Environmental Research 280 (2025) 121912

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Adolescent exposure to benzophenone ultraviolet filters: cross-sectional associations with obesity, cardiometabolic biomarkers, and asthma/allergy in six European biomonitoring studies

Francisco M. Peinado [a,b], Ainhoa Pérez-Cantero [a,b], Alicia Olivas-Martínez [b,c], Lydia Espín-Moreno [a,c], Tomás de Haro [d], Luis D. Boada [e,f], Andrea Rodríguez-Carrillo [b,g], Eva Govarts [g], Susana Pedraza-Díaz [h], Marta Esteban-López [h], Ludek Blaha [i], Lucie Blahova [i], Beata Janasik [j], Wojciech Wasowicz [j], Sanna Lignell [k], Loïc Rambaud [l], Margaux Riou [l], Clémence Fillol [l], Sébastien Denys [l], Aline Murawski [m], Anne Lise Brantsæter [n], Amrit Kaur Sakhi [n], Nina Iszatt [n], Greet Schoeters [o], Marike Kolossa-Gehring [m], Mariana F. Fernández [a,b,c,*], Vicente Mustieles [b,c,p]

[a] University of Granada, Biomedical Research Center (CIBM), Granada, Spain
[b] Instituto de Investigación Biosanitaria (ibs.GRANADA), Granada, Spain
[c] CIBER de Epidemiología y Salud Pública (CIBERESP), Spain
[d] Unidad de Gestión Clínica de Laboratorios, Hospital Universitario Clínico San Cecilio, Granada, Spain
[e] Toxicology Unit, Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria (ULPGC), Las Palmas de Gran Canaria, Spain
[f] CIBER de Fisiopatología de la Obesidad y la Nutrición (CIBERObn), Spain
[g] VITO Health, Flemish Institute for Technological Research (VITO), 2400, Mol, Belgium
[h] National Centre for Environmental Health, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain
[i] RECETOX, Faculty of Science, Masaryk University, Brno, Czech Republic
[j] Nofer Institute of Occupational Medicine, Department of Environmental and Biological Monitoring, Poland
[k] Department of Risk Benefit Assessment, Swedish Food Agency, Uppsala, Sweden
[l] Department of Environmental and Occupational Health, Santé Publique France, French Public Health Agency (SpFrance), France
[m] German Environment Agency (UBA), Berlin, Germany
[n] Department of Food Safety and Centre for Sustainable Diets, Norwegian Institute of Public Health, Oslo, Norway
[o] Department of Biomedical Sciences, University of Antwerp, Belgium
[p] Servicio de Radiodiagnóstico, Hospital Universitario Clínico San Cecilio, Granada, Spain

ARTICLE INFO

Keywords:
Benzophenone
UV filter
Obesity
Allergy
HBM4EU
PARC
Endocrine disruption

ABSTRACT

Background: Exposure to benzophenone-1 (BP-1) and benzophenone-3 (BP-3), widely used as UV filters in personal care products, has been associated with adverse health effects. However, epidemiological evidence is limited and inconclusive, particularly in vulnerable populations such as teenagers.
Objective: To examine the relation between BP-1 and BP-3 concentrations and obesity, cardiometabolic biomarkers, and asthma/allergy outcomes in European teenagers, including possible sex-specific associations.
Methods: A multi-country cross-sectional study was conducted using pooled data from six aligned studies from the Human Biomonitoring for Europe Initiative (HBM4EU). Sociodemographic data, cardiometabolic biomarkers, and asthma/allergy outcomes were collected through questionnaires. Anthropometric data and BMI z-scores were calculated (n = 1339). Plasma/serum cardiometabolic biomarkers and asthma/allergy outcomes were available for a subsample (n = 173–594). Urinary BP-1 and BP-3 concentrations were adjusted for creatinine dilution using the traditional standardization (trad.) and the covariate-adjusted creatinine standardization (CAS) method. Generalized additive models, linear, logistic, and multinomial mixed models were applied, and sex-interaction terms were tested.

* Corresponding author. University of Granada, School of Medicine, Department of Radiology and Physical Medicine; Biomedical Research Center (CIBM), Spain.
E-mail address: marieta@ugr.es (M.F. Fernández).

https://doi.org/10.1016/j.envres.2025.121912
Received 10 January 2025; Received in revised form 18 May 2025; Accepted 19 May 2025
Available online 21 May 2025

Results: Each natural log-unit increase in urinary BP-3 (CAS) concentrations was associated with higher odds of obesity in the whole population (OR: 1.20; 95%CI: 1.04-1.38). Sex-specific associations were also found with BP-1 (CAS) and BP-3 (CAS) concentrations, which were associated with higher odds of obesity in male teenagers (OR: 1.25; 95% CI: 1.01-1.55; OR: 1.34; 95%CI: 1.09-1.65, respectively). Linear mixed models showed consistent findings toward higher BMI z-scores. A negative association was found between BP-1 (CAS) concentration and serum adiponectin levels in females (% change per log_e-unit increase: -3.73, 95%CI: -7.32, -0.10). BP-3 (CAS) concentrations were also associated with higher odds of non-food allergies in males (OR: 1.27; 95%CI: 1.00-1.63). Traditional creatinine adjustment showed similar or slightly attenuated estimates compared to the CAS method.

Conclusions: BP-1 and BP-3 exposure was cross-sectionally associated with higher odds of obesity in European male teenagers, highlighting the need to update regulations and keep exposure levels as low as practically achievable. Longitudinal studies are needed to confirm these findings.

