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Linking Probabilistic Exposure and Pharmacokinetic Modeling To Assess the Cumulative Risk from the Bisphenols BPA, BPS, BPF, and BPAF for Europeans

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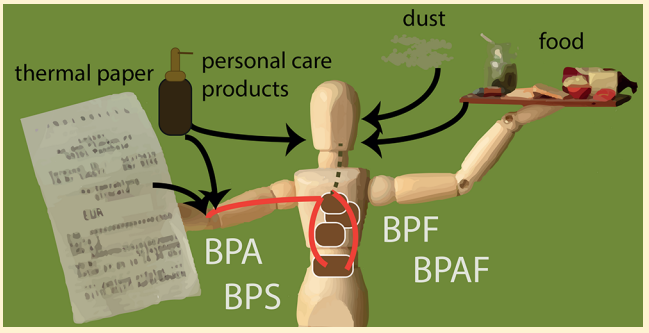
Supporting Information

ABSTRACT: The bisphenols S, F, and AF (BPS, BPF, and BPAF) are used to replace the endocrine disrupting chemical bisphenol A (BPA) while exerting estrogenic effects of comparable potency. We assessed the cumulative risk for the aforementioned BPs in Europe and compared the risk before and after the year 2011, which was when the first BPA restrictions became effective. For this, we probabilistically modeled external exposures from food, personal care products (PCPs), thermal paper, and dust (using the tools MCRA and PACEM for exposures from food and PCPs, respectively). We calculated internal concentrations of unconjugated BPs with substance-specific PBPK models and cumulated these concentrations normalized by estrogenic potency. The resulting mean internal cumulative exposures to unconjugated BPs were 3.8 and 2.1 ng/kg bw/day before and after restrictions, respectively. This decline was mainly caused by the replacement of BPA by BPS in thermal paper and the lower dermal uptake of BPS compared to BPA. However, the decline was not significant: the selected uncertainty intervals overlapped (P2.5−P97.5 uncertainty intervals of 2.7−4.9 and 1.3−6.3 ng/kg bw/day before and after restrictions, respectively). The upper uncertainty bounds for cumulative exposure were higher after restrictions, which reflects the larger uncertainty around exposures to substitutes compared to BPA.



1. INTRODUCTION

Bisphenol A (BPA) is a high-production-volume chemical for the production of polycarbonate (PC) plastics and epoxy resins that are used for the manufacture of packaging materials, such as reusable tableware, storage containers, drinking bottles, and metal cans.[1−3] From there it can migrate into food, beverages, personal care products (PCPs), and finally also into dust and air.[4] Furthermore, BPA is used as a color developer in thermal paper (TP).[5] Growing evidence that BPA can interfere with the hormonal system[6−9] resulted in the inclusion of BPA into the list of substances of very high concern and its official classification as endocrine disruptor by the European Chemicals Agency in 2017.

In 2011, the first European BPA restrictions became effective, which were its prohibition in PC baby bottles[10] and its general limitation in the manufacturing of food contact plastic materials.[11] In view of the increasingly strict legislation, industry has partly turned toward replacement chemicals for BPA, such as structurally similar bisphenols (BPs). In this paper, we focus on bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF) because BPS and BPF are the most widely used replacements and BPAF has a comparatively high estrogenic potency.[12] BPS is used to replace BPA as a color developer in TP.[13] BPF can replace BPA in the production of epoxy resins[14] and occurs naturally in mustard.[15] BPAF can be used as a curing agent in the production of elastomers and was found in 11% of food samples investigated in a U.S. study, which implies that it can migrate from food packaging.[16,17] Recent studies from the U.S. and China have found BPA, BPS, BPF, and BPAF in dust and PCPs.[18,19]

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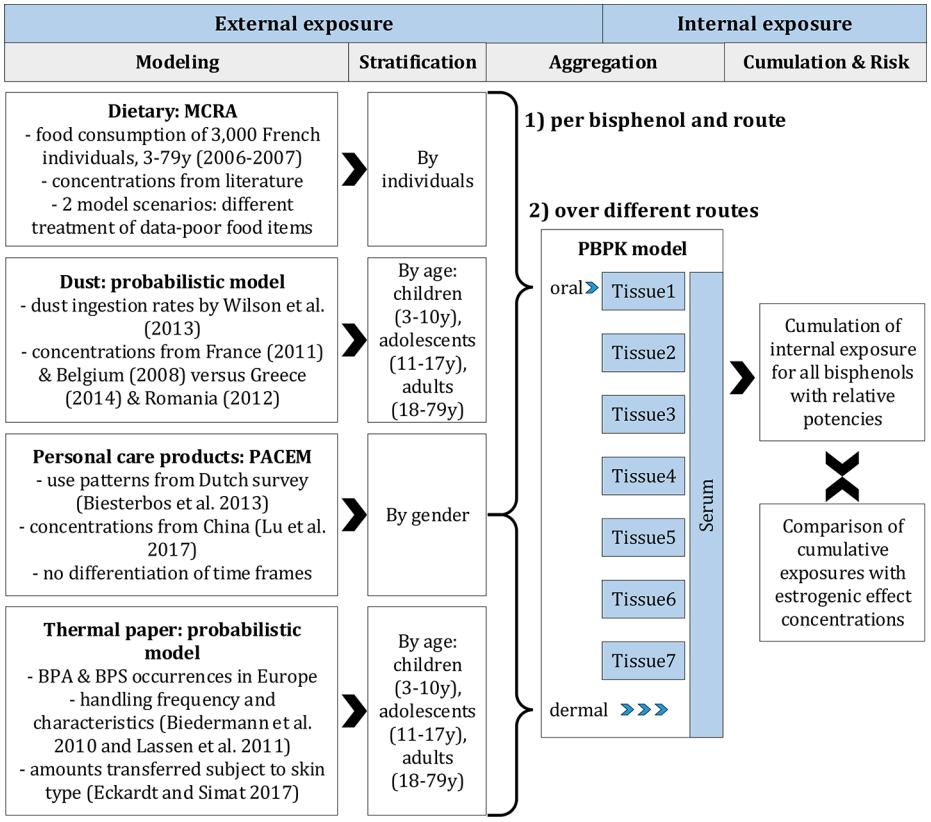

Figure 1. Workflow for modeling aggregate exposure and cumulative risk from the bisphenols A, S, F, and AF before and after the European BPA restrictions in 2011.

