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Risk assessment of food contact materials

Viviana Ramírez[1], Stefan Merkel[2], Thomas Tietz[2] and Ana Rivas[1]

[1]Department of Chemicals and Product Safety, German Federal Institute for Risk Assessment (BfR), Berlin, Germany
[2]Institute of Nutrition and Food Technology "Jose Mataix Verdú", Biomedical Research Centre, University of Granada, Granada, Spain

Abstract

Bisphenol A (BPA) is authorised for use as a chemical compound for the production of plastic food contact materials (FCMs) under Regulation (EU) No 10/2011. But according to requirements of the Regulation (EU) No 2018/213, BPA has been banned in the manufacture of polycarbonate drinking cups or feeding bottles intended for infants and young children. Food has been identified as the main source of human exposure to BPA, followed by dermal absorption, air and dust inhalation, revealing ubiquitous and continuous contact with BPA. Considering that BPA is able to enter the food chain through the migration from food packaging into foodstuffs, assessment of dietary exposure is necessary for accurate estimations and identification of potential exposure from food sources. In 2015, EFSA set a temporary tolerable daily intake (TDI) for BPA of 4 μg/kg body weight (bw) per day and concluded that no health concern from BPA exposure for any age group was to be expected. In 2023, EFSA has re-evaluated BPA safety and the new TDI was reduced by a factor of 20,000 resulting in a TDI of 0.2 ng/kg bw per day. In this case, the CEP Panel concluded that there is a health concern from dietary exposure to BPA. Amongst others, the BfR identified several points of criticism which, in the opinion of the BfR, call into question the risk assessment carried out by EFSA. The BfR derived a TDI of 200 ng/kg bw per day and suggests taking this into account for risk assessment. In the proposed EU-FORA programme, the fellow had the opportunity to gain experience in the exposure assessment and then integrate the data together with the BfR hazard assessment to perform a comprehensive risk assessment. As second objective of the work programme, the fellow was in charge of performing a toxicokinetic analysis in an attempt to correlate external exposure with urinary BPA levels.

Keywords: bisphenol A, chemical exposure assessment, food consumption, food contact materials

Correspondence: eu-fora@efsa.europa.eu

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1. Introduction

Bisphenol A (BPA) is a chemical compound produced in high amounts by the plastic manufacturing industries since 1950 (Akash et al., 2020). BPA is widely used as a basic component for production of polycarbonate plastics and epoxy resins, which are found in a broad range of daily consumer products such as food storage containers, personal care products, kitchenware, toys, thermal paper, dental composites and electronic devices, as well as in inner coating of canned products and jar caps (Hartle et al., 2016; Ramírez et al., 2021). It reveals the ubiquitous and continuous human exposure to BPA.

Food has been identified as the main contributor to BPA exposure of humans, followed by dermal absorption, air and dust inhalation (Rubin et al., 2019). The overall BPA exposure results in quantifiable levels in biological samples including urine, saliva, blood, placenta, breast milk and umbilical cord serum (Berge et al., 2017; Lee et al., 2018). BPA is able to migrate from food contact materials (FCMs) into foodstuffs, and EFSA identified FCM as the main source for BPA entering the food chain (EFSA CEF Panel, 2015).

Evidence from animal and human observational studies has linked BPA exposure to several adverse effects, including reproductive, developmental, cardiovascular, metabolic, immuno, respiratory, renal and hepatic toxicities (Ma et al., 2019). Therefore, BPA is a multitarget compound displaying multiorgan system effects, but the underlying biological mechanisms by which BPA predisposes to disease development remain uncertain in humans. Endocrine disruption has been shown to play an important rule for some of the effects (e.g., reproductive toxicity). BPA analogues (BPS, BPF, BPB, BPE and BPAF) are being utilised as BPA alternatives, but they are structurally similar to BPA and have been found to also show endocrine disruption based on in vivo and/or in vitro studies (Barboza et al., 2020; Heindel et al., 2022). However, there is much less data on these compounds compared to BPA. So far, tolerable daily intake (TDI) has only been established for BPA and there are limited data on exposure to BPA analogues. Future efforts to sample for BPA and its analogues are required to gain a better understanding of current status of overall exposure to bisphenols in all population groups.

