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Lifetime dietary exposure to bisphenol A in the general population and during pregnancy: Foetal exposure and health risk assessment

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Abstract

Bisphenol A is a well-known chemical substance triggering reprotoxic and endocrine disruptor effects. Pregnancy is considered as a critical period of exposure to BPA because of the foetal sensitivity to endocrine disruption. Because of its wide use in food packaging, BPA is found in common foods and in infant formulae.

We used a lifetime approach to simulate dietary exposure trajectories of a French population and to assess the associated health risk. Moreover, a semi-physiological based toxicokinetic model was used to simulate the maternal-foetal exchanges of BPA during pregnancy. Metabolism was taken into account by considering the glucuronidation of BPA by the foetal-placental unit, as well as the reactivation of BPA-glucuronide into BPA in the foetal compartment. From maternal critical daily exposures defined by ANSES based on effects for different endpoints of BPA in the unborn child (*i.e.*

0.083, 0.17, 0.29 and 0.33 µg/kg bw/d, respectively based on effects on mammary gland, brain and behaviour, metabolism and obesity and female reproductive system), resulting concentrations of BPA in the foetal compartment were estimated and health risk was assessed for the sub-population of unborn children.

This work leads to the conclusion that while a health risk due to dietary exposures of the general population can be excluded, this is not the case for the sub-population of pregnant women, in view of the levels of foetal exposure to BPA.

Keywords

Bisphenol A, modelling, health risk assessment, foetal exposure

Abbreviations

ANSES: French Agency for Food, Environmental and Occupational Health & Safety, **BPA**: bisphenol A, **BPA-G**: bisphenol A glucuronide, **ECHA:** European Chemicals Agency, **EFSA:** European Food Safety Authority, **iTDS**: French infant Total Diet Study, **kg bw**: kilogram of body weight, **PI95%**: 95% prediction interval, **t-TDI**: temporary Tolerable Dietary Intake

Introduction

Bisphenol A (BPA, CAS Registry Number 80-05-7) is a substance widely used in industry for the production of polycarbonate or epoxy resin. It is largely used in food contact materials and is therefore present in food (EFSA 2015). Due to its varied uses, the general population is also exposed to BPA by other routes, such as inhalation of indoor and outdoor air or dermal contact with thermal papers (FAO/WHO 2010).

BPA is classified as a category 1B reprotoxic substance (*i.e.* presumed to be toxic for human reproduction) by the European Chemicals Agency and the European Commission (directive 94/33/EC). Moreover, BPA is considered as a substance of very high concern under REACH regulation because of its toxicity for reproduction and its endocrine disrupting properties (ECHA 2020).

Because of its toxicity and the frequent presence of BPA in food, the evaluation of lifetime dietary exposures of the population, and especially exposures during pregnancy, is a necessary step to extrapolate effects demonstrated *in vitro* or *in vivo* in animal models to human. In average, women of childbearing age have dietary exposures to BPA around 41 ng/kg bw/d in Europe (EFSA 2015).

Since there are no threshold values for foetal exposure in the literature, and few foetal biomonitoring data, we propose here to simulate lifetime exposure trajectories as well as maternal-foetal exchanges during pregnancy to predict the health risk related to dietary exposure to BPA for the general population and also for the sub-population of unborn children. Our methodology is based on different models, predicting dietary exposures from socioeconomic profiles (Pruvost-Couvreur et al. 2020) and maternal-foetal internal exposures from dietary exposures during the third trimester of pregnancy (Gauderat et al. 2017). This period of pregnancy is of particular interest because of a maximum placental surface area and a thinner placental barrier, maximizing the foetal exposure (Snoeck 1962).

Materials and methods

Simulation of lifetime exposure trajectories

A previously developed methodology was used to simulate lifetime dietary exposure trajectories. This methodology is based on the relationship between dietary exposures and socioeconomic profiles, studied by general linear regressions (Pruvost-Couvreur et al. 2020). Briefly, a virtual population representative of the French general population, for which the socioeconomic characteristics are known throughout life, is simulated. Considered individual characteristics were

age, gender, body mass index, region of residence, household income, education level and marital status. Then, by time steps of one week, dietary exposures are predicted, according to the profile of the studied individual, and this from the perinatal period to 80 years old. In the present article we simulated a population of 10 000 individuals. Historical evolution of BPA dietary exposures due to changes in the production and consumers' habits consumption could not be taken into account in this work because of the heterogeneity of the data in the literature on this subject.