BPS, BPF, and BPAF have endocrine-disrupting effects, with estrogenic potencies similar to[6,20,21] or even higher than BPA (7−13 fold higher for BPAF[7,22]). BPs are largely metabolized,[23] with glucuronides and sulfates as their most important metabolites. In a recently conducted BPA biomonitoring (BM) study, BPA-glucuronide and BPA-sulfate represented 67% and 23% of total BPA in serum, respectively, with the unconjugated form as a minor serum component (0.56%, with respect to the area under the curve, AUC). In urine, the glucuronide was found at even higher shares (87%, with 3% of the sulfated and 0.03% of the unconjugated form, respectively, discrepancy between sums due to bis-conjugates).[24] In a similar study on BPS, compared to BPA a considerably higher share of the unconjugated form (28.6% of AUC) was present in serum. The remaining share was BPS-glucuronide and BPS-sulfate. Related shares in excreted urine were 97% and 3% of conjugated and unconjugated BPS, respectively.[25] Thus, BPS seems to be metabolized to a lesser extent than BPA. So far no estrogenic activity could be found for BP metabolites.[21,26−28] Therefore, the remaining share of unconjugated BPs is decisive for assessing the potential risk of BPs related to endocrine disruption.

The European Food Safety Authority (EFSA) and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) have conducted risk assessments for BPA exposure from multiple sources.[29,30] ANSES additionally looked into BPS exposure from TP. Furthermore, exposure to BPA and other analogues has been assessed separately for the sources food, dust, and PCPs, mostly focusing on source concentrations from the U.S. and China.[17−19,31,32] In the U.S., BPA has been banned from several food contact materials.[33,34] Together with possible voluntary replacements, this has led to a considerable decline in internal BPA exposures between 2003 and 2012, so that the exposure situation may be different between the U.S. and Europe.[35]

In this paper, we provide the first population-based, cumulative exposure and risk assessment for estrogenic effects from BPs for the European context and investigate the effects of the European BPA restrictions. Since the share of internal unconjugated BPs is decisive for estrogenic effects, we first modeled external exposure to BPA, BPS, BPF, and BPAF via exposure sources identified as the most important sources in previous BPA assessments[29,30] on the basis of two scenarios (before and after the first European restrictions, respectively). Then the external exposures of the different BPs were transformed into internal exposures to unconjugated BPs with substance-specific physiologically based pharmacokinetic (PBPK) models. The internal concentrations were cumulated for the compartments serum and gonads after normalization by relative potency factors (RPFs) related to their estrogenic activity and then compared to effect concentrations. Finally, modeled amounts of total (conjugated plus unconjugated) BPs were compared to BM data.

2. MATERIALS AND METHODS

2.1. Scope. The objective of this work was to assess cumulative exposure to the bisphenols BPA, BPS, BPF, and BPAF and to evaluate as far as possible the effects of the first European BPA restrictions in 2011 on this cumulative exposure. As defined previously,[38] cumulative exposure refers to exposure to multiple substances via multiple routes (here: to BPs), and aggregate exposure refers to exposure to substance

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(here: one BP) via multiple routes. We defined two legislative scenarios: wherever possible, the "before restrictions scenario" (*BRS*) relies on source concentrations measured before the restrictions (*BR*) in 2011, and the "after restrictions scenario" (*ARS*) relies on measurements after the restrictions (*AR*) in 2011. We used the same consumption and use patterns in both scenarios, so that exposure differences would only depend on BP concentrations.

In EFSA's scientific opinion on BPA from 2015, exposure was assessed for different population groups.[29] Dietary intake, dust ingestion, and dermal exposure from PCPs and TP were found to be the most important general exposure pathways (GEP, i.e., exposure pathways from larger product categories).[39] We focused on these pathways, because BPS, BPF, and BPAF are replacement chemicals for BPA (for chemical structures, see Figure S1), and therefore, exposure pathways are expected to be similar. For PCPs, we additionally considered the oral exposure route for lipstick, lip balm, and toothpaste, but not inhalation exposure, since BPs have a low volatility.[40] For TP, different BP occurrence frequencies for *BR* and *AR* have been reported (see Table S1). For a meaningful comparison of possible exposures in the *BRS* and the *ARS* we focused on the highest BPS occurrence found *AR* (50% in France, with a BPA occurrence of 23% in the same study,[41] other BPs are not used in TP), and for the *BRS* we used a BPA occurrence of 73% from a Belgian study,[42] so that the sums of BP occurrences were equal. We focused on the age groups of children (3−10 years (y)), adolescents (11−17 y), and adults (18−79 y). Children below 3 years were not included, because (1) concentrations of BPS, BPF, and BPAF in food items were not available for infant foods, (2) a comprehensive food consumption survey for 3360 French individuals was only available for the range 3−79 y, and (3) BPA has been banned from infant feeding bottles[10] and no migration has been observed for the replacement substance BPS.[43,44]

Since source concentrations and exposure factors were not available consistently for one European country, we aimed at conducting an assessment representative for the general European population.