In 2015, EFSA set a temporary TDI for BPA of 4 μg/kg bw per day and concluded that no health concern from BPA exposure for any age group was to be expected (EFSA CEF Panel, 2015). Nonetheless, EFSA has recently published a re-evaluation of BPA safety in which the TDI was reduced by a factor of 20,000 resulting in a TDI of 0.2 ng/kg bw per day. No current exposure estimation was performed. However, with respect to the low value, the new TDI is expected to be exceeded by all age groups, and the CEP Panel concluded that there is a health concern from dietary exposure to BPA (EFSA, 2023). Amongst others, the BfR identified several points of criticism which, in the opinion of the BfR, call into question the risk assessment carried out by EFSA (BfR, 2022). Therefore, the BfR derived a TDI of 200 ng/kg bw per day (20-fold lower than the former value of EFSA, 2015) and suggests taking this into account for risk assessment (BfR, 2023).

The main objective of this technical report within the EU-FORA work programme 'Risk Assessment of Food Contact Materials' was the estimation of the daily dietary intake of total BPA for Spanish children, adolescents and adults, and the comparing it to the TDI derived by the BfR in 2023.

Likewise, after oral intake in humans, BPA is rapidly transformed into highly hydrophilic BPA-glucuronide by the liver and excreted mainly via urine (Ramírez et al., 2021). The biological half-life of BPA is less than 6 h, and it is totally eliminated from the body in 24 h. Therefore, total urinary BPA excretion (free or unconjugated plus conjugated BPA) can be used as a biomarker tool to reflect the daily dietary BPA exposure (EFSA CEF Panel, 2015; Peng et al., 2019). As second part of the work programme, the fellow was in charge of performing a toxicokinetic analysis in an attempt to correlate external exposure with BPA levels measured in urine.

2. Data and methodologies

2.1. Description of work programme

As part of the EU-FORA fellowship, this study was focused on acquiring knowledge on how to perform a risk assessment for a compound related to FCM based on existing exposure estimates. The experimental work of this project was developed within Institute of Nutrition and Food Technology (INYTA) of the University of Granada (Spain); and the data processing and statistical treatments were carried out at the Department of Chemicals and Product Safety of the BfR with the support of experts in risk and toxicological assessment.

In this way, the fellow was involved in all the activities and methods required to collect, process, and analyse datasets (Figure 1). In the first place, the fellow participated in the recruitment of children; collection of anthropometric measurements and food surveys; and biological sampling. Later on, the fellow was involved in the design of databases containing the food consumption of each participant, chemical determination of BPA in different food matrices and estimation of individual dietary exposure to BPA from each food consumption questionnaire. Besides exposure assessment, the fellow was engaged to address the agreement between urine levels of BPA and external exposure through the dietary intake.

The activities performed and methods applied during the programme are listed below:

1) Recruitment of children collecting all the necessary information: sociodemographic characteristics, dietary recalls, anthropometric data and questions related to different sources of exposure to BPA at home.
2) Preparation of a database reporting the food consumption and concentrations of BPA in each food needed to perform the exposure assessment in children, adolescents and adults.
3) Urine sampling collection, treatment and determination of BPA.
4) Software tools required to data processing and interpretation.

