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REGULATORY TOXICOLOGY

Case study: Is bisphenol S safer than bisphenol A in thermal papers?

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Abstract

The Risk Assessment Committee of the European Chemical Agency released a scientific opinion alerting that the risk associated with dermal occupational exposure to bisphenol A (BPA) via thermal paper might not be adequately controlled because the estimated exposure was around twice the Derived No Effect Level (DNEL) and the European Commission will effectively restrict BPA in thermal paper as soon as 2020. Bisphenol S (BPS) is currently being used as a BPA surrogate and is already widespread in thermal paper receipts. Based on publically available information in the scientific literature, we assessed the risk associated with dermal BPS exposure via thermal paper for the general and occupational populations to compare with BPA situation. We developed two exposure scenarios; one based on the total excreted BPS and another on exposure estimations by transferring BPS from the thermal paper matrix to skin. Both scenarios yielded similar exposures for the general population (0.016–0.013 µg/kg bw/day), but the exposure estimated for the workers in the second scenario (0.96 µg/kg bw/day) was around 17-fold higher than that estimated for the workers in the first scenario. The systemic DNELs for the general and workers populations were 0.45 and 0.91 µg BPS/kg bw/day, respectively, which were 4.6- and 19-fold higher than the respective dermal DNELs. Risk Characterisation Ratio (RCR) (estimated exposure through urinary excretion compared with the systemic DNEL) in the first and most reliable scenario suggested that the risk was adequately controlled. In the second scenario, however, the RCR suggests that the risk might not be adequately controlled for both the general population and workers. This work raises the necessity of generate more toxicodynamic and toxicokinetic information, specially using dermal exposures, to properly assess the risk associated to dermal BPS exposure because the situation might presumably get worse after 2020.

Keywords Bisphenol A · Bisphenol S · Thermal paper · Risk assessment · Dermal absorption

Abbreviations

BMDL	Benchmark dose level
BMDL10	Benchmark dose level lower confidence limit of 10%
BPA	Bisphenol A
BPS	Bisphenol S
DNEL	Derived no effect level
EFSA	European Food Safety Agency
GLP	Good Laboratory Practice
HED	Human equivalent dose
HEDF	Human equivalent dose adjustment factor
LOAEL	Lowest observed adverse effect level
NOAEL	No observed adverse effect level
RAC	Risk Assessment Committee of the European Chemical Agency
RCR	Risk characterisation ratio

Introduction

Bisphenols comprise a family of chemicals with a common chemical structure formed by two phenol rings bonded with a variety of bridges, including a linear or branched alkyl hydrocarbon chain that can also contain other heteroatoms, such as sulphur or oxygen (Fig. 1). These chemicals are widely used to manufacture polycarbonate plastics, epoxy resins and thermal papers. The most representative compound of this family is bisphenol A (BPA). The European Food Safety Agency (EFSA) determined that exposure to BPA by handling thermal paper is the second largest source of exposure to this substance (EFSA 2015).

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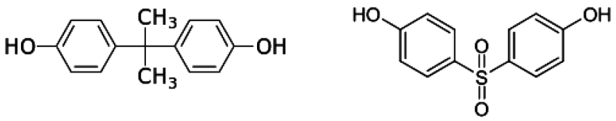
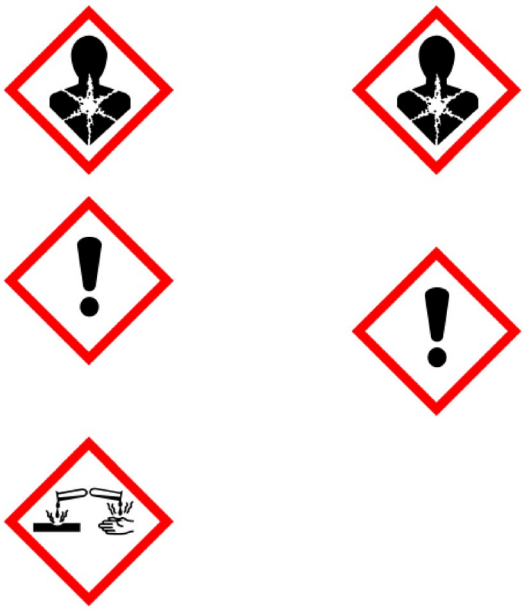


Fig. 1 Chemical structures of bisphenol A (left) and bisphenol S (right)

BPA is a chemical that has caused considerable social and scientific concern about its capability to act as an endocrine disruptor. However, the capability of BPA to alter the oestrogen cycle is very limited because its potency as such is usually several orders of magnitude lower than the positive controls used in studies (Rochester and Bolden 2015).

Table 1 Classification of BPA and BPS according to European CLP Regulation No. 1272/2008

	BPA[a]	**BPS**[a]
CAS number	80-05-7	80-09-1
Classification	Eye Dam. 1 Skin Sens. 1 STOT SE 3 Repr. 1B	Eye Irrit. 2 Repr. 2
Hazard statements	H318 = Causes serious eye damage H317 = May cause an allergic skin reaction H335 = May cause respiratory irritation H360F = May damage fertility	H361 = Suspected of damage fertility or the unborn child H319 = Causes serious eye irritation
Pictograms		

[a]Data taken from the European Inventory available in: https://echa.europa.eu/information-on-chemicals/cl-inventory-database. The BPS classification is still not harmonized

According to European CLP Regulation No. 1272/2008, BPA is classified as a known or presumed human reproductive toxicant (reproductive toxicant category 1B) on the basis of its capability to cause fertility and sexual function impairments (Table 1) and is also classified as a skin sensitizer and as agent that cause serious eye damage. This classification is probably the reason why one of the main concerns of BPA effects lies in its effects on reproduction. However, alterations to reproduction are not the most sensitive effect reported for BPA. Indeed BPA is not considered a selective reproductive or developmental toxicant in mice (Tyl et al. 2008) or rats (Tyl et al. 2002).

BPA also seems able to induce some kind of disruption in organs such as pancreas, adipose tissue and muscle (Rahmani et al. 2018). In its assessment of the risks to public health related to the presence of BPA in foodstuffs, EFSA took the proliferative and morphological changes potentially related to mammary gland carcinogenicity, along with liver and kidney impairments, to be the most likely hazards (EFSA 2015). EFSA was unable to derive a Benchmark Dose Level (BMDL) for the first effect but determined a $BMDL_{10}$ (BMDL lower confidence limit of 10%) of 8960 µg BPA/kg bw/day. This $BMDL_{10}$ was further transformed into a human equivalent dose (HED) of 609 µg/kg bw/day and allowed the estimation of a temporary tolerable daily intake of 4 µg/kg bw/day. Finally, EFSA concluded no health concerns due to BPA dietary exposure (EFSA 2015).