2.2. Modeling Approach. The Monte Carlo Risk Assessment (MCRA) model is a web-based, freely available model for probabilistic exposure and risk assessment. It can also calculate cumulative exposure and risk.[45] It was used for assessing dietary exposure, aggregating exposure from GEPs (e.g., dermal PCP exposure), and cumulating internal BP exposures to BPA equivalents. For aggregating exposures, nondietary exposure estimates were calculated outside MCRA and supplied in input tables.[46] We calculated them with the Probabilistic Aggregate Consumer Exposure Model (PACEM) for PCP exposure[47] and with self-developed probabilistic models for TP and dust (programmed in R, model code provided in the Supporting Information (SI)). Figure 1 illustrates the overall procedure. For each stratum defined by BP and GEP, we performed 10000 Monte Carlo (MC) runs (further information on exposure calculations see the SI).

2.3. Input Data. BP concentrations for the selected exposure sources were gathered from literature. To account for differences in eaten and measured food items, a "food translation table" was used (Table S2). Canned and non-canned items were distinguished (see Tables S3 and Table S4 and Figure S2). Related consumption frequencies were obtained from a French total diet study conducted in 2006/07 (Table S5). Table S6 provides the origin of samples and respective limits of reporting.

For the selection of dietary source concentrations with respect to the legislative scenario we used decision trees (Figures S3 and S4). BP exposure from handling TP depends on the handling frequency, the skin area in contact with TP, the skin type, and the BP occurrence (Table S1). Parameters for dust exposure include BP concentrations, detection frequencies, and ingestion rates (Tables S7−S9). For the *BRS*, input data for TP and dust exposure was only available for BPA. For all BPs, we used the same PCP concentrations for the *BRS* and *ARS* due to limited data (Figure S5 and Tables S10 and S11). Therefore, the comparison between the *BRS* and *ARS* focused on food and on TP and dust for BPA. PCP exposure was included to provide the shares of related GEPs.

2.4. Aggregation. Dietary exposure was modeled with individual-based dietary consumption data. The nondietary exposure was stratified by either age or gender: for TP and dust, the different strata were children, adolescents, and adults. We randomly assigned strata-specific nondietary exposure estimates for each GEP to each individual of the French model population (see Figure 1).

2.5. Conversion of External to Internal Exposures with PBPK Models. For the risk assessment of BPs, the internal unconjugated forms of the BPs are decisive. Further, the risk assessment benefits from assessing the exposure directly in the target organ. Consequently, we used serum and gonadal concentrations of unconjugated BPs as result metrics because the serum concentration of a mother influences the fetal serum concentrations[50] and gonads are susceptible to endocrine effects, especially for younger age groups. To derive organ-specific internal BP exposure estimates from external exposure distributions, PBPK models are needed that account for concentration-dependent conjugation processes. Hence, we constructed analogue-specific PBPK models[36] based on the most recent studies on BP pharmacokinetics[36] and embedded them into MCRA. For feeding into the PBPK models, the daily external exposure estimates were divided into several dosings according to the respective GEP: for oral exposure, we assumed three dosings per day with t_{oral} = 0, 6, and 12 h because it mainly stems from diet. For dermal exposure to PCPs and TP, we assumed two dosings per day with t_{dermal} = 0 and 12 h, respectively, because an average handling frequency of 2.4 TP receipts/day was reported[48] and most contacts to PCPs usually occur in the morning and in the evening.[31,49] Oral and dermal BP absorption were described with absorption fractions (fractions of externally available BPs able to enter the body), absorption half-lives (time needed for half of the available BP amounts to enter the body), and uptake periods (overall time window for absorption after external exposure).[36] Internal concentrations were modeled for 4 days (to reach a steady state).[36]

The PBPK models were run individual-based with 10,000 MC iterations per BP to yield concentration−time curves for the target organ and result metric selected. Since endocrine active substances act in a specific exposure window, for risk assessment the highest single exposure was compared to the effect concentrations. To derive the highest cumulative concentrations possible, we used the maximal concentrations (C_{max}) for each individual (Figure S6 illustrates the approach).

2.6. Cumulation and Risk Assessment. At present, estrogenic effects are the most comprehensively studied effects of BPs,[20,51] and they were therefore used for cumulating

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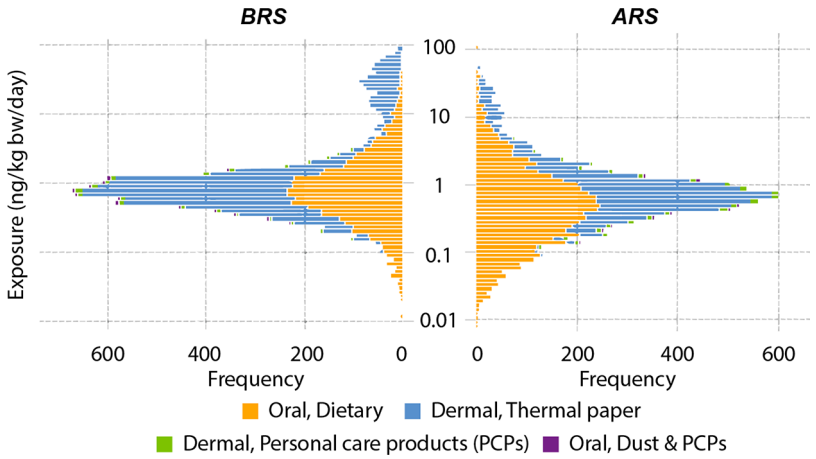

Figure 2. Stacked histograms of the distribution of cumulative exposures (principal runs) to unconjugated bisphenols in serum for days with exposure, differentiating contributions of general exposure pathways for the before restrictions scenario (*BRS*) and the after restrictions scenario (*ARS*).

