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Mothers and children are related, even in exposure to chemicals present in common consumer products

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Abstract

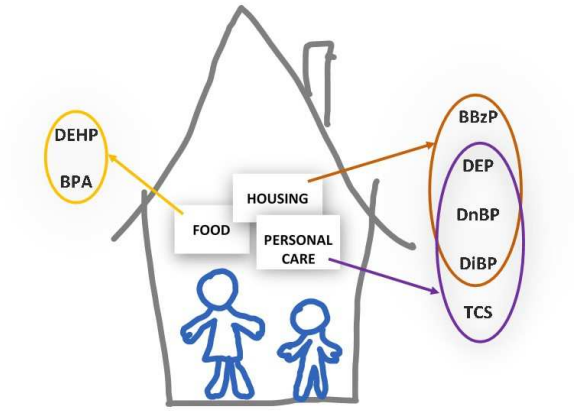
Background. Phthalates, bisphenol A (BPA) and triclosan (TCS) are detectable in the vast majority of people. Most humans are continuously exposed to these chemicals due to their presence in food or in everyday consumer products. The measurement of these compounds in family members may help to explore the impact of major lifestyle factors on exposure. Mothers and (young) children are especially interesting to study, as they mostly share considerable parts of daily life together.

Materials and Methods. Phthalate metabolites, bisphenol A (BPA) and triclosan (TCS) were measured in first morning void urine, collected in mother-child pairs (n=129) on the same day. The mothers (27-45y) and their children (6-11y) were recruited in the Brussels agglomeration and rural areas of Belgium in the context of the European COPHES-DEMOCOPHES human biomonitoring project. Face-to-face questionnaires gathered information on major exposure sources and lifestyle factors. Exposure determinants were assessed by multiple linear regression analysis.

Results. The investigated compounds were detectable in nearly all mothers (92.8-100%) and all children (95.2-100%). The range (P_{90} vs. P_{10}) of differences in urinary concentrations within each age group was for most compounds around 10-20 fold, and was very high for TCS up to 35 and 350-fold in children and mothers respectively. Some participants exceeded the tolerable daily intake guidelines as far as they were available from the European Food Safety Authority (EFSA). Overall, for BPA, the urinary concentrations were similar among both age groups. Most urinary phthalate metabolites were higher in children compared to the mothers, except for monoethyl phthalate (MEP). TCS levels were generally higher in the mothers. Despite the difference in mothers' and children's urinary concentrations, the creatinine-corrected levels were correlated for all biomarkers (Spearman rank r= 0.32 to 0.66, $p<0.001$). Furthermore, for phthalates, similar home and lifestyle factors were associated with the urinary concentrations in both age groups: home renovation during last two years or redecoration during the last year for di-ethyl phthalate (DEP); PVC in home for di-n-butyl phthalate (DnBP), di-iso-butyl phthalate (DiBP) and butyl benzyl phthalate (BBzP), and personal care products use for DiBP and DnBP. Based on questionnaire information on general food type consumption patterns, the exposure variability could not be explained. However, comparing the phthalate intake from the current study with earlier assessed Belgian food intake calculations for both ages, food in general was estimated to be the major intake source for di-ethyl hexyl phthalate (DEHP), with diminishing importance for BBzP, DiBP and DnBP.

Conclusion. Our results confirm, that children and their mothers, sharing diets and home environments, also share exposure in common consumer products related chemicals. By collecting morning urine levels on the same day, and using basic questionnaires, suspected exposure routes could be unraveled.

Key words: phthalate metabolites, bisphenol A, triclosan, mother-child exposure, human biomonitoring



Graphical abstract: Phthalates (BBzP, DEP, DnBP, DiBP, DEHP) and phenols (BPA, TCS) exposure takes place via food and/or everyday consumer products. These compounds were detected in nearly all morning urine samples collected in Belgian mother-child pairs sharing home environments. The levels were clearly correlated among both age groups. Personal care products use, housing and/or food intake were the main determinants of exposure associated with the urinary levels.

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Highlights

- Phthalates, BPA and TCS were measurable in urine of nearly all mother-child pairs
- Analysing morning urine of family members facilitated exploring common exposure patterns
- All urinary levels, especially TCS and MEP were highly variable within both age groups
- Sharing home environments implies sharing exposure in consumer product chemicals

1. Introduction

Phthalates (Sampath et al., 2016) and bisphenol A (BPA) (Corrales et al., 2015) are widely present in consumer products, food, bottled water and even indoor and outdoor air. This results in the exposure of nearly every person to these compounds (Calafat et al. 2008; Wittassek et al. 2011). Phthalates are used as softeners/plasticizers/emulsifyers/stabilizers, BPA is applied in the manufacturing of polycarbonate plastics, epoxy resins and thermal paper, and triclosan (TCS) is a bactericide commonly used as disinfectant and conservation agent, as e.g. used in tooth-paste. The main exposure route can be oral intake (all three chemical groups), or inhalation (phthalates), but also a complex scenario of mixed sources and routes of uptake, including the dermal pathway (Wormuth et al. 2006; Rubin 2011; Sandborgh-Englund et al. 2006; Weschler et al. 2015; Salthammer et al. 2018). Even if exposure to these compounds is widespread in humans (almost 100% detection in urine samples), the exact pattern of both intermittent and concurrent exposure is difficult to unravel for compounds that are rapidly excreted (e.g. within 24 h) (Lorber, Koch, and Angerer 2011; Vandenberg et al. 2007; Sandborgh-Englund et al. 2006; Holger M. Koch et al. 2014; Preau et al. 2010). This is especially of importance for the measured contaminants, as they do not accumulate in the body. Indeed, phthalates have a short half-life of <12 h. For TCS, the major fraction is excreted within 24 hours, with 24% to 83% being excreted within 4 days (Sandborgh-Englund et al. 2006). BPA metabolism and half-life are dependent on the routes of exposure. Rapid metabolism is observed for oral exposure, while other types of exposure (avoiding first pass liver metabolism) may result in longer residence time of BPA in the blood stream (Vandenberg et al., 2007).

Measurement of these present daily-life compounds in individuals and in particular in family members, may help to explore the impact of major lifestyle factors. Mothers and (young) children often share quite some time together and have similar or mutual influenced exposures (Song et al., 2013). In N=258 Taiwanese mother-baby/infant (1-27 months) pairs, 12-hours urine di(2-ethylhexyl) phthalate (DEHP) metabolite levels were higher in the infants compared to the mothers. They observed a low association ($r<0.20$) between the mothers and these young children, which was explained as differences in food intake, mouthing of plastic materials, body surface area relative to body volume, and differences in usage of personal care products (Song et al., 2013). Interestingly mothers having those smaller children had on average 20% higher ∑DEHP metabolite levels. This was interpreted as additional routes of exposure to DEHPs e.g. children's toys and childcare products for mothers with small children. In a North-American study on phthalates in 1-16 month old children and their mothers, medium correlations were found ($r<0.45$), decreasing with increasing age of the infants up to 16 months (Sathyanarayana et al., 2008).

