N/A	N/A	
Consumption of foods							
		g/day	N	Fromdiaries	Fromdiaries	Fromdiaries	Husøy et al., 2019
Body weight	BW	kg	LN	65.2 ± 14.2	65.2 ± 14.2	65.2 ± 14.2	Husøy et al., 2019

LN = Log-normal; T = Triangular; N = Normal distribution. P50, P05 and P95 values were used for triangular distributions. The parameters were normalised taking into account the sample size, and thus larger weighting was given to analyses with bigger sample sizes. N/A = Not applicable due to lack of data

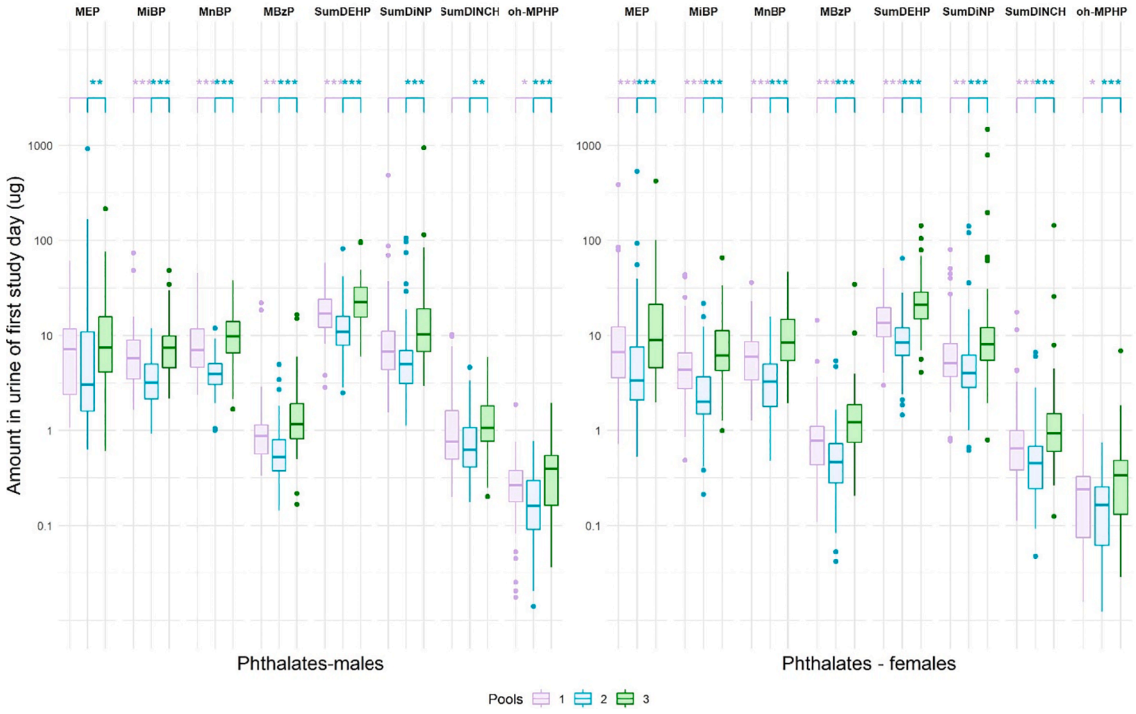

Fig. 1. Phthalate amounts measured in urine in the different time pools (pool 1: 06:00–12:00, pool 2: 12:00–18:00 and pool 3: 18:00–06:00) for males and females on day 1, expressed as their metabolites of DEP (MEP), DiBP (MiBP), DBP (MnBP), BBzP (MBzP), and DPHP (oh-MPHP), or the sum of their metabolites: sumDEHP (MEHP, MEHHP, MEOHP, MECPP, MMCHP), sumDiNP (oh-MiNP, oxo-MiNP, cx-MINP) and sumDINCH (oh-MINCH, oxo-MINCH).

3. Results

3.1. Estimated exposure from food

The exposure was based on twelve food and drink groups, each contributing differently to the total exposure for each phthalate. The food groups were beverages (tap and bottled water, fruit juices, coffee, tea, alcoholic beverages and soft drinks), bread and butter including different types of oils, cakes, cereals, cheese, dairy, fish, fruits and vegetables, meat products, sweets and snacks. The probabilistic estimated exposure was simulated according to equation (1) by performing Monte Carlo modelling with 1000 iterations. The top four food groups with the highest contributions to exposure are shown in Table S9.

There were no statistically significant differences ($p > 0.05$) between the dietary sources of MB exposure between males and females for study day 1. Beverages were the food group that contributed the most to BBP, DBP and DEP exposure, irrespective of gender, while meat contributed considerably to BBP and DiNP exposure. Dairy products also seem to be an important source of all the phthalates. The results for day 2 did not differ significantly from day 1 and can be found in the Supplementary materials (Figure S2).

Phthalate exposure from food was estimated as described in section 2.3 and, as can also be seen in the summary table (Table S10), there were no significant differences between males and females. Exposure from food was ranked as DEHP > DINP > DBP > BBP > DEP.