Table 1. Summary Statistics for Cumulative Exposure to Unconjugated BPs in Serum (Expressed as BPA Equivalents Related to Estrogenicity) for the before Restrictions Scenario (*BRS*) and after Restrictions Scenario (*ARS*) and for the Respective Margins of Exposure (MOEs, in Bold if <100) between the Cumulative Exposures and the Minimal Half-Maximal Effect Concentration (EC_{50}) of BPA, Together with Uncertainty Bands (P2.5−P97.5)

	***BRS*: Internal exposure and risk estimates**			***ARS*: Internal exposure and risk estimates**		
Variability (principal run) and uncertainty bands	Principal run	P2.5	P97.5	Principal run	P2.5	P97.5
Internal exposure estimates	**BPA equivalents for *BRS* (ng/kg bw/day)**			**BPA equivalents for *ARS* (ng/kg bw/day)**		
mean	3.78	2.72	4.85	2.13	1.25	6.34
P50	0.741	0.521	0.853	0.726	0.295	1.53
P90	5.58	2.27	17.0	3.67	2.12	29.4
P95	25.1	18.0	40.8	8.99	4.87	54.7
P99	57.8	45.4	82.9	26.9	14.5	88.9
P99.9	89.9	77.4	150	67.9	42.1	170
P99.99	118	93.0	284	185	69.5	400
Risk estimates	**MOE for *BRS* ***			**MOE for *ARS* ***		
mean	196	272	153	348	592	117
P50	999	1421	868	1020	2510	484
P90	133	326	**43.6**	202	349	**25.2**
P95	**29.5**	**41.1**	**18.2**	**82.4**	152	**13.5**
P99	**12.8**	**16.3**	**8.93**	**27.5**	**51.1**	**8.33**
P99.9	**8.24**	**9.57**	**4.94**	**10.9**	**17.6**	**4.36**
P99.99	**6.28**	**7.96**	**2.61**	**4.00**	**10.7**	**1.85**

[a]The EC_{50} value was converted to the unit of the exposure estimate by using the fractional plasma volume for adults (mean of women and men).

internal exposures of the different analogues. We used BPA as index compound and collected all studies that had compared the estrogenic potencies of BPS, BPF, or BPAF with that of BPA. For cumulation, the RPF approach was used because no synergistic or antagonistic effects were known for the considered BPs so that concentration addition could be assumed.[37,52] For calculating RPFs, we derived the half-maximal effect concentrations (EC_{50}) for receptor activation from all available studies that had measured comprehensive dose−response curves (Table S12). We selected the most probable parameter values for the "principal run" of the cumulation; i.e., for each analogue we used the respective median RPF from all relevant studies and then added up the RPF-corrected C_{max} values for all BP analogs to yield cumulative BP concentrations ($C_{max}(\sum BP)$). Hence, the cumulative exposure is the potency-normalized internal exposure to all BPs.

We determined the minimum of collected EC_{50} values for BPA (i.e., the most sensitive end point related to estrogenic activity) and in the case of sufficient quality of the study (SI) used this EC_{50} value to calculate the margin of exposure (MOE) according to $MOE = EC_{50}/C_{max}(\sum BP)$. This risk ratio

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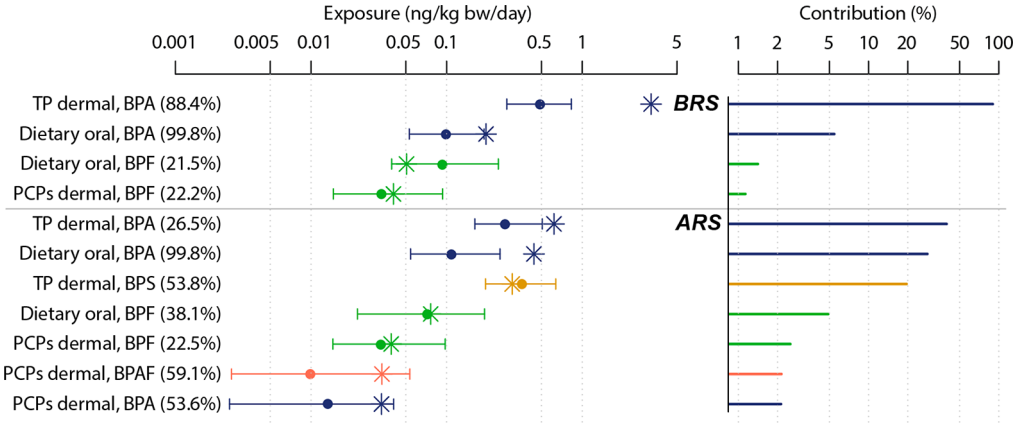

Figure 3. Exposure estimates for days with exposure (left) and contributions to mean cumulative exposure of substance−GEP combinations contributing more than 1% to the combined exposure (right), in the before restrictions scenario (*BRS*, above gray line), and in after restrictions scenario (*ARS*, below gray line), respectively: Median exposure (•), P25−P75 (whiskers) and mean exposure (*); in parentheses on the ordinate axis: percentage of individual days on which exposure to the substance−GEP combination occurred.

was calculated for different exposure percentiles for BP concentrations in serum and gonads.