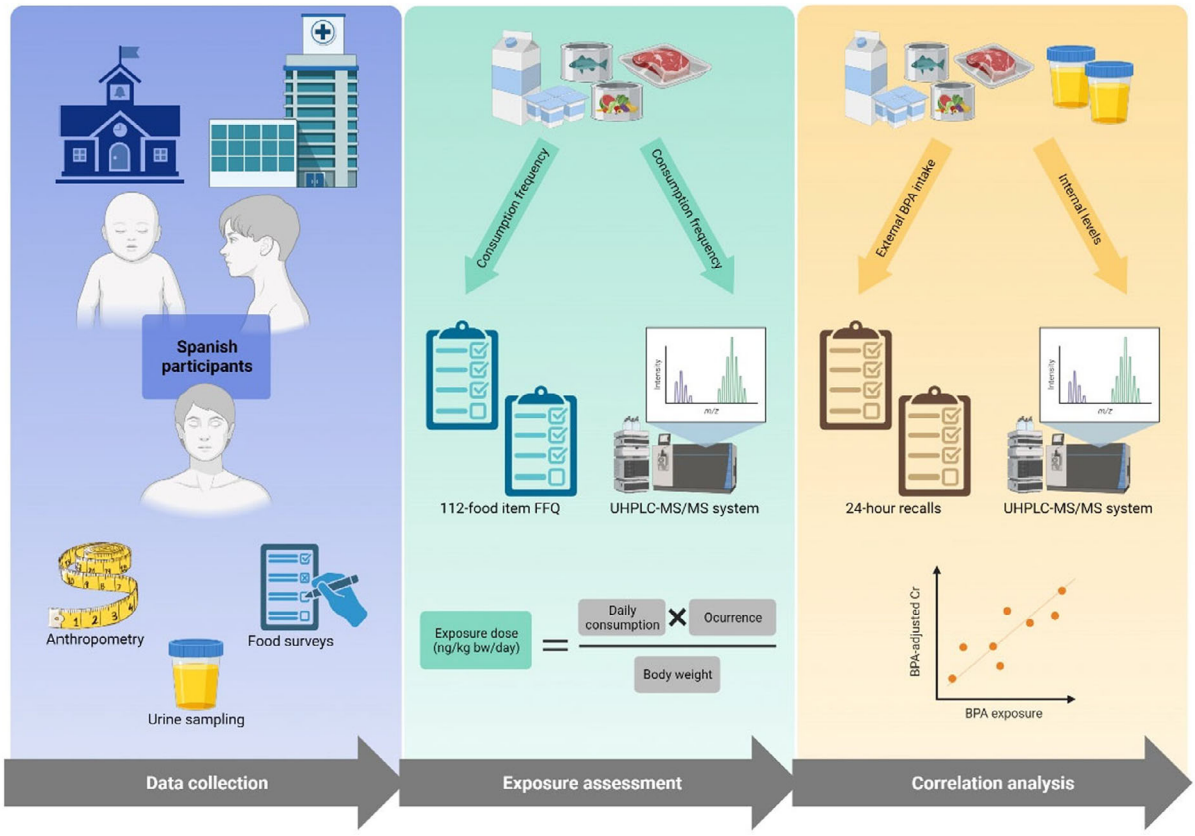

Figure 1: Work programme workflow

2.2. Materials and methods

2.2.1. Study subjects

The study populations included in this report formed part of different previous projects awarded to the research group (GP/EFSA/ENCO/2018/03, PI20/01278 and PE-0250-2019). Children were recruited from different elementary schools and primary care centres in Granada (Spain) between 2020 and 2023. Adolescents and adults from Toledo (Spain) were recruited in 2017–2018. Both projects were approved by Ethics Committee of Provincial Biomedical Research of Granada (CEI).

Then, participants were selected according to the availability of data on weight, height and records on dietary exposure to BPA. The age ranges for children, adolescents and adults were established

following the Spanish Dietary Datasets ENALIA 1 (National Dietary Survey on Children and Adolescents) and ENALIA 2 (National Food Survey on Adults, the Elderly and Pregnant women) that have been included within EFSA Comprehensive European Consumption Database. In this way, approximately 500 participants aged 3 to 39 years were selected for the present exposure assessment. The anthropometric measurements were taken at each follow-up visit using calibrated electronic scales and a wall-mounted stadiometer.