3.2. Exposure modelling and correlation with phthalate metabolites concentrations in the urine

After estimating the individual phthalate exposure from phthalate metabolite concentrations in the urine (measured exposure from day 1), we compare this with the probabilistic intake estimates (day 1) using the three scenarios (Fig. 2). The measured exposure was between the LB and MB probabilistic intake estimates for all phthalates, except for DEP, which was closer to the UB. Additionally, the estimated exposure estimates for day 2 were not significantly different to the ones on day 1, with the exception of DBP ($p = 0.01$) and can be found in the supplementary materials (Figure S3). Finally, there were no significant differences ($p > 0.05$) estimated between males and females for either day.

Under a more detailed exploration of the dietary intake estimates by

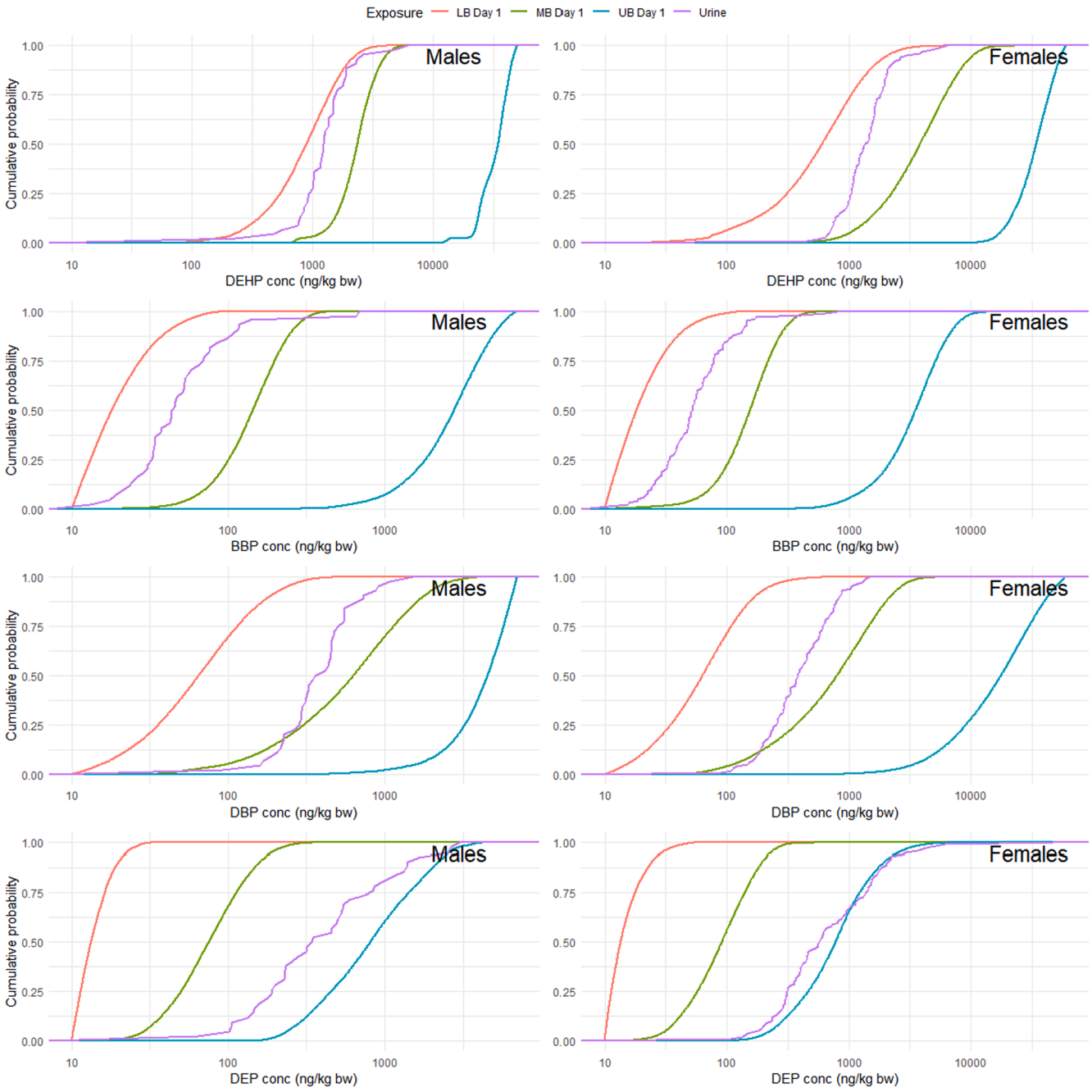

Fig. 2. Cumulative phthalate dietary exposure of males and females on day 1.

time periods within the 24 h, we found that estimated exposure levels for the period 12:00–18:00 were closer to the measured exposure between 18:00–06:00 (pool 3) (Fig. 3). Additionally, there were no significant differences ($p > 0.05$) between males and females for the measured exposure from phthalate metabolite concentrations in urine for pool 2, nor in the phthalate measured in the urine from pools 1 and 3. The exposure estimates for the pools of day 2 were not significantly different ($p > 0.01$) to the ones reported for day 1 and can be found in the supplementary materials (Figure S4).

The individual exposure estimates for MB and UB for both days were also plotted against the respective phthalate exposure measured in the urine (Fig. 4). The individual MB estimated exposure is plotted against each exposure to phthalate measured in the urine for days 1 and 2. The UB individual estimated exposure data (except DEP) depicted a very poor correlation with the measured exposure and can be seen in the supplementary materials (Figure S6). In comparison with the cumulative estimated exposure, the individual estimated exposure does not fit to the exposure model with the same accuracy for most phthalates.