1. Introduction

Benzophenone 3 (BP-3; 2-hydroxy-4-methoxybenzophenone) and its major metabolite, benzophenone 1 (BP-1; 2,4-dihydroxybenzophenone), are chemical compounds widely used as ultraviolet (UV) filters, predominantly found in sunscreens, cosmetics and personal care products (PCPs) (Ding et al., 2018; Li and Kannan, 2022; Tschersich et al., 2021), and to a lesser extent, in food packaging materials building and electronic materials, furniture, textiles, toys and inks (ECHA, 2021; Krause et al., 2018; Zhang et al., 2018). Due to their extensive application, BP-1 and BP-3 are widespread in the environment, with dermal absorption being the primary and most direct human exposure route (Morrison et al., 2017; Song et al., 2020; Zhang et al., 2018), entering rapidly into systemic circulation and avoiding first-pass metabolism (Matta et al., 2020). Despite their short half-lives and relatively rapid urinary excretion within hours to days (Kim and Choi, 2014), chronic and ubiquitous exposure has resulted in urinary detection of BP-1 and BP-3 in 96 % of teenagers and 83–86 % of adults in European biomonitoring studies (Govarts et al., 2023).

Both BP-1 and BP-3 are considered potential endocrine-disrupting chemicals (EDCs) (Krause et al., 2012; Mustieles et al., 2023), exhibiting *in vitro* and *in vivo* agonism of nuclear estrogen receptors alpha (ERα) and beta (ERβ) (Ghazipura et al., 2017; Lee et al., 2018; Molina-Molina et al., 2008), antagonism of the androgen receptor (Kim and Choi, 2014; Molina-Molina et al., 2008; Watanabe et al., 2015), and agonism of the thyroid receptor (Lee et al., 2018; Schmutzler et al., 2007), among other modes of action (Mustieles et al., 2023). Human exposure in young adult males and premenopausal females has been associated with hormonal alterations, including increased levels of progesterone and decreased estrogen levels, follicle-stimulating hormone and luteinizing hormone (Adoamnei et al., 2018; Pollack et al., 2018), as well as increased thyroid hormone levels (Berger et al., 2018). Urinary BP-3 concentrations were also associated with decreased total testosterone levels in U.S. teenagers (Scinicariello and Buser, 2016).

Previous *in vitro* studies have shown that BP-3 also acts as a full agonist of peroxisome proliferator-activated receptor γ (PPARγ), a key nuclear receptor involved in the regulation of lipid homeostasis, energy balance and adipogenesis (Shin et al., 2020; Wnuk et al., 2019). Given the high prevalence of overweight and obesity, currently reaching approximately 50 % of the worldwide population (GBD, 2021), along with its related metabolic disorders, it is crucial to investigate the contribution of environmental risk factors such as exposure to obesogenic and metabolic disruptors (Mustieles et al., 2024). Regarding BP-1 and BP-3, previous epidemiological studies have yielded mixed and inconsistent results with obesity. Thus, a prospective study in Spanish preadolescents found an association between BP-3 and higher BMI z-scores (Güil-Oumrait et al., 2022), while other prospective studies reported inverse associations, particularly when exposure was assessed during pregnancy (Berger et al., 2021; Buckley et al., 2016; Deierlein et al., 2017; Wang et al., 2022). Thus, Berger et al. (2021) and Buckley et al. (2016) examined prenatal exposure to BP-3 and reported lower adiposity in children at age 5 and between ages 4 and 9, respectively. Similarly, Deierlein et al. (2017) found that prenatal BP-3 exposure was associated with reduced adiposity in girls during early adolescence. Wang et al. (2022) investigated children aged 7–15 years observing negative associations between UV filter mixtures (including BP-3) and adiposity measures. In contrast, a small pilot study among Indian children aged 2–14 years found no significant associations (Xue et al., 2015). These variations in results across studies may be related to differences in age groups, exposure windows (e.g., prenatal vs. adolescence), and population characteristics. Additionally, there is limited evidence available regarding human BP-1 and BP-3 exposure in relation to cardiometabolic biomarkers including adipokines, serum lipids, glucose, insulin and hormones (Li et al., 2018; Salamanca-Fernández et al., 2020; Wang et al., 2020). Furthermore, BP-3 has been associated with higher urinary levels of the oxidative stress marker 8-hydroxydeoxyguanosine (8-OHdG) (Ferguson et al., 2019; Rocha et al., 2018), as well as immune-inflammatory markers related to an increased odds of asthma and allergies (Buckley et al., 2018).

Due to its frequent use and potential health risks, the European Union (EU) limited BP-3 content to a maximum of 6 % in sunscreens and up to maximum 0.5 % in other cosmetic products (EU, 2017). However, this limit is currently deemed insufficient to ensure consumer safety (SCCS, 2021). The European Human Biomonitoring Initiative HBM4EU prioritized the measurement of BP-1 and BP-3 in human biomonitoring studies, promoting a more thorough evaluation of their regulatory status within the EU (Santonen et al., 2023; Schoeters et al., 2020), an effort now continued in the Partnership for the Assessment of Risks from Chemicals (PARC) European project.

Adolescence constitutes an understudied critical period of vulnerability to environmental exposures due to significant hormonal and metabolic changes that differ between boys and girls (Buckley et al., 2016; Przybyla et al., 2018). Adolescence is also a period characterized by a higher use of cosmetics and PCPs (Harley et al. 2016, 2019), which can result in higher exposure to BP-1 and BP-3 (Liao and Kannan, 2014; Panico et al., 2019). Given the scarce data available on this field, the aim of this study was to examine the associations of BP-1 and BP-3 exposure with obesity, cardiometabolic biomarkers and asthma/allergy outcomes in a large sample of European teenagers from six HBM4EU Aligned Studies, including the examination of potential sex-specific associations.