2.7. Uncertainty Assessment. To assess uncertainty related to our exposure assessment, we followed a tiered approach.[53] First, we qualitatively evaluated the different sources of uncertainty and classified the related uncertainty on an ordinal scale (see Table S13). Second, for parameters categorized with a medium to high (MH) or high (H) uncertainty and sufficient data availability, we thereafter quantified the joint impact of uncertainty within MCRA. For quantifying uncertainty related to nondietary parameters, uncertainty sets were included into the input files, which were then uploaded to MCRA.[46] Within MCRA, we used empirical bootstrap methods to generate the alternative data sets that reflect the uncertainty in dietary exposure of the model population.[54,55] To account for uncertainty in the cumulation and risk assessment, we used all RPFs reported for the different analogues. Whenever the EC_{50} had not been measured for an analogue, we inserted the median RPF into the uncertainty set of the respective BP.

2.8. Comparison with Biomonitoring. We compared our PBPK model results of total BP exposures with BM data that had been identified for the European context in a thorough literature review by EFSA.[29] For the other BPs, we identified additional studies in a literature search (SI). To calculate the total (unconjugated plus conjugated) amount of absorbed BP from the reported urinary concentrations, we generally used the approach described by EFSA:[29] Urinary concentrations were combined with urinary volumes excreted within 24 h (see the footnote of Table S16) to yield the excreted BP amount. Details on the calculations in the applied PBPK models are described by Karrer et al.[36]

2.9. Computing Software. We used the beta version of MCRA 9—the EuroMix toolbox for modeling dietary exposure and for aggregating and cumulating exposures (as of November 2018, available at mcra-test.rivm.nl). We used PACEM in its R Shiny version (beta 0.9.)[56] for modeling PCP exposure. We used the programming language R (version 3.5.0) for modeling exposure from dust and TP and for data analysis.

3. RESULTS

3.1. Cumulative Exposures before and after Restrictions. The stacked histograms in Figure 2 show distributions of cumulative exposures to unconjugated BPs in serum. Dermal exposure from TP and oral exposure from dietary products were the most important contributors to exposure and most relevant in the higher and lower exposure percentiles, respectively. The shapes of the exposure distributions in the *BRS* and *ARS* are similar, but for the principal runs the mean and median values were lower for the *ARS* than for the *BRS*; e.g., mean cumulative exposures were 3.8 and 2.1 ng/kg bw/day in the BRS and ARS, respectively (Table 1). Moreover, more individuals showed high exposures in the *BRS* compared to the *ARS* (upper local maximum in the *BRS* histogram), and exposure estimates from the P90 to P99.9 were higher in the *BRS* compared to the *ARS* (Table 1). However, as the uncertainty intervals overlapped, these differences between the *BRS* and *ARS* are not significant.

Exposures from the substance-GEP combinations that were most relevant in the principal runs are shown in Figure 3. BPA exposure from TP contributed most to the mean exposures. Exposures related to TP and the respective contributions to overall exposure were considerably higher for the *BRS* than for the *ARS* (mean exposures of 3.2 and 0.62 ng/kg bw/day, contributions of 90% and 40%, in the *BRS* and *ARS*, respectively). While BPA exposure from TP was the only substance−GEP combination with a double-digit contribution to overall exposure in the *BRS*, dietary BPA exposure and BPS exposure from TP were more important in the *ARS* with contributions of 28% and 20%, respectively. Estimates for the P25, P50, and P75 were similar for dietary BPA exposure in the *BRS* and *ARS*, while the mean was considerably higher in the *ARS*. For BPA exposure from TP and food, the mean estimates were higher than the P75 estimates both in the *BRS* and *ARS*. The degree of coexposure was generally higher in the *ARS* than in the *BRS*, due to an increased exposure to BPS, BPF, and BPAF (Figure S7). in particular, BPS contributed to the higher degree of coexposure because the share of BPA and BPS coexposure increased considerably in the *ARS* compared to the *BRS*. In addition, the share of BPA and BPF coexposure decreased with coexposures to BPA, BPS, and BPF increasing at the same time.

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3.2. Contribution of GEPs to Cumulative Exposure. Dietary exposure to BPA and BPF is among the largest contributors to cumulative exposure (Figure 3). BPA concentrations in vegetables, seafood, and milk were considerably higher *AR* than *BR* (Figure S2). Several types of canned vegetables were risk drivers for external dietary exposure (Figure S9), and the resulting exposures were considerably higher in the *ARS*. This also led to higher overall external dietary BPA exposure in the *ARS* compared to the *BRS* (see Figure S8 and Table S14), with BPA as the largest contributor to dietary BP exposure. Main drivers of dietary exposure to BPF, the second largest contributor to overall dietary BP exposure (Figure 3 and Figure S8), were semiskimmed milk (*ARS*) and sweet mustard (*BRS* and *ARS*). However, most of the population was not exposed to BPF in food (the overall P50 of external dietary BPF exposure was zero, Figure S8).

TP was another important contributor to cumulative exposure. BPA exposure from TP was subject to a larger variation in the *ARS* compared to the *BRS*. In some studies that were conducted *AR*, BPA occurrence was higher than *BR* (maximum of 98%, see Table S1), but in most studies BPA occurrence was similar or lower than *BR* (minimum of 8%). BPS has only been investigated in TP *AR*, with an occurrence between 3% and 50%. The shapes of the cumulative distribution functions (CDFs) representing external exposures from TP differed for BPA and BPS exposure (Figure S10) because of different BP amounts transferred per handling event: more BPS than BPA was transferred from TP to normal/dry skin, while more BPA was transferred to humid skin.[57] Therefore, assuming the same occurrence frequency for BPS and BPA, the exposures below the P90 (mostly estimates for normal/dry skin) were higher for BPS. Exposure estimates for BPA were significantly higher beyond the P90. Comparing the importance of BPs in external and internal TP exposure (Figure S8), BPS contributed the most to the mean, P50, and P95 values of external exposure estimates. Yet, BPA contributed most to the cumulative exposure estimates, also due to its higher estrogenic potencies (Figure 3).