BPA is also used in thermal paper receipts at concentrations between 2 and 4% (w/w). For example, Thayer et al. (2016) reported concentrations of 19.6 ± 4.7 mg BPA/g paper [19.3 mg BPA/g paper (median), 7.0–36.0 mg BPA/g paper (range)] in 33 samples collected in USA. Rocha et al. (2015) reported either BPA or BPS in 98% of 190 Brazilian thermal paper receipt samples with up to 4.3% (w/w) (geometric mean of 1.6%). BPA was also found in 44 of 50 thermal paper receipts from the Italian market with concentrations up to 1533 µg BPA/100 mg paper (mean concentration of 107 µg/100 mg paper) (Russo et al. 2017).

Despite the EFSA's assessment for dietary exposure of BPA contained in foodstuff, upon the proposal of France the Risk Assessment Committee of the European Chemical Agency (RAC) determined that the Risk Characterisation Ratio (RCR) [the ratio between exposure and the Derived No Effect Level (DNEL)] in cashiers occupationally exposed to BPA through thermal paper was above one in several reasonable worst cases. RAC proposed to the European Commission the restriction of the use of BPA, which shall not be placed on the market in thermal paper at concentrations equal or exceeding 0.02% per weight (RAC 2015). This restriction proposal was adopted by the European Commission and will be fully operative as from 2020.

One potential alternative to BPA in thermal paper is bisphenol S (BPS), which has no use restrictions to date and is being widely used in thermal paper receipts (Table 2). Liao et al. (2012a) reported that 100% of the 111 thermal receipt paper samples collected randomly in four different countries (USA, Japan, Korea, and Vietnam) contained BPS at concentrations ranging from 0.0000138 to 22.0 mg/g (geometric mean 0.181 mg/g) (Table 2). Japan and the USA were the countries with the highest BPS concentrations in thermal paper receipts, whereas the concentration in Korea and Vietnam was several orders of magnitude lower (Table 2). In another study, 31 of 50 samples of thermal paper receipts collected in Italy contained BPS at a mean concentration of 41.97 µg/100 mg of paper (Russo et al. 2017). The median BPS concentration obtained from 32 thermal paper receipts collected in the USA was 14.6 mg/g paper (mean 15.0 ± 2.6, range 11.9–26.2) (Thayer et al. 2016).

The chemical structure of BPS is similar to that of BPA (Fig. 1) and it still has no harmonised classification set out in European CLP Regulation No. 1272/2008 but has so far been considered a suspected human reproductive toxicant (reproductive toxicant category 2) (Table 1). Therefore, the concern about reproductive impairments seems lower for BPS than for BPA. However, there is also a body of scientific literature that presents BPS as a potentially similar endocrine disruptor to BPA (see for example Rochester and Bolden 2015).

It seems plausible that, although cashiers' occupational exposure to BPA is considered relevant as RAC (2015) highlighted, the exposure of these workers to BPS by a similar route might also be relevant. Therefore, an assessment of

Table 2 BPS content (mg/g) in thermal paper receipts. All data taken from Liao et al. (2012a)

Site	*n*	Geometric mean	Median	95th percentile	Range
USA	81	0.44	7.44	13.4	0.000014–22
Japan	6	0.62	5.50	6.10	0.00055–6.1
Korea	11	0.0007	0.0008	0.0068	0.00009–0.011
Vietnam	3	0.0003	0.0003	0.0005	0.00011–0.00055
All sites	111	0.18	5.0	13.2	0.000014–22

the risk associated with such exposure might be urgently needed.

Methods

In this paper, we developed DNELs for BPS on the basis of reliable publically available toxicological information following similar methodologies to those used by RAC in its opinion of year 2015. We also compared several occupational exposures to BPS reported in the scientific literature with the derived DNELs to make a preliminary assessment of the risk associated with the exposure to BPS of the general population and cashiers through skin contact with thermal paper receipts. We also compared the results with the situation indicated for BPA.

Results

Background information: the BPA case

In 2015, EFSA made a very detailed assessment of the risk associated with exposure to the BPA contained in foodstuffs. This assessment also served RAC (2015) as the main basis to support its view about the need to restrict BPA contents in thermal paper. In the next paragraphs, we present the main conclusions drawn from both scientific opinions as regards the risk associated with occupational exposure to the BPA contained in thermal paper. See both opinions for specific details.

Dermal exposure of cashiers and the general population to BPA via thermal paper

RAC (2015) used several procedures to model the exposure to BPA of the general population and workers via dermal exposure to thermal paper. These models were the "percutaneous absorption flow model" and the "absorption rate model". The first was a probabilistic model, while the second was a deterministic model.

The probabilistic model (percutaneous absorption flow model) was subcategorised by RAC into three different reasonable sub-scenarios according to distinct input parameters. We present here for simplicity reasons the results of the worst scenario, which considers the following parameters (for both workers and the general population): (1) an absorption flow of 0.022 µg/cm^2/h (the maximum value obtained in an in vitro determination with seven human skin explants from two different donors); (2) an area of skin contact sized 6 cm^2 (based on the USEPA default surface area of 2 cm^2 for the thumb and of 1 cm^2 for all the other fingers); (3) a discrete distribution of probabilities to illustrate body weight.

Table 3 Exposure assessment to BPA via dermal exposure in thermal paper according to the percutaneous absorption flow model. All data taken from the opinion of the Risk Assessment Committee of the European Chemical Agency (RAC 2015)

	Exposure (µg/kg bw/day)		
	Arithmetic mean	Geometric mean	95th percentile
Worker	0.21	0.17	0.43
General population	0.02	0.01	0.05

Table 4 Exposure assessment to BPA via dermal exposure in thermal paper according to the absorption rate model. All data taken from the opinion of the Risk Assessment Committee of the European Chemical Agency (RAC 2015)

	Absorption flow (µg/cm^2/h)	Duration (h)	Surface (cm^2)	Body weight (kg)	Total BPA (µg/kg bw/day)
Workers	0.258	10	12	70	0.442
General population	0.258	2	12	70	0.088

The differences in inputs parameters lay in the duration of exposure; uniform distribution was considered up to 2 h/day as the maximum for the general population and a triangular distribution with minimum, mean (mode) and maximum values of 3, 5.5 and 8 h/day, respectively, for workers. The results of the exposure assessment modelled according to this percutaneous absorption flow probabilistic model are summarised in Table 3.

The deterministic model (absorption rate model) was subcategorised by RAC into four different reasonable subscenarios according to several input parameters for the workers and to two sub-scenarios for the general population. Differences were addressed with distinct variations in absorption flow, exposure duration and surface area term. For simplicity reasons, the results of the worst reasonable scenario are presented, which considers (for both workers and the general population): (1) an absorption flow of 0.258 µg/cm^2/h (the 95th value obtained in an in vitro determination with 15 human skin explants from six different donors); (2) an area of skin contact of 12 cm^2 (cumulated surface area of the pads of the ten fingertips); (3) a body weight of 70 kg. The differences in the input parameters lay in the exposure duration, which was considered 2 h/day for the general population and 10 h/day for workers. The results of the exposure assessment modelled according to this percutaneous absorption flow probabilistic model are summarised in Table 4.

RAC also reviewed the data obtained from biomonitoring BPA in urine. Using the correlation between oral daily intake and urinary excretion given by Krishnan et al. (2010), a representative worst case BPA daily intake was estimated in occupationally exposed people to be 400 ng/kg bw/day, which is similar to the values estimated in Tables 3 and 4.