For older, school aged children, the picture may be different. The relationship between N=104 German mothers' and 6-8 y old children's levels was shown to depend on the chemical. The Spearman rank correlation was between r=0.25 and 0.51 for the (or a sum of) phthalate metabolites of di-methyl phthalate (DMP), di-n-butyl phthalate (∑DnBP), di-isobutyl phthalate (∑DiBP), di-isononyl phthalate (∑DiNP), less significant for BPA and di-iso-decyl phthalate (∑DiDP), and not correlated for the phthalates butyl benzyl phthalate (BBzP) and diethyl phthalate (DEP) (Kasper-Sonnenberg, Koch, et al. 2012; Kasper-Sonnenberg, Wittsiepe, et al. 2012). In the European human biomonitoring study COPHES-DEMOCOPHES the relationship between consumer product chemicals measured in N=1844 24-52 y old mothers and their 5-12 y old children was reported for 17 participating European countries (TCS and BPA only analyzed in 6 countries) (Den Hond et al. 2015; Covaci et al. 2015). All mothers and children collected urine simultaneously in the morning. The children had compared to their mothers higher levels of phthalate metabolites (except for MEP), TCS, and similar levels of BPA (Den Hond et al. 2015; Covaci et al. 2015; COPHES 2012). Except for MEP, clearly an indicator of personal care product us, it was observed that 'family' (housing/diet) environment was of importance, causing levels of mothers and children to be correlated in all countries, however with some regional differences (Den Hond et al. 2015; Covaci et al. 2015;Larsson et al. 2014;. Frederiksen et al. 2013; Cutanda et al. 2015; Cullen et al. 2017).

Overall, living in the same (home) environment, sharing the same daily routine, and, to a large extent, eating the same food, can likely cause exposure levels to be similar. However, since early life is an intense period of growth and food intake, rapidly changing behavioural patterns (e.g. playing, mouthing, product use), and/or metabolism may be different in different age groups, also considerable differences in internal exposure were seen despite sharing homes and similar diets (Lunder et al., 2010).

The current manuscript investigates the exposure of mother-child pairs to phthalates, TCS and bisphenol A in the Belgian population of the COPHES-DEMOCOPHES study. Their total daily intake was back calculated from the measured urinary concentrations. Self-reported home environment and lifestyle factors were explored for their influence. For phthalates, the total daily intake could be compared with Belgian daily food intake levels available for both age groups (Fierens et al. 2012; Sioen et al. 2012).

2. Methods

2.1 Study population

The Belgian study population consisted of 129 children and their mothers. N=64 mother-child pairs lived in the urban area of the Brussels capital and N=65 in rural areas 50-65 km south-west of the capital (Brakel, Ellezelles, Frasnes-lez-Anvaing). The rural or urban communities were defined

according to the number of inhabitants (respectively < or >150,000 inhabitants), and the population density (respectively < or >295 inhabitants/km^2). The two major language communities of Belgium were equally represented (Dutch and French speaking). The recruitment was done via schools by two field work teams of those language areas. Field work lasted five months from October 2011 until February 2012. According to the COPHES protocol (Becker et al., 2014) the recruited children were between 6-11 years old and the mothers were between 27 and 45 years old. It was aimed for to recruit ten boys and ten girls per age year, equally distributed between rural/urban residence places. Only one child per family (randomly selected) who lived at least the last 5 years most of the time (> 16 days/month) with the mother was allowed to participate. Mothers or children living in hospitals or institutions, being homeless, or having metabolic disturbances or abnormal urine excretion, were excluded. Pregnant women were also excluded from this study. Mothers had a face-to-face interview with the field workers on their and their children's home environment and residence, smoking behaviour, alcohol consumption, professional occupation, household income and nutrition during the last 4 weeks. The food items included in the questionnaire relevant for phthalate, TCS and bisphenol A exposure were: rice, meat, fast food, milk, cheese, cereals, chocolate, ice, canteen food, chewing gum, fish, shellfish, sea fish and seafood. Height and weight of both mother and child were measured by the field workers. The study was approved by the ethical committees of the University of Antwerp (UA) and the University of Liège (ULg) (registration number: B7072201111787). An application form was submitted to the Belgian Commission for Protection of Personal Privacy (registration number VT005033861).

2.2 Urine collection

The child and mother both collected their first morning urine void on the same day in polypropylene containers of 250 mL (VWR International®, ref 215-5683). The vessels were kept at 4°C,aliquoted in secondary polypropylene tubes within maximum 4 days after sampling, and stored at -20 ^{o}C for maximum 1 month until chemical analysis. To eliminate contamination, previous to sampling, all primary and secondary urine vessels were rinsed overnight in 10% nitric acid, then twice rinsed with purified water and allowed to dry under a laminar flow. Contamination tests were done according to COPHES prescriptions: some vials were filled during 10 min with purified water. These control vessels were then analyzed and found negative for the compounds targeted in the urine.

2.3 Phthalate analysis

In urine, the following phthalate metabolites were measured: mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (5-OH MEHP), mono-2-ethyl-5-oxohexyl phthalate (5-oxo

MEHP), mono-n-butyl phthalate (MnBP), mono-benzyl phthalate (MBzP), monoethyl phthalate (MEP), and mono-iso-butyl phthalate (MiBP).

The frozen samples were thawed, vortexed and sonicated for 5 minutes. The methodology was described in detail in Servaes et al. (2013). Briefly, enzyme buffer (beta-glucuronidase E. coli type K12) and internal standards (^{13}C-MEP, ^{13}C-MnBP, ^{13}C-MBzP, ^{13}C-MEHP, ^{13}C-OH-MEHP, and ^{13}C-oxo-MEHP) were added to 1 mL of sample. This mixture was incubated at 37 °C for 90 min. 10 µL of the solution was injected in a tandem UPLC-MS/MS (triple quadrupole, Waters Acquity UPLC-Waters Xevo TQ-S) equipped with an Acquity UPLC BEH PHENYL 1.7 µm, 2.1 x 100 mm column. Elution was done using A: water + 0.1% acetic acid and B: acetonitrile + 0.1% acetic acid with the following gradient program: 0–0.5 min: 95% A; 0.5–8 min: 95–10% A; 8–8.5 min: 10–95% A (return to initial conditions); 8.5–10 min: equilibration of the column. External calibration using an internal standard was used for quantification. Calibration solutions in a range of 0.1 to 250 µg/L were made in acetonitrile:water (1:9). Twenty samples were measured per run. The limit of quantification (LOQ) equaled: 0.50 µg/L for MEP, MiBP and MnBP, 0.20 µg/L for MBzP, and 0.10 µg/L for 5OH-MEHP and 5oxo-MEHP.

