



## The EuroMix human biomonitoring study: Source-to-dose modeling of cumulative and aggregate exposure for the bisphenols BPA, BPS, and BPF and comparison with measured urinary levels



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### ABSTRACT

**Background:** Bisphenol A (BPA) and, with increasing occurrence, its analogs bisphenol S (BPS) and bisphenol F (BPF) are applied in many consumer products, leading to humans being exposed from a vast number of sources and via several routes. Estrogenic and anti-androgenic effects are exerted by the chemical BPA, and also by its analogs. Therefore, realistic exposure assessments are needed for assessing risks related to cumulative exposure. **Objectives:** Biomonitoring for BPA, BPS, and BPF was conducted in a human study embedded in the EU project EuroMix and the measured urinary concentrations were compared to source-to-dose calculations for source allocation and plausibility test of the model.

**Methods:** For two 24-hour study periods separated by 2–3 weeks, 144 adult volunteers in Norway kept detailed diaries on food consumption, personal care product (PCP) use, and thermal paper (TP) handling. Concurrently, 24 h urine was collected and urinary levels of BPA, BPS, and BPF were analyzed using ultra-high performance liquid chromatography and tandem mass spectrometry (UPLC-MS-MS). In line with the information obtained from the first study day, bisphenol exposure from food, PCPs, TP, and dust was modeled primarily individual-based with probabilistic models. Estimates for BP excretion over 24 h were obtained with the models and compared to measured amounts.

**Results:** Modeled aggregate internal exposures covered the full range of measured urinary amounts for all BP analogs. In general, individual-based medians of modeled BPA exposures were in good agreement with the measurements, but individual-specific correlation was lacking. Modeled exposures mostly underestimated BPS and BPF levels in participants with positive measurements (53% and 8%), except for the P95 values of modeled BPS exposure that were higher than measured amounts if TP was handled. Most likely, diet and TP were the sources contributing the most to BP exposure in this study. Urinary measurements did not reveal a significant correlation between the amounts of canned food consumed, the number of PCPs used, or the number of TP handling events and levels of BPA, BPS, or BPF.

**Conclusions:** The good agreement between the ranges of modeled BPA exposure and measured BPA amounts indicates that available concentrations, especially from the main exposure source food, mirror the exposure situation realistically, and suggests that the exposure model considers the relevant exposure sources. The lack of individual-specific correlations means that the individual measured amounts and modeled exposures did not vary in parallel, e.g. due to mismatch of BP concentrations in food, TP, and other sources, or delayed internal exposure. The underestimation of modeled BPS and BPF exposure suggests that not all relevant sources were included in the respective exposure models. This could be due to a lack of input data, e.g. for food items, or due to an increased replacement of BPA with structural analogs compared to the used concentration and occurrence data.

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## 1. Introduction

Over the years, growing evidence has shown that the industrial chemical bisphenol A (BPA, chemical formula  $C_{15}H_{16}O_2$ , CAS No 80-05-7) can interfere with the hormonal system (Fic et al., 2014; Kitamura et al., 2005; Rubin, 2011; Vandenberg et al., 2009), which recently resulted in the official classification of BPA as an endocrine disruptor by the European Chemicals Agency (ECHA) in their list of substances of very high concern (SVHCs) (ECHA, 2018). BPA has been found to affect kidney and liver weight in animal studies, which led to the inclusion of kidney and liver as critical organs for BPA toxicity in the risk assessment conducted by the European Food Safety Authority (EFSA) in 2015 (EFSA CEF Panel, 2015). BPA is applied in many consumer products, because it is the monomer in the production of polycarbonate (PC) plastics and epoxy resins, and used as an additive in other plastic materials (Vandenberg et al., 2007). PC is commonly used for food contact materials such as bottles and containers for food, tableware, and cookware while epoxy resins are frequently utilized as protective linings for food and beverage cans as well as for coatings in drinking water storage tanks (Geens et al., 2012). Moreover, several non-food items such as paint, printing inks, electronic devices, and thermal paper (TP) used for cash receipts (Bjørnsdotter et al., 2017) may contain BPA. In the European Union, the use of BPA was approved in plastic food contact materials with a migration limit of 600 ng BPA/g food (EC, 2011a), while its use in the production of PC baby bottles was prohibited in 2011 for precautionary reasons (EC, 2011b). BPA regulations got stricter in 2018: the migration limit from plastic food contact materials was lowered to 50 ng/g food (EU, 2018). In addition, its use in coatings applied to food contact materials (e.g. in canned food) is now subject to a migration limit of 50 ng/g food in general and 10 ng/g food (detection limit) for items intended to be consumed by infants and young children (EC, 2016).

In the BPA risk assessment conducted by EFSA, diet and TP were found to be the most important exposure sources, followed by personal care products (PCPs) and dust, while the exact contribution depended on whether external or internal exposures were considered (EFSA CEF Panel, 2015). Numerous studies have investigated the occurrence of BPA in food (e.g. reviewed by Caballero-Casero et al., 2016). Average BPA concentrations were summarized in EFSA's scientific opinion on BPA (EFSA CEF Panel, 2015): canned food contained considerably higher BPA concentrations than non-canned food, with seven out of 17 canned food categories having average concentrations above 30 ng/g. With regard to non-canned food, meat products and fish products had the highest BPA concentrations. In a study on Norwegian food and beverages representative for a typical Norwegian diet, BPA was found in 54% of the analyzed items with levels comparable to other countries worldwide. The major contributing food items to dietary exposure in adults were grain and meat products (Sakhi et al., 2014). Compared to other food groups, bread and other grain products generally contribute the most to the total energy intake in the Norwegian diet (Totland et al., 2012), which implies that even low levels of BPA can become relevant in those food items. Other Scandinavian BPA concentration data are available from three small-scale studies conducted by the Danish Ministry of Food, Agriculture, and Fisheries with a focus on canned food items (Okholm and Legind, 2015, 2014; Pedersen et al., 2013).

BPA is frequently used as a color developer in TP intended for cash receipts and tickets with concentrations for functional use ranging between 0.5 and 3% by weight (Eckardt and Simat, 2018). In this application, BPA reacts with a leuco-dye, a chemical with the ability to transform between two chemical forms, to create color under heat. For being able to react with the leuco-dye, BPA is only loosely bound to the paper surface in TP, which increases the potential uptake from handling of receipts in comparison to contacts with polymerized BPA (Bjørnsdotter et al., 2017). BPA is not permitted as an ingredient in PCPs (EP, 2009). Nevertheless, levels of up to 88 ng/g have been reported in Spanish PCPs (Cacho et al., 2013). The source of BPA in

cosmetics is not known, but may be due to migration from PC packaging or impurity in the ingredients (von Goetz et al., 2017). Presence of BPA in dust (due to migration or abrasion) was reported in several publications from European countries, such as France (ANSES, 2013) or Belgium (Geens et al., 2009).

Because of the strict regulations, BPA is increasingly replaced by structurally similar chemicals of the bisphenol (BP) group. Bisphenol S (BPS) can replace BPA as color developer in TP and its occurrence in TP samples is frequently reported (ANSES, 2013; Liao et al., 2012c; Pivnenko et al., 2015). Bisphenol F (BPF) can replace BPA in the production of epoxy resins (Goodson et al., 2002). In addition, BPF occurs naturally in mustard, probably as a breakdown product of a glucosinolate (Zoller et al., 2016). Recent studies from the U.S. and China have found BPS and BPF in food (Liao and Kannan, 2013), dust (Liao et al., 2012b), and PCPs (Liao and Kannan, 2014). Several studies showed that BPS and BPF exert hormonal effects just like BPA (Fic et al., 2014; Rochester and Bolden, 2015; Skledar et al., 2016). Therefore, it is important to assess exposure to BPA together with the exposure to those structural analogs (Karrer et al., 2018). For doing this, it is crucial to be aware of all sources and source-to-dose relations. With the use of bio-monitoring (BM) data, internal levels of BPA, BPS, and BPF can be examined to identify the possible extent of BPA replacement (Chen et al., 2016). In 2016, the Norwegian Institute of Public Health initiated a human BM study to collect detailed BM and exposure data in Norwegian adults ( $n = 144$ ) (Husøy et al., 2019).