3.3. Uncertainty Assessment and Risk Considerations. Based on the qualitative uncertainty evaluation, the following parameters were selected for quantitative uncertainty assessment: occurrence frequencies of BPA and BPS in TP, RPFs, and BP concentrations in dietary matrices, individuals, and nondietary exposures (see Table S13). Table 1 shows the summary statistics related to different percentiles of the variability distribution (principal run) and uncertainty bands in the *BRS* and *ARS*. For uncertainty, the P2.5 and P97.5 are displayed, which cover 95% of quantified uncertainty. The associated uncertainty was larger for higher percentiles of exposure. Mostly, it had a larger influence on the exposure estimates in the *ARS* than in the *BRS*, which led to a larger spread in the CDFs and boxplots (Figure S11). Table 1 also shows the MOEs between the cumulated exposure estimates and the most sensitive EC_{50} value for BPA[58] (Table S12). Mostly, 100 is considered as a conservative margin.[29] For the percentiles beyond P90, some MOEs were below 100. The MOEs for gonadal concentrations were about a factor of 2 lower than those derived for serum concentrations; e.g., the MOE related to mean cumulative exposures was only 87.5 in the *BRS* (Table S15).

3.4. Comparison with BM Data. According to our literature review, two European BM studies reported urinary concentrations of BPs other than BPA (BPS and BPF, see Table S16).[59,60] To include more measurements for BPA replacements, we additionally considered studies from the U.S..[61] For BPAF, our review did not identify any BM studies.

For all BP analogues, the source-to-dose exposure estimates for children, adolescents, and adults were in good agreement with the corresponding BM data. Modeled exposures for the different age groups were very similar and, therefore, are displayed jointly in Figure S12. For BPA, the agreement between model and measurements was slightly better for the *BRS*. This scenario also includes the majority of consulted BM studies in its time frame (1995−2012 for all studies, see Table S16). The medians of modeled total BPA amounts excreted in urine were 36.8 and 24.5 ng/kg bw/day in the *BRS* and *ARS*, respectively. In comparison, mean internal exposures estimated by backward exposure modeling from BM data were taken from the EFSA BPA opinion[29] and ranged from 13 to 109 ng/kg bw/day for the age groups considered in this work. For BPS and BPF, the agreement was better for the *ARS*. Our medians of modeled total BPS exposure for the whole population were 0.0159 and 11.7 ng/kg bw/day in the *BRS* and *ARS*, respectively, compared to 2.70−9.72 and 7.02−29.2 ng/kg bw/day for median and high internal exposures from BM (derived from the respective BM studies). BPS exposure *AR* was the only exposure type for which exposure for children and the older age groups differed significantly: medians of days with exposure were 0.795, 27.1, and 20.9 ng/kg bw/day for children, adolescents, and adults, respectively. For BPF, the medians of modeled exposures were rather low with 0 and 1.01 ng/kg bw/day in the *BRS* and *ARS*, respectively. The respective P75 values of 4.19 and 15.5 ng/kg bw/day in the *BRS* and *ARS* corresponded better to median internal exposures from BM, which were 1.54−15.4 ng/kg bw/day.

4. DISCUSSION

4.1. Cumulative Exposures and Related Risks. Cumulative exposures for the different BPs were similar in the *BRS* and *ARS* with a considerable decrease of high exposures in the *ARS* (comparison of principal runs, see Figure 2). Oral exposure to food and dermal exposure to TP were the most important contributors with the latter pathway being predominant for high exposures. While TP handling only led to BPA exposure in the *BRS*, it led to both BPA and BPS exposure in the *ARS* (by scenario design). Eckardt and Simat reported that the BPS amount transferred from TP to normal skin was considerably higher than the corresponding BPA amount, while for moist skin the transferred amount was higher for BPA.[57] Since generally the BP transfer to moist skin is higher than to normal skin, high cumulative exposures from TP were mostly driven by high BPA transfers from TP to moist skin, which was a skin type allocated to about 10% of the model population. The partial replacement of BPA with BPS in TP in the *ARS* reduced these high BPA exposure cases. In addition, according to the data collected, the estrogenic effects of BPS are weaker than those of BPA, which reduced the BPS contributions in the RPF-weighted cumulation.

The exposure distributions for single-substance−GEP combinations are skewed to different degrees (see comparison of respective means and medians in Figure 3). The upper tail exposures are most pronounced for dermal BPA exposure from TP (less for AR than BR, for reasons discussed in the paragraph above) and dietary exposure to BPA. High dietary exposures mainly resulted from consuming canned food items

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with high BPA concentrations, and according to the data collected, BPA concentrations in canned food did not decline *AR*, but even increased, especially in canned vegetables.

The degree of coexposure was found to be higher for the *ARS* compared to the *BRS*. In our risk assessment, we assumed dose-additivity because synergistic effects have not yet been reported for coexposure of different BPs. However, synergistic effects may exist and may increase the cumulative risk, since for BPA and 17β-estradiol[62] and BPA and nonylphenol[63] synergistic effects have been reported on the proliferation of MCF-7 human breast cancer cells and on the viability of human prostate epithelial cells, respectively.