2.4 BPA and TCS analysis

The analysis was similar to that described by Geens et al. (2009). Briefly, 3 mL of urine was hydrolyzed adding the internal standards ^{13}C-BPA and ^{13}C-TCS, 50 µL β-glucuronidase/sulfatase and Na-acetate buffer 1M (pH 4.5) for 2 h at 40°C, followed by addition of 200 µL formic acid + 15 min sonication. Extraction was performed by SPE using Oasis HLB (3 mL, 60 mg). Elution was done with 5 mL methanol-dichloromethane (1:1 v/v) and the extract was evaporated to dryness. To the dry extract, 1 mL water + 2 mL hexane + 50 µL KOH + 50 µL pentafluorobenzoylchloride was added and vortexed. The hexane layer was transferred to another tube and the hexane extraction step was repeated, collecting all hexane fractions in one tube. Clean-up of the samples was done by transferring the hexane layer to a 3 mL cartridge containing 1 g acidified silica (10% H_2SO_4) + 200 mg anhydrous Na_2SO_4. Elution was done using 6 mL hexane. After evaporation until dryness, the extract was reconstituted in 100 µL iso-octane. The measurements were done by gas chromatography (Agilent 6890 GC) – electron capture negative ionisation mass spectrometry (Agilent 5973 MS) (GC-ECNI/MS) equipped with a 15 m x 0.25 mm x 0.10 µm DB-5MS column, at 170°C (MS-source) and by injection of 1 µL, cold and splitless, using a PTV injector. The following ions were monitored: ^{13}C-TCS (m/z 494 and 299), ^{12}C-TCS (m/z 482 and 287), ^{13}C-BPA (m/z 628 and 418) and ^{12}C-BPA (m/z 616 and 406) (1 quantifier + 1 qualifier ion) (Geens et al., 2009). Quantification was done using the internal standard method. The LOQ was 0.20 µg/L for BPA, and 0.10 µg/L for free BPA, TCS and free TCS.

Free unconjugated TCS and BPA were analyzed in respectively 11 and 10 randomly selected urine samples of each age group, to check for possible contamination. For all of these samples, the ratio of free versus total TCS or BPA was clearly below 10% , which is speculated to be the maximal share of free over conjugated compounds (Kasper-Sonnenberg et al., 2012b); Völkel et al. 2002). We therefore concluded the influence of possible external BPA/TCS contamination to be minimal and negligible for further interpretation of the results.

2.5 Analytical quality assurance

Each participating laboratory received SOPs for sampling, sample conservation, and chemical analysis within the COPHES project (Schindler et al., 2014). Two interlaboratory comparison investigations and two external quality assessment schemes (ICI/EQUAS) were done with control urine samples sent to all laboratories. In this process, the Belgian laboratories were defined as competent and qualified laboratories (Schindler et al., 2014).

2.6 Data analysis and statistics

2.6.1 Influence of exposure determinants on urinary levels

Biomarker data were natural logarithm (ln-) transformed to a normal distribution. Eight urine samples (4 from mothers, 4 from children) with a creatinine level below <300 mg/L or above 3000 mg/L were excluded from the statistical analysis (WHO, 1996). Since only a minor proportion of the measurements were below the LOQ (7% for MEHP in mothers, 5% for MEHP in children, 2% for TCS in children and 3% for BPA in children), values below the LOQ were replaced by single imputation of half the LOQ. Correlations between exposures in mother and children were assessed using Spearman rank correlation. Multiple linear regression models were constructed, separately for both age groups, for identification of the determinants of exposure, including predefined confounders (urinary creatinine, age, sex) and covariates (Table 1) which were correlated with the biomarker based on ANOVA analysis ($p<0.25$). Quantitative relationships between the covariates and the biomarkers were calculated from the estimates of the multiple linear regression model, assuming that, when quantifying the relation of one covariate with the biomarker, all other covariates in the model are fixed at the population mean. The obtained estimates were presented as multiplicative change in mean biomarker concentration per unit increase of the covariate. Outliers of exposure were assessed using the studentized deleted residuals and outliers with respect to the predictor variables were assessed using the leverages or the diagonal elements of the hat matrix. After identification of the outliers, they were examined to see if they were influential cases using their DFFITS (influence on a single fitted value) and Cook's Distance (influence on all fitted values). Outlying observations which were also considered to be influential cases were considered for further sensitivity analysis, that is

fitting the model excluding them and checking whether there was any significant change in regression estimates of the parameters. All confounders and covariates were included in the models as categorical variables. For the mothers, the variable 'tobacco smoke' was constructed as a combination parameter, being: smokers exposed to environmental tobacco smoke (ETS, at home/elsewhere frequent or sometimes exposed), smokers (daily or occasional) not exposed to ETS, non-smokers exposed to ETS, and the non-smokers not exposed to ETS. As all children indicated to be non-smokers, only ETS was used in the models. Use of personal care products was scored based on the frequency (never to daily) of the use of nine product groups: make-up, shampoo, eye make-up, hair styling products, body lotion & creams, fragrances, deodorants, nail polish and massage oil. For each of the nine groups the frequency was scored as follows: 7 = (almost) every day, 4 = between 3-5 times per week, 1 = up to 3 times per week, 0 = (almost) never. All scores were summed and categorized: score >30: high use, score >5 and <=30: moderate use, score <=5: low use.

2.6.2 Daily intake of compounds

Estimation of the daily intake (DI) of phthalates was done using the urinary (metabolite) concentrations measured in the participants, and the fractional urinary excretion of each compound, the daily intake (DI) of the children and mothers was estimated:

$$DI = [(UE \times CE) / (FUE \times 1000)] \times (MW_{metabolite}/MW_{parent\ compound})$$

With: DI= daily intake, µg/kg bw/day; UE= phthalate metabolite expressed on a creatinine basis, µg/g creatinine; CE= daily creatinine excretion normalized to body weight, mg/kg bw/day; FUE = molar fraction of the urinary excreted metabolite in relation to the ingested parent compound over 24 h after exposure, fraction; 1000 = units conversion factor, mg/g; MW the molecular weights of the metabolites and parent compound, g/mol (Wittassek et al., 2007).

The daily creatinine excretion (CE) used in both calculations, was for adult women equal to 21, 18 and 16 mg/kg bw/day for the BMI category of <25 kg/m^2, 25-30 kg/m^2 and >30 kg/m^2, respectively (Johner et al., 2015). For children the following levels were used: 19 and 21 mg/kg bw/day for boys between 6-8 y and 9-13 y, respectively, and 18 and 19 mg/kg bw/day for girls of those age groups (Remer et al., 2002). The CE was calculated from those values in mmol/kg bw/day using the MW of creatinine being 113.12 mg/mmol. For the phthalates, the fraction of the metabolite excreted in urine (FUE) was taken from human metabolism and excretion studies after oral dosage: 5.9, 23.3 and 15% of DEHP was excreted as MEHP, 5OH-MEHP, and 5oxo-MEHP (Koch et al. 2005), 84% of DnBP was excreted as MnBP, 71% of DiBP as MiBP (Koch et al. 2012), 73% of BBzP as MBzP, and 69% of DEP as MEP (Koch, Drexler, and Angerer 2003).

The calculated DI, based on urinary levels, was compared with phthalate intake levels calculated from a Belgian study in which eight phthalates – the low molecular weight dimethyl phthalate (DMP), DEP, DiBP, DnBP, BBzP, and the high molecular weight DEHP, dicyclohexyl phthalate (DCHP) and di-n-octyl phthalate (DnOP) – were measured (PHTAL study, Sioen et al. 2012). In that study, a phthalate intake assessment for children and adults was done based on a combination of the phthalate concentrations measured in over 550 food products sold on the Belgian market in the year 2009-2010 (Fierens et al., 2012), and a Belgian food consumption databases of preschool children (2.5 to 6.5 years old) or adults (≥15 years old) (Vandevijvere et al. 2009). In the current paper the 50th (P_{50}) and 95th (P_{95}) percentiles of the corrected, long-term intake distributions of DEHP, DEP, BBzP, DiBP and DnBP (separately for the preschool children and the adults) were used to compare with the respective intake values calculated based on the P_{50} and P_{95} urinary metabolite levels in both age groups.