This paper aims to compare measured BP amounts of this Norwegian BM study to individual-based exposures modeled with input data provided by the study participants, using exposure models developed in the European Horizon 2020 project EuroMix (de Boer et al., 2016). We modeled aggregate exposure of BPA, BPS, and BPF from diet, PCPs, TP, and dust for the study participants, using individual-specific input data for food consumption, PCP use, and TP handling. We compared the model estimates with measurements of BPA, BPS, and BPF in 24 h urine collected from the same individuals in the same timeframe. The aim is to examine the plausibility of the source-to-dose calculations and to discuss the strengths and weaknesses of the models and input data. This is the first individual-based comparison of measured and modeled exposure to multiple bisphenols for a general adult population.

## 2. Materials and methods

### 2.1. The EuroMix human BM study

The EuroMix human BM study is described in detail in Husøy et al. (2019). In brief, from September 2016 to October 2017, 144 adult volunteers (100 women aged 24–72 and 44 men aged 25–72) were enrolled. The participants kept detailed diaries on all consumed food items, applied PCPs and handled TP receipts during two 24 h periods separated by two to three weeks. We aimed for a weighed food record, which means that participants gave information on all food items consumed: time points, weights, types/brands, packaging, and type of cookware. In the PCP diaries, the participants reported each PCP used (type of product and brand), and the number and time point of all PCP applications. For TP, the participants indicated all TP handling events within the respective 24 h study periods. The participants collected all urine in separate containers for each void, during both 24 h study periods. For each participant, urine given during the three time slots 6 am–12 am, 12 pm–6 pm and 6 pm–6 am was allocated to three pools according to the total volume of each void, so that each pooled urine sample reflected the total volumes of each void given within the respective time slot. The pooled urine samples were frozen at  $-80\text{ }^{\circ}\text{C}$  until analysis. The data from the food diaries were coded in a food calculation system called KBS (managed by the University of Oslo, Norway) while the cosmetic diaries and the questionnaire data were organized using the web-based system Questback ([www.questback.com](http://www.questback.com)).

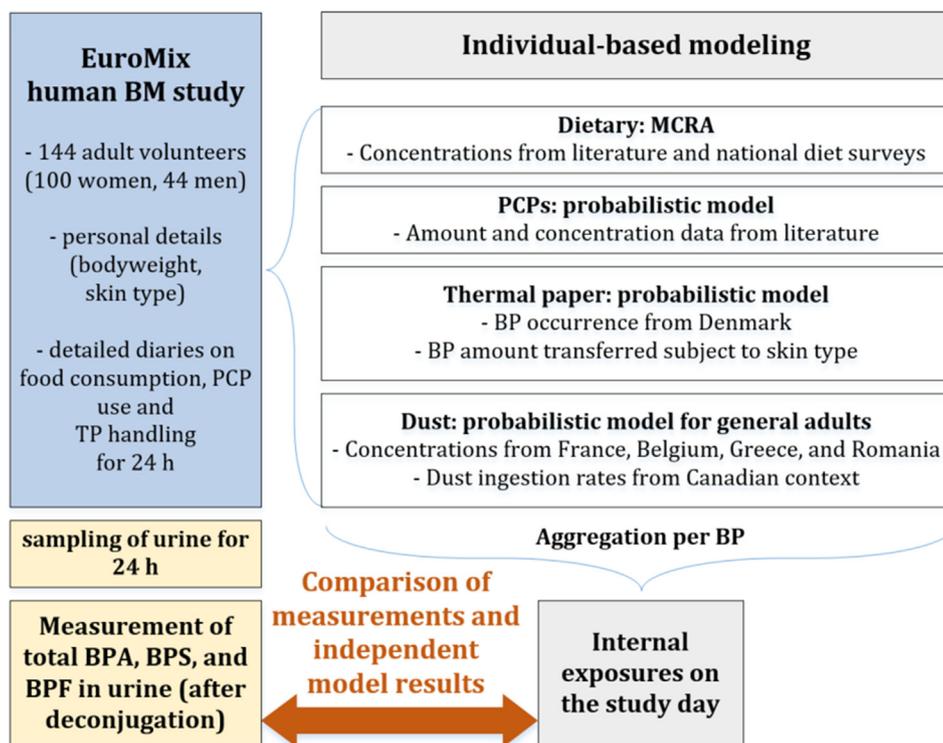


Fig. 1. Workflow for modeling exposures to BPA, BPS, and BPF and comparing the model estimates with measured urinary amounts from BM data.

## 2.2. Quantification of BPA, BPS, and BPF in urine

Husøy et al. (2019) described the analysis of BPA, BPS, and BPF in the urine of the study participants in detail. For this study, BPs were only analyzed in urine collected on study day 1. For most participants (96%), three pooled urine samples were analyzed that represented the time slots described above, while for six participants only two pooled samples were available, because for one of the three time slots no urine was provided. BPA, BPS, and BPF were analyzed as previously described by Sakhi et al. (2018). In brief, the BPs were analyzed by ultra-high performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS-MS) after on-line solid phase extraction. Unconjugated BPs and their respective glucuronides and sulfates were measured as respective summary concentrations (“total” BPA, BPS and BPF, respectively). For deconjugation, enzyme solutions were prepared by dissolving  $\beta$ -glucuronidase/sulfatase in ammonium acetate buffer (pH 5). To 200  $\mu$ L of each pooled urine sample, 50  $\mu$ L of the enzyme solution was added together with a C-13 labelled internal standard of BPA, BPS, or BPF. The enzymatic reaction was stopped by adding formic acid after an incubation of 4 h. Subsequently, the samples were centrifuged at 14,000 rpm for 10 min at room temperature and 80  $\mu$ L of the supernatant was injected into the UPLC-MS-MS system. The method is fully validated with limits of detection (LODs) of 0.04, 0.10, and 0.07 ng/mL and limits of quantification (LOQs) of 0.10, 0.40, and 0.20 ng/mL, for BPA, BPS, and BPF respectively. The accuracy and relative standard deviation in the concentration range of 0.2 to 100 ng/mL were 75–101% and 5.9–34% respectively. The measurements in the three (or two) pools were subsequently combined to obtain an estimate of the amount in 24 h urine for each participant.

## 2.3. Exposure modeling scope

We modeled internal exposures to BPA, BPS, and BPF from food items, PCPs, TP, and dust for the BM study population in the first 24 h study period. Exposure estimates and urinary amounts refer to the same 24 h time window, in view of the rather short time constants of uptake

and elimination observed for BPs (Oh et al., 2018; Thayer et al., 2015). In the following text, the term *modeled BP exposure* will be used for these aggregate internal exposure estimates that can be compared to the measured BP amounts in urine. As elaborated previously (Karrer et al., 2019), inhalation exposure was not taken into account, because of the low volatility of BPs (Staples et al., 1998). Previous exposure assessments have shown that inhalation exposure is of minor importance. For example, in EFSA’s Scientific Opinion on BPA, with 0.2 ng/kg bw/day, inhalation exposure only accounted for about 0.15% of total internal BPA exposure for adults (EFSA CEF Panel, 2015). In a comprehensive study on BP concentrations in indoor air in the U.S., Xue et al. (2016) found a similar magnitude of inhalation exposure for adults of 5.4 ng/day. Since BPS and BPF are replacements for BPA, it was assumed that they have a similar source apportionment as BPA.

### 2.3.1. Modeling software, procedure, and principles

We used the web-based Monte Carlo Risk Assessment (MCRA) model for calculating food exposure and for the individual-based aggregation of exposures from all sources, with absorption factors converting from external to internal exposures (de Boer et al., 2016). The MCRA model was developed for conducting cumulative dietary exposure and risk assessments in a probabilistic way. Its latest version MCRA 9 (beta), the EuroMix toolbox (mcra.rivm.nl/EuroMix/WebApp, account freely available after registration), was used for this work. Exposure calculations used in MCRA and MCRA settings are shown in the Supporting Information (SI) paragraphs 1.3 and 7, respectively. A more detailed description of the MCRA model is provided on the MCRA 9 web page. MCRA input files were prepared in Microsoft Excel 2013. Routines written in the programming language R (version 3.5.0) were used for PCPs, TP, and dust exposure, for aggregation and data analysis. The SI paragraphs 10, 11, and 12 contain the model code used for the exposure calculations. External daily exposures from PCPs and TP were calculated individual-based (see SI paragraphs 2.5 and 3.4). Dust exposure was calculated distribution-based (see SI paragraph 4) as described previously (Karrer et al., 2019), because individual-based information were not available from the BM study. To yield aggregate

exposure, the probabilistic estimates for non-dietary exposures (PCP, TP and dust) were either uploaded to MCRA for an aggregation in MCRA or food exposure estimates were exported from MCRA for aggregation in the programming language R. Fig. 1 shows an overview of the overall modeling scheme.

