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The Norwegian biomonitoring study from the EU project EuroMix: Levels of phenols and phthalates in 24-hour urine samples and exposure sources from food and personal care products

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ABSTRACT

Background: Exposure to multiple chemicals occurs daily through several routes; diet, inhalation and dermal contact. Real-life exposure assessment is needed to understand the risk. Therefore, a human biomonitoring (BM) study was performed to examine the plausibility of source-to-dose calculations for chemical mixtures in the Horizon 2020 EuroMix project.

Objectives: To provide a detailed description of the design of the EuroMix BM study, and to present the initial results for urinary phenols and phthalates and to describe their exposure determinants from foods and personal care products (PCPs).

Method: Adults (44 males and 100 females) kept detailed diaries on their food consumption, PCP use and handling of cash receipts. Urine samples were collected over the same 24-hour period. Urinary levels of four parabens, five bisphenols, oxybenzone/benzophenone-3 (OXBE), triclosan (TCS), triclocarban (TCC) and metabolites of eight phthalates and 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH) were analysed by ultra-high-performance liquid chromatography and tandem mass spectrometry. Multivariable linear regressions were performed between PCPs/food categories and each dependent chemical variable separately, and were only sex-stratified when an interactions between sex and the independent variable was significant.

Results: The detection rate for the metabolites of phthalates and DINCH, and bisphenol A (BPA) and TCS in urine was 88–100%, while bisphenol S (BPS) and bisphenol F (BPF) were only found in 29% and 4% of the urine samples, respectively. Bisphenol B (BPB), bisphenol AF (BPAF) and TCC were not detected. Food groups associated with phenol exposure were meat, bread, beverages and butter and oil. Food determinants for phthalate exposure were sweets, butter and oil, fruit and berries and other foods. The only positive association between the use of PCPs and phenols was found between BPA and lip gloss/balm. Phthalate exposure was associated with the use of shower gel, hand cream (females), toothpaste, anti-wrinkle cream (females) and shaving products (males).

Conclusion: The participants in the EuroMix BM study were exposed to a mixture of phenols and phthalates. A

Abbreviations: BBzP, butyl benzyl phthalate; BM, biomonitoring; BMI, body mass index; BPs, bisphenols; BPA, bisphenol A; BPAF, bisphenol AF; BPB, bisphenol B; BPF, bisphenol F; BPS, bisphenol S; BUPA, butylparaben; cx-MiNP, mono-4-methyl-7-carboxyoctyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DiBP, di-iso-butyl phthalate; DINCH, 1,2-cyclohexane dicarboxylic acid diisononyl ester; DiNP, di-iso-nonyl phthalate; DnBP, di-n-butyl phthalate; DPHP, di(2-propyl heptyl) phthalate; ETPA, ethyl paraben; GM, geometrical means; HDPE, high-density polyethylene; IQR, interquartile range; KBS, food and nutrient calculation system; LDPE, low-density polyethylene; LOD, limits of detection; LOQ, limit of quantification; NIPH, Norwegian Institute of Public Health; FFQ, food frequency questionnaire; MBzP, monobenzyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP, mono-2-ethylhexyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MEP, monoethyl phthalate; MEPA, methyl paraben; MiBP, mono-iso-butyl phthalate; MnBP, mono-n-butyl phthalate; MMCHP, mono-2-carboxymethyl hexyl phthalate; MoBa, Norwegian Mother, Father and Child Cohort Study; oh-MINCH, 2-(((Hydroxy-4-methyloctyl)oxy)carbonyl)-cyclohexanecarboxylic acid; oh-MiNP, mono-4-methyl-7-hydroxyoctyl phthalate; MLR, multivariable linear regression; oh-MPHP, 6-hydroxy monopropylheptylphthalate; oxo-MINCH, 2-(((4-methyl-7-oxyooctyl)oxy)carbonyl)-cyclohexanecarboxylic acid; oxo-MiNP, mono-4-methyl-7-oxooctyl phthalate; OXBE, oxybenzone/benzophenone-3; PBs, parabens; PBMC, peripheral blood mononuclear cells; PBPK, physiologically based pharmacokinetic; PBTK, physiologically based toxicokinetic; PCPs, personal care products; PP, polypropylene; PRPA, propyl paraben; PS, polystyrene; SG, specific gravity; SPE, solid phase extraction; TCS, triclosan; TCC, triclocarban; TP, thermal paper; UPLC, ultra-high performance liquid chromatography

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variety of food categories and PCPs were found to be possible sources of these chemicals. This indicates a complex pattern of exposure to numerous chemicals from multiple sources, depending on individual diet and PCP preferences.

1. Introduction

Exposure to environmental chemicals is of growing global concern, and every day we are exposed to multiple chemicals by several routes of exposure, through diet, inhalation and dermal contact. The effects of chemical pollution on human health are poorly defined and may well be underestimated (Landrigan et al., 2017). Sources of chemical exposure include food packaging and additives to foods and cosmetics. Risk assessments that account for both exposure and toxicity are necessary to monitor and prevent possible adverse effects of chemical mixtures on human health. Risk assessments are usually performed separately for each chemical and for only one route of exposure. Since we are exposed to many chemicals daily through several routes, it is necessary to address the combined risk of exposure to chemical mixtures and their combined risk as set out by European Food Safety Authority (EFSA) (EFSA 2918) and in the EU regulations for plant protection residues, (EC, 2009; EC, 2016).

EuroMix is an EU funded Horizon 2020 project, that aims to develop a tiered, mechanism-based test strategy for refining the risk assessment of combined exposure to multiple chemical using *in-silico* and *in-vitro* tools. These strategies include advanced tools for exposure assessment, such as physiologically based pharmacokinetic/toxicokinetic (PBPK/PBTK) models to facilitate *in-vitro* to *in-vivo* extrapolation (IVIVE) and to estimate internal doses from the different external exposure routes. The toolbox developed in EuroMix will help regulatory agencies to assess the risk of exposure to chemical mixtures. The Norwegian biomonitoring (BM) study performed within this project aims to determine real-life exposure to chemical mixtures from different routes. The BM study was conducted to determine aggregated exposure to chemicals present in foods and PCPs in Norway using 24-hour urine samples over two full days, rather than frequently used spot urines. Exposure levels for chemicals with a short half-life (3–18 h) often vary within a single day and between days for an individual (Johns et al., 2015). Therefore, collection of 24-hour urine is preferred (Aylward et al., 2017) over spot urines to adjust for this daily variation. PCPs can be used on a daily basis, and it is believed that exposure to chemicals in PCPs adds to the overall burden of exposure. However, real-life exposure estimates to chemicals from PCPs are lacking (Craig and Ziv-Gal, 2018).

Phthalates are present in food and in PCPs and have a short half-life in the body. Phthalates are diesters of 1,2-benzenedicarboxylic acid (phthalic acid), and are a class of synthetic chemicals that are widely used in industrial applications, such as in flexible plastic and consumer products, including personal care products (PCPs). Since phthalates are not covalently bound to plastic, they can leach into the environment, foods and PCPs. Phthalates are ubiquitous and humans are exposed throughout life by ingestion, inhalation and dermal contact. After exposure, the phthalates are rapidly metabolised to monoester metabolites, which are excreted in the urine. These monoesters are reliable biomarkers for exposure (Johns et al., 2015; Radke et al., 2018). Exposure to phthalates has been associated with health effects such as reproductive and developmental toxicity, and they are therefore regarded as chemicals of concern (Kay et al., 2013; Lee et al., 2018; Radke et al., 2018).

Other likely candidates are a number of phenolic compounds, such as parabens (PBs), bisphenols (BPs), oxybenzone/benzophenone-3 (OXBE), triclosan (TCS) and triclocarban (TCC), are often used in consumer products. All of these compounds, apart from TCC, have a phenol group in their chemical structure, so they are often referred to as "environmental phenols". Although lacking the phenol group, TCC is included in this group for convenience. Parabens are alkyl or aryl esters of p-hydroxybenzoic acid, and are widely used individually, or in combination, as antimicrobial preservatives in cosmetics, pharmaceuticals and food (Liao et al., 2013). Bisphenol A (BPA) is used as a monomer of polycarbonate plastic, epoxy resins and in thermal paper (Russo et al., 2017), and human exposure from consumer products therefore occurs, partly through migration into foods and PCPs. Due to restrictions on the BPA use, bisphenol analogues, such as bisphenol S (BPS), bisphenol F (BPF), bisphenol B (BPB) and bisphenol AF (BPAF), are used as substitutes for BPA in some consumer products. It has been shown that the exposure to some of these analogous is increasing (Gramec Skledar and Peterlin Masic, 2016). OXBE is mainly used as an UV filter in PCPs but can also be used as UV stabiliser in some food packaging materials (Liao and Kannan, 2014). TCS and TCC are used as antimicrobial and antifungal agents in PCPs (Witorsch and Thomas, 2010).