In order to analyse the agreement between the individual estimated exposure and the individual measured exposure, we performed a Bland-Altman (B&A) plot for males and females for day 1 (Fig. 4) and day 2 (supplementary materials, Figure S6). In the graphs, the mean difference between the two methods is shown, including the 5th and 95th percentiles. For most phthalates, the agreement between the two methods is good, since often more than 95% of the estimates are between the ±2SD of the mean difference, with the exception of DEP in males for day 1 and DINP in females for day 1, where 92.8% and 92.7% of the data fulfilled the above-mentioned criterion.

In comparing the two methods, the B&A method also assists in better identifying possible underestimation or overestimation of the estimated

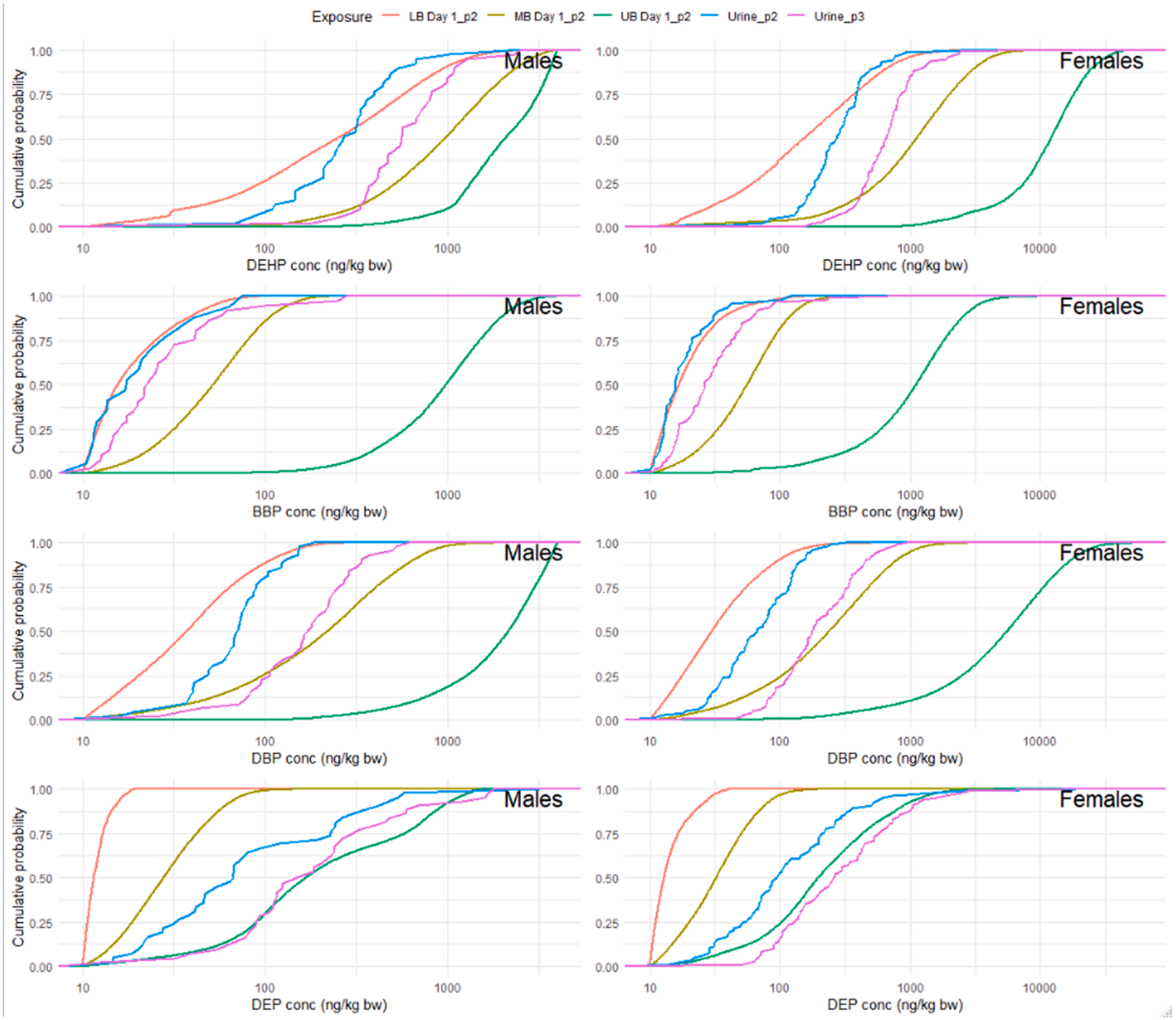

Fig. 3. Cumulative phthalate exposure of males and females between 12:00 and 18:00 (pool 2) compared with urinary concentrations in pool 2 and pool 3.

exposure compared to the measured exposure (from the BM study). All data points above the line of mean difference in Fig. 4 signify that we overestimated the exposure, and all those below that we underestimated the phthalate exposure, in our probabilistic estimates, compared to the measured estimate. For DEHP. there is a trend that, for the low exposure, the estimated exposure is underestimated and, in most of the high exposures, the estimated exposure is overestimated. This trend might be due to an underlying bias (positive 400 for males and 550 for females). The correlation of the measured and estimated exposures was also assessed in R, by using the Spearman correlation coefficient. For all phthalates, the p values were >0.05, except for DINP for males on day 1 ($p = 0.01$). From Fig. 4, we also observe different degrees of bias, shown by how far the mean difference is away from zero. To better visualise the B&A figures for DINP and DEP, we had to remove, from the measured estimates, observations that diverged markedly from the other estimates (outliers), $n = 2$ for DINP and $n = 1$ for DEP respectively.