Parameters not known on an individual basis were drawn from probabilistic distributions wherever possible. Yet, we had to replace censored data deterministically for further calculations, e.g. for BP concentrations in food and BM data. For deriving the most probable exposure values (MPV), we replaced measurements below LOD with 0 and measurements between LOD and LOQ with the average of LOD and LOQ. We additionally derived lower and upper bounds (LB and UB). LBs were derived by replacing measurements below LOD with 0, and measurements between LOD and LOQ with the LOD. UBs were derived by replacing measurements below LOD with the LOD and measurements between LOD and LOQ with the LOQ. The aim of these different replacement methods was to obtain the range of possible concentrations and exposures in view of the small datasets being not suitable for more sophisticated methods such as multiple imputation methods (Chen Haiying et al., 2011; Harel et al., 2014). Replacing measurements below LOD with zero in the MPV was considered the most suitable approach for focusing on products with detected concentrations and not on products with high consumption or use frequencies.

### 2.3.2. External exposure modeling

External exposures from food, PCPs, TP, and dust were modeled probabilistically and independently from each other by considering all individual-based data available in the same 24-hour time frame.

For modeling external dietary exposure, the individual food consumption data from the weighed food records were used. Regarding BP concentration data in dietary matrices, different prioritization approaches are plausible. On the one hand, concentration data from the most suitable studies regarding data origin and representativeness should be considered first, while on the other hand, it is desirable that the exposure to BPA, BPS, and BPF is calculated in a comparable way. Since concentration data for BPS and BPF are scarce, both approaches are mutually exclusive. For the main exposure calculations, we used a concentration dataset previously collected by Karrer et al. (2019) for BPA, BPS, and BPF. Within this dataset, BP-concentrations in food items were preferentially gathered from European studies and, where needed, concentrations were taken from studies not conducted in Europe or extrapolated from similar food items. For BPA, the dataset was supplemented with BPA concentration data measured by national authorities in Norway and Denmark, see Table S1 and Table S2 (Okholm and Legind, 2015, 2014; Pedersen et al., 2013; Sakhi et al., 2014). These measurements were considered the most representative, but unfortunately they were not available for BPS and BPF. For an alternative BPA dataset, we used the data from Norway and Denmark to completely replace entries in the previously collected dataset, which improves the representativeness for the Norwegian study population, but impairs the comparability with BPS and BPF. BPA exposures were found to be very much alike for both datasets and therefore results from the alternative scenario are only presented in the SI. For further information on dietary exposure modeling see SI paragraph 1: consumption data, concentration data and exposure scenarios, exposure model and settings according to scenarios.

For modeling external exposure from PCPs, the individual frequencies of PCP use were available from the BM study, but not the used amounts. Therefore, amount data were gathered from literature (Ficheux et al., 2016) and used according to gender (see Table S3 and Table S4 for distribution parameters of PCP amount data for women and men). Also concentration data were taken from literature (Cacho et al., 2013; Liao and Kannan, 2014; Lu et al., 2018; Miralles et al., 2018; Thomas et al., 2014) and, if needed, concentrations of similar PCPs were used for items without concentration data (see Table S5 for BPA and Table S6 for BPS and BPF). Dermal and oral external exposure

fractions were calculated based on retention factors recommended by the Scientific Committee on Consumer Safety (SCCS, 2016) (see Table S5; for further information on exposure modeling from PCPs see SI paragraph 2: use frequencies and amounts, concentration data, allocation of PCP products, external exposure fractions, exposure model and settings). For modeling external exposure from TP, the number of TP handling events and the skin types (self-reported skin condition of hands, e.g. normal, dry or moist) were available on an individual basis from the questionnaires from the BM study. We used Danish occurrence frequencies of BPA and BPS in TP (Eckardt and Simat, 2018; Pivnenko et al., 2015), and referred to studies by Biedermann et al. (2010) and Lassen et al. (2011) for the number of fingers used for handling TP and to a study by Eckardt and Simat (2017) for the amount of BPA and BPS transferred per finger (see SI paragraph 3 for further information on exposure modeling from TP: handling frequency and skin type, occurrence frequency, number of fingers used for handling and BP amount transferred per finger, exposure model and settings). Dust exposure was modeled with BP concentrations in indoor dust from France (ANSES, 2013; EHESP, CSTB, 2011), Belgium (Geens et al., 2009), Greece, and Romania (Wang et al., 2015). Dust ingestion rates of adults were used as derived by Wilson et al. (2013) (see SI paragraph 4 for further information on modeling dust exposure).

External dietary exposure was modeled in MCRA with 100,000 Monte Carlo (MC) runs in total for the whole BM-study population. External exposure from PCPs and TP was modeled with 1,000 MC runs per person, which led to 144,000 MC runs in total for the 144 participants. This number of runs represented the variability from non-individual-based input data well. Adult-specific oral dust exposure was modeled with 10,000 MC iterations per BP.

### 2.3.3. Conversion of external to internal exposures

We applied absorption factors for converting external to internal exposures. We used a factor of 100% for oral exposure, which is recommended for use in regulatory risk assessments (Pakalin et al., 2010). This is also in accordance with urinary recoveries of 84–109% for deuterated BPA (Thayer et al., 2015) and mean recoveries of 80% with some individual recoveries close to 100% for deuterated BPS (Oh et al., 2018), both found after oral administration. We used 16%, 18% and 20% as LB, MPV and UB, respectively, for the dermal absorption of BPs from PCPs and TP (Demierre et al., 2012; Toner et al., 2018) for the reasons set out in SI paragraph 5 (Review on studies about dermal absorption of BPA).

### 2.3.4. Aggregation of modeled BP exposures from different sources and comparison to measured BP amounts in urine

Dietary exposure estimates were calculated in MCRA. Estimates for PCP, TP, and dust exposure were calculated outside of MCRA with self-developed modeling routines (see chapter 2.3.2 for considered parameters). Exposure estimates for the different sources were combined by individual and exposure percentile, for example to the P95 values of aggregate exposure for all individuals of the study population. Internal BP exposures were compared with measured concentrations of total BPA, BPS, and BPF in 24 h urine to evaluate the performance of the models and related assumptions.

### 2.3.5. Relationship between measured urinary amounts and possible explanatory variables

As seen in the formulas for modeling external exposures of BPA, BPS, and BPF (SI paragraphs 1–4), such estimates are a function of different input variables. We tested to which extent possible explanatory variables investigated in the study population could explain the BP amounts in 24 h urine. Continuous and count variables such as the consumed amount of canned food items, the number of handled TP receipts, and the number of used PCP products were tested with multiple linear regression models and Pearson correlation coefficients. Factorial variables, such as gender and whether or not TP was handled

on the study day, were tested with the non-parametric Mann–Whitney *U* test. Lastly, we investigated possible correlations between the three BPs in urine by calculating Pearson correlation coefficients for the urinary amounts of BPA, BPS, and BPF.

#### 2.4. Uncertainty evaluation

We evaluated uncertainty related to the exposure assessment in a qualitative way using an ordinal scaling approach (Benford et al., 2018). For this, uncertainty sources related to the execution of the BM study and the source-to-dose modeling were identified separately and the associated uncertainty was qualitatively evaluated. In the following, the uncertainty and the impact of the respective uncertainty were classified into five different categories, low (L), low to medium (LM), medium (M), medium to high (MH), and high (H).

### 3. Results

#### 3.1. Comparison between modeled BP exposure and measured urinary BP amounts

Fig. 2 compares measured urinary amounts of BPA, BPS, and BPF with modeled exposures. The cumulative distribution functions (CDFs) depict overall exposure probabilities (for a comparison with the alternative scenario for BPA, see Fig. S1). The ranges of measured amounts are fully covered by the modeled exposures for all BPs. However, for BPS, modeled exposures are lower than measured amounts by up to two orders of magnitude for the percentiles between P0 and P80. Both for measurements and model estimates, BPA contributes by far the most to BP exposure. In addition, the CDFs for measurements and model estimates are best aligned for BPA. The share of censored data was large for BPS and BPF measurements: while BPA was detected in 96.5% of the pooled urine samples, BPS and BPF were only detected in 28.9%, and 4.23% of the samples, respectively (measurements between LOD and LOQ were not treated differently than higher measurements, because the corresponding measured analytical values were used for the comparison). For this reason, the CDFs of BPS and BPF measurements differ considerably depending on whether censored data are replaced by the LOD (UB) or by zero (LB). Beyond the P70 and P95 for BPF and BPS, respectively, the modeled exposure increases faster per percentile (smaller slope). For BPF this can be explained by exposure from food only occurring in 29% of the individual days modeled for the BM

population. For BPS, the smaller slope of the CDF beyond the P95 is a result of TP exposure contributing only to the upper tail, because a relatively low frequency of BPS occurrence in TP was used (as supported by occurrence frequencies from Denmark, see SI paragraph 3.2.) and because TP was only handled by 24% of the study population. On the considered study day, 35 out of the 144 study participants handled TP (12 males, 23 females). Most of them indicated one handling event, five persons indicated two, and two persons indicated three handling events. Three persons (all female) handled TP four, 10, and 41 times, respectively.