For BPA and TCS the DI was calculated under the estimation that BPA and TCS was 100% excreted within 24h (Sandborgh-Englund et al., 2006; Völkel et al., 2002):

DI = UE x CE / 1000

With: DI= daily intake, µg/kg/day; UE= urinary excretion of the compound expressed on a creatinine basis, µg/g creatinine; CE= daily creatinine excretion normalized to body weight (bw), mg/kgbw/day, 1000 = units conversion factor, mg/g.

3. Results

3.1 Study population

Fourteen percent of the people invited to the study wished to participate, but due to stringent inclusion criteria of living area, age and sex classes needed, only 5.3% of the invited individuals could participate. Most of the people wanting to participate were excluded because they did not live long enough in the area, or because of the mother being more than 45 y old. 128 non-responder questionnaires were filled out. The main differences between responders and non-responders were a higher education level (84 vs. 65% tertiary education) and a higher number of working mothers in the responders (92 vs. 80%). There was no difference in smoking habits, frequency of eating fish and number of single mothers.

The median age of the 129 participating mothers and children was 40 years and 8 years, respectively. 9.3% of the mothers were current smokers and none of the children reported to be smoker. 42% of the mothers reported high use and 58% reported moderate use of personal care products (like make-up, shampoo, eye make-up, hair styling products, body lotion, creams, fragrances, deodorants, nail

polish and massage oil). About 1/3rd of the children were moderate users of those products. The rest of the children were low users (64.6%). Half (52%) of the families indicated that they had the last year redecoration, or the last two years renovation activities in their house. PVC flooring or wall paper was present in 24% of the houses (see also Table SI-1 and SI-2).

3.2 Children and mothers internal exposure

The targeted urine metabolites were detectable in almost all mothers and their children. Most phthalate metabolite urinary concentrations, expressed on volume base, were higher in children compared to the mothers: MEHP + 5oxoMEHP + 5OHMEHP (geometric mean 36.7 vs. 21.3 µg/L), MBzP (8.78 vs. 6.47 µg/L), MiBP (58.2 vs. 38.1 µg/L) and MnBP (39.0 vs. 30.9 µg/L). The phthalate MEP (26.2 vs. 36.3 µg/L) and TCS (1.23 vs. 2.72 µg/L) were lower in children compared to the mothers, whereas for BPA there was no difference between both age groups (2.35 vs. 2.55 µg/L) (Figure 1). The difference in concentrations between the highest and lowest exposed individuals (P_{90} vs. P_{10}) was considerable for most phthalate metabolites, namely a factor 10, and highest for MEP (factor 13-20 for children and mothers respectively) (Table SI-3).

The health-based guidance value HBM-I for the sum of 5oxo-MEHP and 5OH-MEHP of 300 µg/L, set for women at child-bearing age (Schulz et al. 2011; Apel et al. 2017) was not exceeded by any of the mothers. One girl living in the city center, had a urine level of the sum of 5oxo-MEHP+5-OHMEHP of 1337 µg/L, distinctly above the HBM I of 500 µg/L for children (Schulz et al. 2011; Apel et al. 2017). Such high level of DEHP exposure could only be speculated to originate from contaminated food intake (or possible intensive mouthing of a PVC product). There were no other indications of possible sources based on the questionnaire info. It was apparent that also the mother of that child had rather elevated levels for the sum of 5oxo-MEHP+5-OHMEHP i.e. 94 µg/L, which was around the P_{95} in the mothers' population (in the same way as the MEHP levels of both mother (36µg/L) and child (19 µg/L)). Metabolites of all other phthalates in that girl were within the normal concentration range. Also in some other mother child pairs with both elevated levels, it was difficult to explain them based on the questionnaire data. This was so for a mother having a urinary MBzP level of 164 µg/L, where also the child had the highest value of 120 µg/L. A group of ten mother-child pairs, each had high levels for MiBP between 97 and 1940 µg/L. For MnBP and MEP, the synchronic increase was less pronounced.

For BPA, the levels in the mothers and the children were comparable: GM 2.55 vs 2.35 µg/L. The difference in concentrations between the higher (P_{90}) and lower (P_{10}) exposed individuals within an age group were moderate (factor 4 in the mothers and 10 in the children). This indicated a rather homogeneous exposure among the population. One mother had a high exposure of 456 µg/L, and in the same way, the female child had a high urinary value of 445 µg/L. These were the only

participants, that had levels above the HBM-I threshold of 0.1 and 0.2 mg/L BPA for children and mothers respectively (Apel et al., 2017).

For TCS, the mothers had two-fold higher levels compared to the children, GM 2.72 vs. 1.23 µg/L. The variability in concentrations within each age group, between the higher (P_{90}) and lower (P_{10}) exposed individuals was very high with a factor 350 and 35 in mothers and children, respectively. This may be due to a high variability in individual use and TCS levels in different trademarks of consumer products. Three mothers had urinary TCS levels higher than 800 µg/L, unlike their children that were low in urinary TCS (<2.0 µg/L). The children with the highest levels of 645 (girl), 434 (boy) and 427 (girl) µg/L, had mothers with high TCS levels of respectively 427, 290 and 177 µg/L. None of the mothers or children had urinary levels above the biomonitoring equivalent of 6.4 mg/L (based on USA reference dose) or 2.6 mg/L (based on European NOAEL) (Krishnan et al., 2010).

Overall, mothers' and children's urinary concentrations were correlated (Spearman rank r= 0.43 to 0.66, p<0.001) in decreasing order from MiBP, MBzP, MnBP, TCS, MEP to BPA. The metabolites of DEHP were less correlated, r=0.40 for MEHP, and r=0.32 and 0.35 for the oxidative metabolites of MEHP, namely 5oxo-MEHP and 5OH-MEHP (Table SI-3; Figure SI-1).

3.3 Exposure determinants

Factors of influence, and significant in both age groups were reported PVC flooring and/or wall paper in the house (significant for MEP, MBzP, and MiBP, with estimates between 16 and 2 fold increase for individuals having PVC), and home renovation the last two years or redecoration in the last year (MEP, estimate of 1.8 in children and their mothers) (Table 1) (Figure 2). Use of personal care products could be shown to be of influence for MnBP, MiBP, and TCS in the children (respectively estimates of 1.3, 1.5, and 2.7 fold increase). Sunscreen use influenced TCS levels in the children's urine (estimate of 6.1 fold). In the mothers, MEP was influenced by their personal care product use (1.8 fold higher in high vs. moderate users) (Figure 2). For the children, the use of flexible plastic toys daily compared to never, appeared to increase the urinary MEP level almost 2-fold (Table 1).

Unlike of the observed association of the urinary levels vs. the use of consumer goods, the influence of the intake of food contaminants could not be demonstrated using the questionnaires. Although DEHP is overall present in food, none of the questioned food items was of significance for the urinary metabolites. Canned food being one of the major exposure routes for BPA, did not appear significant in children, but proved to be of importance in the mothers (estimate of 1.6 for mothers using it several times per week compared to <=1 per week) (Table 1) (Figure 2).