2. Methods

2.1. Study population

A multi-country cross-sectional study was conducted, including teenagers from the HBM4EU Aligned Studies. Detailed information on study selection and data harmonization within HBM4EU was previously reported (Gilles et al. 2021, 2022; Govarts et al., 2023). Briefly, the HBM4EU Aligned Studies consist of a survey conducted across 23 countries aimed at generating harmonized and comparable human biomonitoring data at EU level to characterize internal exposure to

priority environmental chemicals. The inclusion criteria were (i) studies with available biobanked samples collected between 2014 and 2021, (ii) studies that fully adhered to HBM4EU protocols, (iii) studies targeting the general population, (iv) availability of a basic set of covariates, and (v) chemical analyses performed in the qualified laboratories of the HBM4EU Quality Assurance/Quality Control (QA/QC) program laboratories (Esteban López et al., 2021; Gilles et al. 2021, 2022).

Out of the initial eleven Aligned Studies focusing on teenagers (12–19 years old), six provided available data on urinary concentrations of BP-1 and/or BP-3. Therefore, ESTEBAN (*Etude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition*, France, n = 299), BEA (*Biomonitorización en Adolescentes*, Spain, n = 282), Riksmaten Adolescents (Sweden, n = 300), POLAES (Polish Aligned Environmental Study, Poland, n = 249), NEB II (Norwegian Environmental Biobank II, Norway, n = 149) and GerES V (subsample of the fifth cycle of the German Environmental Survey, Germany, n = 60) were included in this study, resulting in a total study population of 1339 (685 female and 654 male) European teenagers (Fig. 1). All participants signed and provided their informed consent, and all studies were approved by their local ethical committees, in accordance with the Principle of the Declaration of Helsinki.

2.2. BP-1 and BP-3 exposure

First-morning (ESTEBAN and GerES V), random spot (Riksmaten adolescents, POLAES, and NEB II), and a combination of first-morning and random spot (BEA) urine samples were collected and immediately frozen at −20 °C or −80 °C until analyses. Urinary concentrations of BP-1 and BP-3 were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) in accordance with HBM4EU QA/QC protocols (Esteban López et al., 2021). Due to variability in the limits of detection (LOD) and quantification (LOQ) across different studies, the LOQ was used as a cut-off value for reporting quantifiable data. LOQ of urinary BP-1 concentrations were 0.01 μg/L (ESTEBAN, BEA, Riksmaten adolescents and POLAES) and 0.5 μg/L (GerES V). LOQ of urinary BP-3 concentrations were 0.03 (ESTEBAN, BEA, Riksmaten adolescents, and POLAES), 0.10 μg/L (NEB II), and 2.00 μg/L (GerES V).

To adjust for urine dilution, urinary creatinine (mg/dL) was determined, and two dilution-adjustment approaches were applied: the traditional standardization method, calculated by division of the urinary BP-1 or BP-3 concentration by the measured creatinine concentration (μg/g creatinine), and the novel covariate-adjusted creatinine standardization (CAS) method (μg/L) (O'Brien et al., 2016). The CAS method aims to remove the influence of causal creatinine predictors such as age, sex and body mass index (BMI), before the standardization is performed. First, we predicted the urinary creatinine concentration (Pred_Ucr) that would have been obtained if all participants had similar characteristics, by regressing age, sex and BMI on natural-log-transformed urinary creatinine concentrations. Second, we divided the Pred_Ucr by the measured urinary creatinine (Ucr) concentration to obtain the creatinine ratio. Finally, the benzophenone concentration was multiplied by the creatinine ratio to calculate CAS levels, as represented in the following formula (O'Brien et al., 2016):

CAS BP concentration = [Urinary BP concentration] x (Pred_Ucr/Ucr)

2.3. Cardiometabolic biomarkers and asthma/allergy outcomes

BMI (kg/m^2) was considered our primary outcome (n = 1339) and was calculated using the continuous variables weight and height, which were available in all studies. To standardize comparisons with international studies and align with adult thresholds for overweight and obesity, age- and sex-specific BMI z-scores were calculated using the 2007 World Health Organization (WHO) growth reference standards (de Onis et al., 2007). This approach accounts for the significant age- and sex-dependent variability in BMI among adolescents, ensuring consistency and accuracy in classifying overweight and obesity across populations. BMI z-scores were categorized into different weight categories (severe thinness, thinness, normal weight, overweight and obesity), based on WHO BMI z-score cut-offs (de Onis et al., 2007). A grouping of categories was used for further analyses, including (i) dichotomous outcome: normal weight or lower versus overweight-obesity, and (ii) categorical outcome: normal weight or lower versus overweight, and obesity.