For an individual-based comparison of modeled and measured BP exposures, we zoomed into the medians of modeled exposure for each individual. In addition, we looked at the individual-based P95 values, which represent a realistic upper bound. Fig. 3, Fig. 4, and Fig. 5 compare modeled exposures with measured amounts of BPA, BPS, and BPF on an individual basis. BPA was detected in all study participants. In contrast, BPS and BPF had low detection frequencies (DF). Only for 76 and 12 individuals, at least one measurement of BPS and BPF was above LOD, respectively. If individuals had measurements below LOD in at least one of their pooled samples, two measurement points are connected with a horizontal line in Figs. 3–5. The left and right measurement points show LB and UB, respectively.

Measured BPA amounts in 24 h urine spanned over two orders of magnitude (4.06–297 ng/kg bodyweight (bw)/day) with a median of 35.6 ng/kg bw/day (Fig. 3). Individual-based medians of modeled BPA exposure under- or overestimated the measured amounts less than 10-fold for 95.1% of the individuals (median 41.7 ng/kg bw/day, range 4.58–391 ng/kg bw/day). Fig. S2 shows the comparison with the alternative food concentration scenario (less than 10-fold under- or overestimation for 89.6% model range 1.67–389 ng/kg bw/day, median 30.2 ng/kg bw/day). Individual-based P95 values of modeled BPA exposure overestimated the measurements to a higher extent (see Fig. S3). Because food was the main BPA exposure source, TP handling did not substantially change the degree of under- or overestimation.

For individuals with at least one BPS measurement above LOD in the three pools (measurement range 0.716/2.50–343/345, median 6.38/7.53 ng/kg bw/day, LB/UB), the median values of modeled individual exposures underestimated exposure for all but three individuals (Fig. 4). Respective P95 values mostly over- and underestimated BPS exposures for participants that handled TP on the study day or not, respectively. The exact degree of over- or underestimation was different for LB and UB, because the occurrence of censored data in

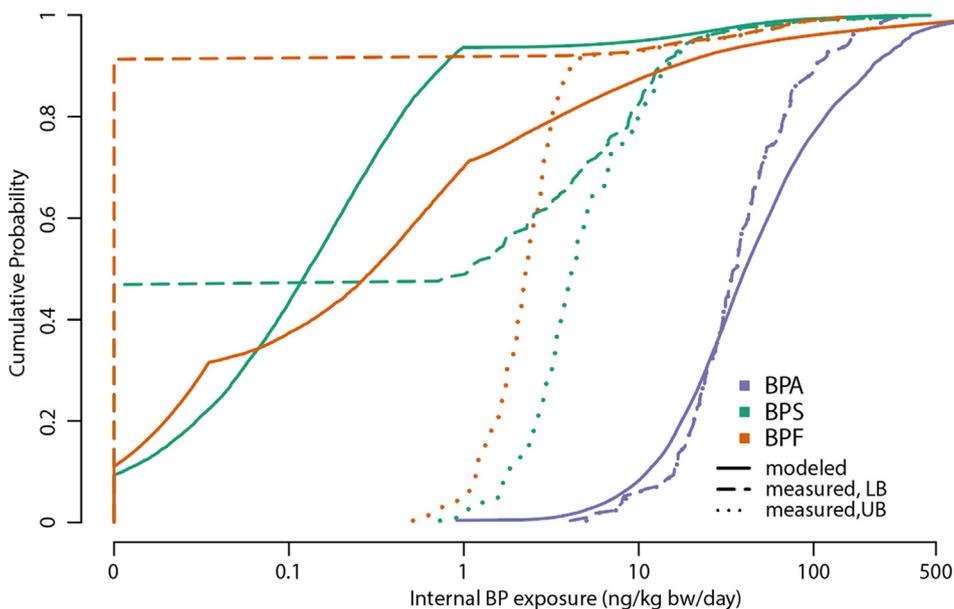
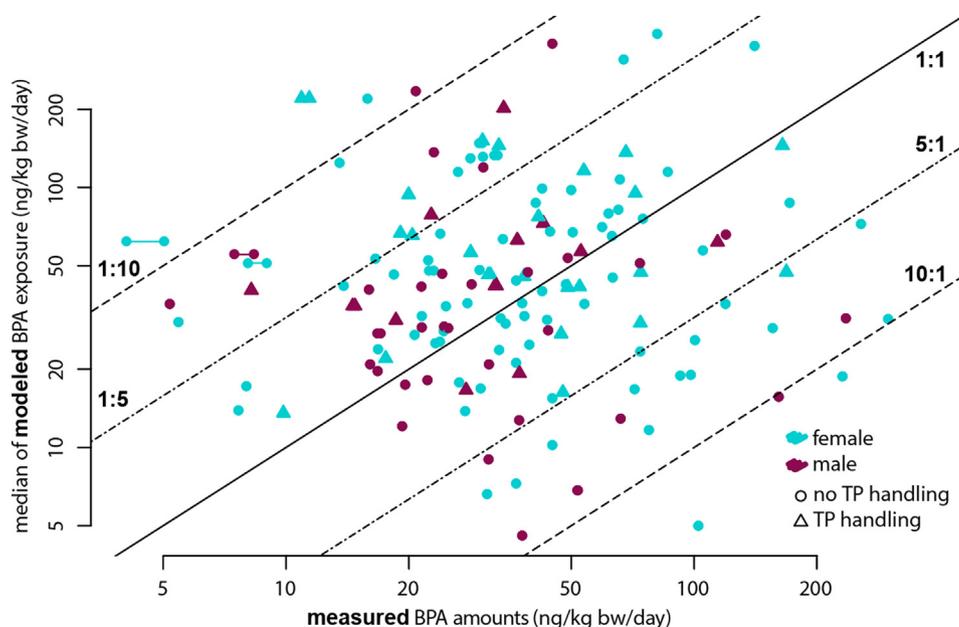
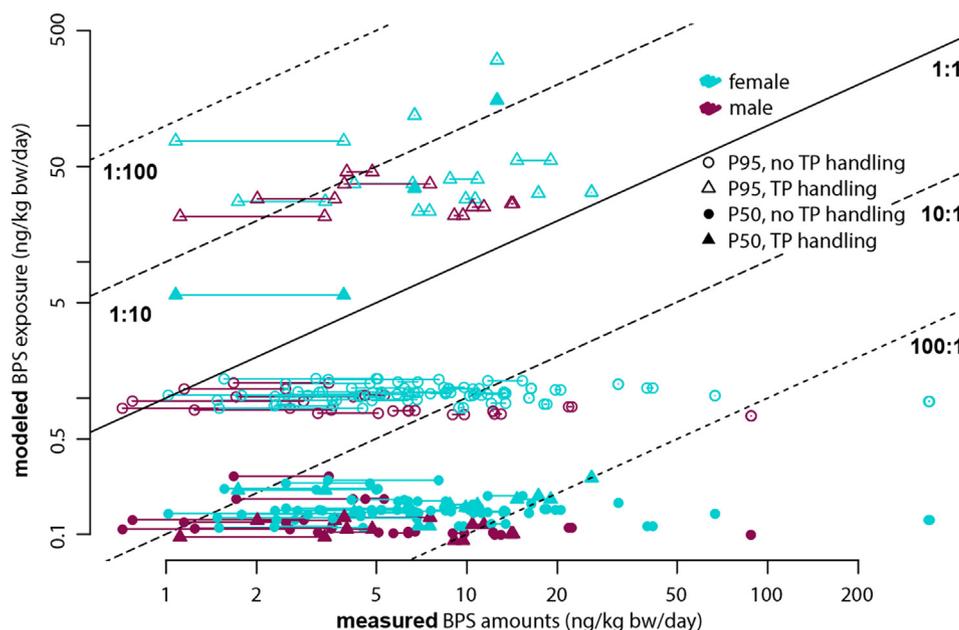


Fig. 2. Cumulative distribution functions of modeled BP exposures from food, PCPs, TP, and dust and of measured amounts in 24 h urine (dashed and dotted lines show LB and UB respectively; for BPA these lines overlap). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 3.** Individual-based comparison of urinary BPA amounts versus median values of modeled exposure. If two measurement points are displayed for one person (connected with horizontal line), at least one measurement of the three pools was below LOD and the two points show LB and UB, respectively. The diagonal lines show ratios of measured to modeled exposure. Ratios below 1 (e.g. 1:10) and ratios above 1 (e.g. 10:1) stand for overestimations and underestimations of modeled exposure compared to measured amounts, respectively.