Hazard identification

EFSA (2015) assessed the available evidence to determine the likelihood of a specific hazard occurring in humans (Table 5). EFSA determined as "likely" the general toxicity (mainly nephrotoxicity and hepatotoxicity) reported in two and three generation reproductive toxicity studies performed in mice and rats. EFSA derived a $BMDL_{10}$ of 8960 µg/kg bw/day for these effects. This hazard was considered by EFSA and RAC to be the risk characterisation end-point.

In addition, the general toxicity proliferative and morphological changes potentially related to carcinogenesis in mammary gland were also considered "likely" by EFSA. However, no dose-response could be derived and this effect was accounted for in the risk assessment using additional assessment factors.

Five hazards were labelled by EFSA with the likelihood of "as likely as not likely", which were: immune effects, neurological, neurodevelopmental and neuroendocrine effects, reproductive and developmental effects, metabolic effects and cardiovascular effects (Table 5). Once again, no dose-response could be derived for these hazards and the corresponding risk was addressed using additional assessment factors.

Finally, the likelihood of carcinogenicity and genotoxicity occurring was considered "unlikely to as likely as not" and "unlikely"; respectively (Table 5). These two hazards, together with cardiovascular effects, were not taken into account by RAC (2015) in its assessment of the risk associated with BPA exposure via thermal paper.

Overall, the critical point considered for the risk assessment of the effects to human health was nephrotoxicity, an effect considered not associated with endocrine disruption, fertility or developmental impairments (effects that lead to more social concern). However, with less likelihood, a variety of additional effects was also be accounted for and was considered in the risk assessment using additional assessment factors to cover any uncertainties in the database.

Oral DNEL derivation

The process for DNEL derivation is overall in Table 6. EFSA (2015) considered the HED approach to transform animal doses into human doses, which was also accepted and adopted by RAC (2015) in its assessment. The HED

Table 5 Hazard identification associated to exposure to BPA. EFSA (2015) categorised the likelihood of occurrence of each hazard in humans on the basis of weight of evidence and considered 7 different categories

Hazard description	Dose-response	Likelihood[a]
General toxicity: increase in the mean relative kidney weight in male mice of the F0 generation in Tyl et al. (2008). Other nephrotoxicity signs at doses: mild renal tubular. Other signs of general toxicity: Increase of relative liver weight in rats and mice both absolute and relative liver weight in mice and hepatocyte hypertrophy in mice	YES $BMDL_{10}$ = 8960 µg/kg bw/day	Likely
Mammary gland: ductal hyperplasia and effects on the architecture of the mammary gland, including effects on terminal end buds	NO	Likely
Immune effects: failure to induce a proper cellular immune response, deregulation of TH1/Th2 cytokines profile	NO	As likely as not to likely
Neurological, neurodevelopmental and neuroendocrine effects: altered child behaviour, anxiety-like behaviour, learning and memory, social behaviour and sensory-motor function, loss of midbrain TH-immunoreactive neurons and loss of hippocampal spine synapses	NO	As likely as not
Reproductive and developmental effects: increase in the occurrence of ovarian cysts, increase in the frequency of endometrial hyperplasia, disruption of ovarian cycles	NO	As likely as not
Metabolic effects: Obesogenicity: effects on glucose or insulin regulation or lipogenesis and body weight gain	NO	As likely as not
Cardiovascular effects	NO	As likely as not
Carcinogenicity	NO	Unlikely to as likely as not
Genotoxicity	NO	Unlikely

[a]Likelihood according to weight of evidence: Very likely, Likely, As likely as not to likely, As likely as not, Unlikely to as likely as not, Unlikely and Very unlikely

Table 6 Overall of oral DNEL derivation performed by RAC for assessment of the risk associated to dermal BPA exposure via thermal paper. Data taken form RAC (2015)

Starting point: $BMDL_{10}$= 8960 µg/kg bw/day
Critical end-point: nephrotoxicity
Key study: Two-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD-1 (Swiss) Mice (Tyl et al. 2008)

	Workers	General population
Human equivalent adjustment dose factor	0.068	0.068
Human equivalent dose (µg/kg bw/day)	609	609
Assessment factors		
Interspecies allometric factor	1	1
Interspecies remaining factors	2.5	2.5
Intra-species	5	10
Additional factor (quality of data base)	6	6
Derived oral DNEL (µg/kg bw/day)	**8**	**4**

Bold indicates the staring points and the final derived DNELs

represents dose (D) in an animal species that a human would require to obtain an equivalent area under the curve of toxicokinetic experiments. Therefore;

$$\mathrm{HED} = D \times \mathrm{HEDF}; \quad (1)$$

where the HEDF (human equivalent dose adjustment factor) is defined by a common relationship between the external dose given to an animal and the resultant area under the curve, and the external dose given to a human and its area under the curve.

The area under the curve for oral BPA administration to adult mice was 0.244 nmol/h/l, while the area under the curve for humans was estimated by physiologically-based pharmacokinetic modelling in monkey, and was estimated as 3.6 nmol/h/l (RAC 2015). Thus the HEDF for estimating the HED according to Eq. 1 starting with a mice dose was a factor of 0.068 (0.244/3.6).

EFSA considered the HED approach to replace the default uncertainty factor for the interspecies extrapolation of toxicokinetics, although the 2.5 assessment factor (out of 10) for toxicodynamics is still needed. RAC (2015) considered an extra assessment factor to cover the uncertainties associated with accounting for effects on mammary gland, reproductive, neurobehavioral, immune and metabolic systems. EFSA (2015) indicated that these effects could occur starting with doses from 100 µg/kg bw/day, which corresponds to an HED of 6.8 µg/kg bw/day according to Eq. 1 (100 µg/kg bw/day × 0.068). RAC finally set this extra assessment factor at 6.

Table 7 Overall of dermal DNEL derivation performed by RAC for assessment of the risk associated to dermal BPA exposure via thermal paper. Data taken form RAC (2015)

Starting point: $BMDL_{10}$ = 8960 µg/kg bw/day
Critical end-point: nephrotoxicity
Key study: Two-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD-1 (Swiss) Mice (Tyl et al. 2008)

	Workers	General population
Human equivalent adjustment dose factor	0.00074	0.00074
Human equivalent dose (µg/kg bw/day)	6.63	6.63
Assessment factors		
Interspecies allometric factor	1	1
Interspecies remaining factors	2.5	2.5
Intra-species	5	10
Additional factor (quality of data base)	6	6
Derived dermal DNEL without biotransformation (µg/kg bw/day)	0.088	0.044
Rounded DNEL (µg/kg bw/day)	0.10	0.05
Biotransformation factor (%)	50	50
Derived dermal DNEL (µg/kg bw/day)	**0.2**	**0.1**

Bold indicates the staring points and the final derived DNELs

Dermal DNEL derivation

The DNEL derivation process is overall in Table 7. RAC (2015) derived a DNEL for dermally absorbed BPA using toxicokinetic information about the fraction of an external dermal dose reaching systemic circulation. RAC used to convert the starting point into the dermal HED areas under the curve of 0.244 nmol/h/l for an oral dose of 100 µg BPA/kg bw in mice, and of 329.5 nmol/h/l for a dermal dose of 100 µg BPA/kg bw in humans. Therefore, the HEDF for estimating the dermal HED according to Eq. 1 starting from a mice dose was a factor of 0.00074 (0.244/329.5).