3.4 Daily intake of chemicals

From the urinary biomarker levels, the daily intake of all compounds was calculated. Overall the median daily intake of phthalates in the children of the current study was highest for DEHP (median=1.8 µg/kg bw/day). In the mothers the intake was highest for DEP (median=1.2 µg/kg bw/day) (Figure 3, Table SI-4). The children had on average a higher phthalate intake compared to the mothers, except for DEP. One girl had a calculated DEHP daily intake level, which was 127.5 µg/kg bw/day i.e. 2x above the European Food Safety Authority (EFSA) tolerable daily intake (TDI) value of 50 µg/kg bw/day. For DnBP and BBzP, the respective EFSA TDI levels of 10 and 500 µg/kg bw/day were not exceeded by any of the participants. For BPA and TCS the median intake in mothers and children was similar, 0.04 and 0.02 µg/kg bw/day, respectively. One mother and her female child had a BPA daily intake of 10.8 and 5.2 µg/kg bw/day, respectively. This was above the EFSA t-TDI of 4 µg/kg bw/day (EFSA, 2015).

For the phthalates, Belgian daily food intake levels for preschool children and adults were available from the PHTAL study (Sioen et al., 2012). The median of the DEHP long-term intake via food calculated in that study was comparable or higher than the median daily intake of DEHP intake, calculated based on the urinary levels of the children and mothers in the current study. Contrary to that, for the other phthalates (DEP, BBzP, DiBP and DnBP) the daily intake levels from food (PHTAL study) were considerably lower than the total daily intake levels calculated from the urinary concentrations (Figure 3; Table SI-4).

4. Discussion

In a group of Belgian mothers and primary school children (6-11 y), we examined the urinary levels of phthalates and phenols, the determinants of exposure, and the correspondence among both family members of which first void urine was collected at the same day. Indeed, concentrations of those generally in daily-life used compounds, was earlier reported to show similarity in mothers and their young children (e.g. Kasper-Sonnenberg, Koch, et al. 2012; Kasper-Sonnenberg, Wittsiepe, et al. 2012; Den Hond et al. 2015; Covaci et al. 2015).

4.1 Urine levels and daily intake

Almost all participants (>92.8%) had detectable levels of the analyzed phthalates and phenols, in agreement with reports from all over the world (e.g. Covaci et al. 2015; Frederiksen et al. 2013; Den Hond et al. 2015; Kasper-Sonnenberg et al. 2012; Sathyanarayana et al. 2008; Song et al. 2013). The variability among urine levels within the group of mothers or children was highest for the phthalate MEP (respectively 20 and 10-fold difference between P_{10} and P_{90}) and for TCS (respectively 350 and 35-fold). These are chemicals omnipresent in personal care products, of which the use and the

451 resulting exposure may be quite variable among individuals (Wormuth et al. 2006; Geens et al. 2012;
452 Holger M Koch et al. 2014; Preau et al. 2010)
453 The daily intake of the phenols and phthalate metabolites were calculated from the measured spot
454 urine levels and available urinary excretion fractions of the metabolite relative to the parent
455 compound. Such a calculation, based on a single spot urine sample, may, due to rapid elimination
456 kinetics, substantially over- or underestimate the exposure of the individual (Holger M. Koch et al.,
457 2014), i.e. may not necessarily be representative for their average daily exposure. On the other hand,
458 Philippat et al. (2015) reported, when repeating urine collection in the same individuals after 1 year,
459 the levels were well correlated for TCS (r=0.71) and MEP (r=0.44), and moderate for MnBP (r=0.25)
460 and MiBP (r=0.39), suggesting that urine levels of short-lived metabolites may also represent a
461 'persistent behavior' of an individual. In the current study, for most of the participants the calculated
462 daily intake was below the TDI values set by EFSA i.e. below 50, 10, 500 and 4 µg/kg bw/day for
463 DEHP, DnBP, BBzP and BPA, respectively (Table SI-4). The median calculated daily intake levels of
464 DEHP, DnBP, BBzP, DEP were rather low, or similar for DiBP as reported for several countries in
465 Wittassek et al. (2011) and Clark et al. (2011). The DiPB intake of mother and child were also similar
466 to those calculated in a Danish population within the current European COPHES/DEMOCOPHES
467 campaign (Frederiksen et al., 2013). For BPA, the median total intake was both, for mothers and
468 children 0.04 µg/kgbw/day. This was in line with median levels of <0.1 µg/kgbw/day calculated from
469 biomonitoring data collected in the general population of different countries and summarized in
470 Geens et al. (2012).
471 Unfortunately, the individual exposure outliers could not be clearly explained based on the
472 questionnaires, probably because there was not enough detailed information on specific food items
473 consumed and/or on trademarks of the used consumer products or of the indoor materials present
474 in the homes. On group level, the main exposure determinants were either indoor housing
475 parameters (home renovation, PVC flooring/wall paper) and/or consumer products (personal care
476 products, flexible plastic toys).
477 This was also earlier reported in other studies, and on European scale within the
478 COPHES/DEMOCOPHES study (Covaci et al. 2015; Geens et al. 2012). For the different phthalates, we
479 could compare the calculated total intake based on the urinary levels, with phthalate food intake
480 data from the Belgian PHTAL study. The Belgian food intake calculation was done one year before the
481 current human biomonitoring campaign (Fierens et al. 2012; Sioen et al. 2012). From the PHTAL
482 study DEHP appeared to be the most abundant phthalate compound in food, followed by DiBP, DnBP
483 and BBzP (Fierens et al., 2012). The daily DEHP food intake calculated from Belgian food
484 concentrations was in the same range, or even higher than the total intake calculated in our study
485 (based on the urinary metabolites MEHP, 5OH-MEHP, 5oxo-MEHP): 88% and 312% food vs. total

intake for respectively children and mothers (Table-SI-4, Figure 3). The comparison is indicative. Among others, urinary excretion of the primary phthalate monoesters underestimates exposure to phthalates for e.g. the long alkyl chains, such as DEHP and di-iso-nonyl phthalate (DINP) (but also for the low molecular weight MiBP and MnBP) which undergo further metabolism (oxidation, hydroxylation, carboxylation) prior to excretion (Koch et al. 2012).

For the shorter chain phthalates, DiBP, DnBP and BBzP, consumer products seem of the same or even higher importance compared to food (Wittassek et al. 2011; Holger M Koch et al. 2013) . Based on the comparison between the PHTAL food intake levels and the total intake back-calculated from the urine levels, the food intake route of DiBP, DnBP, and BBzP covered 26-64% and 9-24% of respectively the mothers' and children's daily intake (Table-SI-4, Figure 3). Wormouth et al. (2006) reported especially exposure to DEP being mainly via personal care products use. It was therefore not surprising to observe the discrepancy between the total intake and the food related intake being highest for DEP (only <10% food vs. total intake) (Table-SI-4, Figure 3). The metabolite MEP is a clear indicator of personal care use (Nassan et al., 2017). This chemical is indeed omnipresent in fragrances, lotions, creams, and was hardly measured in Belgian foodstuff (Fierens et al., 2012).

4.2 Mothers and children: related but not equal in exposure

The current study showed that children's urine levels may be partly predicted from adult measurements. Indeed, individual mothers having higher urinary concentrations of DEHP metabolites, MBzP, MiBP, BPA and TCS, also showed to have children with levels in the higher end range of their age group. For the phthalate metabolites MnBP and MEP the similarity was less pronounced.