3.3. Aggregate exposure modelling

The dermal MB phthalate exposure (from PCPs) was estimated in R using equation (2), as previously described. The phthalate concentrations in PCPs, PCP amounts used, frequency of application, dermal absorption and rinse factor were all coupled to Monte Carlo equations, using 1000 iterations and a triangular type of distribution based on P5, P50 and P95 as parameters values.

The estimated MB exposure to phthalates from PCPs was calculated for both sexes and the two study days. The 24 different personal care products under consideration ranged from shampoos and conditioners to hand creams, make-up and shaving products. The cumulative exposure from PCPs was then compared with the estimated dietary exposure, the aggregate exposure and the measured exposure from the urine for study day 1 (Fig. 5) and study day 2 (in supplementary materials Figure S10). Dietary exposure is the dominant source of most phthalates, with the exception of DEP, where the estimated exposure levels are predominately due to the DEP concentrations found in PCPs. This accords with current knowledge on PCPs being the main source of this phthalate. The PCPs that contributed most to female DEP exposure were, in descending order: deodorants, perfumes, hair-styling products, shower gels, shampoos and hand cream. Similarly, for males, the PCPs that contributed most to DEP exposure were: hair styling products, deodorants, shower gels and shampoos.

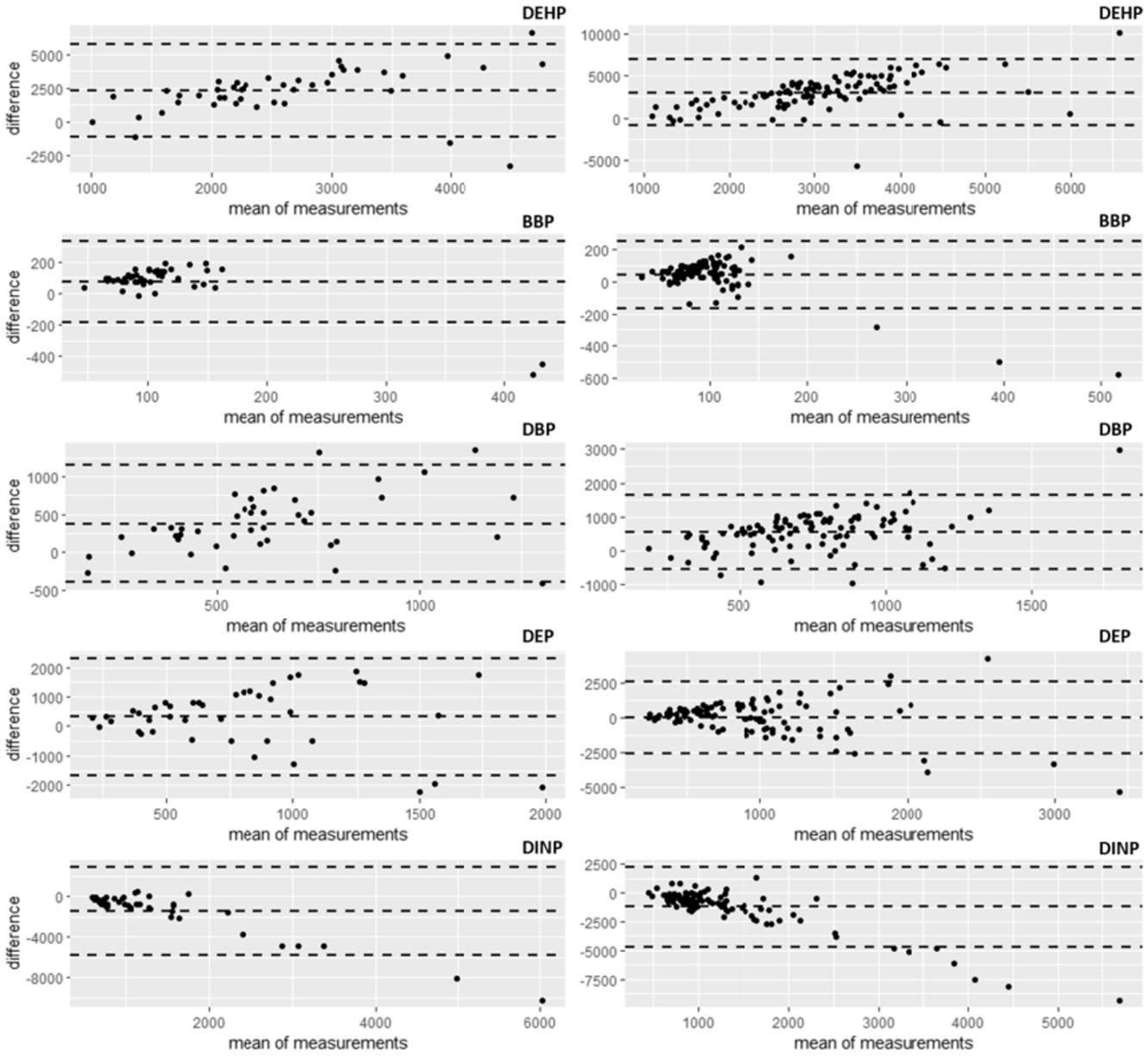

Fig. 4. Bland-Altman middle bound individual exposure estimates for males (left) and females (right) correlated with measured exposure in samples of urine, with the exception of DEP, where the UB exposure estimate is presented.