This paper provides a detailed description of the design of the

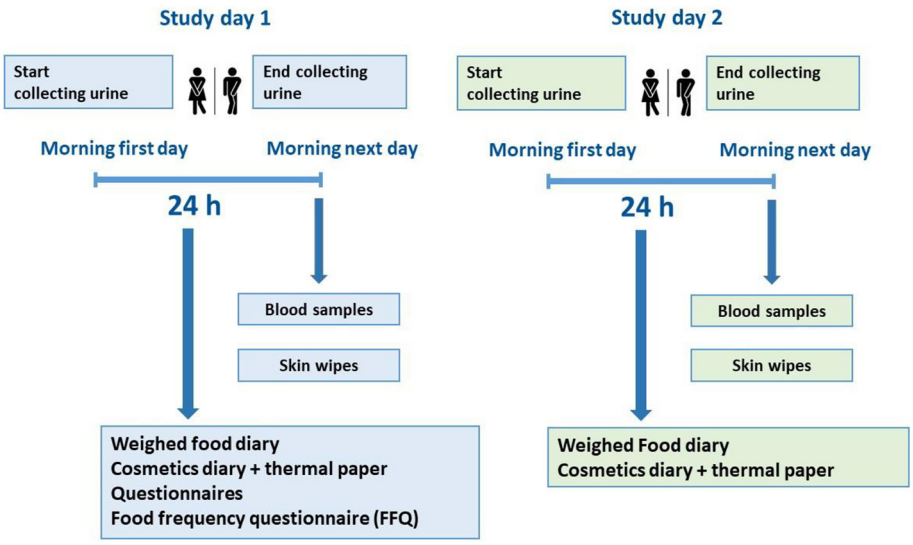

Fig. 1. A graphical presentation of the design of the human biomonitoring study.

EuroMix study, and presents the initial results of chemical mixtures of phenols and phthalates determined in urine, together with their possible exposure sources from foods and PCPs.

2. Materials and methods

2.1. Study subjects and sample collection

The current biomonitoring study is a part of the EU project "European Test and Risk Assessment Strategies for Mixtures" (EuroMix, 633172-2), which is funded by the H2020 programme. Established at the Norwegian Institute of Public Health (NIPH), the study is investigating exposure to chemical mixtures from foods, PCPs and thermal paper (TP) for two full days (separated by 2–3 weeks), and to validate PBPK/PBTK models of chemicals developed in the EuroMix project. Participants were recruited among employees from governmental institutes and authorities, and universities in the counties of Oslo and Akershus in Norway between September 2016 and November 2017. Recruitment campaigns used e-mails, targeted campaigns in social media and oral presentations of the project. The recruited participants might not be a representative sample of the overall Norwegian population but this was not the aim of our biomonitoring study. The study recruited 144 participants (44 males aged 25–72 years and 100 females aged 24–72 years) who completed day one, but only 140 (43 males and 97 females) of these participants completed both full 2-day collections. Given the effort required by the participants, a sample size of approximately 150 was considered to be sufficient. Similar studies conducted at the NIPH with comparable sample collections had similar sample sizes (Papadopoulou et al., 2016; Sakhi et al., 2017). The recording and sampling period consisted of two non-consecutive 24-hour intervals, with 2–3 weeks between the two sampling periods, as described in Fig. 1. The 2–3 weeks interval between the sampling points was considered to be an appropriate delay for excretion of chemicals with short half-lives. During the two study periods, participants kept detailed, weighed food records on food consumption and the usage of personal care products and handling of thermal paper receipts. All urine was collected during the recording period and blood samples were taken at the end of the 24 h period, as described below. The study was approved by the Regional Committees for Medical and Health Research Ethics (REK ID no 2015/1868) and all the participants provided their written informed consent.

2.2. Data collection, registration and processing

During the two sampling periods, the participants were asked to complete a diary of their weighed food record, a cosmetic diary, a food frequency questionnaire (FFQ) (only on the first day) and a questionnaire for socio-demographic and lifestyle characteristics (only first day). A 24-hour weighed food record was developed specifically for this project. The participants were instructed to register all relevant information regarding any foods and beverages consumed, *i.e.* the type and weight of the consumed food and beverages, the time of consumption, recipes (if applicable) and brand names. In addition, the participants were asked to record any food packaging (plastic box/bag/wrap, aluminium foil, paper/carton, or original package) and/or cookware used (utensils with non-stick coating or other, or microwaved in plastic or other) in the food preparation. In this food record, the number and times that cash receipts (thermal paper, TP) were touched throughout the day were also registered.

The used FFQ was a modified version of the validated FFQ developed for the Norwegian Mother, Father and Child Cohort Study (MoBa). In this version, all questions related to diet changes in pregnancy were removed, and participants were asked to report the frequency of food eaten over the last year (Brantsæter et al., 2008). Frequency of consumption was then combined with standard portion sizes to calculate daily consumption in grams.

The recorded consumption from the weighed food records and FFQ were registered and coded separately by a dietician into the food and nutrient calculation system (KBS) at the University of Oslo (UiO). Intake of foods and nutrients, separate from both the weighed food record and the FFQ, were then estimated using the KBS AE14 food composition database. Finally, a comparison between estimated food intake in our study population and the general Norwegian population was conducted.

The cosmetic diary recorded the use of all personal care products (PCP) used during the 24-hour intervals for both days, including the time of use and brand names of the products. In addition, the participants recorded the number, duration and the temperature of showers, and how often they washed their hands during that day. The participants were not asked to record the amount of PCP products applied in the diaries since this would be too complicated. Personal information, such as gender, education, age, height, weight, smoking habits, consumption of tap water, visits to swimming pools, skin types of hands (dry, normal, greasy) and number of childbirths were recorded in the personal questionnaire, in addition to certain health outcomes.

Participants were asked to report whether they had experienced asthmatic symptoms, hay-fever, eczema, food allergy and if they had a cold, influenza, pneumonia, ear infection, gastrointestinal infection or urinary infection during the last year. They were also asked whether they had been diagnosed with asthma or allergies by a physician, and if they had been taken any medications for these specific health conditions. If participants had been sick during the week before the first study day, they were asked to return at a later stage to avoid any effects of recent illness.

2.3. Collection of blood, urine and hand wipes

On the study day, the 24-hour urine sampling started in the morning, typically between 6:00–8:00, and continued until the same time next morning, including the morning urine the next day. The participant collected every urination during the period in separate containers and marked them with time and date. The samples were stored without addition of preservatives in a refrigerator by the participant until delivery the next day. The urine sample containers used were made of high-density polyethylene (HDPE) to avoid chemical contamination of the samples. The next day, the volumes of each sample were measured and immediately stored individually, as pools of urine combining all the voids into three time periods (6:00–12:00, 12:00–18:00 and 18:00–6:00 the next day) and a pool representing the 24-hour interval. Urinary pools of 30 ml in total were prepared from the samples for given time periods adjusted for volume, as described below.

$$\text{Volume pipetted out from individual sample for inclusion in the pooled sample (ml)} = \text{Volume of individual sample of urine (ml)} / \text{Total urine volume for time period (ml)} \times 30\ \text{ml}$$

Small (1.8 ml) and medium (10 ml) aliquots of urine (each sample, pooled and 24-hour) were stored at −80 °C, while larger volumes of urine were stored at −20 °C. Blood samples (in total 70 ml per participant per study day) were collected at the end of the recording and sampling period at NIPH, to obtain serum, plasma, white and red blood cells, as well as RNA/DNA which were all stored at −80 °C. Blood collected in tubes with EDTA was used to prepare peripheral blood mononuclear cells (PBMC), as described elsewhere (Sonnet et al., in preparation). Vials, pipettes and vacutainers made of HDPE, low-density polyethylene (LDPE), polypropylene (PP) or polystyrene (PS) were used to avoid chemical contamination from plastic laboratory equipment (see overview Table S1). All samples (urine and blood) were immediately handled and aliquoted into smaller quantities to avoid unnecessary sample handling, and repeated thawing and freezing. After

blood sampling, the participants' fingers and upper side of both arms were washed with wipes. The same technicians washed all the participants with pre-wet wipes (brand MeSoft, soaked in 5 ml 50/50% water and ethanol in a glass petri-dish), while wearing nitrile gloves and using a stencil with fixed area of 3 × 7 cm. Each fingertip was also washed with pre-wet wipes, and all the wipes were put in 50 ml tubes (Sarstedt) and frozen immediately at −20 °C. This strict procedure was followed to avoid contamination of the samples. The wipes were not analysed for this paper.

Out of 144 participants, 8 and 10 subjects did deliver incomplete 24-hour urine collection, for day 1 and 2, respectively. Two and 3 participants did not agree to give blood samples on day 1 and 2, respectively. All participants provided wipes on both days.

2.4. Determination of specific gravity in urine samples

In order to correct for urinary dilution, specific gravity (SG) was measured in all urine samples. SG-adjusted concentrations were used in all statistical analyses because they are less affected by age, gender, body mass index (BMI), muscle mass, diet, activity and season compared to, for example, creatinine-adjusted concentrations (Johns et al., 2015).

SG adjustment used the following formula (Bertelsen et al., 2013).

Adjusted Urine Concentration (ng/ml)

= Measure Urine Concentration (ng/ml) × (Mean SG − 1)/(SG − 1).

The mean SGs were calculated for males and females separately and were 1.018 and 1.013 for the pooled urine from day 1, respectively.

2.5. Determination of phthalate metabolites in urine

Thirteen different phthalate metabolites (monoethyl phthalate (MEP), mono-isobutyl 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)) (see Table S2) were determined in the three urine time pools (see Section 2.3) and a 24-hour concentration of each metabolite was estimated by averaging the three time pools of urine from study day 1, after adjusting for SG. The analyses of the time pools, which include all the voids from that 24-hour period, therefore equal the analysis of a 24-hour urine sample. The determination of phthalate metabolites in urine were performed using an on-line column switching liquid chromatography coupled to tandem mass spectrometry as described elsewhere (Sabaredzovic et al., 2015). In brief, labelled internal standard solution and enzyme solution to deconjugate glucuronidates (beta glucuronidase 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 which 20% formic acid was added. The samples were centrifuged, and the supernatant was injected into the system. The limits of detection (LOD) were between 0.07 and 0.7 ng/ml (Table S2). The accuracy of the method ranged from 70% to 120%. In-house pooled urine samples and standard reference material from National Institute of Standards and Technology (NIST) were analysed along with the samples and the precision was below 20% for the phthalate metabolites.