RAC used the same assessment factors to derive the dermal DNEL but noted how published papers described for low dermal exposures the dermal metabolism can reduce up to 40% of the original dose. Thus, a compromise approach was used and a biotransformation rate of 50% was considered (i.e., only 50% of the dose reached the potential target organs in an unconjugated form) to correct the dermal DNEL.

Risk characterisation

The RCRs (the ratios between exposure and DNELs) for workers and consumers based on both probabilistic exposure modelling and deterministic modelling are summarised in Tables 8 and 9, respectively. Both approaches yielded similar results, with an RCR for workers slightly above 2 in a reasonable worst case, and with RCRs of 0.1 and 0.88 for the general population.

The BPS case

We reviewed the scientific literature to assess the risk associated with dermal BPS exposure through contact with thermal paper in cashiers and the general population. One of the main inconveniences was that available information is considerably reduced compared with BPA, especially in terms of exposure assessment, toxicokinetics and risk characterisation after skin exposure and, consequently, the risk assessment will necessarily have greater uncertainties.

Table 8 Risk characterisation for workers and consumers exposed to BPA through dermal contact with thermal paper

	Exposure[a] (µg/kg bw/day)		DNEL[b] (µg/kg bw/day)	RCR (exposure/DNEL)	
	Geometric mean	95th percentile		Geometric mean	95th percentile
Workers	0.17	0.43	0.2	0.85	**2.15**
General population	0.01	0.05	0.1	0.1	0.5

Bold indicates the staring points and the final derived DNELs

[a]Estimated according to the percutaneous absorption flow model (Table 2)

[b]DNEL was derived as described in Table 7

Table 9 Risk characterisation for workers and consumers exposed to BPA through dermal contact with thermal paper

	Exposure[a] (µg/kg bw/day)	DNEL[b] (µg/kg bw/day)	RCR (exposure/DNEL)
Workers	0.442	0.2	**2.21**
General population	0.088	0.1	0.88

Bold indicates the staring points and the final derived DNELs

[a]Estimated according to the absorption rate model (Table 3)

[b]DNEL was derived as described in Table 7

Dermal exposure of cashiers and the general population to BPS via thermal paper

Two well-defined strategies were found in the literature to estimate BPS exposure. One was based on biomonitoring BPS excretion in urine and the second on estimations of transfer rates of BPS from the thermal paper matrix to skin.

Biomonitoring The literature has clearly determined that BPS can be biomonitored in the urine taken from both the general and worker populations. Ndaw et al. (2018) found significant differences (3.7-fold) between BPS contents in the urine of the general population and cashiers, and was consistently detected in the general population (Table 10).

Liao et al. (2012b) found BPS in 81% of 315 urine samples collected in the USA, China, India, Japan, Korea, Kuwait, Malaysia and Vietnam. The BPS concentrations ranged from below the limit of quantitation (0.02 ng/ml) to 21 ng/ml (geometric mean 0.168 ng/ml) (Table 11). A clear correlation between high BPS content in thermal paper in some countries (Table 1) and high urinary BPS in the citizens of these countries (Table 11) was observed.

Estimation of daily BPS exposure by biomonitoring urinary excretion This methodology estimates the total daily exposure as:

$$\text{Exposure} = \text{urinary BPS concentration } (\mu g/l) \times \text{urine excretion rate } (l/\text{day}). \quad (2)$$

Table 10 Urinary concentrations of BPS (µg/l) in general and worker population in France. Data taken from Ndaw et al. (2018)

Population	Individuals	Samples	Median	95th percentile	Geometric mean
Workers	17	80	2.53	19.9	2.48
General	15	73	0.67	12.6	0.72

Table 11 BPS content in urine (μg/l) of general population of 8 different countries. Data taken from Liao et al. (2012b)

Site	*n*	Geometric mean	Mean	95th percentile	Occurrence (%)
USA	31	0.30	1.12	2.65	97
China	89	0.23	0.53	1.73	82
India	38	0.07	0.17	0.71	76
Japan	36	1.18	2.27	7.76	100
Korea	33	0.03	0.10	0.17	42
Kuwait	30	0.17	0.79	1.65	70
Malaysia	29	0.07	0.13	0.25	76
Vietnam	29	0.16	0.20	0.39	100

Table 12 Estimated exposure (μg BPS/l urine) in general population of eight different countries. Data taken from Liao et al. (2012a)

Country	*N*	Mean	Median
US	31	1.48	0.32
China	89	0.71	0.34
India	38	0.24	0.08
Japan	36	3.47	1.67
Korea	33	0.15	0.023
Kuwait	30	1.10	0.292
Malaysia	29	0.18	0.122
Vietnam	29	0.28	0.217
All countries	315	0.93	0.248

Using this methodology, Liao et al. (2012a) concluded that the mean and median exposures of BPS for the general populations in eight different countries were collectively 0.930 and 0.248 μg/day, respectively, with Japan, US, China and Kuwait having the highest exposures (Table 12).

The two highest exposures estimated in Table 12 for the general population were similar to the exposure estimated for two different cashiers in France after collecting urine at 24 h, with 3.42 and 1.5 μg BPS/day (Ndaw et al. 2018).

Estimation of daily BPS exposure starting with BPS contents in thermal paper Several papers have estimated exposure to BPS as:

$$\text{Exposure (ng/day)} = k \times C \times \text{HF} \times \text{HT} \times \text{AF}/10^6 \quad (3)$$

where k is the paper-to-skin transfer coefficient for BPS (21,522.4 ng/s) (the same value reported for BPA because this parameter is unknown for BPS); C is the BPS concentration in paper samples (μg/g); HF is handling frequency (2–3 times/day for the general population and 150 times/day for the workers population); HT is the handling time of paper (5 s/handling); AF is the absorption fraction of BPS (set at 27% in all the reviewed studies). The estimations of the exposures found in the recent literature are summarised in Table 13.

By the same procedure, Rocha et al. (2015) estimated the 95th percentile of bisphenol exposure to be 2000 and 101,000 ng/day for the general population and the worker population, respectively, while the median exposure for these populations was, respectively, 1420 ng/day and 71,000 ng/day. These values were considerably higher than those reported in Table 13. However, it was remarkable that these authors determined total bisphenols, and that it was not possible to discriminate the specific exposure to both BPA and BPS separately. Therefore, these figures were considered unsuitable for our purposes.