3.4. Risk characterisation for the phthalate mixture with respect to reproductive toxicity

A summary of the median estimated exposure for males and females for the scenarios LB, MB and UB for day 1 is presented in Table S11. The highest estimated median exposure was 35 μg/kg bw per day for the UB of DEHP and the lowest was the LB of 0.003 μg/kg bw per day for DEP.

Regarding dermal exposure from PCPs, due to lack of concentration data, only MB exposure was estimated. In Table S12, P5, P50 and P95 values from the estimated MB dermal exposure from PCPs is summarised for males and females for day 1. The highest median exposure was the P95 estimated exposure of 0.59 μg/kg bw per day for DEP, and the lowest was the P5 exposure of $3.81e^{-5}$ μg/kg bw per day estimated for DEP. The estimated exposure levels of phthalates from PCPs are significantly lower than their respective dietary levels, except for DEP where the levels are higher from PCPs.

In order to proceed to the risk characterisation, the RPFs were estimated (equation 4) for each phthalate, and then the potency-related exposure was calculated as shown in Table S8 using the same approach described by EFSA (2019a). For most of the phthalates, the TDIs were selected from EFSA (2019a) as HBGVs. DEP was an exception where the TDI was calculated by WHO (2003).

The estimated exposure was converted to RPF-adjusted exposure estimates by using equation 4. The individual and mixture dietary and aggregate phthalate estimated exposures were subsequently compared to their TDI and the TDI of DEHP, respectively (Table 2). When the phthalates are assessed individually, it can be seen that their MB levels are lower than their respective TDIs, implying that there is no risk even when considering both exposure routes. When comparing the estimated exposure for the UB, all phthalates with the exception of DBP are at lower levels than their TDI. DBP's levels are slightly above the TDI for both males and females. In comparing the MB phthalate mixture exposure to its respective TDI (0.05 mg/kg bw day) for DEHP, the levels are lower for both males and females (0.0055 and 0.0075 mg/kg bw day respectively). On the other hand, on taking into account the UB mixture exposure, then both males and females are exposed to higher amounts