2.6. Determination of phenols in urine

Twelve environmental phenols (see Table S3) were determined using on-line solid phase extraction (SPE) prior to ultra-high performance liquid chromatography (UPLC) coupled to tandem mass spectrometry (MS-MS). The present method included 4 parabens (methyl paraben (MEPA), ethyl paraben (ETPA), propyl paraben (PRPA) and butyl paraben (BUPA)), 5 bisphenols (BPA, BPS, BPF, BPB and BPAF), OXBE, TCS and TCC, as described elsewhere (Sakhi et al., 2018). In brief, labelled internal standards and enzyme solution (beta-glucuronidase/sulfatase in ammonium acetate buffer, pH 5.0) were added to 200 µl of the sample. After 4 h, 40% formic acid was added to stop the enzymatic reaction. The samples were then centrifuged and 80 µl of the supernatant was injected into the UPLC-MS-MS system. The ionisation of the analytes was performed in an electrospray source in negative mode. A signal to noise (S/N) ratio of 10 was considered as the limit of quantification (LOQ). The LOD (S/N ratio of 3) was calculated from the respective LOQs and varied from 0.02 to 0.10 ng/ml (Table S3). The accuracy of the method ranged from 75% to 120%. In-house pooled urine samples and standard reference material from National Institute of Standards and Technology (NIST) were analysed along with the samples and the precision was below 26% for the phenols.

2.7. Statistical analysis

Determination of phthalate metabolites and phenol concentration in the urine samples were only performed for study day one. Concentrations < LOD were replaced with the value of LOD for each chemical. For concentrations between the LOD and LOQ, the values calculated by the software programme of the instrument were used. The number of samples below LOD and between LOD and LOQ are reported in Tables S14 and S15 for the phenols and phthalates, respectively. For each chemical, the average concentration of the SG-adjusted concentrations of the three time pools provided the mean 24-hour urine concentrations of day one for each participant. These mean 24-hour values were used in all the statistical analyses. Wilcoxon rank sum test was used to test statistical significance in the urinary concentration of chemicals between males and females. Multiple comparison were performed using the Sidak correction $1-(1-\alpha)^{1/n}$, where n was the number of chemicals multiplied by gender, leading to a significance level of $P \leq 0.001$. The non-parametric Spearman's rank correlation coefficient (rho) was used to study correlations between non-normal distributed chemicals or metabolites in urine, after checking normality using the Shapiro-Wilk test.

To identify dietary determinants of measured concentrations of contaminants, multivariable linear regression (MLR) was performed between the concentration of chemicals in the urine and the main categories of the determinants foods and PCPs. Urinary concentrations of the chemicals were the dependent variables and were log-transformed to approach normal distribution. Only chemicals with a concentration > LOD in > 50% of the samples were included in the statistical analyses. Exposure to the phthalate compounds (di(2-ethylhexyl)phthalate e (DEHP), di-iso-nonyl phthalate (DiNP) and DINCH) was represented by several metabolites. Therefore, DEHP, DiNP and DINCH concentrations in urine were estimated by summing their metabolites (ng/ml) after adjusting for molecular weight, denoted sumDEHP (MEHP, MEHHP, MEOHP, MECPP, MMCHP), sumDiNP (oh-MiNP, oxo-MiNP, cx-MiNP) and sumDINCH (oh-MINCH, oxo-MINCH).

Two groups of determinants were considered based on the mostly likely exposure sources and were used as the independent dependent variables in MLR: PCP use (in counts per day) and food intake (in g/day). Variables with < 10% of participants were excluded from the MLR analyses. Fifteen independent food variables were included for both genders; bread, grain, cakes, potato, vegetables, fruit/berries, meat, fish, egg, dairy, cheese, butter/oil, sweets, beverages and other foods. The category “sweets” includes foods like sweet sandwich

spread, chocolate, deserts and ice-cream. Seventeen independent PCP variables were included for both genders; shower gel, shampoo, conditioner, deodorant, facial cleanser, facial moisturiser, body lotion, mouthwash, toothpaste, perfume, lip gloss/balm, foundation, hand cream, hair styling, eye make-up, rouge powder and hand soap. Nineteen independent PCP variables were included for females; shower gel, shampoo, conditioner, deodorant, facial cleanser, facial moisturiser, body lotion, anti-wrinkle cream, sunscreen, mouthwash, toothpaste, perfume, lip gloss/balm, foundation, hand cream, hair styling, eye make-up, rouge/powder and hand soap, while eleven independent PCP variables were included for men; shower gel, shampoo, conditioner, deodorant, facial moisturiser, mouthwash, toothpaste, perfume, hair styling, shaving products and hand soap. The intake of different foods was used as categorical variables with 2–3 groups, depending on the distribution of each variable. The use of PCPs was also categorised in 2–3 groups. Groups with low count (< 10% of the participants) were merged with neighbouring categories. The lowest food intake or PCP use categories were used as the reference group in MLR.

First, simple linear regressions between each food and PCP variable and each chemical were performed for all participants, adjusted for gender, age, education and including any interaction between gender and independent food/PCP variable. Any linear regressions with an association with P-value < 0.2 were included in the MLR models for each chemical. When the interaction between gender and independent PCP/food variable were statistically significant ($P \leq 0.05$), MLR were performed separately for each gender and adjusted for age and education. The beta coefficients from all models were exponentiated (base 10) to produce the ratio of the geometric mean (GM) of contaminant concentrations of each category in respect to the geometric mean of the reference category. The associations were regarded as significant with a $P \leq 0.05$. Multiple comparisons were performed using the Sidak correction $1\text{-}(1\text{-}\alpha)^{1/n}$, where n represented the mean tests performed for each chemical, multiplied by the number of chemicals and gender, leading to a significance level of $P \leq 0.0004$.

A multiple t-test was used to compare the mean food intake and mean use of PCPs between males and females, after correcting for multiple comparisons using the Holm-Sidak method.

StataSE 15 (StataCorp LLC, Texas, USA), R version 3.6.0 and GraphPad Prism 7 (GraphPad Software, CA, USA) were used for the statistical analyses and figures.

3. Results

3.1. Descriptive data

The demographic characteristics of the participants are shown in Table 1. The participants of the study were recruited from governmental institutes and universities in the Oslo area so the population was highly educated, with nearly 80% of the participants having a university degree. This was also reflected in smoking habits, where > 60% of the participants reported that they never smoked, 24% had quit smoking and 13% smoked occasionally. There were no regular smokers in the study population. The mean weight of males and females were 82 (SD = 8.5) and 65 (SD = 8.9) kg, respectively. The age of the participants ranged from 25 to 72 years for males and from 24 to 72 years for females.

3.1.1. Diet from weighed food record and FFQ

The food intake of the main food categories (mean grams per day) estimated from the two 24-hour weighed food records, for male and females, are shown in Fig. 2 and Table S4. The food categories with the highest absolute intake in grams per day were beverages > fruit/berries > dairy > vegetables > bread > grain. There were no statistically significant differences between males and females regarding intake of the main food categories. There were significant differences between genders in total energy intake and intake of several micronutrients based on the weighed food records (Tables S5–S6). The energy percentage from energy providing nutrients and a detailed description and the estimated food intake from the FFQ are described in Supplementary information (Tables S7–S8).

The diet of the study population in EuroMix, as derived from the 24-hour diaries, was compared with that of the study population from the national dietary survey, Norkost 3 (Tables S9 and S10). The largest differences in the diet between EuroMix and Norkost 3 were found for females. Females in EuroMix ate on average more vegetables ($P < 0.000001$), grain ($P < 0.0001$) and cheese ($P < 0.001$), but consumed less beverages ($P < 0.001$), butter/oil ($P < 0.001$) and meat ($P < 0.01$). On average, the men's diet was more similar to the men in Norkost 3 but the EuroMix men consumed less butter/oil ($P \leq 0.01$), beverages ($P \leq 0.05$) and dairy products ($P \leq 0.05$).

3.1.2. Use of personal care products and handling of thermal papers

The mean number of PCP applications for males and females from study day one is presented in Fig. 3, while the percentage of users for the PCP categories and the usage frequency of PCPs for males and females (users only) are presented in Tables S11 and S12. There was a significant difference between the type of PCP use and frequency of use between males and females. Females used a wider variety of PCP products and had a higher frequency of use for those PCP categories that were used by both males and females. Females had a significantly higher use of the following PCPs: conditioner, deodorant, facial cleanser, facial moisturiser, body lotion and toothpaste (Fig. 3). Most of the participants (66.2%) had taken one shower, while some had taken none (17.9%), two (7.6%) or three (1.4%) showers. The average number of hand washes was 10 ± 5.4.

The overview over the number of participants touching TP is shown in Table S13. Most participants did not touch thermal paper at all, with 76% and 80% of the participants not touching any TP on study day one and two, respectively.

3.2. Data analysed

This paper presents the initial results of chemical mixtures of phenols and phthalates determined in urine of day one of the study, together with their possible exposure sources from foods and PCPs. The data included are presented in an overview in Fig. 4. Concentrations of phenols and phthalates were analysed in the three time pools of urine, and combined as 24 h measures from study day 1 (see Materials and methods).

3.2.1. Phenols and phthalates in urine samples from the first study day

The detection rate of BPA above LOD was 96% of the samples analysed, while BPS was found in 29% and BPF in 4% of the urine

Table 1
Demographic characteristics of the participants in the present study.