For most of the model population, the MOE related to serum concentrations was above 100, and therefore, from this informal first tier risk assessment no detrimental effects would be expected. However, MOEs derived from exposures in higher percentiles (from the P95 onward) and the upper uncertainty bound were lower, so that a refined risk assessment would be needed for concluding on risks for susceptible groups. In addition, risks related to estrogenic effects are not the only effects suitable for describing risks of BPs. For example, the temporary Tolerable Daily Intake (t-TDI) of BPA of 4 μg/kg bw/day was derived from kidney effects in a two-generation study in mice.[29] Yet kidney effects are so far not well studied for other BP analogues so that to date they cannot be used for assessing cumulative risks (changes in kidney weights have only been investigated in one BPF study[64]).

4.2. Comparison with Other Source-to-Dose Exposure Assessments and Biomonitoring. Deterministic source-to-dose calculations for the age groups considered in this work were presented in EFSA's scientific BPA opinion, with mean and high internal exposures of 134−301 and 393−876 ng/kg bw/day, respectively.[29] In our assessment, means of modeled total BPA exposure were 131 and 102 ng/kg bw/day in the *BRS* and *ARS*, respectively. In this respect, our *BRS* results correlate better with the results of the EFSA opinion, especially with the mean internal exposure for adults that ranged from 134 to 140 ng/kg bw/day. High estimates of internal total BPA exposure derived from our assessment were 213 and 191 ng/kg bw/day for the P90 and 760 and 432 ng/kg bw/day for the P95 for the *BRS* and *ARS*, respectively. Thus, for both the *BRS* and *ARS*, the P95 exposure estimates are in the range of high internal exposures reported in the EFSA opinion, which corresponds to EFSA's goal to deterministically construct a P95 exposure estimate with the high scenario.[38]

Our BPS and BPF exposure estimates for the *ARS* matched the BM data better than the estimates for the *BRS*. This can be explained by the limitations in concentration data for some exposure sources: BPS concentrations in dust and TP were only available *AR*. Therefore, related BPS exposures were only modeled in the *ARS*, with TP being the most important source for BPS exposure. However, those additional exposure sources could have been relevant contributors to BPS exposure already in the BM studies conducted *BR*,[59] although no such *BR* measurements exist. In addition, dietary exposure to BPS might be more relevant than suggested by the available concentration data. For BPF, *BR* exposures were modeled for food and PCPs. For the *ARS*, in addition BPF concentrations in dust and in more dietary matrices were available. This led to higher exposure estimates in the *ARS* that better reflect the exposure situation observed in the BM studies. Because the BPF BM studies were conducted partly *BR* and partly *AR*, it is likely that comparable BPF exposures have also occurred *BR*.

4.3. Limitations in Model Parameters. For the assessment of cumulative exposures, concentrations and other chemical-specific parameters for the different chemicals should ideally be selected on the basis of data of similar quality and should cover the same exposure sources. However, dietary concentration data were primarily available for BPA, while concentrations of other BPs were only available for a limited number of food items. The assumption of zero concentrations in the nonanalyzed food items may result in an underestimation of the contributions of BPs other than BPA and, consequently, the underestimation of the cumulative exposure.

Regarding the comparison of *BR* and *AR* exposures, the paucity of data for noncanned food items meant that most concentrations for noncanned items had to be used for both legislative scenarios, so that the differences between *BR* and *AR* may be underestimated. In addition, for both scenarios different types of dietary studies have been used. For *BR*, some BPA measurements of canned food items were available from a French Total Diet study (TDS) with representative sampling, while for *AR* concentrations of canned food items were only available from single studies with convenience sampling, which may result in higher substance concentrations. Therefore, overestimation due to publication bias may be higher for the *ARS* than for the *BRS*. An optimal data set would consist of representative data for all BP analogues for both legislative scenarios. While the French consumption patterns used in the assessment are not necessarily representative for other European subpopulations, the large number of 3360 individuals ensures a good representation of variability in France. All in all, we consider the unquantified uncertainty around the consumption data less influential than the uncertainty from the dietary concentration data (Table S13).

With regard to BP concentration data in general, we tried to use European data wherever possible, but in some cases we had to use data from outside Europe, which might reduce the explanatory power for assessing exposure for the general European population. Regarding food concentration data, all but two considered studies investigating European samples (see Table S6). The two exceptions were from Canada and reported measurements of BPs in juice *BR*[65] and in salmon and tuna *AR*.[66] In the latter study, a significant BPA reduction in comparison to a previously conducted study was observed, which corresponds well to the pattern seen in Europe. For both TP and dust, we solely used European occurrence frequencies and concentrations. However, for PCP concentrations, the only study investigating all BPs of interest and disclosing individual measurements was from China. Because of potential BPA concentration differences, we did not use another European study for BPA concentrations in the *BRS*, but the same Chinese data for both the *BRS* and the *ARS*. In this manner, the comparison between the *BRS* and *ARS* was not influenced by the Chinese data, but the PCP exposure term represents realistic worst-case BP exposures from PCPs for the sake of illustration and completeness. Still, food and TP are the most important contributors to BP exposure and PCPs are of minor importance (see, e.g., Figures 2 and 3).

Several parameters related to TP exposure are associated with a considerable variability and/or uncertainty (described in Table S13). The uncertainty in TP occurrence was addressed in our quantitative uncertainty assessment. BPA and BPS occurrence reported *AR* show a large spread (Table S1), with the spread for BPA occurrence being considerably larger *AR* than *BR* (8−98% compared to 58−85%). This could be due to

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nonrepresentative sampling techniques of TP receipts and/or different strategies pursued in different EU countries. In some instances, the BPA occurrence was higher *AR* than *BR* (86−98% in Germany, Denmark, and Italy), but also low occurrences have been reported *AR* (8−49% in Italy, France, Denmark, and Germany), which suggests that BPA has partly been replaced. However, findings varied between different studies conducted in the same countries (e.g., in Denmark, France, Germany, and Italy), which complicates the comparison of replacement patterns. Additionally, color developers other than BPA and BPS are increasingly used, such as Pergafast201 and D8, which can also lead to lower BPA occurrences.[57] Besides the occurrence, the daily handling frequency and the area of contact with TP are also variable and uncertain,[29] and the manner of handling is of importance, which we could not include in our assessment due to missing data. Since the BP transfer from TP to skin was found to be related to skin properties,[48,57,67] such properties need to be known for the population considered. We estimated the frequencies of different skin types in general,[68−71] but these shares are not necessarily representative for specific populations, such as those from the BM studies. In addition, we separated the skin types deterministically, but a fluent transition of different skin types and related BP transfers is probably more realistic. However, in comparison to other sources of uncertainty this source is minor.