Blood plasma/serum levels of triglycerides (mg/dL), total cholesterol (mg/dL), high-density lipoproteins (HDL) (mg/dL), low-density lipoproteins (LDL) (mg/dL), leptin (μg/L), adiponectin (μg/mL), glucose

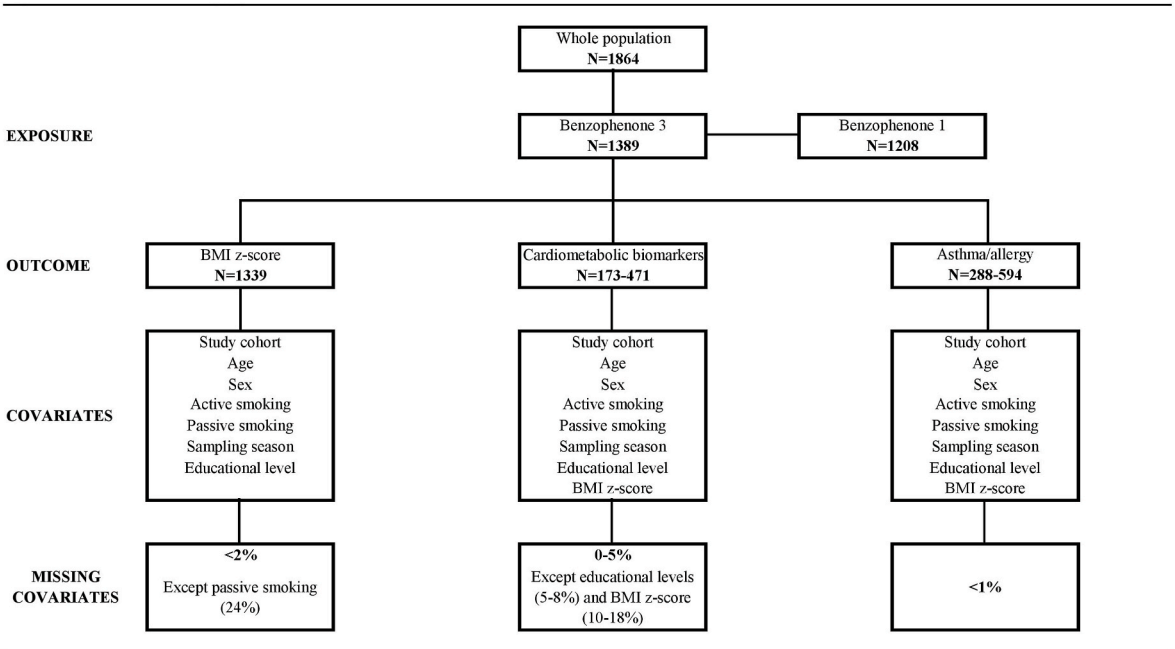


Fig. 1. Flow chart of study population.

(μg/L), insulin (μIU/mL), homeostasis model assessment of insulin resistance (HOMA-IR), and kisspeptin 54 (pg/mL) were determined in both BEA and NEB II studies (n = 173–471). These measurements were conducted at the Hospital Universitario Clínico San Cecilio (HUSC) of Granada (Spain), except for leptin, adiponectin, and kisspeptin 54, which were quantified at the Center of Biomedical Research (CIBM) at the University of Granada (Spain). Urinary concentrations of 8-hydroxydeoxyguanosine (8-OHdG) were only determined in BEA at the Research Centre for Toxic Compounds in the Environment (RECETOX), Masaryk University (Czech Republic), using LC-MS/MS (Bláhová et al., 2023), and were adjusted for urine dilution using both standardized and CAS methods.

Triglycerides, total cholesterol, HDL, and LDL levels were measured using colorimetric enzymatic assays (TRIGL, CHOL 2, HDLC3, LDLC3 tests, respectively), and glucose was assessed by UV radiation (GLUC3 test), following Beckman Coulter protocols. Leptin and adiponectin levels were determined using enzyme-linked immunosorbent assay (ELISA) kits from ENZO Life Sciences (Farmingdale, NY), while kisspeptin 54 levels were measured with an ELISA kit from Biotek Synergy HT, MyBiosource (San Diego, CA). Insulin levels were quantified using the electrochemiluminescence immunoassay Elecsys iNSULIN (Roche Diagnostics, Basel), and HOMA-IR was calculated using the following formula (Matthews et al., 1985):

HOMA-IR = [insulin levels (μIU/mL)*glucose levels (mmol/L)]/22.5

Asthma and allergy outcomes were only available in ESTEBAN, POLAES and GerES V cohorts (n = 288–594). Information was gathered from parental interviews, including asthma, eczema, food and non-food allergies. Questions focused on whether participants had ever received a medical diagnosis at any point in their life.

2.4. Covariates

Covariates were gathered through self-reported questionnaires from the Aligned Studies and then harmonized according to the HBM4EU Aligned Studies codebook (https://hbm.vito.be/peh-data-platform). The covariates included in this study were age (years), sex (male/female), sampling season (spring, summer, autumn, and winter), highest education level of the household according to the International Standard Classification of Education (ISCED) [low (ISCED 0–2), medium (ISCED 3–4), and high (ISCED 5–8], family income as the monthly total gross income of household at time of sampling (low, medium and high), and current and passive smoking (Yes/No). The missing covariate percentage ranged from 0 % to 5 %, with the exception of education level (5–8 %) and passive smoking (24 %).

2.5. Statistical analysis

A descriptive analysis was conducted on teenager's sociodemographic characteristics, cardiometabolic biomarkers, and asthma/allergy outcomes, considering both the whole population and sex-stratified groups. Continuous variables were expressed as means ± standard deviation (SD), while frequencies (percentages) were used for categorical variables. Raw, creatinine-standardized, and CAS urinary BP-1 and BP-3 concentrations were reported as means ± SD, along with minimum and maximum values and the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. For values below the LOQ (<5 % of all measurements), single-value random imputation was applied using a log-normal distribution, as described by Lubin et al. (2004). Urinary concentrations of BP-1 and BP-3, cardiometabolic biomarkers, and continuous covariates with skewed distributions were natural log-transformed to standardize their distributions and minimize the influence of extreme values.