We also observed correlation coefficients of r=0.40-0.66 for creatinine-corrected urine values (except for the lower r=0.32 and 0.35 for secondary oxidation products of DEHP), between the children's and their mothers' first void urine levels. It was to be expected as they normally share diet and home environments. Interestingly, excluding mother-child pairs not always sharing diet - i.e. of which either the mother or the child consumed canteen food several times a week - resulted in a higher correlation only for the DEHP metabolites (N=58 mother-child pairs). Indicating that mainly for DEHP, food intake was an exposure contributor. Still, even sharing life environment, the complex interplay between age, contaminant user patterns, and environmental partitioning may cause the exposure to be different (Lunder et al., 2010). Indeed, similar to what was previously shown in other studies (e.g. Lin et al. (2011) for DEHP metabolites), the children in the current study had higher morning urinary levels of DEHP metabolites (1.7x higher), MiBP (1.5x), MnBP (1.2x) and MBzP (1.4x) compared to their mothers (resulting in higher total intake levels calculated from the urine levels, Figure 3). Knowing that children have a higher urine volume compared to adults (i.e. more dilution per urinary

volume) (Wittassek et al., 2011), enforces that the uptake levels of those compounds was higher in children. This may be a result of a higher exposure, such as increased food uptake in relation to body size in children. It may hold for the parent compounds DEHP and DiBP and DnBP, known to be substantially originating from food contamination throughout its processing (Wormuth et al., 2006). Higher urinary MBzP (as well as MiBP and MnBP) in children, compared to their mothers – even presuming them both exposed to equal concentrations of phthalates in indoor air – might be partly explained by higher phthalate inhalation uptake rates in children (100%) compared to teenagers and adults (75%) (Wittassek et al. 2011; Wormuth et al. 2006). On the other hand, it has to be noted, that the higher levels of those butyl phthalates in the children might also be partly because of the fact that they sleep more hours. Their morning urine may reflect a longer exposure time (Kasper-Sonnenberg et al., 2012b), assuming continued exposure during the night. For sources such as indoor PVC flouring and wall paper, the latter may be plausible.

We furthermore saw a slight increase in proportional amount of 5oxo-MEHP in children (40%) compared to mothers (36%). Kasper-Sonnenberg (2012) and Song et al. (2013) observed similar higher excretion levels for most of the secondary phthalate metabolites in children of that age compared to adults. This may be due to a more effective oxidative metabolism in children (Becker et al. 2004, Koch et al. 2004, 2006; although not observed by Wittassek et al. (2007)), but it may also simply be due to the longer urination time lag as mentioned above. The latter makes that especially secondary metabolites, such as 5OH- and 5oxo-MEHP, with a much longer elimination time in the range of 10-15 hours, compared to 5 hours for MEHP, accumulate more in morning urine of children (Lorber, Koch, and Angerer 2011; Kasper-Sonnenberg, Wittsiepe, et al. 2012). In our study, the time between the last urination and the morning urine void collected, was on average three hours longer for children compared to their mothers (median 10.5h vs. 7.6h).

It was earlier reported, that families having PVC floors or PVC wall paper in their homes, had significantly increased levels of MBzP in children (Sweden (Carlstedt, Jönsson, and Bornehag 2013); Spain (Cutanda et al. 2015); European wide (Den Hond et al. 2015)), of MiBP in children and mothers, and of MnBP in children (Den Hond et al., 2015). The strong mother-child correlation of urinary butyl phthalate monoesters (r=0.66, 0.63 and 0.54 for MiBP, MBzP and MnBP) points to similar 'within-family' exposure. It supports the knowledge, that apart from food as major source for these phthalates, ingestion of dust and/or inhalation may be quite important in children and even in adults (Wormuth et al., 2006).

For TCS and MEP - two compounds which are, as the other chemicals almost completely excreted in urine within 24 h - the situation was however somewhat different. Firstly, the levels were higher in the mothers compared to the children (respectively 2x and 1.4x). This was most probably due to an

on average higher level of personal care products' use in the female adult group, as was also seen in other studies (e.g. in Frederiksen et al. 2013;Cutanda et al. 2015). In the regression models of the current study, the sum of the personal care products and or sunscreens explained the variability in urinary MEP only in the mothers, and for TCS only in the children (Table 1). Possibly the more general use of hand soaps, mouth wash products and disinfection gels among the mothers (most mothers were moderate to high users) made it difficult to identify personal care products as TCS exposure determinants.

Secondly, TCS and MEP urinary levels also differed from the other measured compounds in that they showed the highest variability within each of the age groups: difference of a factor >30 between the 10^{th} and 90^{th} percentile of each age population. For the other phthalate metabolites and BPA, this difference in urinary concentrations within an age group was 'only' of the order of 10. This was also reported by Sandborgh-Englund (2006), and Den Hond et al. (2015). It emphasizes that the MEP and TCS levels were influenced by individually very different exposures. Personal care products' exposure could be one of those variable exposures, as there is a large variation in quantity, frequency and timing of individual exposure and/or a high variability in types of products used. For TCS, other potentially individually variable sources, such as wearing of sportswear, socks, shoes, and household articles impregnated with TCS to limit bacterial growth (Allmyr et al., 2006) were potentially of importance (NB: these were not covered by the questionnaire). Furthermore, the fraction of lipid-soluble TCS excreted within 24h was found to be highly individually different as described in Sandborgh-Englund et al. (2006). It was therefore to some extent remarkable that children and mothers' urinary concentrations of MEP and of TCS were relatively good correlated (respectively Spearman rank r= 0.49 and r=0.52, $p<0.001$). Certainly there is also for these chemicals a common exposure pattern as e.g. children and mothers may use some personal care products such as shampoo, tooth paste (NB: not asked for in the current study) and lotions within the family. At least for TCS (but not for MEP), we observed that children with the highest levels (645, 434 and 427 µg/L), had mothers with high TCS levels (respectively 427, 290 and 177 µg/L).

For urinary BPA, there were no clear differences in urinary levels between mothers and their children This was also seen on European level, with furthermore also no clear differences in the levels among the countries (Covaci et al., 2015). We did not observe any tendency of higher BPA levels in the children's youngest age category (6-8 y) compared to the older age group (9-11 y) as observed in the European data (Covaci et al., 2015). The correlation between mothers' and children's urinary BPA levels was moderate with r=0.43. We may speculate that exposure was determined by common life style factors such as food consumption pattern of the family, as well as individually differences in use of e.g. medication and convenience food.

Overall, our results confirm mainly previously reported phthalate exposure findings, that in case adults and children live together in the same home environment and the urine samples are collected at the same time point, the values are different, but the correlation between the mothers' and child exposure can be considerable (Sathyanaryana et al. 2008; Song et al. 2013; Wittassek et al. 2011 and Frederiksen et al. 2013).

4.3 Strengths and limitations of the study

Since single spot urine causes moderate to large intra-individual variability in exposure levels (Barr et al., 2005), certainly it was a strength of the study, that the spot urine sample collection was synchronized for mother and child. This allowed to a certain extent, capturing similar (possibly substantial), and elucidating dissimilar daily life exposure sources and/or uptake rates in both age groups.

We collected only one urine sample i.e. the first morning void of the day and may have missed the rise in urinary concentrations following personal care product use (Philippat et al., 2015) or food intake. For this reason, the current study may have underestimated the associations between life style factors and urinary concentrations. Furthermore, home environmental and/or food levels were not measured and the types/trademarks of consumer products were not asked for. For example, personal care products use was only reported in general terms as 'use of' make-up, shampoo, eye make-up, hair styling products, body lotion, creams, fragrances, deodorants, nail polish, massage oil and sun screens. These products, as well as food items, may contain various levels dependent on addition of the chemical, or contamination by packaging and processing.