Discussion about BPS exposure Exposure estimated by BPS excreted in urine might be more representative of systemic (internal) exposure, but the respective figures can be underestimated if the substance bioaccumulates. This is not expected if we consider: (1) the water solubility of BPS (1.1 g/l) and a log Pow of 1.2 (BPS dossier for registration according to the REACH Regulation); (2) the high excretion in humans after a single oral administration (92% in males; 72% in females) (Oh et al. 2018); (3) the slight retention in tissues following a single gavage dose in mice and rats, which anticipates a lower accumulation potential with repeated dosing (Waidyanatha et al. 2018). Therefore, we used the exposures estimated by this procedure to make a comparison with the DNEL derived from the oral dose to be assimilated to the systemic DNEL by assuming 100% oral absorption, which is typically considered for the pharmacokinetic modelling of bisphenols (Karrer et al. 2018).

For our assessment, we took the reasonable worst cases to be the highest exposure that derived from one cashier after the 24-h urine collection employed in the study of Ndaw et al. (2018) (3.4 μg BPS/day) (Table 14) and, for the general population, the mean exposure derived from monitoring

Table 13 BPS exposure (ng/day) estimated assessing transfer rate from thermal paper to skin according to Eq. 3

	General population			Occupational population		
	Geometric mean	Median	95th percentile	Geometric mean	Median	95th percentile
Liao et al. (2012a)	10.5	291	767	787	21,804	57,493
Russo et al. (2017)	–	24.4	–	–	15,600	–

urine in eight different countries (0.93 µg/day) (Tables 12, 14).

The exposures derived from assessing BPS paper-skin transference (Table 13) were clearly higher than those obtained from BPS urinary excretion (Table 12). As we see it, this estimation procedure might overestimate real exposure basically for two reasons: (1) the paper-to-skin transfer coefficient for BPS is unknown and the coefficient for BPA was taken by default; (2) the absorption fraction of BPS through skin was considered by several authors to be 27%, while the potentially absorbed dose determined in one ex vivo study using human skin *stratum corneum* samples was considerably lower ($8.79 \pm 3.24\%$) (BPS dossier for registration according to the REACH Regulation). For our assessment, we considered the 95th percentile for the general population and the workers in the study of Liao et al. (2012a) to be reasonable worst cases (Table 14).

The general population exposures shown in Table 14 were lower (for both scenarios), but of the same order of magnitude as the BPA exposures estimated by RAC (2015) (Tables 3 and 4). However, the exposure estimated by assessing the amount of BPS that came into contact with the workers' skin approximately doubled the estimated BPA exposure. The workers' exposures shown in Table 14, estimated by urine excretion, are around eightfold lower than the BPA exposures estimated by RAC (2015) (Tables 3 and 4).

Hazard identification

A 90-day repeated dose toxicity study The results of this repeated dose toxicity study are summarised in Table 15. The highest dose had to be reduced by day 70 and onwards due to excessive body weight reduction in animals. At this high dose, in addition to this body weight and body weight reduction, other effects were reported: (1) slight haematological impairments (red blood cell, haemoglobin, haematocrit, mean corpuscular volume and relative reticulocyte counts); (2) changes in clinical chemistry (increases in creatinine and alkaline phosphatase and reductions in bilirubin; (3) increases in organ weights (adrenals, brain, epididymis, heart, kidneys, liver, spleen, thyroid, thymus, testes and ovaries) in males and/or females; (4) histopathological alterations in caecum, spleen, mammary gland, liver and uterus of females.

Increases in organ weights were found for kidney in males, and for adrenals, kidney, liver and spleen in females. The only relevant effect noted at the lowest dose was a focal squamous cell metaplasia of glandular epithelium in the uteri of two females, which was also found in two females at the mid dose and in five females at the highest dose, but not in the control females (Table 15).

According to the registrant, the No Observed Adverse Effect Level (NOAEL) of this study should be 100 mg/kg bw/day, based on the alterations of organ and body weight and body weight gain reported at 300 mg/kg bw/day [dose considered to be the Lowest Observed Adverse Effect Level (LOAEL)]. We noted that the focal squamous cell metaplasia of glandular epithelium in the uterus reported at 100 mg/kg bw/day was not contemplated because a similar incidence was reported for 300 mg/kg bw/day. However, we also noted that this effect was not reported in the control animals and, based on a more conservative approach; we considered that 100 mg/kg bw/day should be taken as the LOAEL of this 90-day repeated toxicity study, while no NOAEL could be set.

Toxicity to reproduction: screening for reproductive/developmental toxicity An experimental study performed, which observed OECD Guideline 421 and GLP compliance, was found in the BPS dossier for registration according to the REACH Regulation. This study was conducted with Crj: CD(SD) rats and presented a deviation from the standard protocol because the high dose group only included seven pregnant females, which diminished the study's reliability. The total exposure in this study was 45 days in males (including a 14-day pre-mating period) and 40–46 days in females (from mating to the gestational period and parturition to day 3 of lactation). Animals without delivery were administered until day 25 after confirming copulation. The study results are summarised in Table 16.

Severe body weight gain reduction, together with alterations in the relative weight of liver, pituitary gland, and the absolute weight of seminal vesicles and histopathological alterations in caecum and liver were reported at the highest dose. At this same dose, reproductive performance, the implantation index and the total number of offspring at birth were also statistically reduced, as observed in the controls. The same gross pathology and histopathology were described for the mid dose, but with lower incidences than for the top dose.

Table 14 Exposure figures taken for risk assessment in this paper. It was considered a corporal default weight of 60 kg for estimating µg/kg bw/day

Procedure	General population		Workers	
	µg/day	µg/kg bw/day	µg/day	µg/kg bw/day
Systemic exposure (urine excretion)	0.93[a]	0.016	3.4[b]	0.057
Dermal exposure (BPS in contact with skin)	0.77[c]	0.013	57.5[c]	0.96

[a]Liao et al. (2012b)

[b]Ndaw et al. (2018)

[c]Liao et al. (2012a)

Table 15 Summary of the 90-days repeated dose toxicity study with BPS. Data taken from BPS dossier for registration under REACH Regulation. Assay performed observing OECD Guideline 408 and with Good Laboratory Practice (GLP) compliance. Animals (10 Wistar rats/sex/dose) were dosed by gavage

	100 mg/kg bw/day	300 mg/kg bw/day	1000 mg/kg bw/day (days 0-70) 600 mg/kg bw/day (days 71-90)
Clinical signs and mortality	No mortalities Short salivation immediately after dosing in 6/10 males and 4/10 females	No mortalities. Soft and discoloured (light brown) faces were observed in all animals (starting on day 84-85) Short salivation immediately after dosing in 9/10 males and 10/10 females	No mortalities. Soft and discoloured (light brown) faces were observed in all animals (starting on day 15) Short salivation immediately after dosing in 10/10 males and 9/10 females
Body weight	No treatment related changes	Males = -10% by day 84 No treatment related changes in females	Males = -20% by day 70 No treatment related changes in females
Body weight gain	No treatment related changes	Males = -15% from day 0 to 84	Males = -33% from day 0 to 63 No treatment related changes in

Table 15 (continued)