Basic characteristics		Males (n = 44)	Females (n = 100)
Age (years, mean ± SD)		43.4 ± 11.7	42.2 ± 12.3
Weight (kg, mean ± SD)		82.0 ± 8.5	65.2 ± 8.9
Height (m, mean ± SD)		1.81 ± 0.06	1.68 ± 0.06
BMI (kg/m^2, mean ± SD)		25.0 ± 2.34	22.8 ± 3.78
Smoking status (n)	Non-smokers	26	64
	Ex-smokers	11	24
	Occasional smokers	7	12
Education (n)	University/college up to 4 years	8	22
	University/college > 4 years	36	78
Women with children (n)	No children	–	45
	1 child	–	19
	2 children	–	26
	3–4 children	–	10

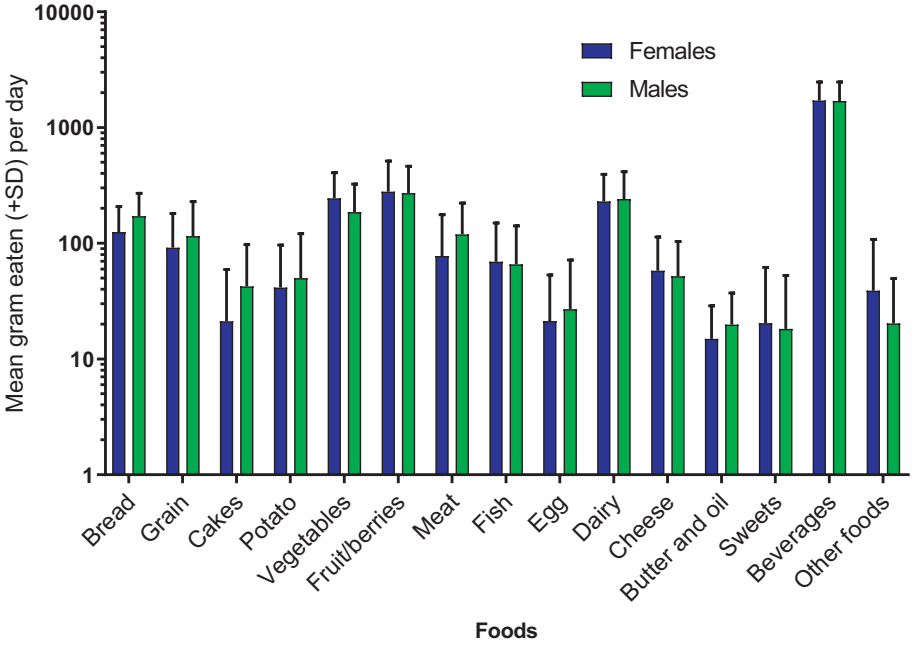

Fig. 2. Consumption of main food groups (g/day), from both days of the weighed food records. Food intake presented in grams/day of the main food categories for males (blue) and females (green), for both study days. Significant differences between male and females (* = $P < 0.05$) were tested using a multiple *t*-test correcting for multiple comparison using the Holm-Sidak method. There were no significant differences between males and females. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

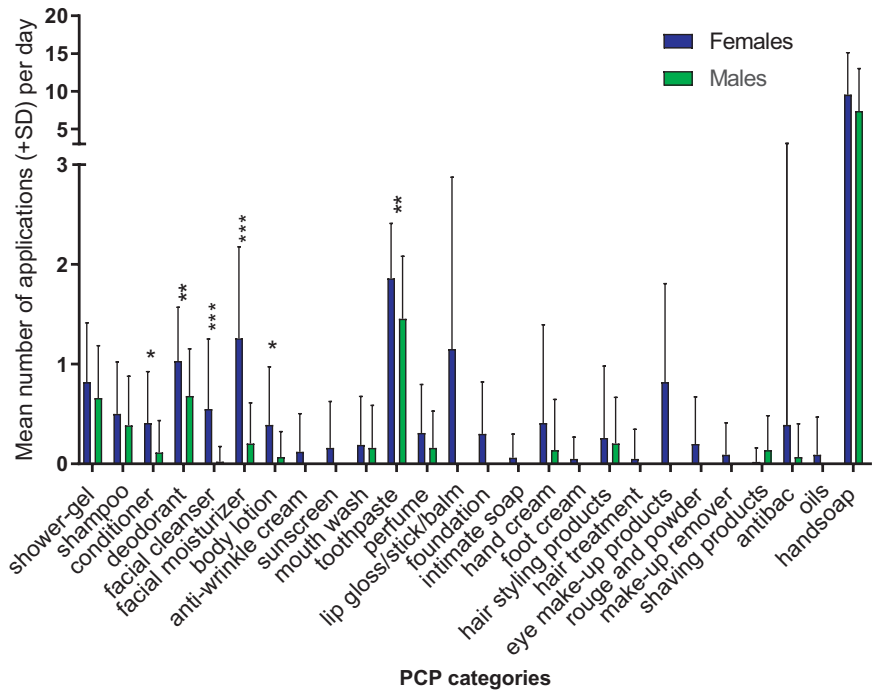

Fig. 3. Use of PCPs on the first study day. The mean number of PCP applications on the first study day, shown for males (green) and females (blue). Significant differences between male and females (* = $P \leq 0.05$, ** = $P \leq 0.01$, ***$P \leq 0.0001$) were tested using a multiple *t*-test correcting for multiple comparisons using the Holm-Sidak method. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

samples, respectively. BPB, BPAF and TCC were not detected in any urinary samples. OXBE, TCS, MEPA and ETPA were detected in 90–100% of the samples and PRPA and BUPA in 65% and 50%, respectively. Higher concentrations of parabens were measured in the urine of females compared to males (Fig. 5). The highest concentrations found among the different chemicals analysed were found for MEPA (significantly different between genders, $P \leq 0.05$), ETPA and PRPA (significantly different between genders, $P \leq 0.01$) of 9.4, 1.1 and 0.7 ng/ml in females and 5.2. 1.0 and 0.07 ng/ml in males, respectively. Concentrations of TCS and OXBE were also found at a comparable level to the parabens, with a higher concentration for OXBE in females (4.3 ng/ml) than in males (2.6 ng/ml) (non-significant). Using multiple comparison, only the concentration of PRPA remained significantly different between the genders. A detailed description of phenol levels is presented in Table S14.

The detection rate was 100% for ten of the phthalate metabolites, while for the remaining phthalate metabolites and the metabolites of DINCH, the detection rate was between 88 and 97%. The number of samples between LOD and LOQ is presented in Table S15, which also shows the SG adjusted median concentrations of the phthalate and DINCH metabolites in urine. Phthalates (DEHP and DiNP) and DINCH concentrations in urine were estimated by summing their metabolites (ng/ml) after adjusting for molecular weight, denoted sumDEHP, sumDiNP and sumDINCH. The concentrations of phthalates and DINCH expressed as their metabolites or the sum of their metabolites in the urine are shown in Fig. 6. For all the phthalates metabolites, except for DEP, statistically significant higher concentrations were observed in males compared to females. The concentration pattern for the

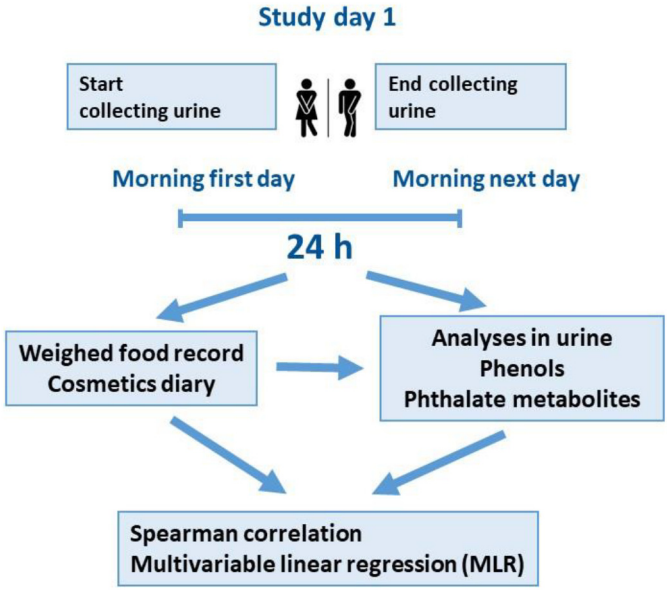

Fig. 4. A graphical presentation of the part of the study used for data analyses in this paper.

phthalates and DINCH were DEHP > diethyl phthalate (DEP) ~ di-n-butyl phthalate (DnBP) ~ di-isobutyl phthalate (DnBP) ~ DiNP > DINCH > butyl benzyl phthalate (BBzP) > di(2-propyl heptyl) phthalate (DPHP). For more details on phthalate metabolite concentrations in urine see Table S15.

Fig. 7 shows correlations between different urinary phthalate metabolites and the phenols in males and females, shown as a heat map. There was a clear difference in the correlations between males and females. In men, there were significant positive correlations between MEPA and the DINCH metabolites oh-MINCH ($r = 0.35$) and oxo-MINCH ($r = 0.43$). There were also significant correlations between BPA and the metabolites of DEHP (r between 0.3 and 0.38), TCS ($r = 0.37$) and OXBE ($r = 0.49$). The same correlations were not found for females, with the exception of a significant correlation between BPA and OXBE ($r = 0.27$). See also Tables S16–18 for detailed information about the correlation.

3.2.2. Determinants of phenol exposure

MLR for between phenol concentrations in urine and consumption of the major food categories determined from the weighed food record is shown in Table 2. Since no significant ($P \leq 0.05$) interactions between gender and independent variables were observed, only MLR for all participants was performed. Positive significant associations were found between MEPA and meat ($\beta = 1.88$, $P = 0.04$) and between BUPA and bread ($\beta = 1.92$, $P = 0.00$) and beverages ($\beta = 1.52$, $P = 0.04$). Negative significant associations were found between MEPA and bread ($\beta = 0.47$, $P = 0.02$), BPA and dairy products ($\beta = 0.64$, $P = 0.01$) and BUPA and butter and oil ($\beta = 0.63$, $P = 0.01$). Other significant associations were also found but these did not show a relationship with increased or decreased consumption of food.