2.2.2. Exposure assessment

Total dietary exposure to BPA (ng/kg of body weight (bw) per day) was calculated on an individual basis, following the next steps: (1) estimation of daily intake of different foods (g/day), (2) determination of mean BPA concentration found in these foods (ng/g of food), (3) calculation of daily BPA intake through different food items (ng/day), and (4) calculation of individual overall daily BPA exposure.

Estimation of daily food intake

A semi-quantitative food frequency questionnaire (FFQ) was completed by each participant thorough a face-to-face interview. The FFQ has shown to be the most convenient dietary assessment tool for estimating exposure to food contaminants in epidemiology (Notario-Barandiaran et al., 2020). Considering geographical, cultural and age differences, the FFQ should be validated for each specific population. In our case, 24-h dietary recalls (24H-R) were previously used as validation method (Robles-Aguilera et al., 2021). The FFQ was designed to ask about 112 food items classified into 13 categories, e.g. dairy products, meat and meat products, vegetables and cereals.

Consumption frequency was categorised as never or hardly ever, once a week, 2–4 times per week, 5–6 times per week, once a day, 2–3 times per day, 4–6 times per day and more than 6 times per day. The type of food packaging (plastic, glass, metal or cardboard) was also recorded. Then, mean daily intake (g/day) was obtained by multiplying the consumption frequency of each item (servings/day) by its corresponding portion size (g/serving). The recommended amounts of each food group are established for Spanish children, adolescents and adults (Monteagudo et al., 2021).

Determination of BPA concentration found in food

Based on FFQ responses, the foods most frequently consumed by the whole population were identified by stepwise regression model. This analysis shown those foods providing more than 95% of daily energy intake; consequently, they were purchased from different national and local supermarkets and their BPA content was chemically analysed via ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS) system, according to the methodology previously described Galvez-Ontiveros et al. (2021). For left-censored data, i.e. samples with concentrations below the LOD or LOQ, the lower bound (LB) and upper bound (UB) approaches were used.

Calculation of daily BPA intake through different food items

BPA content (ng/g) after applying both substitution methods was multiplied by the daily food intake (g/day) for all individual study participants. This resulting daily BPA intake per food item (ng/day) was divided by body weight (kg) obtaining the daily dietary exposure to BPA for all food items (ng/kg bw per day) for each participant. Afterwards, food items were grouped into different food categories according to EFSA Food Classification (Level 1 of exposure hierarchy) (EFSA, 2015) in order to identify the greatest contributor to the total exposure to BPA.

Calculation of overall BPA exposure for all study participants

For all individuals, total exposure dose was estimated by summing up BPA exposure from all food items. Afterwards, statistical analysis was performed for the different age groups in order to compare the outcome between different age groups and to the BfR TDI.

In addition, first steps to include the exposure data in the risk assessment, both by deterministic and probabilistic approaches, were undertaken.

2.2.3. Correlation analysis

The goal of the second part of the work programme was to evaluate the correlation between the dietary exposure and the urinary BPA levels on an individual basis. For this analysis, all children aged 3–13 years with available urinary BPA and creatinine levels, dietary and anthropometric records were

selected. External exposure through dietary intake was estimated from the 24H-R following the same procedure as for the FFQs. On the other hand, a urine sample from each participant's first morning void was collected in a sterile polyethylene container and stored at −80°C until analysis. Total BPA was extracted as previously described by Moscoso-Ruiz et al. (2022). Each sample was analysed in duplicate, with and without glucuronidase pre-treatment in order to receive values for total and free BPA. In the non-enzymatic process, 4 mL of urine, 4 mL of NaCl aqueous solution (10%, w/v) and 100 μL of HCl (6 N) were mixed to pH 2. The dispersive liquid–liquid microextraction was followed. A mixture of 400 μL of acetone plus 600 μL of chloroform was rapidly injected into the urine sample. The low phase was collected after vortexing and centrifugation. This step was repeated four times, and the final organic layer was evaporated to dryness. The solid residue was reconstituted in ultrapure water/MeOH mixture (80:20; v/v), centrifuged and directly injected into the UHPLC–MS/MS system. For the enzymatic treatment, 4 mL of urine was incubated with 25 μL of β-glucuronidase/sulfatase and 100 μL of β-glucuronidase for 24 h at 37°C. Then, the protocol follows as the free form.