<table>
<tr><td></td><td></td><td>No treatment related changes in females</td><td>females</td></tr>
<tr><td>Food consumption</td><td>No treatment related changes</td><td>No treatment related changes</td><td>Males reduced from study day 7 to 70 (maximum of -18% on day 63). After the reduction of the dose within the usual range.</td></tr>
<tr><td>Haematology</td><td>No treatment related changes</td><td>No treatment related changes</td><td>
<table>
<tr><th></th><th>Males</th><th>Females</th></tr>
<tr><td>Red blood cell</td><td>-7.2%</td><td>-5.6%</td></tr>
<tr><td>Haemoglobin</td><td>-4.4%</td><td>-9.1%</td></tr>
<tr><td>Haematocrit</td><td>-</td><td>-6.8%</td></tr>
<tr><td>Mean corpuscular volume</td><td>+5.5%</td><td>-</td></tr>
<tr><td>Relative reticulocyte counts</td><td>+21%</td><td>-</td></tr>
</table>
</td></tr>
<tr><td>Clinical chemistry</td><td>No treatment related changes</td><td><u>Males</u>
Cholesterol = -34%</td><td><u>Males</u>
Cholesterol = -44.3%
Creatinine = +11%
Bilirubin = -22%

<u>Females</u>
Alkaline phosphatase = + 35%</td></tr>
<tr><td>Organ weights</td><td colspan="3">
<table>
<tr><th></th><th colspan="3">Males</th><th colspan="3">Females</th></tr>
<tr><td>Dose (mg/kg)</td><td>100</td><td>300</td><td>600 (1000)</td><td>100</td><td>300</td><td>600 (1000)</td></tr>
<tr><td>Adrenals</td><td>96</td><td>109</td><td>177**</td><td>101</td><td>121*</td><td>131**</td></tr>
<tr><td>Brain</td><td>100</td><td>103</td><td>120**</td><td colspan="3">No effect</td></tr>
<tr><td>Epididymes</td><td>101</td><td>103</td><td>112**</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Heart</td><td>98</td><td>101</td><td>109*</td><td>101</td><td>107</td><td>109*</td></tr>
</table>
</td><td></td></tr>
</table>

Table 15 (continued)

Kidneys	110*	122**	125**	112	113*	118**
Liver	No effect			109	120**	149**
Spleen	97	94	119**	105	113**	111*
Thyroid	89	104	116*	92	105	121**
Thymus	No effect			100	87	79*
Testes	104	102	116*	-	-	-
Ovaries	-	-	-	102	109	130*
Uterus	-	-	-	124	185	95

Histopathology

	Males				Females			
Dose (mg/kg)	0	100	300	600 (1000)	0	100	300	600 (1000)
Cecum dilation	0	0	0	10	0	0	1	10
Spleen	0	0	0	8	2	1	4	10
Mammary gland	0	0	0	0	0	0	7	10
Liver, hypertrophy	0	0	0	0	0	2	5	10
Liver, foci	0	0	0	0	1	1	1	6
Uterus	-	-	-	-	0	2	2	5

The NOAEL for parental toxicity was set at 10 mg/kg bw/day based on the gross pathology and histopathology reported at 60 mg/kg bw/day (the dose considered to be the LOAEL). The NOAEL for reproductive toxicity was 60 mg/kg bw/day based on alterations in oestrous cycles, the fertility index, the implantation index and the number of live offspring reported for 300 mg/kg bw/day (the dose considered to be the LOAEL).

Developmental toxicity One prenatal developmental toxicity study, performed by observing OECD Guideline 414 and GLP compliance, was found in the BPS dossier for registration according to the REACH Regulation. Twenty-five pregnant Wistar rats per dose were treated by gavage with 30, 100 or 300 mg BPS/kg bw/day from gestation day (GD) 6 through to GD 19.

Reversible salivation was found in 7/25 females at the highest dose. This top dose caused reductions in body weight gain from gestation day 8 to 10 (− 29%) and from gestation day 6 to 19 (− 8%). The corrected body weight of the animals treated with 300 mg BPS/kg bw/day was 10% lower than the corrected body weight of the control animals. This difference was not statistically significant. No signs of maternal toxicity were reported for the animals dosed with 30 and 100 mg BPS/kg bw/day.

Neither significant differences in the mean placental weight among the various groups, nor incidences of external variations and soft tissue malformations, were observed. The

Table 16 Summary of the study for screening for reproductive/developmental toxicity with BPS. Data taken from BPS dossier for registration under REACH Regulation. Assay performed observing OECD Guideline 421 (with some deviations that do not compromise the results) and with GLP compliance. Animals (12 Crj: CD(SD) rats/sex/dose) were dosed by gavage

	10 mg/kg bw/day	60 mg/kg bw/day	300 mg/kg bw/day
P generation			
Clinical signs	No treatment-related changes	No treatment-related changes	Reversible salivation in 7 males and 1 female
Body weight gain	No treatment-related changes	No treatment-related changes	Severe reductions up to day 35
Organ weights	No treatment-related changes	No treatment-related changes	Relative weights of liver (12%) and pituitary gland (19%) were increased and absolute weight of seminal vesicles (14%) were decreased in males
Gross pathology	No treatment-related changes	Distension of the caecum in one male and female	Distension of the caecum and in all males and 4 females
Histopathology	No treatment-related changes	*Caecum* Mucosal epithelium diffusion in 1 females	*Caecum* Mucosal epithelium diffusion in caecum in 11 males and 4 females Cell necrosis of absorptive epithelium in 5 males and 1 females *Liver* Hypertrophy of centrolobular hepatocytes 5 males and 3 females
Reproductive performance	No treatment-related changes	No treatment-related changes	5/10 females with extended oestrus cycle [5.57 ± 1.81 days vs 4.08 ± 0.21 on controls ($p < 0.01$)] Fertility index 58.3% (91.7% in controls)
Implantation index	No treatment-related changes	No treatment-related changes	$64.89 \pm 26.57\%$ vs 95.80 ± 5.75 in controls ($p < 0.01$)
F1 generation			
Total number of offspring at birth	No treatment-related changes	No treatment-related changes	4.1 ± 1.7 vs 6.6 ± 1.3 in controls ($p < 0.05$)

incidences in soft tissue variations, external malformations, skeletal malformations, skeletal variations and foetuses with skeletal malformation/litter did not statistically differ from the concurrent control or fell within the historical control data or no dose response was observed. Therefore, these effects were not considered dose-related.

The maternal NOAEL was set at 100 mg/kg bw/day based on the severe alterations in body weight gain reported at 300 mg/kg bw/day (dose considered to be the LOAEL for maternal toxicity). No dose-related teratogenicity was detected in this study. Therefore, the NOAEL for developmental toxicity was the highest tested dose (300 mg BPS/kg bw/day) and no LOAEL could be derived.

Setting critical end-points for assessment The repeated dose toxicity studies caused severe reductions in body weight and bodyweight gain, alterations in the weight of several organs, and histopathological alterations in caecum, spleen, mammary gland, liver, and uterus and fertility impairments. No teratogenicity was reported for BPS. Table 17 summarises the risk assessment end-points.