From birth to the age of 3, BPA exposure data originated from the French infant total diet study (iTDS), which focused on dietary exposures of non-breast-fed children under the age of 3 to more than 400 chemical substances (ANSES 2016). From the age of 3 years, the exposure data were those of Bemrah et al. (2014); they were produced as part of the characterization of the dietary exposure of the French population to BPA, from different consumption surveys and food samplings. All dietary exposure values include exposure to BPA via food and beverages.

Heath risk assessment from exposure trajectories

Once exposure trajectories were simulated, the health risks associated with the presence of BPA in food were assessed by comparing the simulated exposure trajectories with five reference values, one for the general population (EFSA 2015) and four for the specific population of pregnant women, given the effects on the health of the unborn child (ANSES 2013):

- The temporary tolerable dietary intake (t-TDI) of 4 µg/kg bw/d set by EFSA (2015) for the general population, based on effect of BPA on the kidney (Tyl et al. 2002; Tyl et al. 2008);
- The critical maternal exposure of 0.083 µg/kg bw/d set by ANSES (2013) for pregnant women, based on the effects of BPA on the mammary gland morphology of the unborn child identified by Moral et al. (2008);
- The critical maternal exposure of 0.17 µg/kg bw/d set by ANSES (2013) for pregnant women, based on the effects of BPA on brain and behaviour of the unborn child characterised by Xu et al. (2010);
- The critical maternal exposure of 0.29 µg/kg bw/d set by ANSES (2013) for pregnant women, based on the effects of BPA on metabolism and obesity of the unborn child identified by Miyawaki et al. (2007);
- The critical maternal exposure of 0.33 µg/kg bw/d set by ANSES (2013) for pregnant women, based on the effects of BPA on the female reproductive system of the unborn child according to the results of Rubin et al. (2001).

In this work, we used the expression “external” risk assessment for health risk estimated from dietary exposures.

Simulation of maternal-foetal plasma concentrations during pregnancy

To estimate foetal exposures to BPA, and to assess the associated adverse health effects in unborn children, foetal exposures were modelled during the third trimester of pregnancy using a semi-physiological model (Figure 1 in Gauderat et al. 2017). Concerning the placenta, the exchange surface is maximal and the thickness of the barrier is minimal during the third trimester of pregnancy, maximizing foetal exposures to BPA (Snoeck 1962). In addition, Veiga-Lopez et al. (2015) observed higher concentrations of BPA in maternal blood during later stages of pregnancy compared with earlier stages. Focusing on the third trimester therefore appears protective. The model, developed from a physiologically-based toxicokinetic model in sheep, was humanized and validated using a data set from monkey experiments (Gauderat et al. 2017). This model takes into account the specific kinetics of BPA and its glucuronidation form in the foetal compartment.

In this model, the maternal compartment includes a central and a peripheral compartment for BPA and BPA-glucuronide (BPA-G), and the foetal compartment includes a central compartment for BPA and BPA-G and a peripheral compartment only for BPA-G. Maternal-foetal exchanges are represented by flows between compartments.

The maternal dietary exposure was divided in 3 doses per day simulating the different meals. Moreover, an equation was added to the model to consider the mother's weight gain during pregnancy, as recommended by the National Research Council (NRC 2010). In order to validate the model by comparing the simulated values with urinary concentration data from the literature, maternal urinary excretion of BPA was simulated.

Mother exposure trajectories during the third trimester of pregnancy were randomly selected between 18 and 45 years old, from the previously simulated trajectories for women, according to the distribution of fecundity in France (INSEE 2020). This represented 4 941 exposure trajectories of 13 weeks.

Using the model, 4 941 trajectories of BPA and BPA-G plasma concentrations in the maternal and foetal compartments were generated, by time steps of one hour, during 13 weeks.

Heath risk assessment from plasma concentration trajectories

To estimate the risk associated with foetal plasma concentrations of BPA and BPA-G, reference plasma concentrations are needed. To estimate these values, the previously selected critical exposures (*i.e.* 0.083, 0.17, 0.29 and 0.33 µg/kg bw/d) were applied as daily exposures to a female of childbearing age with a mean body weight. The maximum plasma concentrations of BPA and BPA-G estimated during the third trimester of pregnancy in the foetal compartment were considered as reference concentrations. In order to adopt a conservative approach, the 5th percentile of these peak plasma concentrations was considered as the value used in the comparisons with estimated plasma concentrations.

In this work, "internal" risk assessment relates to the health risk estimated from BPA plasma concentrations.