**Fig. 4.** Individual-based comparison of urinary BPS amounts versus median and P95 values of modeled exposure for individuals with at least one BPS measurement above LOD in the three pools. If two measurement points are displayed for one person (connected with horizontal line), at least one measurement of the three pools was below LOD and the two points show the LB and UB, respectively. The diagonal lines show ratios of measured to modeled exposure. Ratios below 1 (e.g. 1:10) and ratios above 1 (e.g. 10:1) stand for overestimations and underestimations of modeled exposure compared to measured amounts, respectively.

the pooled samples was rather high. Yet, with regard to the P95 model estimates, both over- and underestimations were mostly 1- to 10-fold and with regard to median model estimates, the underestimation was mostly 10- to 100-fold.

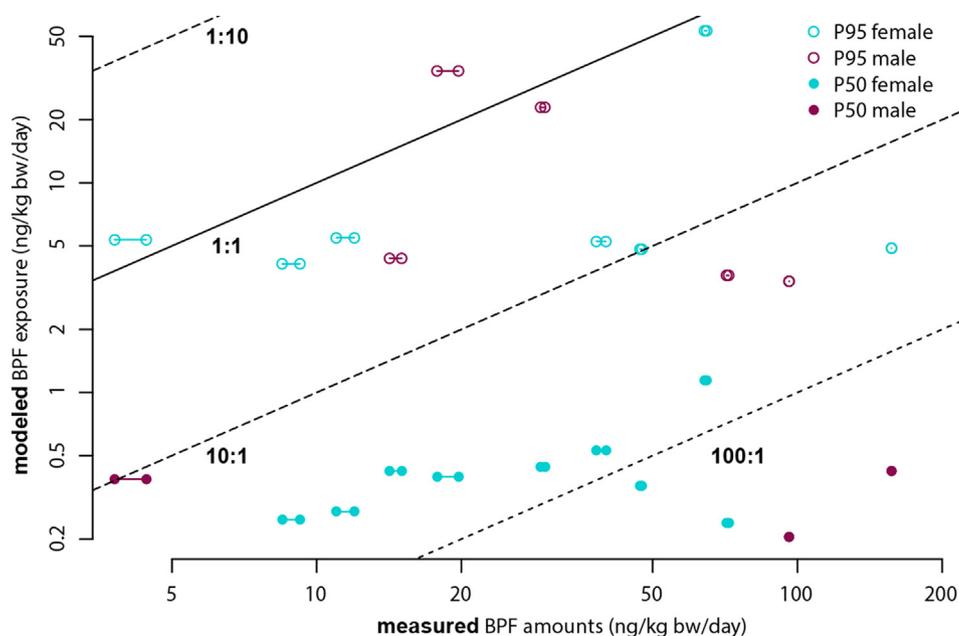
For individuals with no BPS detected in the three pools, UB estimates for urinary BPS amounts ranged between 0.731 and 6.53 ng/kg bw/day with multiplying the LOD with the urine amount excreted in 24 h (see Fig. S4). Our model predictions were in general not lower for individuals with no BPS detects than for those with BPS detects in urine. Only for individuals with a high number of TP handlings, modeled exposures were considerably higher, and BPS had also been detected in the related BM samples. In general, modeled BPS exposure was very similar for participants with an equal number of TP handling events, while the measured urine concentrations varied more between participants.

Only 12 individuals had at least one BPF measurement above LOD in the three pools, with urinary BPF amounts spanning from 3.80/4.42-157, and medians of 33.7/34.9 ng/kg bw/day (LB/UB, see Fig. 5).

Median and P95 values of modeled BPF exposure were mostly 10–100 and 1–10 times lower than the measurements for individuals in this subgroup, respectively. P50 and P95 values of UB model estimates were partly higher for individuals with no BPF detects in the three pools than for such with BPF detects (see Fig. S5).

### 3.2. Contribution of different sources to modeled exposure

Fig. 6 shows the contribution of different sources to modeled exposures for BPA, BPS, and BPF. Food contributed the most to BPA exposure, followed by exposure from TP. TP exposure was only present in the upper tail, because only 24% of the participants handled TP on the study day. For this subgroup, BPA exposure occurred in 79% of modeled days. BPA exposure via PCPs and dust was negligible. TP contributed the most to modeled BPS exposure of those individuals that handled TP on the study day and for whom a TP with BPS occurrence was drawn in the MC calculation. However, since BPS occurrence was only 17.2%, this only influences the upper percentiles. Food did not



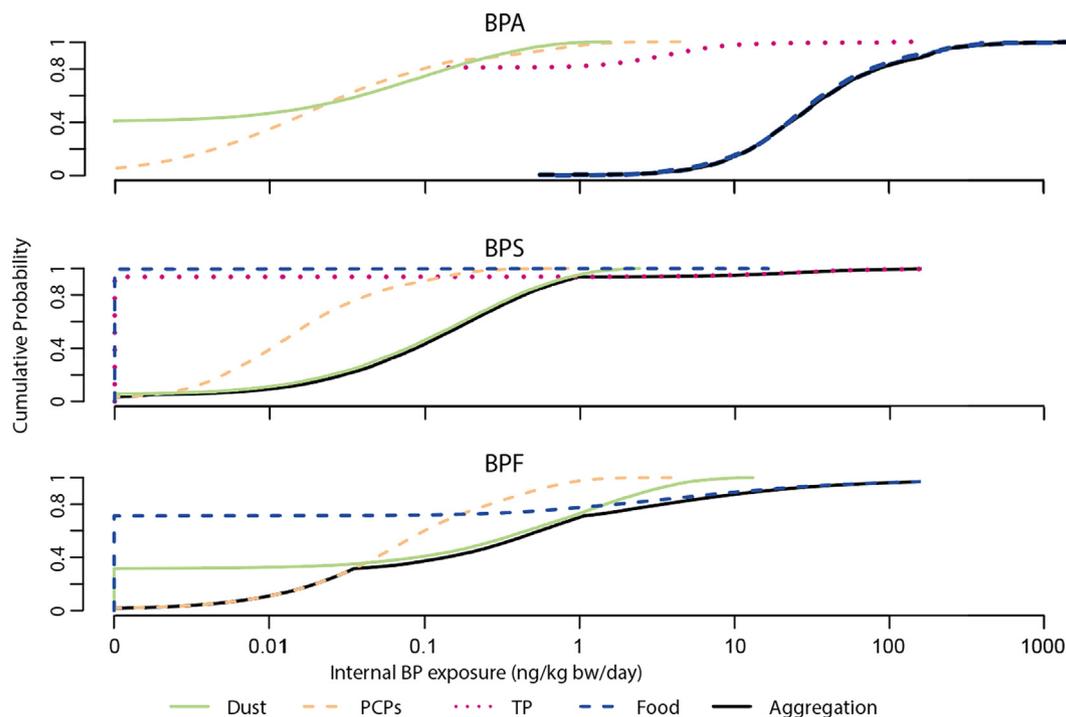
**Fig. 5.** Individual-based comparison of urinary BPF amounts versus median and P95 values of modeled exposure for individuals with at least one BPF measurement above LOD in the three pools. If two measurement points are displayed for one person (connected with horizontal line), at least one measurement of the three pools was below LOD and the two points show the LB and UB, respectively. The diagonal lines show ratios of measured to modeled exposure. Ratios below 1 (e.g. 1:10) and ratios above 1 (e.g. 10:1) stand for overestimations and underestimations of modeled exposure compared to measured amounts, respectively.

contribute to BPS exposure in 99.5% of the modeled days. Dust and PCPs contributed to all BPS exposure percentiles, with dust being the most important exposure source in percentiles without TP contribution. Food contributed the most to modeled internal BPF exposure if dietary products containing BPF were consumed (only in 72% of modeled exposure days). The contribution of PCPs to BPF exposure was higher than to BPA and BPS exposure, but still less important than the contribution of dust if dust exposure occurred (BP occurrence in dust depended on the DFs in the considered studies, see SI paragraph 4).