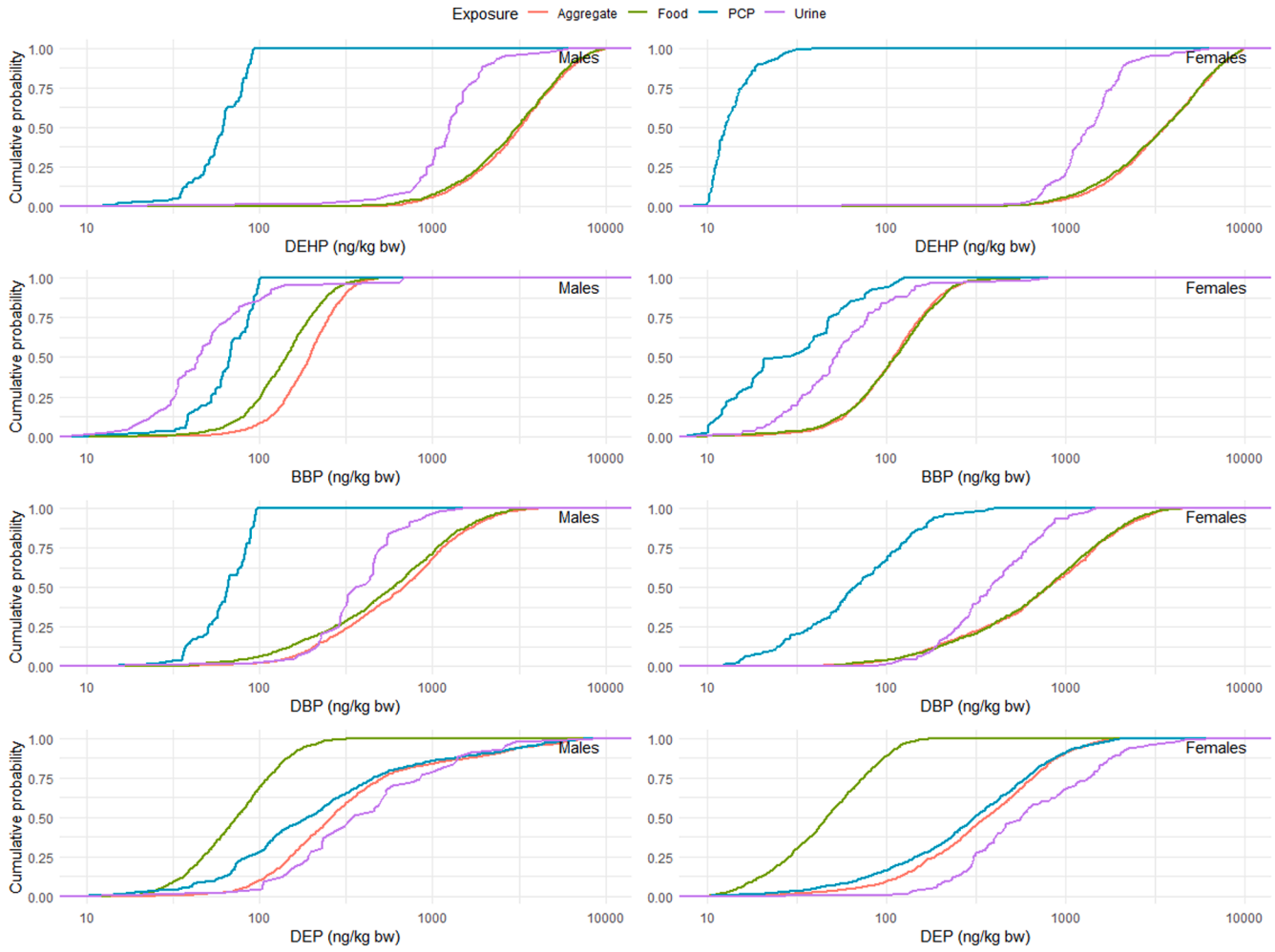

Fig. 5. Food, PCP and aggregate MB exposure estimates vs measured exposure in the urine for day 1.

Table 2
Individual and mixture phthalate exposure estimates (mg/kg bw/day) for males and females on study day 1 compared with TDI (mg/kg bw/day).

Phthalate	TDI	Measured median (females)	Measured 3rd quartile (females)	Estimated MB dietary exposure (males)	Estimated MB aggregate exposure (males)	Estimated MB dietary exposure (females)	Estimated MB aggregate exposure (females)	Estimated UB dietary exposure (males)	Estimated UB dietary exposure (females)
DEHP	0.05	0.0014	0.0018	0.0031	0.0032	0.0038	0.0038	0.035	0.035
DEP	5	0.00057	0.0014	0.00007	0.00027	0.00009	0.00037	0.0008	0.0007
DBP	0.01	0.00039	0.00061	0.0006	0.00068	0.00079	0.00082	**0.014**	**0.018**
BBP	0.5	0.000052	0.000079	0.0001	0.00019	0.0001	0.00011	0.0028	0.0035
DINP	0.15	0.0014	0.0023	0.0007	N/A	0.0006	N/A	N/A	N/A
Mixture	0.05	0.0038	0.0055	0.0055	0.0066	0.0075	0.0079	**0.105***	**0.125***

*The P95 of the DINP exposure (MB) was used for the mixture estimate.

than the TDI (Table 2).

4. Discussion

4.1. Phthalate exposure estimates in food

Probabilistic estimated exposure was performed for five phthalates in food using 144 and 140 participants from the EuroMix study for study days 1 and 2 respectively. In Table 3, the estimated exposure (P5, P50, and P95) for all scenarios is compared against the estimated exposure from three total diet studies (TDSs) summarised by EFSA (2019), and from a study performed in Norway by Sakhi et al., in 2014. TDSs (Bradley et al., 2013; FSAI, 2016; ANSES, 2016a; 2016b) were performed in three different countries (UK, Ireland and France) with data referring to 2007, 2012 and 2011–12. The estimated exposure for the LB and the MB from the EuroMix BM study was in most cases in the same range as the estimates from TDSs. The estimates for the UB are significantly higher in our study, which can be attributed to a variety of factors such as: limited concentration data base, cases where only limited descriptive values were available, the addition of water to the beverages food group leading to high consumption values and very high exposure estimates when combined with the P95 concentration values used for the calculation of the UB. By taking such high concentration values into consideration, the exposure estimates (UB) were much higher than estimates reported in the literature (Table 3) and led to an overestimation of the risk. This is also supported by the poor correlation

Table 3
P5, P50, P95 exposure estimates (μg/kg bw per day) compared with exposure estimates (LB) summarized by EFSA (2019a) (Bradley et al., 2013; FSAI, 2016; ANSES, b, 2016a) and a study in Norwegian foods by Sakhi et al. (2014).

Phthalate	Scenario	P5 (males, females)	P50 (males, females)	P95 (males, females	Sakhi et al., 2014 (P50)	Sakhi et al., 2014 (P95)	EFSA 2019a mean (min–max)	EFSA 2019a P95 (min–max)
DEHP	LB	0.23, 0.08	0.6, 0.6	2.23, 2.1	0.366	0.751	0.446–3.459	0.902–6.148
	MB	1.12, 1.0	2.3, 3.8	4.13, 10.3	0.384	0.78		
	UB	21.9, 17.4	35, 35	56.0, 66.0	0.406	0.809		
DEP	LB	0.0014, 0.0013	0.003, 0.003	0.013, 0.012	0.00151	0.00711	N/A	N/A
	MB	0.029, 0.031	0.07, 0.09	0.188, 0.228	0.0112	0.022		
	UB	0.239, 0.226	0.8, 0.7	2.55, 2.53	0.0203	0.0395		
DBP	LB	0.01, 0.089	0.06, 0.059	0.23, 0.22	0.024	0.052	0.042–0.769	0.099–1.503
	MB	0.09, 0.11	0.6, 0.7	2.196, 2.675	0.0296	0.0593		
	UB	3.078, 3.483	14, 18	47.5, 58.4	0.0352	0.0678		
BBP	LB	0.0024, 0.0022	0.01, 0.008	0.041, 0.042	0.00581	0.15	0.009–0.207	0.021–0.442
	MB	0.05, 0.055	0.1, 0.1	0.3, 0.34	0.0184	0.16		
	UB	0.88, 0.97	2.8, 3.5	6.78, 8.21	0.0308	0.173		
DINP	LB	N/A	N/A	N/A	0.392	1.08	0.232–4.27	0.446–7.071
	MB	0.3, 0.24	0.7, 0.6	1.62, 1.43	0.402	1.09		
	UB	N/A	N/A	N/A	0.412	1.10		

between the UB individual estimated exposure and the individual measured exposure in the urine.