Results and discussion

Dietary exposure trajectories and associated health risk

The correlation between dietary exposures to BPA and socioeconomic characteristics highlighted that individual exposure depends on the profile defined by age, gender, region of residence, education level, household income, marital status and body mass index, according to general linear regressions (p-value < 0.05). For example, exposures increase with age from birth to 3 years old, decrease from 3 years old to adulthood and then remain constant. Furthermore, exposures of men are, on average, higher than those of women, and households in which the head of the household has a high level of education or a high income have higher dietary exposures to BPA than the rest of the population.

The differences of dietary exposures can be partly explained by different consumption behaviours. For example, on average, men consume more canned foods than women (ANSES 2014). Because canned foods are major contributors to dietary exposure to BPA, that may explain differences of exposures between genders (ANSES 2014).

Table 1 summarises simulated lifetime exposure trajectories as well as exceedances of different critical values selected to assess the health risk related to the dietary exposure to BPA. Dietary exposures to BPA in European populations were in the same order of magnitude and were estimated on average to 81 µg/kg bw/d for children, 55 µg/kg bw/d for adolescents and 42 µg/kg bw/d for adults between 45 and 65 years old (EFSA 2015).

Table 1: Durations of exceedance of the critical exposures throughout life in the general population and the women of childbearing age

	Critical exposures (weeks)	**Mean**	**Min**	**P5**	**P25**	**P50**	**P75**	**P95**	**Max**
General population (0-80 years old)	**4 µg/kg bw/d**	0	0	0	0	0	0	0	0
	0.33 µg/kg bw/d	0.3	0	0	0	0	0	1	11
	0.29 µg/kg bw/d	0.6	0	0	0	0	1	3	17
	0.17 µg/kg bw/d	8.3	0	0	3	6	11	23	100
	0.083 µg/kg bw/d	117.8	3	31	71	109	155	232	468

The duration of exceedance was the number of weeks during which simulated trajectories of weekly exposures exceeded the reference value. This duration was computed for each studied virtual individual before being summarised in the table.

Lifetime exposure trajectories never exceeded the t-TDI of 4 µg/kg bw/d set by EFSA for the general population. In light of these results, a health risk for French consumers related to the ingestion of BPA via the diet could therefore be excluded. Focusing on the sensitive sub-population of women of childbearing age, it appeared that dietary exposures of women between 18 and 45 years old regularly exceeded the critical exposure values set by ANSES for pregnant women. In view of these values, a risk for the health of potential unborn children cannot be excluded.

In order to refine the health risk assessment of unborn children, foetal exposures to BPA were simulated during the last trimester of pregnancy using the semi-physiological model developed by Gauderat et al. (2017), briefly described in the materials and methods section. Predicted maternal and foetal plasma concentrations are presented in Table 2.

An example of BPA and BPA-G plasma concentration profiles during pregnancy is given on Figure 1. BPA-G concentrations were higher than those of unconjugated BPA, both in the maternal and foetal compartments. Moreover, on average, both free and conjugated BPA plasma concentrations were higher in the foetal compartment than those in the maternal plasma. It can also be noted that BPA plasma concentrations in maternal and foetal compartments, as well as BPA-G plasma concentrations in the maternal compartment significantly fluctuated over a 24-hour period (a factor of 100 can be observed between the estimated maximum and minimum values) because of the short elimination half-life of BPA. Thus, BPA maternal plasma concentrations increase immediately after a

food intake and decrease in the next hour. On the other hand, BPA-G plasma concentrations showed little fluctuations and accumulated in the foetal compartment; on average, BPA-G foetal concentrations were 3 times higher at the end of the 39th week of pregnancy than those at the beginning of the 28th week. Due to its relative stability, BPA-G may be a better marker of foetal exposure than fluctuating unconjugated BPA and values of foetal BPA-G plasma concentrations were the ones to be considered to evaluate foetal exposure.

Unfortunately, data on BPA concentrations in the foetal compartment are relatively scarce in the literature. Two studies measuring BPA-G concentrations in cord blood during pregnancy were identified (Gerona et al. 2013; Liu et al. 2017). These two studies reported high left censoring rates, making them difficult to interpret. However, it can be noted that the geometric mean of simulated BPA-G concentrations in the foetal compartment (*i.e.* 0.058 ng/mL) was of the same order of magnitude than that estimated in the study of Liu et al. (2017) (*i.e.* 0.04 ng/mL) and lower by a factor of 2 than the geometric mean computed in the study of Gerona et al. (2013) (*i.e.* 0.14 ng/mL). These results partially validate the relevance of the model we used.