Since no significant ($P \leq 0.05$) interactions between gender and independent PCP variables were observed, only MLR for all participants was performed, (Table S19). A significant positive association was found between the use of lip gloss and lip balm and the concentration of BPA in the urine ($\beta = 1.44$, $P = 0.05$). No other statistically significant associations were found between the phenols and the use of PCP (Table S19). However, a positive association was found between PRPA and eye make-up and hand soap, with a β well above 2 that nearly reaches statistical significance.

3.2.3. Determinants of phthalate exposure

MLR for some of the phthalates was presented separately for males and females, since significant interactions ($P \leq 0.05$) between gender and independent food variables were observed, as shown in Table 3. The major positive significant associations that increased with consumption were found for females between oh-MPHP and sweets ($\beta = 1.46$, $P = 0.03$), and sumDEHP and fruit and berries ($\beta = 1.30$, $P = 0.01$) and butter and oil ($\beta = 1.26$, $P = 0.01$). For all participants there was a significant positive association between MiBP and fruit and berries ($\beta = 0.32$–0.43, $P = 0.01$–0.04) and other foods ($\beta = 1.27$, $P = 0.04$). No significant associations were found between the phthalates and DINCH and foods for males.

As for foods, MLR for several of the phthalates was presented

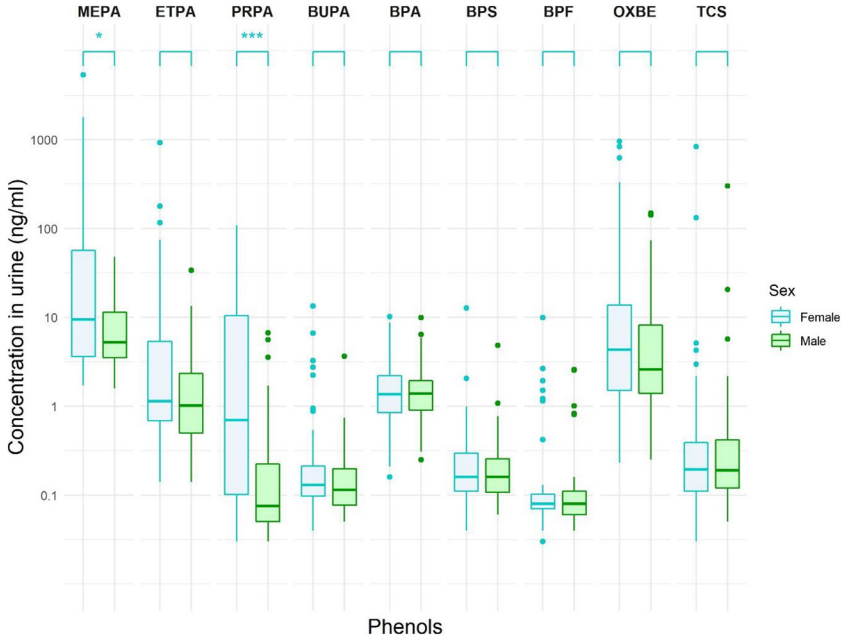

Fig. 5. Concentrations of phenols in the 24 h urine of the first study day. Parabens (MEPA, ETPA, PRPA, BUPA), bisphenols (BPA, BPS, BPF), OXBE and TCS (all SG adjusted) were measured (ng/ml) in 24-hour urine. Significant differences between male and females (* = $P \leq 0.05$, *** = $P \leq 0.001$) using Wilcoxon rank sum test.

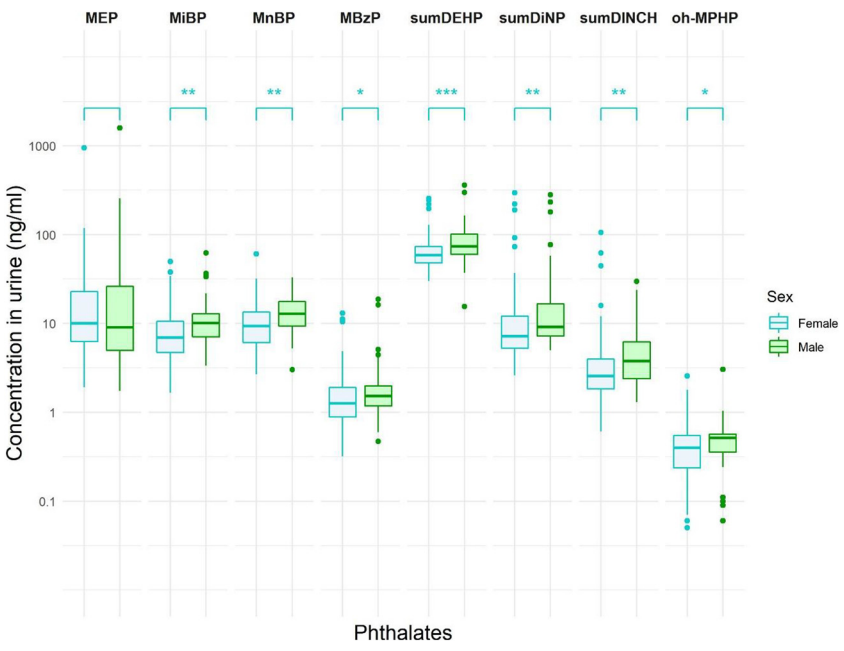

Fig. 6. Concentrations of phthalates and DINCH in the 24 h urine of the first study day. The phthalates (ng/ml) expressed as their metabolites (SG adjusted) of DEP (MEP), DiBP (MiBP), DnBP (MnBP), BBzP (MBzP), and DPHP (oh-MPHP), or the sum of their metabolites sumDEHP (MEHP, MEHHP, MEOHP, MECPP, MMCHP), sum DiNP (oh-MiNP, oxo-MiNP, cx-MINP) and sumDINCH (oh-MINCH, oxo-MINCH). Significant difference between male and females (* = $P \leq 0.05$, ** = $P \leq 0.01$, *** = $P \leq 0.001$) using Wilcoxon rank sum test.

separately for males and females, since significant interactions ($P \leq 0.05$) between gender and independent PCP variables were observed, as shown in Table 4. In females, significant positive associations were found between the uses of anti-wrinkle cream and MEP (β = 2.43, $P \leq 0.01$) and sumDINCH (β = 1.82, $P = 0.02$), hand cream and MiBP (β = 2.26, $P \leq 0.001$), and toothpaste and MnBP (β = 1.51, $P \leq 0.01$) and MBzP (β = 1.47, $P = 0.03$) (Table 4). A significant positive association was found for males between MBzP and shaving products (β = 1.87, $P \leq 0.05$). Significant associations between MBzP and the use of shower gel were found for both males (β = 0.59, $P = 0.01$) and females (β = 0.59, $P = 0.05$). A negative association was also found between sumDiNP and the use of toothpaste (β = 0.69, $P = 0.04$) for all participants.

4. Discussion

4.1. Concentrations of phenols and phthalates in 24-hour urine

In 144 participants, urinary biomarkers of 20 different chemicals were measured in pooled urine samples from a 24-hour sampling period, and 12 of these chemicals were found above LOD in > 90% of the participants. Most published biomonitoring studies report on concentrations of chemicals in one or more spot urines and might underestimate the exposure to chemicals with short biological half-lives. Due to the endocrine potential of the phenols and phthalates, analyses are mostly done in spot urines from mother and child cohorts. To our knowledge, this is the case in Norway, with some exceptions (Papadopoulou et al., 2016). In EuroMix, we studied an adult population of both genders. Compared to concentrations in spot urines of women in Norway by Sakhi et al. (2018), the concentrations of the phenols and TCS were in the same range as the concentrations in urine from females in the EuroMix study. Comparison of TCS concentration in urine across countries shows that Denmark (median in adults = 0.64 ng/ml) has concentrations in the same range as Norway, while USA and Canada have > 10 times higher TCS concentration in urine (Juric et al., 2018). The concentrations of BPA in spot urines from males and females in the NHANES study were slightly higher than the concentrations in the EuroMix study, expressed as geometrical means (GM) (Hartle et al., 2016). However, GM from spot urines have been found to overestimate the long-term exposure of chemicals with short

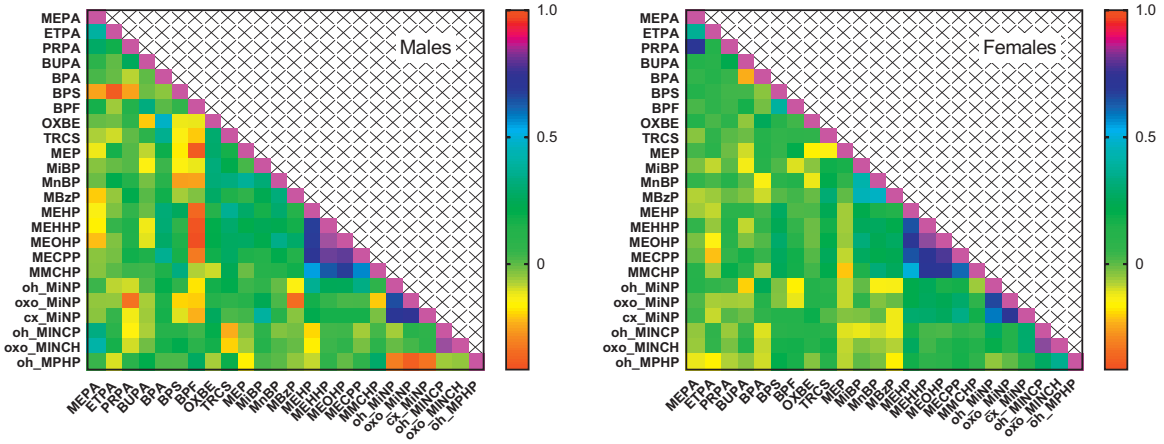

Fig. 7. A heat map of the Spearman correlation coefficients. Spearman correlation coefficients were calculated between all the metabolites of phthalates and DINCH, and the phenols in urine. From green to blue shows an increased positive correlation, while yellow to red shows no correlation to negative correlation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Multivariable linear regression (MRL) analysis showing the association between the dependent variables urinary phenols (SG-adjusted and log transformed) and the independent main categorical food variables from the weighed food records (all participants).