Sakhi and colleagues (2014) analysed food samples and estimated the food groups with the highest contribution to phthalate exposure to be: milk and dairy (DEP), beverages (DBP), meat and meat products (BBP) and bread (DEHP, DINP). These categories appear often in the literature as the ones associated with high phthalate concentrations. Serrano et al. (2014) reviewed several food monitoring surveys from North America, Europe and Asia with data from between 1990 and 2013. High phthalate concentrations (>300 μg/kg) were often observed for DEHP in different types of meat, oils and fatty products (butter, cooking oils, animal fat). On the other hand, low phthalate concentrations (<LOD) were reported for dairy, grain products and fruits. Fifteen different phthalates were determined in a TDS from the UK, with the most important being DEHP, DBP, DiBP, DEP and BBP. The most important food groups with the highest prevalence of DEHP were fish, poultry and other meat products. Nuts, bread, oils, fats and meat products contained DBP, and DEP and BBP were present only in cereal and bread respectively (Bradley et al., 2013). In this study, we found that beverages, dairy and cheese products, meat and meat products, and fish products contributed most to phthalate exposure. This agreed relatively well with reported results, except for beverages, which in our assessment also included water. The food groups contributing to phthalate exposure were more or less the same in males and females

4.2. Comparing estimated exposure with measured levels in urine

The measured exposure showed a rather good fit when correlated with the cumulative estimated exposure for the whole study population. The measured exposure distribution was between the LB and the MB for all phthalates that are most commonly found in food. In comparing the measured and estimated exposure, we observed that the measured dietary exposure of DEP approached the estimated UB exposure, so we hypothesize that the main contributors to DEP exposure are PCPs. The measured exposure in urine correlated with the estimated exposure from food for DEHP and DBP, while, for BBP and DEP, it correlated with the exposure estimates from PCPs. Our estimated exposure was able to reasonably predict the potential phthalate exposure for this population, making it a useful tool for the risk assessment of phthalates in humans. In 2018, Giovanoulis et al. compared the estimated exposure with the measured exposure in a Norwegian cohort by using median and P95 intake estimations. The authors reported that the total daily intakes for DMP (dimethyl phthalate), DiBP and DBP were 1.3–2.6 times higher than the measured exposure using the BM data (Giovanoulis et al., 2018). Additionally the authors not only collected BM data on DINCH, which were not significantly different from the levels presented in this study (approx. 0.8 μg/kg), but they were also able to calculate a total daily intake of 0.366 μg/kg, which is much lower than the TDI of EFSA (1 mg/kg bw) for renal toxicity (EFSA, 2006). In another study, human BM data (24 h) collected in Germany over a period of 9 years (1988–2003) were back-calculated to daily intakes from urinary phthalate metabolites. The observed high levels for DBP exceeded the TDI in a small group of the subjects (Wittassek et al., 2007).

Regarding within-day variation, after assessing the phthalate levels measured in urine within a day, there were no significant differences within the time pools. Additionally, the phthalate levels in the urine were not significantly ($p > 0.05$) different between the two days. The exposure estimate of the time for pool 2 was compared with the phthalates found in urine pools 2 and 3. The measured exposure of pool 3 was better correlated to the estimated exposure than pool 2. This accords with current knowledge on the short half-life of phthalates. In a study performed by Sakhi et al. (2017), in Norwegian mothers and children, the phthalates measured in the morning urine were significantly higher than the concentrations in afternoon and evening samples for all phthalates, with the exception of MEHP (Sakhi et al., 2017).

The individual estimated exposure to phthalates showed an overestimation when compared with the individual measured exposure, apart from DINP where our estimates underestimated the measured exposure. When analysing the agreement between the measured and the estimated exposures with the B&A method, we observed quite good correlation in the two methods. The agreement between the two methods was compared using a methodology agreement criterion established by Bland and Altman (1986) stating that more than 95% of the estimates should be within ± 2SDs. For most phthalates, the agreement between the two methods is good since more than 95% of the estimates are between the ± 2SD of the mean difference for most phthalates. Exceptions were observed for DEP in males for day 1 and DINP in females for day 1, where only 92.8 and 92.7% of the data fell within the criterion.