The mother part of the model could be validated by comparing simulated excretion of BPA-G and urinary concentrations found in the literature. To this end, an average diuresis of 1.2 L/d was considered in the model (Valentin 2002). Moreover, because unconjugated BPA concentrations are negligible compared to BPA-G concentrations in maternal urine (Foster et al. 2019), BPA-G and total BPA urinary concentrations could be compared. Under these assumptions, the average simulated maternal urinary excretion of BPA of 1.5 µg/L (95% prediction interval of [0.7; 2.7]) found in our model was similar to the geometric mean of 1.78 µg/L (PI95% [1.62 ; 1.94]) provided by Covaci et al. (2015).

Table 2: Description of simulated BPA and BPA-G plasma concentrations (ng/L) in maternal and foetal compartments during the third trimester of pregnancy

BPA or metabolite	Compartment	Minimum plasma concentration	Arithmetic mean plasma concentration	Maximum plasma concentration
BPA free	**Maternal**	4.38×10^{-3} [1.53×10^{-3} ; 8.22×10^{-3}]	5.70×10^{-2} [2.93×10^{-2} ; 9.33×10^{-2}]	0.483 [0.208 ; 1.00]
	Foetal	5.19×10^{-3} [1.05×10^{-3} ; 1.58×10^{-2}]	5.56×10^{-2} [2.26×10^{-2} ; 1.13×10^{-1}]	0.266 [0.093 ; 0.619]
BPA-G	**Maternal**	0.241 [0.086 ; 0.501]	7.31 [3.71 ; 12.0]	104 [44.4 ; 215]
	Foetal	1.16 [0.244 ; 3.31]	53.3 [23.3 ; 99.4]	99.6 [39.0 ; 209]

Values given between brackets correspond to 95% prediction intervals.

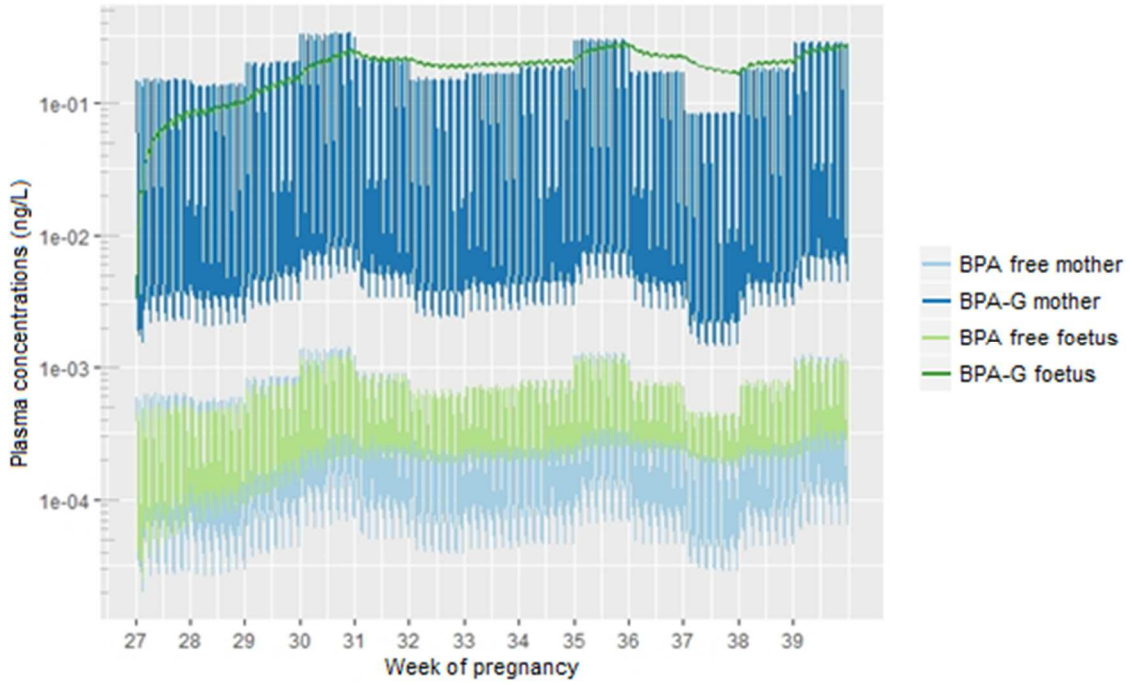

Figure 1: Example of simulated BPA and BPA-G plasma concentrations in maternal and foetal compartment during the third trimester of pregnancy

As there are no established critical values for foetal BPA and BPA-G exposure in the literature, the critical values set by ANSES for maternal exposures were used to determine the associated plasma concentrations in the foetal compartment. Considering maternal exposures of 0.33, 0.29, 0.17 and 0.083 µg/kg bw/d, the maximum BPA plasma concentrations in the foetal compartment were estimated to be, on average, 1.05, 0.91, 0.54 and 0.26 ng/L, respectively. To be protective for the majority of the population, the 5th percentiles of the maximum foetal concentrations were selected as reference plasma concentrations. The estimated reference values of BPA and BPA-G concentrations are presented in Table 3.