2.5.1. Associations between BP-1/BP-3 and obesity

BMI z-score and obesity, available for a larger sample size (n = 1339) compared to cardiometabolic biomarkers (n = 173–471) and asthma/allergy outcomes (n = 288–594), were the primary outcomes of this study. Generalized Additive Models (GAMs) between exposure concentrations and BMI z-scores showed no departures from linearity (Figs. S1 and S2). Associations between BP-1 and BP-3 concentrations and each outcome were evaluated using multivariable generalized linear mixed models (for continuous outcomes), mixed-effects logistic (for binary outcomes) and multinomial regression models (for categorical outcomes), with study cohort included as a random effect to account for both within- and between-cohort variability. Exposure variables were standardized for creatinine dilution using both the traditional and CAS methods. Potential sex interactions were evaluated by including cross-product terms (exposure × sex) in the models. Sex-stratified analyses were performed when interaction terms yielded a p-value <0.10, indicating potential sex-specific associations.

2.5.2. Associations between BP-1/BP-3 and cardiometabolic biomarkers

GAM models showed evidence of linearity for most associations (Fig. S2). Multivariable linear regression mixed models were applied. When data were available from a single study, standard linear/logistic regression models were used instead of mixed models. Sex-stratified analyses were performed when exposure-sex interaction terms yielded a p-value <0.10.

2.5.3. Associations between BP-1/BP-3 and asthma/allergy outcomes

Multivariable mixed-effects logistic models were performed to explore the associations between exposure concentrations and asthma, as well as food and non-food allergies. A standard logistic regression model was conducted for eczema, since this outcome was available in only one cohort. Sex-stratified analyses were performed when exposure-sex interaction terms yielded a p-value <0.10.

2.5.4. Covariate adjustment

Potential confounders were selected in advance based on prior evidence from epidemiological research using a directed acyclic graph (DAG) specified in the HBM4EU project's statistical analysis plan (Govarts et al., 2020). Age (continuous), sex (binary), active smoking (binary), passive smoking (binary), sampling season (categorical), household educational level based on the International Standard Classification of Education [ISCED: low (0–2), medium (3–4) and high (≥5)] and family income (categorical), were identified as potential confounders and were included in the models as fixed effects, while study cohort was included as a random effect to account for both within- and between-cohort variation. To explore the associations between exposure concentrations and cardiometabolic biomarkers or asthma/allergy outcomes, BMI z-score was also included as a fixed effect in the models. The few missing data for covariates were imputed using the mode for categorical variables and the median for continuous variables.

2.5.5. Effect estimation

Beta coefficients and 95 % confidence intervals (CIs) from linear regression mixed models were reported for BMI z-score, while for cardiometabolic biomarkers, the percentage change for each natural log-unit increase (equivalent to each 2.7-fold increase) in BP-1 and BP-3 concentration was calculated $[(e^{\beta}-1)*100]$. For logistic regression models, multivariable-adjusted odds ratios (ORs) with 95 % CIs were reported to assess the odds of categorical outcomes (obesity and asthma/allergy) for each log-unit increase in BP-1/BP-3 concentration.

2.5.6. Sensitivity analyses

The influence of the additional inclusion of log-transformed creatinine as a covariate was examined in all exposure-BMI z-score models, as well as in exposure-cardiometabolic biomarkers and exposure-asthma/allergy models. Additionally, we considered the exclusion of extreme

values (values lower and higher than the 5th and 95th percentiles) for both exposure and effect variables. As an additional sensitivity analysis, BP-1 and BP-3 concentrations were categorized into tertiles in mixed-effects models with BMI z-scores and obesity (the primary outcome). Finally, given that BP-1 is the primary metabolite of BP-3, we conducted exploratory analyses by creating a cumulative benzophenone exposure metric (∑BPs), calculated as the molar sum of BP-1 and BP-3 concentrations, obtained by dividing each concentration by its respective molecular weight, and expressed in ng/mL equivalents of BP-3 (Deierlein et al., 2017).

2.5.7. Software

SPSS v28.0.1.0 (IBM, Chicago, IL) and the R statistical computing environment v4.4.1 (http://www.r-project.org/) were used for data analyses. Statistical significance was set at a two-tailed p-value <0.05.

3. Results

3.1. Characteristics of the study population

A detailed description of the participants' sociodemographic characteristics is provided in Table 1. Briefly, 1339 teenagers (51 % females) were included. The mean (SD) age of the whole, male and female population was 14.07 (1.53), 14.02 (1.50) and 14.13 (1.56) years, respectively. Most teenagers reported a high family educational level (63 %), and a medium/high family income (39 %). Up to 7 % of adolescents were active smokers, while up to 26 % were exposed to environmental tobacco smoke. Sociodemographic characteristics of each individual study are shown in Table S1A.

The mean (SD) BMI z-score for the whole population was 0.24 (1.08), being 0.27 (1.12) for males and 0.22 (1.05) for females. The prevalence of overweight/obesity in the 1339 adolescents was 25.0 %, 27.7 %, and 22.5 %, for the whole population, males and females, respectively (Table 1). Cardiometabolic biomarker levels were quantified in a subset of the population (n = 173–471) (Fig. 1), and sex-dependent differences were found with females showing higher cholesterol, HDL, LDL, leptin, insulin and kisspeptin 54 levels than males (Table 1). The prevalence of asthma, eczema, food allergies and non-food allergies were 11.3 %, 39.9 %, 3.90 %, and 32.6 %, respectively, available in 288–594 participants (Table 1). The prevalence in each individual cohort is shown in Table S1A.