The model results discussed here depend on the used PBPK models and their parameters, which were presented and discussed by Karrer et al.[36] Among other parameters, absorption fractions, half-lives, and uptake periods were derived from the literature (Karrer et al.[36] Table 5, e.g., absorption fractions of 100%, 20%, and 60% for oral exposure, dermal TP exposure, and dermal PCP exposure, respectively), and the uncertainties of the oral and dermal absorption parameters for BPA were classified low to medium and medium to high, respectively.[36] For the other BP analogues, the uncertainties of these parameters are even higher. Due to a lack of specific dermal uptake studies for BPS, BPF, and BPAF, for calculating dermal exposure from TP and PCPs the same BPA-specific parameter values were used in the PBPK models for all BP analogues for the extent of dermal absorption, the absorption half-life for dermal penetration, and the dermal uptake period.[36] However, it is likely that the uptake characteristics differ among BPs, e.g., because of different lipophilicities and molecular weights. This may have an impact on the comparison of cumulative exposures *BR* and *AR* because different shares of BP amounts may cross the dermal barrier, which could change the relative importance of external exposure to different BPs. Yet, the same PBPK models and parameters were used in the *BRS* and *ARS*, and therefore, related uncertainties do not influence the comparison between *BRS* and *ARS* exposures.

Despite the presence of several limitations in the parametrization of the models, the present work shows a valid tendency of BP exposure changes as a result of BPA restrictions, and it can be used as an orientation to identify areas in which further research is most urgently needed.

4.4. Model Limitations. Within the models MCRA and PACEM, exposures were calculated for different age strata, i.e., for French individuals 3−79 y and Dutch adults, respectively. The allocation of individuals from the different models results in uncertainty in exposure estimates. However, for children and adolescents only dietary exposure was modeled (not PCP exposure), so that this uncertainty source is only relevant for adults. Furthermore, since PCPs contributed little to exposure, related uncertainties are minor.

The uncertainties from the PBPK models have not been quantified here because they have been evaluated in detail with a two-dimensional Monte Carlo analysis in a previous assessment,[36] and a reiteration was beyond the scope of this work. According to the previous assessment, the P95 uncertainty bound of the P95 for variability in internal estimates was less than 1 order of magnitude higher than the respective medians for all PBPK models. This means that the PBPK model parameters entail less quantified uncertainty than the exposure model parameters. Another limitation related to the PBPK models is that we used dermal absorption fractions, absorption half-lives, and dermal uptake periods for describing the dermal uptake instead of more sophisticated kinetic models. However, this uncertainty source presumably is minor in comparison to those described previously.

4.5. Considerations Related to BPA Legislation. According to the collected data, the use of BPA for internal coatings of cans did not decline in the *ARS*. This suggests that neither has the production process of the cans been optimized to minimize BP transfer nor has there been a proactive BPA replacement. Therefore, more binding regulations or better incentives may be needed if BPA exposure should be reduced further. New legislative measures became binding very recently in the EU; i.e., BPA migration limits for plastics were lowered from 600 to 50 ng/g and BPA migration limits were introduced for epoxy resins from September 2018 onward.[72] The respective migration limit was set to 10 ng/g (detection limit) for items intended to be consumed by infants and young children and to 50 ng/g for other items. Even the higher limit has been exceeded by many food samples used in the *ARS* (Figure S2). This means that the new legislation should effectively decrease BPA concentrations in canned food compared to the measurements used for this assessment but, in case of replacement by other BPs, not necessarily the cumulative exposure to BPs. For TP, the same issue is likely: From 2020 onward, BPA will be practically banned from use as a color developer in TP because BPA concentrations in TP will have to be smaller than 0.02%.[73] However, no legally binding measures were announced for BPS, and therefore, a regrettable substitution[74] with this substance might be a possible scenario in the future. Even though the estrogenic effects of BPS were lower than those of BPA in the studies considered, it still exerts estrogenic activity. Furthermore, the BPS amount transferred from TP to normal skin was found to be higher than the corresponding BPA amount,[57] and the glucuronidation in liver and gut was found to be lower for BPS than for BPA, so that more of the chemical remains in the endocrine active, unconjugated form.[36] To the best of our knowledge, dermal uptake parameters for BPS that would further improve the risk comparison between BPA and BPS have not yet been published. While more and more data for BPA exposure assessments became available in the last years, the knowledge about source concentrations and uptake characteristics is comparatively poor for its analogues. Our findings of larger uncertainty around exposure estimates for substitutes compared to BPA (Table 1 and Figure S11) highlights the problem of such substitutions and indicates which parameter values need to be assessed to reduce this uncertainty.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.9b01749.

Details on the approaches for modeling BP exposure from food, PCPs, TP, and dust; approach and keywords of conducted literature searches; quality assessment of studies reporting endocrine effects of BPs; MCRA settings; R code for modeling TP and dust exposure; supporting tables and figures (PDF)

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