Given the different duration of the studies and the various types of end-points (one NOAEL and one LOAEL), we derived DNELs for both to later consider the lowest one for the risk characterisation.

DNEL derivation RAC used a procedure for transforming animal doses into the HED. This approach is more questionable for BPS because there was much less toxicokinetic available information than for BPA. Indeed the basic toxicokinetics in vivo study is not presented in the BPS dossier for registration according to the REACH Regulation because it is "ongoing" (checked in December 2018).

Nevertheless, we decided to derive two DNELs (with and without HED transformation) to be as conservative as possible. For such transformations, we used the same factors employed for BPA (0.068 for the oral DNEL and 0.00074 for the dermal DNEL) by EFSA (2015) and RAC (2015). Other assessment factors were considered according to the ECHA procedures for deriving DNELs for threshold end-points (ECHA 2012).

Table 17 End-points for risk assessment of BPS according to data provided in Tables 15 and 16

Study	Critical effect	mg BPS/kg bw/day	
		NOAEL	LOAEL
Sub-chronic study in rats (90-days exposure)	Focal squamous cell metaplasia in uterus	–	100
Reproductive/developmental toxicity (45-days exposure)	Female fertility	10	60
Developmental toxicity (maternal effects) (14-days exposure)	Maternal toxicity	10	60
Developmental toxicity (teratogenicity) (14-days exposure)	Teratogenicity	300	–

Oral systemic DNEL The DNEL derivation for the critical end-point of the 90-day repeated dose toxicity study is summarised in Table 18. We considered an allometric factor of 4, an interspecies remaining differences factor of 2.5, an intra-species difference of 5 (for the workers) or 10 (for the general population), adjustment sub-chronic to chronic of 2, a LOAEL to NOAEL extrapolation of 3 and an additional factor due to poor quality (only two studies by a single route) of the database of 10 (RAC used a factor of 6 to cover BPA assessment uncertainties but we considered that the uncertainties for BPS were larger than for BPA). We considered 100% oral absorption for the transformation of oral DNEL into systemic DNEL, as did Karrer et al. (2018).

The DNEL derivation for the critical end-point of the reproductive/developmental toxicity study is summarised in Table 19. We considered similar assessment factors to those discussed above but took into account that the critical end-point was a NOAEL. Therefore, no additional assessment factor was needed, exposure was 45 days and we assigned this duration to a subacute study to consider an assessment factor of 6 to extrapolate from subacute exposure to chronic exposure.

In both cases, the transformation of animal doses into the HED yielded lower DNELs than when using an allometric factor for derivation. The DNEL derived from the reproductive/developmental toxicity study in rats was one order of magnitude lower than that derived from the 90-day oral repeated dose toxicity study in rats. Therefore, to characterise the worst possible scenario, we made our risk characterisation of systemic DNELs and obtained 0.91 and 0.45 µg/kg bw/day for the workers and the general population, respectively (Table 19). These DNELs were around one order of magnitude lower than the oral DNELs derived by RAC (2015) for BPA (Table 6), which suggests that our assessment might be conservative.

Table 18 Derivation of systemic oral DNEL for BPS from the reproductive/developmental toxicity in rats. The starting end-point was taken from Table 17 and deduced from data presented in Table 15

Starting point: LOAEL = 100 mg/kg bw/day
Critical end-point: focal squamous cell metaplasia in uterus
Key study: 90-days oral repeated toxicity study in rats (BPS dossier for registration under REACH Regulation)

	With HED adjustment		Without HED adjustment	
	Workers	General population	Workers	General population
Human equivalent adjustment dose factor	0.068	0.068	1	1
Human equivalent dose (mg/kg bw/day)	6.8	6.8	100	100
Assessment factors				
Interspecies allometric factor	1	1	4	4
Interspecies remaining factors	2.5	2.5	2.5	2.5
Intra-species factor	5	10	5	10
Adjustment to chronic	2	2	2	2
Additional factor (quality of data base)	10	10	10	10
LOAEL to NOAEL	3	3	3	3
Oral DNEL (mg/kg bw/day)	0.0091	0.0045	0.033	0.017
Oral absorption factor	1	1	1	1
Derived systemic DNEL (mg/kg bw/day)	0.0091	0.0045	0.033	0.017
Derived systemic DNEL (µg/kg bw/day)	**9.1**	**4.5**	**33**	**17**

Bold indicates the staring points and the final derived DNELs

Dermal DNEL The dermal derivation was performed using the same factor as for BPA, while the derivation without transformation into the HED yielded the same DNELs outlined in Tables 18 and 19 (not shown here for simplicity reasons). The dermal DNEL estimation is summarised in Tables 20 and 21. As we did not consider biotransformation factor as RAC (2015) did for BPA, our work is as conservative as can be reasonably assumed.

Following the same conservative approach used for the systemic DNELs, we considered the data derived from the reproductive/developmental toxicity study in rats (respectively 0.0098 and 0.0049 mg/kg bw/day for workers population and general population). These DNELs were around 20-fold lower than the dermal DNELs derived by RAC (2015) for BPA, which once again suggests that our assessment is conservative.

Risk characterisation

The RCR was estimated, as in the case of BPA, to be the ratio between exposure and the DNEL. We estimated RCR for both considered cases: the exposures estimated from urinary excretion versus the derived systemic DNEL, and the exposure estimated from dermal contact versus the derived dermal DNEL (Table 22).

For dermal exposure, the RCR was higher than for both workers and the general population, which suggests that the risk, especially for workers, might not be adequately controlled.

Discussion

RAC (2015) released a scientific opinion which demonstrated that the risk associated with the dermal exposure of cashiers to BPA via thermal paper receipts might not be adequately controlled. Consequently, a restriction in BPA contents in thermal paper will come into force in Europe as of 2020. Here we made a preliminary assessment of the risk associated with the exposure of the general population and workers to BPS via dermal contact with thermal paper receipts. We concluded that, for one of the scenarios that we considered, and as in the case of BPA, once again the situation might not be adequately controlled because exposure was around threefold the DNEL for the general population and around 100-fold for workers.

We based our assessment on publically available information in the scientific literature as we recognised many uncertainties, which we attempted to overcome using an assessment factor. This means that our assessment might be extremely conservative and the situation is probably not as bad as suggested by the data displayed in Table 22.