Raw, traditional creatinine-standardized [BP-1 (trad.) and BP-3 (trad.)], and CAS [BP-1 (CAS) and BP-3 (CAS)] urinary concentrations of BP-1 and BP-3 are displayed in Table 2 and Table S1B. Both BP-1 and BP-3 were detected in over 95 % of the study population. Median (P25-P75) raw concentrations were 1.06 (0.37–3.37) μg/L for BP-1 and 2.43 (0.83–7.39) μg/L for BP-3. Traditional creatinine-adjusted median concentrations (P25-P75) were 0.88 (0.31–2.57) μg/g for BP-1 and 2.05 (0.71–5.79) μg/g for BP-3. CAS concentrations were 1.10 (0.39–3.21) for BP-1, and 2.50 (0.89–7.18) for BP-3. For both BP-1 and BP-3, regardless of the creatinine adjustment method, females showed higher concentrations compared to males (e.g., median BP-3 (trad.): 2.83 μg/g in females vs 1.50 μg/g in males) (Table 2). Spearman correlation coefficients indicated a strong correlation between BP-1 and BP-3 (r = 0.81–0.87) (Table S2).

3.2. Associations between BP-1/BP-3 and obesity (n = 1339)

In the whole population, each natural log-unit increase in urinary BP-3 (CAS) concentrations was associated with a higher BMI z-score (β = 0.03; 95 % CI: 0.00–0.06) (Fig. 2, Table S3). In the dichotomized model (normal weight or lower versus overweight-obesity), urinary BP-3 (trad.) was marginally associated with increased odds of overweight-obesity (OR = 1.06; 95 % CI: 0.99–1.14), while BP-3 (CAS) was significantly associated (OR = 1.07; 95 % CI: 1.00–1.15). In the multinomial model (normal weight or lower versus overweight, and obesity), higher urinary concentrations of both BP-3 (trad.) and BP-3 (CAS) were associated with increased odds of obesity (OR = 1.17; 95 % CI: 1.02–1.35; and OR = 1.20; 95 % CI: 1.04–1.38, respectively) (Fig. 2, Table S3).

We found evidence of a potential interaction by sex (p-int<0.10) in almost all BMI and obesity associations (Table S4). Sex-stratified models showed that urinary BP-1 (trad.), BP-1 (CAS), BP-3 (trad.) and BP-3 (CAS) concentrations were significantly and positively associated with higher BMI z-scores only in male teenagers (β = 0.07; 95 % CI: 0.02–0.013; β = 0.08; 95 % CI: 0.03–0.13; β = 0.08; 95 % CI: 0.03–0.12; and β = 0.08; 95 % CI: 0.04–0.13, respectively) (Fig. 3, Table S5). Among males, higher BP-1 (CAS) concentrations were marginally associated with the odds of overweight/obesity in logistic models (OR = 1.11; 95 % CI: 0.99–1.24) and significantly associated with obesity in multinomial models (OR = 1.25; 95 % CI: 1.01–1.55). Higher BP-3 (trad.) and BP-3 (CAS) concentrations were associated with increased odds of overweight/obesity in binary logistic models (OR = 1.14; 95 % CI: 1.03–1.27; and OR = 1.16; 95 % CI: 1.04–1.28, respectively), and with obesity in multinomial logistic models (OR = 1.32; 95 % CI: 1.07–1.62; and OR = 1.34; 95 % CI: 1.09–1.65, respectively) (Fig. 3, Table S5).

3.3. Associations between BP-1/BP-3 and cardiometabolic biomarkers (n = 173–471)

In the whole population, higher BP-3 (CAS) concentrations were marginally associated with higher 8-OHdG urinary levels (% change = 2.43; 95% CI: -0.40-5.34). No significant associations were found between BP-1 and BP-3 exposure and other cardiometabolic biomarkers (Fig. S3, Table S6).

Sex-specific associations between urinary concentrations of BP-1 and BP-3 (trad. and CAS) in relation to HDL serum levels were found (Table S4), with a positive trend in males and a negative trend in females, although these associations did not reach statistical significance (Fig. S4, Table S5). Sex-specific associations between BP-1 (trad.) and BP-1 (CAS) concentrations in relation to adiponectin levels were also found, with a non-significant positive association in males (% change = 0.40; 95% CI: -4.78-5.87) and a significant negative association in females (% change = -3.73; 95% CI: -7.32– -0.10) (Fig. S4, Table S5).

3.4. Associations between BP-1/BP-3 and asthma/allergy outcomes (n = 288–594)

No associations between urinary concentrations of BP-1 and BP-3 and asthma, eczema, food and non-food allergies were found (Fig. S5, Table S7). However, sex-specific associations were observed between BP-3 (trad.) and BP-3 (CAS) concentrations and the odds of non-food allergies (Fig. S6, Table S5), showing a positive trend in males (OR = 1.27; 95 % CI: 1.00–1.63), and a non-significant negative trend in females (OR = 0.89; 95 % CI: 0.74–1.09) (Fig. S6, Table S5).

3.5. Sensitivity analyses

Sensitivity analyses, including creatinine as an adjustment variable in the models (Tables S8A and S9A) and removing outliers (Tables S8B and S9B), did not substantially change the effect estimates or the significance of the associations. Minor changes were observed, with some associations being slightly attenuated, such as those between BP-1 (trad.) and BP-1 (CAS) concentrations and adiponectin levels in females after including creatinine as an adjustment variable. Tertile-based models (Table S10) showed consistent associations compared to results of models evaluating benzophenone concentrations as continuous variables. In males, positive associations were found between the third tertile of BP-1 (Trad.), BP-3 (Trad.), and BP-3 (CAS) and BMI z-score (β = 0.31; 95 % CI: 0.07–0.55; β = 0.33; 95 % CI: 0.09–0.57 and β = 0.28; 95 % CI: 0.06–0.50, respectively), compared to the first tertile. In addition, higher odds of obesity were found in the third tertile of BP-3

Table 1
Sociodemographic characteristics and outcome variables of the study population.