Food variable[a]	Chemical	Gender	Category 1			Category 2		
			Beta	95% CI	*P*-value	Beta	95% CI	*P*-value
Bread	MEPA	MF	0.57	0.31,1.05	0.07	0.47	0.26,0.88	**0.02**
	BUPA	MF	1.14	0.78,1.68	0.49	1.92	1.28,2.86	**0.00**[#]
	OXBE	MF	1.54	0.76,3.14	0.23	1.58	0.77,3.21	0.21
Grain	PRPA	MF	1.69	0.67,4.22	0.26	1.88	0.74,4.79	0.19
	BPA	MF	0.95	0.69,1.31	0.77	1.07	0.78,1.48	0.67
Fruit and berries	ETPA	MF	0.80	0.42,1.54	0.50	0.59	0.31,1.14	0.12
	BUPA	MF	1.06	0.74,1.53	0.74	1.21	0.82,1.76	0.33
Meat	MEPA	MF	1.34	0.74,2.43	0.34	1.88	1.04,3.40	**0.04**
Fish	OXBE	MF	0.55	0.30,1.01	0.06	NA	NA	NA
Dairy	MEPA	MF	1.41	0.80,2.49	0.23	1.77	0.98,3.18	0.06
	PRPA	MF	1.44	0.58,3.58	0.43	2.27	0.89,5.78	0.09
	BUPA	MF	1.26	0.88,1.82	0.21	1.43	0.98,2.08	0.06
	BPA	MF	0.79	0.58,0.58	0.08	0.64	0.46,0.88	**0.01**
	OXBE	MF	0.97	0.48,1.93	0.92	1.59	0.78,3.26	1.18
Cheese	MEPA	MF	2.07	1.14,3.75	**0.02**	1.52	0.82,2.82	0.18
	PRPA	MF	1.89	0.71,4.98	0.20	1.16	0.44,3.06	0.77
	BUPA	MF	0.64	0.43,0.96	**0.03**	0.79	0.52,1.18	0.24
	BPA	MF	1.23	0.90,1.69	0.20	1.27	0.92,1.76	0.15
Butter and oil	MEPA	MF	0.61	0.33,1.10	0.10	0.67	0.38,1.18	0.16
	ETPA	MF	0.72	0.37,1.41	0.34	0.54	0.28,1.03	0.06
	BUPA	MF	0.64	0.44,0.94	**0.02**	0.63	0.44,0.91	**0.01**
	OXBA	MF	1.52	0.75,3.09	0.24	1.64	0.82,3.29	0.16
	TCS	MF	1.63	0.90,0.90	0.11	1.65	0.92,2.94	0.09
Sweets	BPA	MF	0.85	0.65,1.12	0.26	NA	NA	NA
Beverages	ETPA	MF	1.53	0.78,3.00	0.21	1.68	0.85,3.28	0.13
	PRPA	MF	0.59	0.24,1.50	0.27	0.85	0.32,2.30	0.75
	BUPA	MF	1.00	0.69,1.46	0.98	1.52	1.02,2.26	**0.04**
	TCS	MF	1.91	1.06,1.06	**0.03**	1.32	0.73,2.40	0.36
Other foods	BPA	MF	1.22	0.92,1.61	0.16	NA	NA	NA
	OXBE	MF	1.66	0.90,3.08	0.11	NA	NA	NA

NA: not applicable, only category 1 for this variable. In bold – significant correlations ($P \leq 0.05$).
MF: males and females.
Models are adjusted for age, gender and education.
-significant correlation after multiple comparison using the Sidak correction ($P \leq 0.0004$).
[a] Categories for each food variable (gram of food for reference category, category 1 and category 2, n = 45–51): All participants; bread; 0–78; 79–162; 165–508, grain; 0–41; 43–137; 142–714, fruit and berries; 0–180; 182–315; 318–1653, meat; 0–10; 12–105; 106–634, fish: 0–84; 87–740, dairy: 0–130; 131–291; 300–1045, cheese; 0–19; 20–61; 64–517, butter and oil; 0–3; 4–20; 20–96, sweets; 0–11; 12–147, beverages; 0–1395; 1400–2050; 2061–6069, other foods; 0–21; 22–557.

elimination half-life compared to concentrations in 24-hour urine (Aylward et al., 2017). Compared to the results reported here, the concentrations of phthalate metabolites in spot urines (n = 6) from Norwegian women were mostly higher for MEP, MiBP, MnBP, MBzP and metabolites from DEHP, but at the same level for metabolites from DiNP (Sakhi et al., 2017). Metabolites from DINCH and DPHP were not reported in the Sakhi study.

It is suggested that the concentrations from one or more spot urines will not necessarily give a good estimate of long-term exposure. This is highly dependent on the chemical tested and the elimination half-life of the chemical. The chemicals analysed in this paper have a relatively short half-life, and the elimination half-lives reported for some of the chemicals are from 4 to 11 h (Aylward et al., 2017). Therefore, the concentration in 24-hour urine is likely to give a better surrogate estimate for long-term exposure. As Aylward et al. (2017) pointed out, the controlling factor regarding the use of spot urine as a reliable exposure estimate for individuals is the half-life of elimination and frequency of exposure.

4.2. Exposure to chemicals from foods and PCPs

The exposure of the chemicals studied depends on their use and presence in foods and PCPs. Chemicals used in plastic, such as bisphenols and phthalates, can migrate into PCPs and foods, while chemicals like parabens, TCS, TCC and OXBE have been added to foods or PCPs. However, all these chemicals are present in both PCPs and foods.

The external exposures to phenols and phthalates from diet are mostly in the ng-µg range, but can be up to mg from cosmetics. In a Norwegian cohort, the median intake of phthalates in adults ranged from 0.13 to 0.89 µg/kg bw/day (Giovanoulis et al., 2016). The mean exposure to total parabens from diet (MEPA, ETPA, PRPA, BUPA and benzyl paraben) was estimated as 307 ng/kg bw/day in adults (Liao et al., 2013), while daily external exposure to parabens from PCP in adults was estimated as 2.4 mg/kg bw/day (Bledzka et al., 2014). However, it can be assumed that only a small fraction of this amount from PCP is absorbed through skin, leading to lower internal concentrations.

As we all are exposed to many of these chemicals on a daily basis from different routes of exposure, co-exposure to some of these chemicals is likely, despite their different uses. Significant correlations were found between levels of phthalates, parabens and TCS in urine samples for some of the participants. This indicates that exposure to one chemical may increase the likelihood for exposure to another chemical, for example, because they are present in the same food or product. Pairwise correlation between BPA concentrations in urine and phthalates were also found in mothers by Larsson et al. (2014).

4.3. Diet and associations with urinary concentrations of phenols and phthalates

A positive association was found between urinary MEPA and BUPA concentrations with meat and bread consumption, respectively, for all

Table 3
Multivariable linear regression (MLR) analysis showing the association between the dependent variables urinary phthalates metabolites (SG adjusted and log transformed) and the independent main categorical food variables from weighed food records.