5. Conclusion

Analyzing morning urine collected at the same day in two age groups living in the same household allowed to compare exposure to phthalates (BBzP, DEP, DnBP, DiBP, DEHP) and phenols (BPA, TCS). Although the levels were not similar they were clearly correlated among the mother-child pairs. This confirmed the finding that exposure routes such as food and/or home life environment were considerable determinants.

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820 **Table 1:** Factors of influence on levels of the urinary compounds (µg/L) analysed via linear multiple regression analysis. The estimate and 95% confidence interval reflect the
821 times increase in biomarker for a unit increase of the factor of influence. All models were corrected for creatinine level of the urine, age, and also sex in case of the children
822 (the latter two variables are listed in the table in case they were significantly associated with the biomarker levels)

Compound	Metabolite	Major human exposure source of parent compound	Tested determinants of exposure for all compounds	Additional tested determinants of exposure	Significant variables (estimate (95% CI)		
					Determinant	Mothers	Children
DEHP	**MEHP+ 5OH-MEHP+ 5oxo-MEHP**	Food: contact materials, food processing. PVC polymer and plastisol applications[1]	-Creatinine[3] -Sex -Age -Urinary volume -Time urine collection -Food consumption in last 4 weeks: o Rice o Meat o Convenience food/snacks o Canteen food o Milk o Cheese o Cereals o Chocolate o Ice cream o Chewing gum -Water consumption in last 4 weeks (tap, own source) -Educational level - Rural/urban	-BMI -Home renovation last 2 years/redecoration in last year -PVC in floors and wall paper -Use PCP -Contact with (rubber-like non-latex) gloves -Contact child with flexible plastic toys -Age of car and time/day spent in it -Industry in neighborhood	none	-	-
DEP	**MEP**	PCP, such as fragrances, deodorants, hair products, detergents, lotions			Home renovation (y/n)	1.83 (1.23-2.73)**	1.80 (1.20-2.71)**
					PVC in floors/walls (y/n)	1.99 (1.25-3.18)**	1.72 (1.10-2.70)*
					Use PCP[2] (high/moderate)	1.81 (1.20-2.73)**	NS
					Canteen food (several times/wk vs. <=1/wk)	1.98 (1.09-3.59)**	NS
					Chewing gum (several times/wk vs. <1/wk	NS	1.74 (1.02-2.98)*
					Flexible toys use (daily/ never)	-	1.95 (1.14-3.33)*
BBzP[5]	**MBzP**	PVC flooring, tiles, artificial leather. Often used also in non-PVC applications such as PCP, paints, adhesives or enteric-coated tablets + food contact materials/food processing			PVC in floors/walls (y/n)	1.60 (1.14-2.24)**	1.79 (1.22-2.63)**
DnBP	**MnBP**				Use PCP (high/moderate)	NS	1.28 (1.00-1.65)*
					PVC in floors/walls (y/n)	NS	1.33 (1.01-1.75)*
DiBP	**MiBP**				Lower vs. higher age group[4]	NS	1.44 (1.06-1.97)*
					Use PCP (high/moderate)	NS	1.48 (1.07-2.06)*
					PVC in floors/walls (y/n)	1.75 (1.25-2.45)***	1.85 (1.29-2.65)***
BPA	**BPA**	Polycarbonate: construction material, food cans, drinking bottles; Epoxy resins: e.g. lining of food/drink cans, flooring, adhesives, composite dental filling		- Home renovation last 2 years/redecoration in last year - Contact with plastic toys by child	Canned food (several times/wk vs. <= 1/wk)	1.62 (1.07-2.44)*	NS

Compound	Metabolite	Major human exposure source of parent compound	Tested determinants of exposure for all compounds	Additional tested determinants of exposure	Significant variables (estimate (95% CI)		
					Determinant	Mothers	Children
				-(Environmental tobacco) smoking			
TCS	**TCS**	PCP (disinfection, mouth wash, creams, lotions, tooth paste…), (fatty) food, sportswear, shoes and household articles impregnated with TCS against bacterial growth		-Use PCP -Disinfection use: hand, body, mouth -Use sunscreens	Lower vs. higher age group*	NS	0.48 (0.26-0.89)*
					Use PCP (high/moderate)	NS	2.75 (1.45-5.22)**
					Use sunscreen (moderate/low)	NS	6.11 (1.33-28.07)*
					Urban/rural	2.44 (1.13-5.25)*	NS

*: <0.05, **: <0.01, ***:<0.001

[1] building and construction materials, cables and wires, floorings, clothing, furnishings, car interiors/coatings, toys

[2] PCP= personal care products use categorized into three groups of users (low, moderate and high) based on questionnaire data on frequency of (never to daily) use of (eye) make-up, shampoo, hair-styling products, body lotions and creams, fragrances, deodorant, massage oil, and nail polish.

[3] Creatinine was included in the models in the following categories0.3-1g/L, 1-2 g/L and 2-3 g/L

[4] comparison of age 5-8 vs 9-11years

[5] BBzP is metabolized both to MBzP and to MnBP

Figure 1: Geometric mean (±95 confidence interval) of urinary phthalate metabolites: MEHP, 5OH-MEHP+ 5oxo-MEHP, MBzP, MiBP, MnBP, MEP, and the phenols BPA and TCS in Belgian mothers and their children (µg/L)

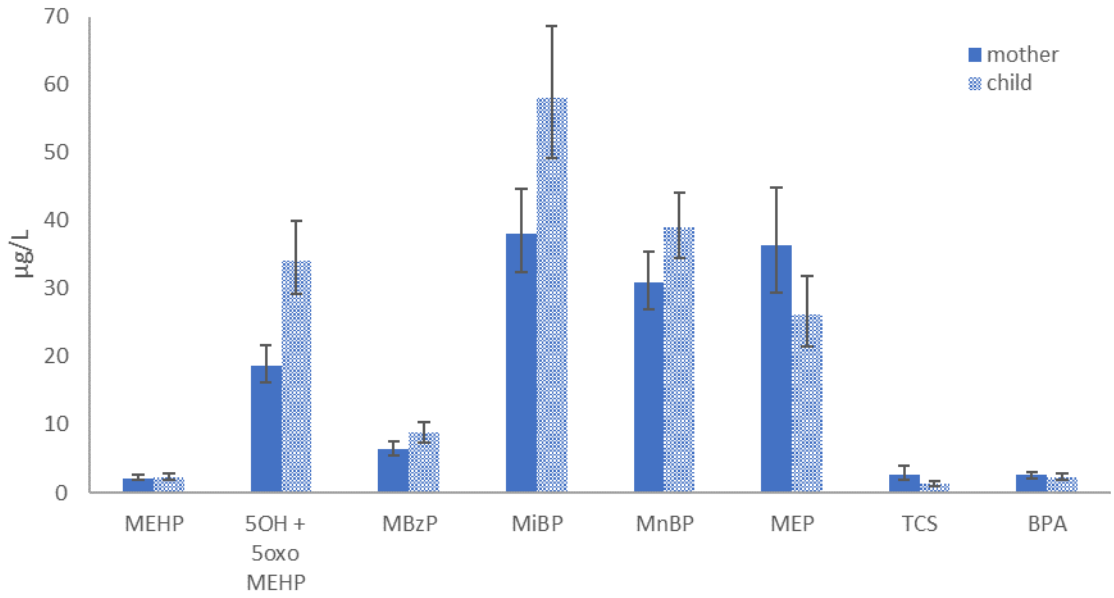


Figure 2: Geometric mean (±95 confidence interval) of MiBP, MEP, TCS and BPA in mothers and children, stratified for significant determinants of exposure (NB: Canned food was not significant for BPA in children, but the same trend was seen as for mothers)