Sociodemographic characteristics		Whole population			Male population			Female population			p-value[a]
		N/Mean	%/SD	Sample size	N/Mean	%/SD	Sample size	N/Mean	%/SD	Sample size	
Age (years)		14.1 ±	1.53	1339	14.02 ±	1.50	654	14.13 ±	1.56	685	0.153
Creatinine (mg/L)		1.40 ±	0.64	1339	1.41 ±	0.61	654	1.39 ±	0.67	685	0.355
Cohort	ESTEBAN (France)	299	22.3	1339	144	22.0	654	155	22.6	685	0.055
	BEA (Spain)	282	21.1		134	20.5		148	21.6		
	Riksmaten Adolescents (Sweden)	300	22.4		150	22.9		150	21.9		
	POLAES (Poland)	249	18.6		140	21.4		109	15.9		
	NEB II (Norway)	149	11.1		61	9.30		88	12.8		
	GerES V (Germany)	60	4.48		25	3.80		35	5.10		
Sampling season	Spring	241	18.0	1339	116	17.7	654	125	18.2	685	0.092
	Summer	156	11.7		64	9.80		92	13.4		
	Autumn	710	53.0		366	56.0		344	50.2		
	Winter	232	17.3		108	16.5		124	18.1		
Family educational level	Low education (ISCED 0–2)	99	7.50	1316	35	5.40	643	64	9.50	673	**0.018**
	Medium education (ISCED 3–4)	389	29.6		198	30.8		191	28.4		
	High education (ISCED≥5)	828	62.9		410	63.8		418	62.1		
Family income	Low	40	6.90	579	17	6.10	277	23	7.60	302	0.113
	Medium	224	38.7		118	42.6		106	35.1		
	High	151	26.1		75	27.1		76	25.2		
	Don't know/don't want to share	164	28.3		67	24.2		97	32.1		
Active smoking	Yes	72	7.30	989	31	6.30	496	41	8.30	493	0.211
Passive smoking	Yes	267	26.2	1021	128	25.9	495	139	26.4	526	0.837
OUTCOMES											
BMI z-score and cardiometabolic biomarkers											
BMI z-score		0.24 ±	1.08	1339	0.27 ±	1.12	654	0.22 ±	1.05	685	0.323
Categorized BMI z-score[b]	Severe thinness	1	0.07	1339	1	0.20	654	0	0.00	685	0.119
	Thinness	27	2.02		15	2.30		12	1.80		
	Normal	976	72.9		457	69.9		519	75.8		
	Overweight	270	20.2		147	22.5		123	18.0		
	Obesity	65	4.85		34	5.20		31	4.50		
Cardiometabolic biomarkers	Triglycerides (mg/dL)	76.0 ±	43.5	464	65.9 ±	41.1	215	75 ±	45.2	249	0.623
	Cholesterol (mg/dL)	188 ±	64.9	463	178 ±	61.1	215	196 ±	67.2	248	**0.002**
	HDL (mg/dL)	50.8 ±	12.8	472	49.3 ±	12.6	217	52.0 ±	12.9	255	**0.003**
	LDL (mg/dL)	94.8 ±	23.8	472	90.4 ±	19.9	217	98.2 ±	26.4	255	**<0.001**
	Leptin (μg/L)	10.5 ±	9.99	173	6.15 ±	5.97	76	13.9 ±	11.2	97	**<0.001**
	Adiponectin (μg/mL)	10.6 ±	5.59	469	10.3 ±	5.33	217	10.9 ±	5.81	252	0.281
	Glucose (mg/dL)	46.7 ±	21.7	295	46.2 ±	22.7	141	46.9 ±	21.0	154	0.645
	Insulin (μIU/mL)	14.8 ±	15.0	467	12.8 ±	12.3	216	16.5 ±	16.8	251	**0.004**
	HOMA-IR	1.62 ±	2.58	291	1.43 ±	2.29	140	1.79 ±	2.83	151	0.241
	Kisspeptin 54 (pg/mL)	2224 ±	318	463	2175 ±	230	215	2266 ±	374	248	**<0.001**
	8-OHdG (μg/L)	5.68 ±	3.29	299	5.64 ±	3.20	143	5.71 ±	3.37	156	0.876
	8-OHdG (Trad.) (μg/g)	4.43 ±	1.49	299	4.27 ±	1.32	143	4.59 ±	1.67	156	0.233
	8-OHdG (CAS) (μg/L)	5.03 ±	1.67	299	4.94 ±	1.64	143	5.08 ±	1.84	156	0.814
Asthma/allergy outcomes											
Asthma	Yes	67	11.3	594	27	12.3	300	30	10.2	294	0.404
Eczema	Yes	115	39.9	288	56	41.2	136	59	38.8	152	0.739
Food allergies	Yes	21	3.90	543	8	2.90	278	13	4.90	265	0.224
Non-food allergies	Yes	179	32.6	549	85	30.2	281	94	35.1	268	0.239