Food variable[a]	Chemical	Gender	Category 1			Category 2		
			Beta	95% CI	*P*-value	Beta	95% CI	*P*-value
Bread	MiBP	MF	0.76	0.59,1.00	**0.05**	0.69	0.52,0.91	**0.01**
	sumDEHP	F	0.88	0.71,1.07	0.20	0.84	0.67,1.04	0.10
	sumDINCH	MF	1.06	0.75,1.49	0.75	0.89	0.62,1.29	0.54
	oh_MPHP	M	1.18	0.61,2.31	0.61	1.20	0.60,2.41	0.59
		F	0.86	0.58,1.28	0.46	0.72	0.48,1.07	0.11
Grain	sumDINCH	MF	1.37	0.99,1.90	0.06	1.14	0.81,1.61	0.45
	oh_MPHP	M	0.78	0.41,1.47	0.43	0.74	0.37,1.49	0.39
Potato	oh_MPHP	F	0.76	0.54,1.07	0.11	NA	NA	NA
Vegetables	MEP	M	0.87	0.28,2.69	0.81	0.42	0.15,1.20	0.10
	MnBP	M	1.32	0.92,1.89	0.13	1.02	0.70,1.49	0.92
	oh_MPHP	M	1.19	0.64,2.22	0.57	0.73	0.39,1.38	0.32
Fruit/berries	MiBP	MF	1.43	1.11,1.84	**0.01**	1.32	1.01,1.72	**0.04**
	sumDEHP	F	1.09	0.89,1.33	0.42	1.30	1.06,1.60	**0.01**
	oh_MPHP	F	0.72	0.49,1.06	0.10	1.01	0.68,1.52	0.96
Meat	MiBP	MF	1.33	1.02,1.73	**0.04**	1.12	0.86,1.45	0.40
	MBzP	MF	1.29	0.98,1.72	0.07	0.93	0.70,1.24	0.62
	sumDEHP	M	0.98	0.68,1.40	0.89	0.73	0.51,1.04	0.08
	sumDEHP	F	0.86	0.72,1.02	0.08	NA	NA	NA
Fish	MEP	F	1.28	0.84,1.96	0.25	NA	NA	NA
	oh_MPHP	M	0.69	0.40,1.18	0.17	NA	NA	NA
Dairy	MEP	M	0.49	0.17,1.42	0.18	1.31	0.42,4.13	0.63
	MiBP	MF	0.94	0.73,1.21	0.64	0.84	0.65,1.09	0.19
	sumDEHP	M	1.14	0.80,1.62	0.45	0.83	0.57,1.20	0.31
	sumDiNP	M	0.39	0.19,0.79	**0.01**	0.69	0.34,1.41	0.30
Cheese	MEP	M	0.58	0.20,1.65	0.29	0.51	0.17,1.54	0.23
	MiBP	MF	1.11	0.85,1.44	0.45	0.96	0.73,1.26	0.76
	MBzP	MF	0.91	0.69,1.19	0.47	0.74	0.56,0.98	**0.03**
	sumDEHP	F	0.89	0.73,1.09	0.25	0.84	0.68,1.04	0.12
	sumDINCH	MF	0.89	0.64,1.25	0.49	0.86	0.61,1.21	0.38
Butter/oil	MiBP	MF	1.22	0.93,1.58	0.15	1.26	0.98,1.63	0.07
	MnBP	M	1.21	0.86,1.71	0.27	0.92	0.64,1.33	0.66
	MnBP	F	1.21	0.93,1.58	0.16	1.23	0.95,1.60	0.12
	sumDEHP	F	1.26	1.03,1.55	**0.03**	1.32	1.08,1.60	**0.01**
	sumDiNP	M	0.45	0.22,0.92	**0.03**	0.52	0.23,1.16	0.11
	sumDiNP	F	1.78	1.18,2.67	**0.01**	1.44	0.96,2.15	0.08
	sumDINCH	MF	1.40	1.01,1.94	**0.05**	1.23	0.89,1.69	0.20
	oh_MPHP	F	1.36	0.92,2.01	0.12	1.12	0.76,1.65	0.57
Sweets	MBzP	MF	0.84	0.67,1.07	0.16	NA	NA	NA
	MnBP	F	0.85	0.68,1.08	0.18	NA	NA	NA
	sumDiNP	F	0.73	0.51,1.04	0.08	NA	NA	NA
	oh_MPHP	M	1.31	0.77,2.23	0.30	NA	NA	NA
	oh_MPHP	F	1.46	1.04,2.05	**0.03**	NA	NA	NA
Beverages	MEP	M	0.47	0.17,1.25	0.13	0.64	0.22,1.85	0.40
	MEP	F	1.29	0.79,2.10	0.30	1.34	0.83,2.19	0.23
	MnBP	M	1.27	0.88,1.81	0.19	0.99	0.70,1.41	0.97
	sumDiNP	M	0.76	2.64,1.54	0.44	0.67	0.32,1.40	0.28
	oh_MPHP	M	1.02	0.55,1.90	0.96	1.50	0.76,2.96	0.24
Other foods	MiBP	MF	1.27	1.01,1.59	**0.04**	NA	NA	NA
	sumDEHP	F	1.16	0.97,1.39	0.11	NA	NA	NA
	sumDiNP	M	1.45	0.74,2.84	0.27	NA	NA	NA

NA: not applicable, only category 1 for this variable. MF: males and females, M: males, F: females.
In bold – significant correlations ($P \leq 0.05$).
All models are adjusted for age and education, and including gender for models with all participants.

[a] Categories for each food variable (gram of food for reference category, category 1 and category 2): All participants, n = 45–51; bread; 0–78; 79–162; 165–508, grain; 0–41; 43–137; 142–714, potato 0–20; 25–350, vegetables; 0–135; 136–291; 293.7–1432, fruit and berries; 0–180; 182–315; 318–1653, meat; 0–10; 12–105; 106–634, fish: 0–84; 87–740, dairy: 0–130; 131–291; 300–1045, cheese; 0–19; 20–61; 64–517, butter and oil; 0–3; 4–20; 20–96, sweets; 0–11; 12–147, beverages; 0–1395; 1400–2050; 2061–6069, other foods; 0–21; 22–557.

Males, n = 13–29; bread; 0–104; 110–223; 232–508, grain; 0–51; 56–161; 213–580, potato 0–20; 25–350, vegetables; 0–135; 136–291; 293.7–1432, fruit and berries; 0–180; 182–315; 318–1653, meat; 0–10; 12–105; 106–634, fish: 0–84; 87–740, dairy: 0–130; 131–291; 300–1045, cheese; 0–19; 20–61; 64–517, butter and oil; 0–3; 4–20; 20–96, sweets; 0–11; 12–147, beverages; 0–1395; 1400–2050; 2061–6069, other foods; 0–21; 22–557.

Females, n = 32–66; bread; 0–64; 65–144; 145–412, grain; 0–38; 40–120; 123–714, potato 0–28; 50–282, vegetables; 0–137; 140–294; 297.7–1432, fruit and berries; 0–180; 182–301; 302–1653, meat; 0–82; 95–634, fish: 0–84; 87–740, dairy: 0–131; 148–280; 282–1045, cheese; 0–19; 20–60; 64–415, butter and oil; 0–2; 3–16; 19–96, sweets; 0–13; 14–147, beverages; 0.5–1395; 1400–2050; 2061–6069, other foods; 0–23; 26–430.

participants. Parabens were found in foods in USA, with the highest concentrations of total parabens in grains (18.6 ng/g), beverages (14.2 ng/g), dairy products (9.6 ng/g) and meat (7.67 ng/g), and with the lowest concentrations in fruit (Liao et al., 2013). Parabens are also found in fish and shellfish (Fussell et al., 2014; Liao et al., 2013). The association between MEPA and meat consumption conforms to the EU-authorised use of parabens (E214–E219) as preservatives in a few meat products described in the Annex II to R 1333/2008. Liao et al. (2013)

Table 4
Multivariable linear regression (MLR) analysis showing the association between the dependent variables urinary phthalate metabolites (SG-adjusted and log transformed) and the independent main categorical cosmetic variables.

Cosmetic category	Chemical	Gender	Category 1			Category 2		
			Beta	95% CI	*P*-value	Beta	95% CI	*P*-value
Shower gel	MEP	MF	1.37	0.91,2.05	0.13	NA	NA	NA
	MnBP	F	0.77	0.50,1.19	0.23	NA	NA	NA
	MBzP	M	0.59	0.39,0.89	**0.01**	NA	NA	NA
	MBzP	F	0.59	0.35,1.00	**0.05**	NA	NA	NA
	sumDEHP	F	0.76	0.55,1.06	0.11	NA	NA	NA
Shampoo	MnBP	F	0.85	0.60,1.19	0.34	NA	NA	NA
	sumDEHP	M	0.90	0.67,1.20	0.45	NA	NA	NA
	sumDEHP	F	0.96	0.73,1.25	0.75	NA	NA	NA
Conditioner	MnBP	M	1.24	0.77,2.02	0.37	NA	NA	NA
	MnBP	F	1.05	0.74,1.47	0.79	NA	NA	NA
	MBzP	F	0.94	0.70,1.25	0.66	NA	NA	NA
	sumDEHP	F	0.92	0.70,1.20	0.53	NA	NA	NA
Deodorant	MEP	MF	0.59	0.37,0.95	**0.03**	0.59	0.29,1.22	0.15
Facial cleanser	MiBP	MF	0.85	0.66,1.10	0.21	NA	NA	NA
Facial moisturiser	MnBP	M	1.20	0.82,1.75	0.33	NA	NA	NA
	MnBP	F	0.84	0.63,1.13	0.25	0.74	0.55,0.99	**0.04**
	sumDiNP	MF	0.75	0.51,1.11	0.15	0.93	0.60,1.44	0.75
Anti-wrinkle cream	MEP	F	2.43	1.27,4.66	**0.01**	NA	NA	NA
	MiBP	F	1.28	0.84,1.96	0.25	NA	NA	NA
	sumDiNP	F	1.30	0.74,2.28	0.36	NA	NA	NA
	sumDINCH	F	1.82	1.09,3.04	**0.02**	NA	NA	NA
Toothpaste	MnBP	F	1.51	1.14,2.01	**0.01**	NA	NA	NA
	MBzP	F	1.47	1.04,2.08	**0.03**	NA	NA	NA
	sumDiNP	MF	0.69	0.49,0.98	**0.04**	NA	NA	NA
Perfume	MEP	MF	1.46	0.96,2.22	0.08	NA	NA	NA
	sumDEHP	F	0.86	0.71,1.04	0.12	NA	NA	NA
	sumDiNP	MF	0.76	0.53,1.08	0.13	NA	NA	NA
Lip gloss and balm	sumDiNP	MF	0.97	0.60,1.56	0.89	1.44	0.95,2.17	0.08
	oh_MPHP	F	1.35	0.96,1.90	0.08	0.57	0.35,0.91	**0.02**
Hand cream	MiBP	F	2.26	1.50,3.42	**0.00**[#]	1.16	0.75,1.80	0.49
	MBzP	F	1.40	0.92,2.13	0.11	0.85	0.55,1.31	0.46
Hair styling	sumDEHP	F	1.33	1.05,1.69	**0.02**	NA	NA	NA
	sumDINCH	MF	1.21	0.84,1.74	0.31	NA	NA	NA
Shaving products	MBzP	M	1.87	1.01,3.47	**0.05**	NA	NA	NA
Eye-makeup	MEP	F	1.19	0.75,1.90	0.45	1.30	0.80,2.11	0.29
	MiBP	F	1.28	0.94,1.74	0.11	1.09	0.78,1.52	0.60
Rouge and powder	MnBP	F	0.81	0.59,1.09	0.16	NA	NA	NA
Hand soap	MEP	MF	1.33	0.83,2.14	0.24	0.98	0.62,1.54	0.92
	MiBP	MF	0.87	0.66,1.16	0.36	0.82	0.62,1.07	0.15
	oh_MPHP	F	0.68	0.45,1.04	0.08	0.76	0.50,1.16	0.20