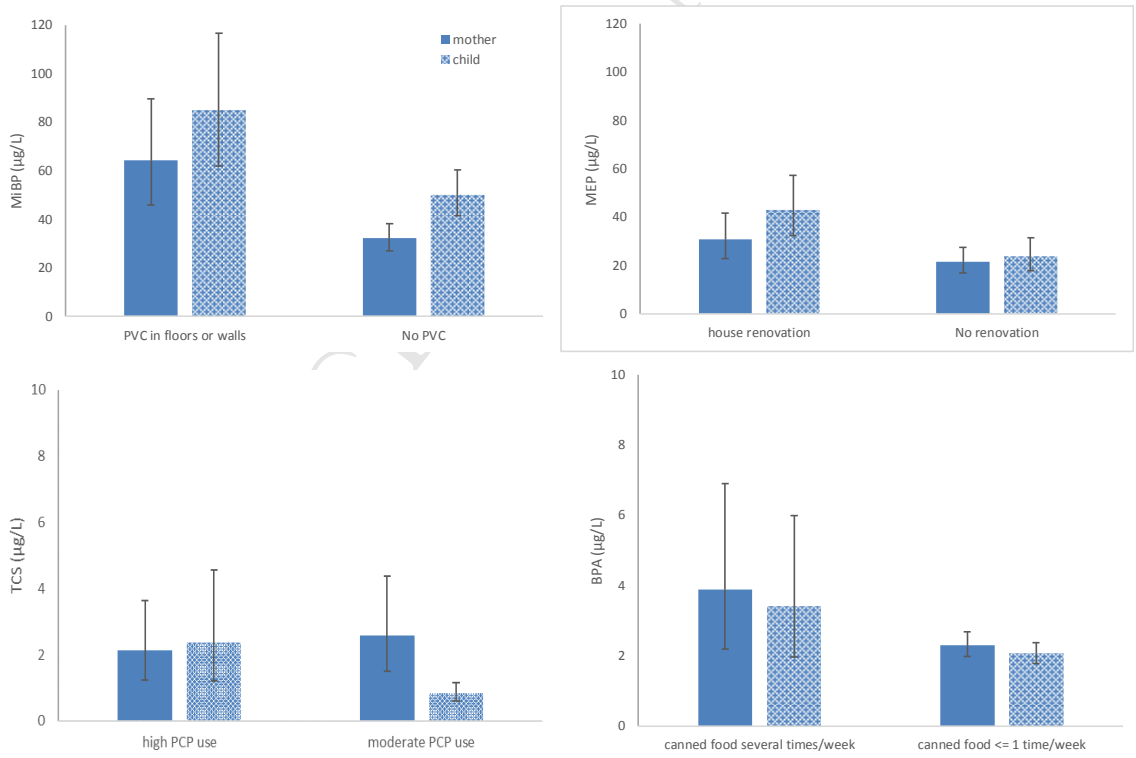
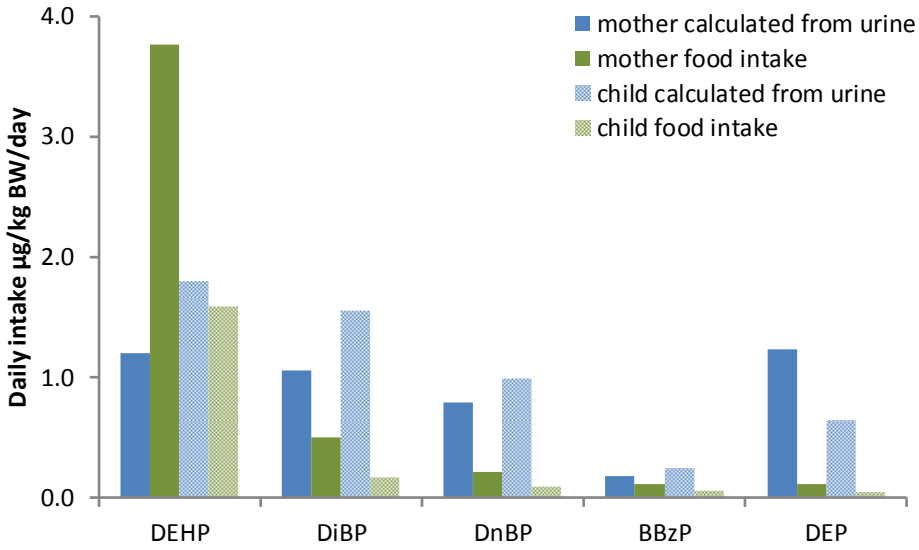


Figure 3: Calculated median daily intake of phthalates (µg/kg bw/day), either: (i) based on the median urine levels measured in mother and child within the current study (for DEHP, all measured metabolites were included in the calculation), and (i) based on median food intake levels estimated from a previous study on phthalate exposure via measurements in Belgian food items (PHTHAL study)



Gudrun Koppen: Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Supervision, Project Administration. **Eva Govarts:** Software, Formal Analysis, Data Curation, Writing - Review & Editing. **Guido Vanermen:** Validation, Formal Analysis, Investigation, Data Curation. **Stefan Voorspoels**: Investigation, Data Curation. **Malarvannan Govindan:** Investigation, Writing - Review & Editing. **Marie-Christine Dewolf:** Resources. **Elly Den Hond**: Software, Resources. **Pierre Biot**: Supervision, Project Administration, Funding Acquisition. **Ludwine Casteleyn**: Conceptualization, Methodology, Project Administration. **Marike Kolossa-Gehring**: Conceptualization, Methodology, Project Administration, Writing -Review & Editing. **Gerda Schwedler:** Methodology, Writing - Review & Editing. **Jürgen Angerer:** Conceptualization, Methodology. **Holger M. Koch**: Conceptualization, Methodology, Supervision, Writing - Review & Editing. **Birgit K. Schindler:** Conceptualization, Methodology, Supervision, Writing - Review & Editing. **Argelia Castaño**: Conceptualization, Methodology, Supervision, Writing - Review & Editing. **Marta Esteban López**: Conceptualization, Methodology, Writing -Review & Editing. **Ovnair Sepai**: Conceptualization, Methodology. **Karen Exley**: Methodology. **Louis Bloemen**: Conceptualization, Methodology. **Lisbeth E. Knudsen**: Conceptualization, Methodology. **Reinhard Joas**: Conceptualization, Methodology, Supervision, Project Administration, Funding Acquisition. **Anke Joas**: Conceptualization, Methodology, Supervision, Project Administration, Funding Acquisition. **Greet Schoeters**: Conceptualization, Methodology, Supervision, Project Administration, Funding Acquisition, Writing - Review & Editing. **Adrian Covaci**: Validation, Investigation, Data Curation, Writing - Original Draft.