**3.3. Modeled exposures from different sources and relationships between possible explanatory exposure variables and measurements**

Zooming in to modeled exposure from food, BPF was the second

largest contributor to external dietary cumulative BP exposure after BPA, while BPS only contributed marginally (see Fig. 7). For BP-exposure via food, the food items pepper, salmon, canned hake (referring to canned mackerel in tomato, a common Norwegian bread spread, canned tomatoes, and a pasta dish contributed more than 2% to the total exposure distribution (see Fig. 8, also the case for the alternative scenario for BPA, see Fig. S6). BPA in semi-skimmed milk and BPF in mustard were the most important BP-food item combinations (Fig. 8). With regard to the alternative scenario for BPA, canned hake and a pasta dish contributed the most (Fig. S6). In the BM measurements, the amount of canned food eaten by the participants did not correlate to the urinary amounts of BPA, BPS, or BPF (see SI paragraph 6: Relationship between measured urinary amounts and possible explanatory variables).



**Fig. 6.** Contributions of the exposure sources food, TP, PCPs and dust to modeled aggregate exposures for BPA, BPS, and BPF.

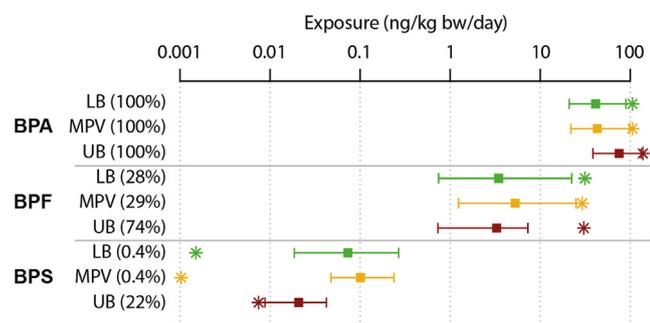


Fig. 7. External dietary exposures of BPA, BPF, and BPS for modeled days with exposure (medians with P25 and P75 values as whiskers, stars display average values). The estimates for LB, MPV, and UB are shown in green, yellow, and red, respectively. The share of modeled days with exposure is displayed in brackets behind the calculation methods. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Zooming in to PCPs, modeled exposures were higher for women than for men for all BPs and percentiles (see Fig. S7). For most percentiles, BPS and BPF exposures were the lowest and the highest contributors to external total BP exposure, respectively, differing by about one order of magnitude. Facial moisturizer and body lotion were important contributors to BP exposures from PCPs both for men and women, with the related BPF exposures being the highest (see Table S7). For men, mouthwash (BPA and BPS), toothpaste (BPS), and hand soap (BPF) were also of importance, while sunscreen played an additional role for women exposure. However, in the comparison to the BM measurements, multiple linear regression analyses did not show a correlation between the number of PCPs and the urinary amounts of BPA and BPS in the participants (see SI paragraph 6). For BPF, gender had an effect on the intercept of urinary amounts (p-values 0.0895/0.0958, LB/UB), which was dependent on the number of PCPs used (p-values for interactions 0.0702/0.0729, LB/UB).

The CDFs of external BPA and BPS exposure from TP for the 24.3% of the TP-handling participants mirror the BP occurrence frequencies and transferred amounts used in the distributions: about 79% and 26% of the individuals were exposed to BPA and BPS, respectively (see Fig.

S8). These numbers were slightly higher than the occurrence frequencies used, because multiple handling events increase the probability of BPA and BPS exposure on an individual basis. In the upper tails, BPS exposure was mostly higher than BPA exposure, because of higher amounts being transferred to normal skin. Multiple linear regression analyses did not reveal a significant correlation between the number of handled TP receipts and urinary amounts of BPA or BPS. In addition, the independent 2-group Mann-Whitney U tests did not show significant differences between urinary amounts of BPA and BPS for individuals that handled or did not handle TP (see SI paragraph 6), unlike suggested by the P95 values of modeled internal exposures of BPS (Fig. 4). For 17 out of 35 persons that had handled TP on the study day, BPS was not detected in any of the three pooled urine samples, while measurements were not particularly high for the remaining 18 persons in comparison to the measurements of other participants with BPS detects.

### 3.4. Uncertainty evaluation

A comparison of uncertainties related to the BM study execution (Table S8) and the source-to-dose modeling (Table S9) reveals that the uncertainty related to the modeling was generally higher. Study design was the parameter classified with the highest uncertainty and highest impact related to the BM study execution (medium to high, MH, classification for both), because both the exposure data and the urine were collected in the same time period. To improve the comparison between measurements and modeled exposures, the time needed for BP uptake and elimination should be taken into account. Especially the durations of dermal exposure (Demierre et al., 2012) and elimination (Oh et al., 2018; Thayer et al., 2015) could lead to a mismatch between exposure events and the BP-occurrence in urine. This uncertainty could not be eliminated within this study, because MCRA, the model used for calculating food exposure, only had a daily resolution and because of missing information on exposure on the day before the urine sampling. With regard to source-to-dose modeling, several parameters were classified with a MH or high (H) uncertainty and/or impact on the exposure assessment: BP concentrations in dietary matrices, occurrence frequency of BPA and BPS in TP, exposure from handling TP, and BP concentrations in PCPs.

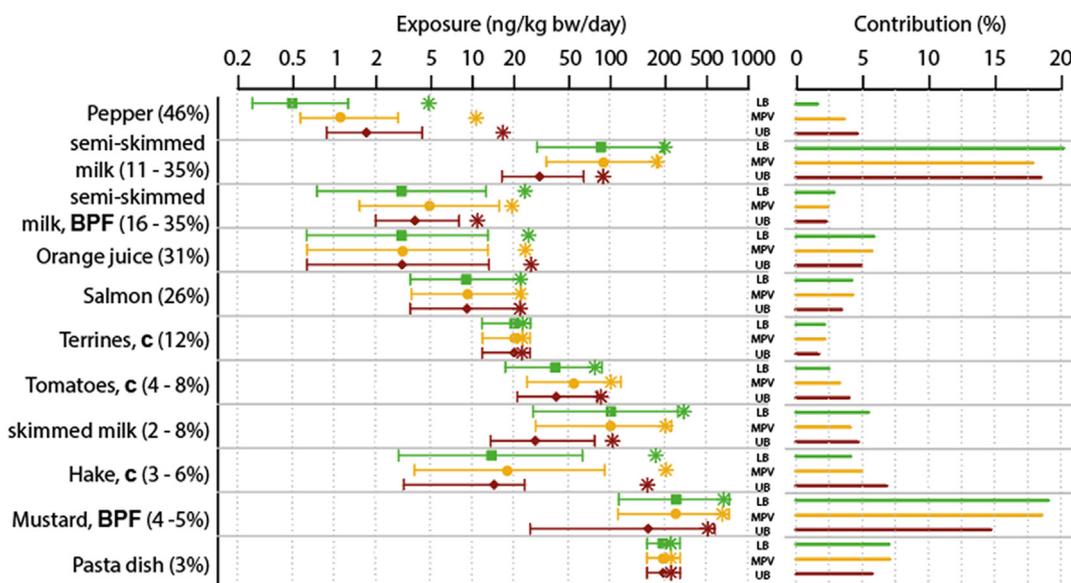


Fig. 8. External exposure estimates (medians with P25 and P75 values as whiskers, stars display average values) for modeled days with exposure, and contributions to the total exposure distribution for food items contributing more than 2% to exposures from BPA, BPF, and BPS. The estimates for LB, MPV, and UB are shown in green, yellow, and red, respectively. The share of modeled days with exposure (due to study diet and concentration data) is displayed in brackets behind the different food items. If not specified otherwise, exposure estimates and contributions are displayed for BPA and non-canned food items (c stands for canned food items). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

## 4. Discussion

### 4.1. Comparison between measured and modeled BP exposures

Measured BPA amounts and modeled BPA exposures were generally in good agreement, both in individual-based comparisons (Fig. 3) and when considering overall exposures (Fig. 2). This suggests that the main exposure sources for BPA are well characterized and used input data are sufficient and up-to-date. However, the cloud of dots in Fig. 3 suggests that even if the agreement between modeled exposures and measured amounts is generally good, individual-specific correlations were not strong. For risk assessment purposes, a good prediction of average exposures might be a sufficient basis for the application of additional uncertainty factors (Meek et al., 2011). However, a model able to depict individual-specific correlations would be needed for tracking down and monitoring specific exposure sources that would for example be required for effects such as an allergic contact dermatitis (Garcia-Hidalgo et al., 2018).