Urinary BPA concentrations were adjusted by creatinine content and body weight (μg/g Cr per kg of body weight). Creatinine in urine was determined by Ángel Méndez Soto Clinical Analysis Laboratory (Granada, Spain). After this adjustment, correlations of external exposure to BPA and internal adjusted levels were tested by Spearman's rank correlation.

3. Conclusion

The EU-FORA programme was a great opportunity for the fellow to go deep into chemical exposure assessment of FCM. The fellow acquired theoretical and practical knowledge from expert assessors on FCM safety. This programme offered the fellow the opportunity to learn about the different methods for assessing dietary exposure to food contaminants and how to analyse the datasets by putting her data science related knowledge into practice.

Importantly, the programme has not only allowed the fellow to deal in real exposure data, but has also been a special stay to build connections with outstanding professionals in the field of Food Risk Assessment, leading to promising improvements on the analyses in the near future.

In addition to the work at INYTA and BfR, the fellow attended to the five training modules organised by EFSA, AGES and BfR. The additional scientific activities developed during the fellowship are detailed in Appendix A.

4. Disclaimer

The results of the exposure assessment and correlation study are intended to be published in other scientific journals. To avoid copyright claims, they were described only very briefly in this report.

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Abbreviations

24H-R	24-h dietary recall
AESAN	Spanish Agency for Food Safety and Nutrition
AGES	Agency for Health and Food Safety
BfR	Bundesinstitut für Risikobewertung
BPA	bisphenol A
BPAF	bisphenol AF
BPB	bisphenol B
BPE	bisphenol E
BPF	bisphenol F
BPS	bisphenol S
bw	body weight
CEI	Ethics Committee of Provincial Biomedical Research of Granada
Cr	creatinine
D	detected
ENALIA 1	National Dietary Survey on Children and Adolescents
ENALIA 2	National Food Survey on Adults, the Elderly and Pregnant women
FCM	food contact material
FFQ	food frequency questionnaire
HCl	hydrochloric acid
INYTA	Institute of Nutrition and Food Technology
LB	lower bound
LDR	linear dynamic range
LOD	limit of detection
LOQ	limit of quantification
MeOH	methanol
NaCl	sodium chloride
ND	not detected
TDI	tolerable dietary intake

UB	upper bound
UHPLC–MS/MS	ultra-high-performance liquid chromatography–tandem mass spectrometry system
WHO	World Health Organization

Appendix A – Scientific activities

Event	Title	Contribution	Location	Date
Congress	XL Congress of the Spanish Society of Physiological Sciences. Joint meeting between Spanish and Portuguese physiologists	Poster	Badajoz, Spain	19–22 September 2022
Congress	XXI Scientific Meeting of the Spanish Society of Chromatography and Related Techniques	Oral communication	Almería, Spain	25–27 October 2022
Congress	'XIV Congreso Español de Toxicología y VIII Iberoamericano'	Poster	Córdoba, Spain	11 November 2022
Congress	'III Jornadas de Jóvenes Investigadores'	Poster	Granada, Spain	17–18 November 2022
Meeting	Spanish Agency for Food Safety & Nutrition (AESAN) Meeting	Attendance	Madrid, Spain	17–18 January 2023
Congress	'XXVII Jornadas Internacionales de Nutrición Práctica/XVI Congreso Internacional de SEDCA'	Poster	Madrid, Spain	15–16 March 2023
Congress	'V Jornada de Avances en Investigación en Epidemiología y Salud Pública'	Poster	Granada, Spain	23 June 2023