Table 3: Estimated foetal reference BPA and BPA-G plasma concentrations and corresponding percentages of fetus exceeding the reference concentrations

Critical maternal exposure *Health effect*	**Estimated foetal reference BPA plasma concentration[a] (ng/L)**	**Percentage of foetuses exceeding the estimated foetal reference BPA concentration[b]**	**Estimated foetal reference BPA-G plasma concentration[a] (ng/L)**	**Percentage of foetuses exceeding the estimated foetal reference BPA-G concentration[b]**
0.33 µg/kg bw/d	0.62	2.5%	341	0.1%

Female reproductive system		[2.1 ; 2.9]		[0.01 ; 0.2]
0.29 µg/kg bw/d *Metabolism and obesity*	0.54	4.3% [3.7 ; 4.9]	303	0.3% [0.1 ; 0.5]
0.17 µg/kg bw/d *Brain and behaviour*	0.32	26.2% [25.0 ; 27.4]	176	6.0% [5.3 ; 6.7]
0.083 µg/kg bw/d *Mammary gland*	0.16	78.6% [77.5 ; 79.7]	86.6	54.5% [53.1 ; 55.9]

.[a]: 5th percentiles of the maximum foetal concentrations

[b]: Values given between brackets correspond to 95% prediction intervals

This internal approach for risk assessment confirmed that a risk for health of unborn children cannot be excluded as, regardless of the critical maternal exposure, a part of simulated foetuses showed BPA and BPA-G plasma concentrations exceeding the corresponding foetal reference concentrations during the third trimester of pregnancy. Indeed, when considering the reference concentration based on the effects of BPA on the architecture of the mammary gland (*i.e.* corresponding to 0.083 µg/kg bw/d for maternal dietary exposure), more than half of the unborn children had excessive BPA and BPA-G body burdens at the end of the pregnancy. *Ex vivo* studies highlighted BPA adverse effects on human foetal testes and mammary gland cells (22.8 µg/L for mammary gland cells and 2.28 µg/L for foetal testes) but with BPA concentrations higher than the reference concentrations estimated here (0.16 ng/L for mammary gland) (Atlas et Dimitrova 2019; Maamar et al. 2015). The presented approach appears therefore protective.

However, it should be noted that the model used in this article only allows the simulation of BPA and BPA-G concentrations in the maternal and foetal compartments during the third trimester of pregnancy. It therefore does not take into account the changes in the architecture of the placental barrier (decrease in placental thickness and increase in placental surface area) or in the foetal liver metabolic capacity during pregnancy. All sensitive periods for the development of the unborn child are therefore not covered. For example, in humans, the anatomical development of the mammary gland begins during the first trimester of pregnancy and continues until the eighth month (Macias and Hinck 2012). The study of foetal exposure to BPA during only the third trimester of pregnancy is therefore not sufficient to cover the period of susceptibility related to the formation and the development of mammary glands. Finally, since the model has been developed using a humanised sheep experimental model, additional data on the human foetal metabolism of BPA might be necessary to fine-tune the model (Corbel et al. 2015).

Conclusion

Dietary exposure to BPA varies according to socioeconomic profile, which highlights the importance of an individual-level lifelong approach to assess health risk.

An external risk assessment approach makes it possible to exclude a health risk for the general population, due to dietary exposure to BPA when considering the t-TDI set by EFSA. However, a risk cannot be excluded for some unborn children, given maternal exposures, according to the critical values set by ANSES. This assessment is confirmed by the internal approach, taking into account the metabolism and maternal-foetal exchanges of BPA during pregnancy, using modelling tools.

Finally, it should be noted that this work can be improved by considering the entire duration of pregnancy with additional data on the foetal metabolism of BPA. In addition, even if diet is the main contributor to the exposure of pregnant women (on average 84%, ANSES 2013), other routes of exposure (inhalation of BPA present in dust or skin contact by thermal paper, for instance) should be considered with a view to refine the assessment of the associated risks.

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