For BPS and BPF, the CDFs of aggregate BPS and BPF exposures varied for modeled exposures and measured amounts (Fig. 2). In individual-based comparisons the median values and even the P95 values of modeled exposures underestimated measured amounts in most cases. This implies that the model seems to miss relevant sources for BPS and BPF exposure. Such missing sources could be food items for which BPS and BPF concentrations had not been determined or even entirely different source types. For example, recent studies showed elevated BPS levels in textiles, which might contribute to aggregate BPS exposure (Li and Kannan, 2018; Xue et al., 2017). The modeled exposures might underestimate exposure even more taking into account that a worst-case oral absorption factor of 1 was used. If smaller fractions of incorporated BPS and BPF were excreted, an even higher external exposure would be needed to result in the BPS and BPF concentrations measured in the urine of the study participants. Additionally, the model could not predict which participants were exposed to BPS and BPF and which ones not, because the model results were similar for participants with and without detects. A likely explanation is that individuals with a high intake of liquids produced large urinary volumes that diluted BP amounts below the LOD. The large urinary volumes have, in turn, led to high exposure in the UB. A related problem in the comparison was the relatively small number of participants with BPS and BPF detects in urine samples.

Most likely, diet and TP were the sources contributing the most to BPA exposure. However, measured BPA amounts were not correlated to exposure variables that might have been explanatory for exposure, such as amount of canned food consumed, number of PCPs used, and number of TP handling events on the study day. Only between BPF exposure and gender a correlation was found (significantly different intercept in model with interactions), which depended on the number of PCPs used on the study day. Yet, the correlations were not conclusive, only suggestive (significant only at the  $p < 0.1$  level). In a BPA risk assessment conducted by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES (2013)), the consumption of meat products and seafood products accounted for 17% and 3% of the dietary exposure, respectively, which implies that non-canned food of animal origin could be an important contributor and maybe also predictor for BP exposure (ANSES, 2017). However, such correlations were not found for the Norwegian study population, but Husøy et al. (2019) found a negative correlation between measured BPA exposure and the consumption of dairy products.

### 4.2. Limitations in model parameters

The exposure parameters for food consumption, number of PCPs used (per item), and TP handling events were available on an individual basis for the 24 h of the study day for which urinary BP concentrations were measured and exposure was modeled.

A first limitation of this parameter set is the assumption of external and internal dermal exposure occurring in the same time frame (see also Table S8). While BPA uptake after oral exposure was found to be fast with an uptake period of 15 min (Tsukioka et al., 2004; Völkel et al., 2002), uptake after dermal exposure is probably considerably slower with reported absorption half-lives of 0.2 (Biedermann et al., 2010) to 6 h (Demierre et al., 2012) and an uptake period of 24 h (Demierre et al., 2012). Therefore, the timing of contact with dermal exposure sources might influence the agreement between modeled exposures and measured amounts to a larger degree than the timing of contact with oral exposure sources. However, such information were not available and we assumed that external exposures on the study day resulted in internal exposures on that same day. Yet, in reality TP handling and PCP use on the day before might have had influence on internal exposures on the study day. In addition, the time delay due to elimination may have impaired the comparison between measurements and modeled exposures. For BPA and BPS, half-lives of urinary excretion were found to be 1–3 h (Thayer et al., 2015) and 4–7 h (Oh et al., 2018), respectively. Therefore, elimination half-lives are likely to vary for BP analogs resulting in varying deviations between measurements and models. Furthermore, in addition to the number of used PCPs, the related data on used PCP amounts would have been a valuable information (Ficheux et al., 2016), but unfortunately it was not available for the participants in the BM study.

Exposure factors that were not collected in the BM study were obtained from literature, which adds uncertainty to these input parameters (Table S9): BP concentrations in food were mostly from European countries other than Norway and country-specific concentration differences might be present. If food exposure occurred, food was the most important source for modeled BPA and BPF exposure (Fig. 6) and therefore the uncertainty around food concentration data probably has a large impact on modeled exposures (thus classified high in Table S9). Another important limitation in model parameters was the absence of representative food concentration data for BPS and BPF. Such data were only available for a small subset of the food items consumed by the BM population, while BPA concentrations covered all consumed food items. BPS and BPF concentrations have mainly been measured in canned food items that are suspected to contain comparatively high concentrations, and for most non-canned food items data were not available and therefore set to zero. However, non-canned food items were most frequently consumed, so that the missing input data presumably resulted in an underestimation of exposure estimates. Missing BPS and BPF exposure from not-analyzed food items could therefore be a possible reason for the underestimation of modeled exposures. In addition, concentrations might also have increased since the measurements were conducted, because the attention to new European BPA restrictions (EU, 2018) may have encouraged BPA replacements by BPS and BPF in the years before the restrictions came into force.

For dust exposure, no individual parameters were known and it was therefore modeled for adults in general, like in a previous study (Karrer et al., 2019). BP concentrations in indoor dust were used from France, Belgium, Greece, and Romania together with dust ingestion rates by Wilson et al. (2013) In lower to middle percentiles, dust was an important exposure contributor for BPS and BPF (Fig. 6), most likely also because other exposure sources were missing in the model for the lower percentiles. Therefore, the uncertainty around the input parameters for dust exposure might have a considerable influence on BPS and BPF exposure.

With regard to TP, two studies on occurrence frequencies of BPA and BPS in Danish receipts were used (Eckardt and Simat, 2018; Pivnenko et al., 2015). However, the studies had relatively small sample sizes (16 and 13) and are therefore not necessarily representative for the occurrence of BPA and BPS in TP in Denmark. In addition, occurrence of BPA and BPS in TP on the Norwegian market might differ from the Danish market. Also, the number of fingers used for handling and the transferred BP amount were taken from literature

and are subject to uncertainty. If BP exposure from TP occurred, it was the most and second most important contributor to modeled aggregate exposure for BPS and BPA, respectively, and therefore the uncertainty surrounding these input parameters might influence related exposures substantially, especially in higher percentiles. Yet, a difficulty in modeling TP exposure for the present study population in particular was the short study duration of 24 h, in which most participants touched TP only once, if at all. Depending on their occurrence frequencies, BPA and BPS were either present or not present in the handled receipt. The impact of TP as an additional source becomes evident when comparing the medians of modeled BPS exposures with the respective P95 values (Fig. 4): Because of the low BPS occurrence frequency, the median TP exposure for participants who have handled TP only once is zero and modeled BPS exposure is similar to that for participants that have not handled TP. In the P95, BPS exposure from TP is always present if TP was handled and therefore P95 exposure estimates differ between participants that have handled TP and those who did not handle TP.

Concentration data on BPs in PCPs were scarce: concentrations for BPS and BPF were only available from the U.S. and China (Liao and Kannan, 2014; Lu et al., 2018), and for BPA only few data from Europe were available (Cacho et al., 2013; Miralles et al., 2018; Thomas et al., 2014), which did not allow for an exposure assessment using data from Europe only. PCP amount data were used from a French study (Ficheux et al., 2016) that might not fully resemble amounts used in Norway. However, as PCPs were no major source of exposure for BPA, BPS, or BPF, the uncertainties around related input data might not affect aggregate exposures to a large extent (impact rated low to medium, LM, in Table S9).

Lastly, for exposure from TP and PCPs via the dermal route, absorption factors for BPA were also used for BPS and BPF, because no studies were available for these analogs. However, it is likely that the dermal absorption is different for BPA, BPS, and BPF, e.g. because of their different lipophilicities (Choi and Lee, 2017).

#### 4.3. Model limitations

In our exposure assessment, we only considered sources that were considered important in a risk assessment conducted by the EFSA CEF Panel for BPA (2015). However, for BPS and BPF some sources might be more important (Li and Kannan, 2018; Xue et al., 2017) and additional applications may exist, because they might not only be used as replacements for BPA or they might be formed naturally in break-down processes (Zoller et al., 2016).

We used MCRA for modeling dietary exposure and for aggregating different internal exposure sources on an individual basis. One disadvantage of MCRA is that exposures are modeled with a daily resolution only. Food consumption data, PCP use data, TP handling data, and urinary concentration data were available with a better resolution, but the higher resolution could not be considered due to the model limitations.