NA: not applicable, only category 1 for this variable. MF: males and females, M: males, F: females.
In bold – significant correlations ($P \leq 0.05$).
Categories for each PCP variable (frequency of use for reference category, category 1 and category 2): All participants; shower gel: 0, n = 44; 1–2, n = 100, deodorant; 0, $n = 27$; 1, $n = 101$; 2, $n = 16$, facial cleanser; 0, $n = 100$; 1–2, $n = 44$; facial moisturiser; 0, $n = 57$; 1, $n = 47$; 2, $n = 40$; toothpaste: 0–1, $n = 40$; 2–3, $n = 104$, perfume; 0, $n = 107$; 1–2, $n = 37$, lip gloss and balm; 0, $n = 94$; 1, $n = 20$; 2–5, $n = 30$, hair styling; 0, $n = 121$; 1–4, $n = 23$, hand soap; 0–6, $n = 41$; 7–9, $n = 45$; 10–33, $n = 57$.
Males; shower gel: 0, $n = 16$; 1–2, $n = 28$, shampoo; 0, $n = 27$; 1, $n = 17$, conditioner; 0, $n = 39$; 1, $n = 5$, facial moisturiser; 0, $n = 35$; 1, $n = 9$, shaving products; 0, $n = 38$; 1, $n = 6$.
Females; shower gel: 0, $n = 28$; 1, $n = 64$; 2, $n = 10$, shampoo; 0, $n = 51$; 1–2, $n = 49$, conditioner; 0, $n = 60$; 1–2, $n = 40$, deodorant; 0, $n = 13$; 1, $n = 71$; 2, $n = 16$, facial cleanser; 0, $n = 57$; 1, $n = 31$; 2, $n = 12$, facial moisturiser; 0, $n = 22$; 1, $n = 38$; 2–4, $n = 40$, anti-wrinkle cream; 0, $n = 90$; 1–2, $n = 10$, sunscreen; 0, $n = 87$; 1–2, $n = 12$, toothpaste: 0–1, $n = 19$; 2–3, $n = 81$, perfume; 0, $n = 70$; 1–2, $n = 30$, lip gloss and balm; 0, $n = 50$; 1–2, $n = 37$; 3–5, $n = 13$, foundation: 0, $n = 73$; 1–2, $n = 27$, hand cream; 0, $n = 79$; 1, $n = 11$; 2–5, $n = 10$, hair styling; 0, $n = 85$; 1–4, $n = 15$, eye-makeup; 0, $n = 49$; 1, $n = 29$; 2–4, $n = 22$, rough and power; 0, $n = 83$; 1–2, $n = 17$, hand soap; 0–6, $n = 20$; 7–10, $n = 40$; 11–30, $n = 39$.
All models are adjusted for age and education, and including gender for models with all participants.
[#] Significant correlation after multiple comparison using the Sidak correction ($P \leq 0.0004$).

suggest that foods are a minor source of total paraben exposure, contributing only 0.57% of the total. BPA in urine was previously associated with the intake of meat and fish (Larsson et al., 2014). However, urinary BPA was negatively associated with the intake of dairy products in the EuroMix study. Food is a major source of phthalate exposure (Cao et al., 2014; Wormuth et al., 2006). Since phthalates are lipophilic, they are more likely to be present at high concentrations in fatty foods. Cao et al. (2014) gives a broad overview over phthalates present in foods, and the highest concentrations are in oily foods. This is supported by Wormuth et al. (2006), where the highest phthalate concentrations were found in animal fat, vegetable oil and spices. This correlates well with our findings in the EuroMix study, where fats and oils were positively associated with concentrations of DEHP. The phthalates DPHP and DiBP were also associated with the consumption of sweets. This is in accordance with the findings by Larsson et al. (2014), who found a positive association between phthalates and chocolate and ice cream, which were parts of the sweet food category in our study. However, only low concentrations of phthalates were found in candy and chocolate (Cao et al., 2014).

4.4. Use of PCPs and associations with urinary concentrations of phenols and phthalates

Parabens are widely used as preservatives in PCPs. The urinary concentrations of parabens were associated with the use of PCPs, such as lotion, skin make-up, eye make-up and mouth wash (Larsson et al., 2014). Sakhi et al. (2018) also reported an association between parabens and the use of hand cream, face cream, shower soap, deodorant and hair products. The only significant positive association was found between the use of lip gloss and lip balm and the concentration of BPA in urine for all participants. However, a positive association was found between PRPA and eye make-up and hand soap, with a β well above 2 that approaches statistical significance. An association between OXBE and the use of hand cream was previously reported (Sakhi et al., 2018). In Sakhi et al. (2018), BPA concentration in maternal urine was not positively associated with any PCP use, but was significantly negatively associated with the use of hand soap, which might indicate that hand washing reduced BPA exposure. Phthalates are used as a plasticiser in plastic packaging and may therefore leak into PCPs, so PCP use may therefore be an important source to phthalate exposure. Wormuth et al. (2006) suggests that > 80% of exposure to DEP is caused by dermal application of PCPs. In the EuroMix study a significant association was found for phthalates and the use of shower gel for both males and females, but mostly the PCP determinant for phthalate exposure differed between the genders. For males, a significant association was found between phthalates and the use of shaving products, while for females, a significant association was found between phthalates and anti-wrinkle cream, hand cream and toothpaste. Perfume has been found to be a determinant for phthalate exposure in several previous studies (Braun et al., 2014; Giovanoulis et al., 2016; Parlett et al., 2013; Sakhi et al., 2017), but was not found to be associated with phthalate exposure in EuroMix. Several other studies also reported an association between the use of PCP and concentrations of phthalates in urine (Giovanoulis et al., 2016; Larsson et al., 2014; Sakhi et al., 2017), but the determinants seemed to differ. This might be due to differences in the concentrations of phthalates in products within a PCP category, and differences in PCP use between countries.

4.5. Diet and use of PCPs

To our knowledge, this is the first Norwegian biomonitoring study to provide detailed knowledge of both diet and PCP use from records/diaries accompanied by 24-hour urine sampling over two non-consecutive days. The study population is not representative for the general Norwegian population and several significant differences between the diet of the EuroMix population and the national survey population (Norkost 3) were observed (Totland et al., 2012). Sakhi et al. (2017) and Papadopoulou et al. (2016) have earlier reported on PCP use in two different Norwegian studies, the first with a study group of 48 mothers and 56 children and the second with a study group of 61 adult males and females. Both registered the PCP used through a FFQ, where usage was grouped into defined categories. Due to differences in registration, it is difficult to compare the PCP use directly with our study. However, it seems that the PCP use by the mothers in Sakhi et al. (2017) is consistent with our results, whereby the usage frequency of most PCPs is between 1 and 2 per day, with the exception of products such as hand soap, hand cream and lip balm/lipstick.

4.6. Strengths and limitations

Euromix participants may not be representative for the Norwegian population with regards to their diet or their demographics. There were no regular smokers in the study population, and the EuroMix population contained mostly highly educated people. This is a deviation from the general Norwegian population, where 15% of the population smoke daily (Totland et al., 2012).

A major strength of the EuroMix study is the detailed information by diary recording of PCP use, in combination with weighed food records on food consumption. Also, the fact that a full day's urination was collected for both study days as spot urines, three pooled time slots and total 24-hour urine, strengthens the use of this study for assessing the exposure for chemicals with a short half-life. A weakness is that the food record and the PCP diary, and the urinary collection were performed during the same time intervals, not accounting for the time needed for a chemical to be absorbed and metabolised before excretion. This lack of time shift is probably most important for the assessment of PCP use, since dermal absorption takes longer than oral ingestion. However, all spot urines have been stored separately and the times of food consumption and PCP use have been recorded, which makes it possible to perform more detailed and time-shifted comparison between exposure estimates and urine concentrations in the future. An additional benefit of the EuroMix study is that the participants recorded food consumption using both an FFQ and a weighed food record. These methods of recording food consumption have both advantages and disadvantages. All self-reported food consumption data are prone to errors. The nutrient intake was slightly higher using an FFQ than using a 3-day diet record (Talegawkar et al., 2015). Dietary self-reporting has previously shown to be under reporting (Freedman et al., 2014). Reported food consumption may be affected by the participants' personal characteristics, including BMI, age, gender, educational level, health awareness, dieting and degree of obesity (Maurer et al., 2006; Tooze et al., 2004). Under-reporting is observed more frequently among females than in males (Rennie et al., 2006), with a tendency to under-report foods high in fat or sugar (Mirmiran et al., 2006). Correct reporting of diet is needed to describe the real food sources of the environmental chemicals.

5. Conclusions

The participants in the EuroMix study were exposed to a mixture of phenols and phthalates. A variety of foods and PCPs were found to be possible sources of these chemicals. This indicates a complex pattern of exposure to numerous chemicals on a daily basis, originating from multiple sources and depending on individual diet and PCP preferences. This BM study will be used to further examine exposure to a wide variety of chemicals, including results about variation in exposure within a day and between days. Forward and backward exposure modelling and estimation of internal organ doses based on the BM data will be performed using PBPK models.

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Appendix A. Supplementary data

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