Table 19 Derivation of systemic oral DNEL for BPS from the reproductive/developmental toxicity study in rats. The starting end-point was taken from Table 17 and deduced from data presented in Table 16

Starting point: NOAEL = 10 mg/kg bw/day
Critical end-point: female fertility
Key study: reproductive/developmental toxicity in rats (BPS dossier for registration under REACH Regulation)

	With HED adjustment		Without HED adjustment	
	Workers	General population	Workers	General population
Human equivalent adjustment dose factor	0.068	0.068	1	1
Human equivalent dose (mg/kg bw/day)	0.68	0.68	10	10
Assessment factors				
Interspecies allometric factor	1	1	4	4
Interspecies remaining factors	2.5	2.5	2.5	2.5
Intra-species factor	5	10	5	10
Adjustment to chronic	6	6	6	6
Additional factor (quality of data base)	10	10	10	10
LOAEL to NOAEL	1	1	1	1
Oral DNEL (mg/kg bw/day)				
Oral absorption factor	1	1	1	1
Derived systemic DNEL (mg/kg bw/day)	0.00091	0.00045	0.0033	0.0017
Derived systemic DNEL (µg/kg bw/day)	**0.91**	**0.45**	**3.3**	**1.7**

Bold indicates the staring points and the final derived DNELs

Table 20 Derivation of systemic oral DNEL for BPS from the reproductive/developmental toxicity in rats. The starting end-point was taken from Table 17 and deduced from data presented in Table 15

Starting point: LOAEL = 100 mg/kg bw/day
Critical end-point: focal squamous cell metaplasia in uterus
Key study: 90-days oral repeated toxicity study in rats (BPS dossier for registration under REACH Regulation)

	Workers	General population
Human equivalent adjustment dose factor	0.00074	0.00074
Human equivalent dose (mg/kg bw/day)	0.074	0.74
Assessment factors		
Interspecies allometric factor	1	1
Interspecies remaining factors	2.5	2.5
Intra-species factor	5	10
Adjustment to chronic	2	2
Additional factor (quality of database)	10	10
LOAEL to NOAEL	3	3
Derived DNEL (mg/kg bw/day)	9.8×10^{-5}	4.9×10^{-5}
Derived systemic DNEL (µg/kg bw/day)	**0.098**	**0.049**

Bold indicates the staring points and the final derived DNELs

Table 21 Derivation of systemic oral DNEL for BPS from the reproductive/developmental toxicity study in rats. The starting end-point was taken from Table 17 and deduced from data presented in Table 16

Starting point: NOAEL = 10 mg/kg bw/day
Critical end-point: female fertility
Key study: reproductive/developmental toxicity in rats (BPS dossier for registration under REACH Regulation)

	Workers	General population
Human equivalent adjustment dose factor	0.00074	0.00074
Human equivalent dose (mg/kg bw/day)	0.074	0.074
Assessment factors		
Interspecies allometric factor	1	1
Interspecies remaining factors	2.5	2.5
Intra-species factor	5	10
Adjustment to chronic	6	6
Additional factor (quality of data base)	10	10
LOAEL to NOAEL	1	1
Derived DNEL (mg/kg bw/day)	9.8×10^{-6}	4.9×10^{-6}
Derived systemic DNEL (µg/kg bw/day)	**0.0098**	**0.0049**

Bold indicates the staring points and the final derived DNELs

Uncertainties associated with exposure assessment

We contemplated two well-defined exposure scenarios. One was based on an exposure assessment based on urine-excreted BPS, while the other one was based on an exposure assessment by estimating the BPS transfer rate between thermal paper and skin. We considered that the first scenario was much more reliable as it suggested that the risk could be adequately controlled. We based our reliability in this scenario on the fact that urine-excreted BPS was necessarily absorbed and could theoretically reach target organs. This assessment could underestimate exposure by not considering the bioaccumulation of this substance. However, such bioaccumulation was not expected given the basis of both the substance's physical properties and the toxicokinetic results obtained with humans (Oh et al. 2018). Moreover, the potential bioaccumulation, if any, would probably not be able to increase exposure by a factor of 17, which is what will be needed to reach a systemic DNEL for the workers.

The exposure scenario characterised based on the transfer of BPS from the matrix to skin has, to our understanding, several great uncertainties as: (1) the percentage of dermal absorption used in the literature (27%) is considerably higher than the dermal absorption rate found in the BPS dossier for registration according to the REACH Regulation (9%); (2) dermal absorption rates are not the best way to estimate

Table 22 Risk characterisation for dermal exposure to BPS in thermal papers. RCR was estimated as the ratio between exposure and DNEL. Both exposures and DNEL were expressed in µg BPS/kg bw/day. Exposures were taken from Table 14. DNELs were taken from Tables 19 and 21

	General population			Workers		
	Exposure	DNEL	RCR	Exposure	DNEL	RCR
Systemic exposure (urinary excretion)	0.016	0.45	0.036	0.057	0.91	0.06
Dermal exposure	0.013	0.0049	**2.6**	0.96	0.0098	**98**

Bold indicates the staring points and the final derived DNELs

dermal absorption because it assumes that transfer is constant with time and independent of the amount of substance that comes into contact with skin, which is not completely true; (3) the paper-skin transfer rate for BPS was unknown and the figure for BPA was used as a surrogate, which could also introduce severe uncertainty because BPS is presumably much more polar than BPA and, therefore, BPS would cross membrane barriers by diffusion at much lower rates than BPA.

The uncertainties-associated database

BPA is the most widely studied bisphenol and BPS has attracted interest only in recent years because several restrictions on the use of BPA have been imposed in regulations in developed countries. However, many reports warn that BPA and BPS might exhibit a comparable endocrine disruption potential. For example, it has been demonstrated that BPS has similar anti-androgenic effects to those of BPA (Eladak et al. 2015), and that BPS has similar toxic and estrogenic effects to BPA insofar as inducing developmental deformities (cardiac oedema, spinal malformation and craniofacial deformities) in fish larvae (Moreman et al. 2017). A review has also pointed out that BPS is as hormonally active as BPA (Rochester and Bolden 2015). This suggested that we should include an additional larger assessment factor than the assessment factor used by RAC for BPA assessments, which could lead to a lower DNEL than that needed.

Moreover, the use of the HED still cannot be as appropriate as BPA because lack of toxicokinetic information for BPS brings about additional uncertainties in transformation as we assumed that BPS would display similar toxicokinetic behaviour to BPA in both humans and rats, which has not yet been demonstrated.

The inappropriateness of the transformation of animal dose into HEDs can be particularly notable in the dermal DNEL because it is well-known that dermal absorption is markedly influenced by the polarity of the substance, and that the solubility of BPS in water is 3.7-fold higher than the solubility of BPA, while the log Kow for BPA is 2.8-fold higher than it is for BPS (BPA and BPS dossiers for registration according to the REACH Regulation). These data suggest a very different polarity. In our assessment, we considered that both behave similarly way in dermal terms, which might be the largest uncertainty introduced into calculations.

Conclusions

We created two different BPS dermal exposure scenarios: the risk of that considered more realistic seemed to be adequately controlled, while the worse scenario implied greater uncertainties, which suggests a very worrying situation. Moreover, it should be assumed that the situation might presumably get worse with the European Union restriction fully operative if the reduction in BPA contents causes an increment in the BPS in thermal paper receipts.

This work highlights that more studies on BPS are urgently needed, specially related to toxicokinetics but also related to test the substance in a second species and in a 2-generation reproductive toxicity study, to properly assess the risk associated to dermal exposure via thermal paper.

This work also warns that it might be dangerous to ban the use of certain substances when alternatives might not be safer than banned substances. However, the RAC scientific opinion (2015) did not propose banning BPA in thermal paper but suggested the need to reduce it. This might be a good option as the risk associated with BPS is still not well assessed and controlled, as we reflect in this paper.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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