In the case of DEP, the phthalate levels found in the urine for pools 2 and 3 were close to the UB level and even higher for females. This can be explained by the fact that DEP is more commonly used in PCPs and its levels found in the urine include other sources besides food. The correlation between measured and estimated phthalate levels ranged from zero (BBP) to low (± < 0.30) for DINP to moderate (between 0.30 and 0.49) for DBP, DEHP and DEP. These differences between the two methods may be affected by different sources of uncertainty such as: inter- and intra-day variations, availability of concentration data and back-calculation of phthalate metabolites to external dose. In our study, we did not identify significant differences in the phthalate exposures between the two days and the sexes. The phthalates are non-persistent chemicals with short half-lives and therefore the urinary phthalate

concentration is expected to change considerably throughout the day for a given person. However, this can be eliminated by continuous exposure to the phthalates from different sources throughout the day. There are multiple studies in the literature addressing the high variability of individual exposure to phthalates due to daily variation in diet, PCPs etc. (Fromme et al., 2007; Preau et al., 2010; LaKind et al., 2019). Another source of uncertainty is differences in the availability of data. While consumption data is well documented in the EuroMix study, the concentration studies from the literature addressing the European market were rather limited and contribute to considerable uncertainty. Due to this lack of concentration data, especially for DINCH, we were unable to perform either descriptive or probabilistic exposure estimates for this compound. In order to compare the phthalate measured in the urine with its respective exposure estimates, a back-calculation of the phthalate metabolite concentrations to the external dose of the parent compound was needed. This is a source of uncertainty since only absorption and percentage of dose excreted in urine were considered without examining other toxicokinetic factors such as distribution and faecal excretion. The largest percentage of phthalate elimination occurs in the urine, but there are papers in the literature reporting faecal excretion as a minor route of elimination. For instance, 10% of DEHP, 5% of DBP and <20% of BBP are excreted in the faeces (Peck and Albro, 1982; Frederiksen et al, 2007; Domínguez-Romero and Scheringer, 2019).

4.3. Phthalate mixture exposure

Our results on the risk characterisation of the phthalate mixture showed that the MB estimated exposure of the study population was approximately 10-fold lower than the TDI of the mixture, indicating a low level of risk. The estimated mixture dietary exposure was 0.0055 mg/kg bw for males and 0.0075 mg/kg bw for females, respectively. The mixture aggregated exposure was 0.0066 mg/kg bw for males and 0.0079 mg/kg bw for females. The risk characterisation of DBP, BBP, DEHP and DINP performed by EFSA showed mixture estimated exposure ranging from 0.0009 to 0.0072 mg/kg bw for mean consumers and 0.0016–0.0117 mg/kg bw for the high (P95) consumers (EFSA, 2019). The worst-case estimates (UB) reported in this study were 10 times higher (0.105 for males and 0.125 females) than the P95 estimates from EFSA, and they were also higher than the TDI (0.05 mg/kg bw). This is probably due to our approach to estimating the UB, which was based on very high concentrations (P95) reported in the literature for each food group and the treatment of the ND values (ND = LOD or LOQ), which would lead to an overestimate of exposure.

4.4. Strengths and weaknesses

In the collection of phthalate concentrations in food and PCPs, the concentration data points were normalised with the number of samples analysed, giving more weight to the studies with a high number of samples and thus reducing the power of some possible outliers. Using a similar approach for our statistical analyses, P5 and P95 were used instead of minimum and maximum values. It is well known in the literature that probabilistic estimates (Monte Carlo distributions) are more reliable than a simple deterministic approach that uses only point estimates, and indeed our estimates for LB and MB agreed with previously published studies. For the MB estimates, only medians were used as a statistical descriptor and studies including only means were not included. The reason is that, when these studies were included, the final exposure estimate was even more imprecise, especially when comparing with the individual phthalate levels from the BM study. This can be attributed to the fact that a mean estimate can be more affected by maximum values, thus making it a less reliable descriptor. The consumption data used in this study may under- or over-report the food consumption of the whole population. The continuous bias in the selection of the study group has to be taken into account. Our group comprised only educated adults in good health and does not necessarily represent the whole Norwegian population. There are studies in the literature showing that people of low education and income have different dietary habits, which often leads to unhealthy diets and poorer health (French et al., 2019; Rippin et al., 2020). This limitation had an effect on the accuracy of results on individual estimated exposure (Sioen et al., 2012). Additionally, using concentration data from different studies in the literature adds uncertainty to the exposure estimate. For some phthalate and food category combinations there was only one descriptive value reported in the literature. This adds to the uncertainty of the exposure estimate. Finally, the concentration database was less detailed and less diverse than the consumption database.

5. Conclusion

This study presents the estimated dietary and dermal exposure to five phthalates, namely DEHP, BBP, DBP, DEP and DINP, on two different days of a Norwegian adult population. Concerning the phthalate substitute DINCH, due to lack of concentration data, we were not able to estimate aggregate exposure from food and PCPs. The median exposure estimates were significantly lower than their respective TDI values established by EFSA and WHO. Additionally, beverages, dairy and meat products were the major dietary contributors of phthalate exposure, and deodorants, perfumes, hair styling products, shower gels and shampoos for females, and hair styling products, deodorants, shower gels and shampoos for males, were the major DEP exposure contributors. The dietary estimated exposure correlated better with pool 3 measured exposure from the urine samples. The measured urinary exposure did not differ from the estimated dietary exposure, except for DINP in males. Finally, when assessing the phthalates as a mixture, the MB estimates were 10 times lower than the TDI. On the other hand, for the UB, the exposure estimates are approximately double the TDI; however, this is regarded as a worst-case estimate and has low correlation with the measured exposure estimate.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106598.

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