#### 4.4. Comparison of our BM study with other BM studies

The here-described EuroMix study population is not representative for the general Norwegian population. Yet, the population represents a healthy group of Norwegians with a high level of education (Husøy et al., 2019). Still, a comparison with other BM studies might show spatial and temporal differences of BP exposures. Multiple studies exist that measured urinary concentrations of BPA, BPS, and BPF in recent years. However, we could only identify two studies that were conducted in Europe, with BM data for all the three BPs. In a study among 50 Norwegian mother-child pairs in 2012 (Sakhi et al., 2017), the DFs in the first maternal morning urine samples were 100%, 42%, and 15% for BPA, BPS, and BPF, respectively (Sakhi et al., 2018), with the same LODs as in our measurements, and thus higher than the DFs of all BPs found in our study (96.5%, 28.9%, and 4.23%). Related urinary

concentrations ranged from 0.94 to 14.4 ng/mL for BPA, from below LOD – 0.75 ng/mL for BPS, and from below LOD – 7.67 ng/mL for BPF. Maximal urinary concentrations in our study were 10.2, 12.7, and 9.92 ng/mL for BPA, BPS, and BPF respectively. Therefore, maximal BPA and BPF concentrations observed in our study were similar to values observed for women in Sakhi et al., but maximal BPS concentrations were considerably higher in our study. In a population-based cohort of 1,400 pregnant women in the Netherlands, conducted 2004–2005, BPA, BPS, and BPF were detected in 79.2%, 67.8%, and 40.2% of the samples, respectively (LODs of 0.15, 0.05, and 0.18 ng/mL) (Philips et al., 2018). These DFs were lower for BPA and higher for BPS and BPF than the DFs found in our study. The medians of detected values were 1.66, 0.36, and 0.57 ng/mL for BPA, BPS, and BPF respectively. In our study, medians of detected values were similar for BPA and BPS (1.32 and 0.33 ng/mL), but higher for BPF (2.43 ng/mL), which was only detected in 18 of the pooled samples.

In a recent U.S. National Health and Nutrition Examination Survey (NHANES, 2013–2014), BPA, BPS, and BPF were detected in 95.7, 89.4, and 66.5% of urine samples from U.S. adults ( $n = 1,800$ , LODs of 0.2 ng/mL for BPA and BPF, and 0.1 ng/mL for BPS) (Lehmler et al., 2018). Medians of all urine samples were 1.24, 0.37, and 0.35 ng/mL for BPA, BPS, and BPF respectively. In our study, medians of all samples were 1.29 ng/mL for BPA and below LOD for both BPS and BPF. Therefore, DFs and medians of BPA were similar in our study and the study by Lehmler et al. (2018), but the DFs of BPS and BPF were considerably higher in the U.S. cohort. Also in other U.S. cohorts, DFs of BPS in urine were found to be high, such as 97% reported by Liao et al. (2012a). In summary, the DFs of BPS and BPF from our study were the lowest compared to the other studies described, while the DFs and medians for BPA from literature and our study mostly corresponded well.

With regard to the influence of TP handling on BPA and BPS levels, another U.S. BM study was conducted from 2011 to 2013 that focused on the effect of TP handling on BPA and BPS levels in urine and serum of 77 cashiers (Thayer et al., 2016). For BPS a correlation between TP handling at work and increased exposure was observed. For BPA no direct shift-related exposure increase could be found, but BPA exposure of cashiers was higher than BPA exposure of a control group of non-cashiers.

#### 4.5. Risk considerations

The EFSA established a temporary Tolerable Daily Intake (t-TDI) of 4 µg BPA/kg bw for external oral exposure based on kidney effects in mice (EFSA CEF Panel, 2015). With a worst-case absorption factor of one this can lead to an internal exposure at the same level. In the Norwegian BM study, the highest BPA amount measured in 24 h urine were 0.30 µg/kg bw, which is a factor of 13 lower than the t-TDI.

For BPS and BPF no TDIs were established yet. Assuming the same effect and concentration addition, the maximal cumulative BP-exposure observed in the BM study would be 0.38 µg BP/kg bw, which is still 10-fold lower than the t-TDI. A cumulation of the highest BPA, BPS and BPF exposures measured in the study population (in different individuals) would lead to 0.80 µg BP/kg bw. This worst-case cumulation of occurred exposures is still 5-fold below the t-TDI established for BPA.

In conclusion, the BPA, BPS, and BPF concentrations measured in the Norwegian study population do not pose a risk according to the present state of knowledge if the same t-TDI is assumed for all investigated BPs. However, TDIs for BPS and BPF might be different than for BPA (Rochester and Bolden, 2015), possibly leading to higher or lower margins, and also the BPA t-TDI might be subject to change in the future, e.g. due to an increasing number of studies on endocrine effects being conducted.

While BPA was classified as an endocrine disruptor by the ECHA (ECHA, 2018), no related limit value has yet been established by EFSA. However, several publications have already assessed the endocrine

potency of BPs. In this BM study, BPs were not measured in serum and thus no comparisons with half-maximal effect concentrations ( $EC_{50}$ ) are possible. In a previously conducted exposure assessment for a general European population, margins between cumulative exposure to BPA, BPS, BPF, and BPAF and the lowest  $EC_{50}$  gathered from literature were well above 100 until the P95 (Karrer et al., 2019). Thus, for most of the BM population in this study margins smaller than 100 are not likely.

#### 4.6. Possible implications

BPS and BPF are important replacement chemicals for BPA. For exposure and risk assessment purposes it is crucial to be aware of all sources and source-to-dose relations. The observed mismatch for measured and modeled exposure to BPS and BPF shows that the used input data and/or the exposure models and underlying assumptions do not fully portray occurring exposures. Therefore, in future more input data such as concentration data should be acquired and models and underlying assumptions should be reviewed and refined. For example, for dermal exposure routes a timely delay of exposure events and urine measurements could lead to improved correlations.

Our DFs for BPS and BPF of 29% and 4.2% were lower than the DFs reported in other studies investigating non-occupational exposure to these BP analogs, but they were the closest to those in another study conducted in Norway (Sakhi et al., 2018). The highest DFs for BPS and BPF of 89 and 67% were from the U.S. NHANES study that was conducted 2013–2014 and is the second most recent BM study after ours. This comparison suggests that the DFs for BPS and BPF are to a larger extent dependent on the sampling location than on the sampling time (in the narrow timeframe 2004–2017).

The BP concentrations observed in our BM study population are likely to be biased: the participants were not randomly or representatively selected, but were recruited among employees from governmental institutes, authorities, and universities in the Oslo area (Husøy et al., 2019). Therefore, the test population was highly educated and possibly health-conscious. In addition, the self-reporting could have biased the behavior of the participants during the study period, e.g. fewer TP receipts might have been handled because the participants were aware that they had to note these events. Therefore, BP exposure of the participant might be different in their daily life.

In the near future, it would be important to measure BP levels in representative cohorts of European adults and other age groups to evaluate the effects and consequences of BPA regulations. New EU restrictions recently lowered BPA limits for the migration from plastics from 600 to 50 ng/g (EU, 2018). In addition, limits for the migration of BPA from epoxy resins were introduced (EU, 2018) and BPA concentrations in TP will be restricted from 2020 onwards to below 0.02% by weight (EC, 2016). Therefore, the use of replacements for BPA, such as BPS and BPF, is likely to increase and measures should be taken to increase knowledge about their occurrence, source concentrations and resulting internal exposures in different subpopulations. Important first steps to meet this objective are the collection of representative food concentration data, TP occurrence data, and the study of dermal absorption characteristics for all BP analogs, as well as the realization of comprehensive BM studies to monitor levels of different BP analogs in the long term.

#### CRediT authorship contribution statement

**Cecile Karrer:** Conceptualization, Methodology, Software, Investigation, Writing - original draft. **Monica Andreassen:** Conceptualization, Methodology, Investigation, Writing - original draft. **Natalie von Goetz:** Conceptualization, Supervision, Writing - review & editing. **Friederike Sonnet:** . **Amrit Kaur Sakhi:** . **Konrad Hungerbühler:** Conceptualization, Supervision, Writing - review & editing. **Hubert Dirven:** Conceptualization, Supervision, Writing - review & editing. **Trine Husøy:** Conceptualization, Supervision, Writing -

review & editing.

#### Declaration of Competing Interest

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

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#### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2019.105397>.

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