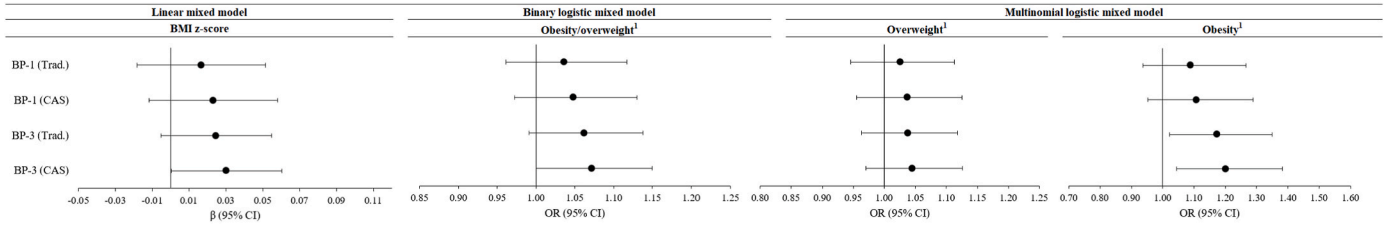
[a] p-value was calculated using the Mann-Whitney and Chi-square tests, for continuous and categorical variables, respectively. SD: standard deviation; BMI: body mass index; ISCED: international standard classification of education; HDL: high density lipoproteins; LDL: low density lipoproteins; HOMA-IR: homeostatic model assessment for insulin resistance; 8-OHdG: 8-hydroxydeoxyguanosine; Trad: creatinine-adjusted benzophenone concentrations (μg/g) were calculated by dividing benzophenone concentrations by urinary creatinine levels (traditional method); CAS: creatinine-adjusted benzophenone concentrations (μg/L) were calculated using the covariate-adjusted standardization method.

[b] BMI categorization according to the World Health Organization. Bold text indicates p-value <0.05.

Table 2
Urinary concentrations of benzophenones (μg/L).

Whole population												
	DF (%)	Mean	SD	Min	Percentile							Max
					5	10	25	50	75	90	95	
BP-1 (μg/L)		6.70	27.7	<LOD	0.07	0.15	0.37	1.06	3.37	12.3	26.0	563
BP-1 (Trad.) (μg/g)	96.4	5.60	27.0	<LOD	0.05	0.12	0.31	0.88	2.57	9.7	19.7	531
BP-1 (CAS) (μg/L)		6.92	32.6	<LOD	0.07	0.15	0.39	1.10	3.21	12.2	25.5	615
BP-3 (μg/L)		26.5	274	<LOD	0.15	0.34	0.83	2.43	7.39	27.4	64.4	9422
BP-3 (Trad.) (μg/g)	95.6	19.9	180	<LOD	0.09	0.27	0.71	2.05	5.79	22.2	49.3	5866
BP-3 (CAS) (μg/L)		24.3	218	<LOD	0.12	0.34	0.89	2.50	7.18	27.1	64.1	7083
Male population												
	DF (%)	**Mean**	**SD**	**Min**	**Percentile**							**Max**
					5	**10**	**25**	**50**	**75**	**90**	**95**	
BP-1 (μg/L)		3.33	10.0	<LOD	0.05	0.12	0.26	0.69	2.17	6.20	15.5	144
BP-1 (Trad.) (μg/g)	96.0	2.71	9.95	<LOD	0.04	0.09	0.22	0.58	1.58	5.17	12.8	189
BP-1 (CAS) (μg/L)		3.45	12.6	<LOD	0.06	0.11	0.28	0.72	2.06	6.52	16.5	237
BP-3 (μg/L)		24.9	370	<LOD	0.13	0.28	0.67	1.78	5.27	15.4	39.2	9422
BP-3 (Trad.) (μg/g)	95.7	16.5	229	<LOD	0.08	0.23	0.55	1.50	4.07	11.0	30.7	5866
BP-3 (CAS) (μg/L)		20.2	276	<LOD	0.11	0.30	0.70	1.83	5.05	13.3	38.9	7083
Female population												
	DF (%)	**Mean**	**SD**	**Min**	**Percentile**							**Max**
					5	**10**	**25**	**50**	**75**	**90**	**95**	
BP-1 (μg/L)		10.1	37.6	<LOD	0.09	0.20	0.58	1.63	4.89	18.8	39.5	563
BP-1 (Trad.) (μg/g)	96.7	8.48	36.6	<LOD	0.07	0.20	0.51	1.36	4.02	13.3	26.0	531
BP-1 (CAS) (μg/L)		10.4	44.1	<LOD	0.09	0.25	0.61	1.64	5.02	16.0	31.7	615
BP-3 (μg/L)		28.0	128	<LOD	0.17	0.41	1.08	3.31	10.4	41.6	92.9	2090
BP-3 (Trad.) (μg/g)	95.5	23.2	116	<LOD	0.11	0.34	0.94	2.83	7.92	31.3	67.7	2020
BP-3 (CAS) (μg/L)		28.3	141	<LOD	0.14	0.42	1.15	3.35	9.34	38.2	79.5	2396

DF: detection frequency; SD: standard deviation; LOD: limit of detection; BP-1: benzophenone 1; BP-3: benzophenone 3; Trad.: creatinine-adjusted benzophenone concentrations (μg/g) were calculated by dividing benzophenone concentrations for urinary creatinine levels (traditional method); CAS: creatinine-adjusted benzophenone concentrations (μg/L) were calculated using the covariate-adjusted standardization method. Significant differences were found between the male and female population for benzophenone 1 and 3, regardless of the creatinine adjustment method (p-value <0.01).



[1]Reference category: normal/thinness/severe thinness. β: beta coefficient; OR: odds ratio; CI: confidence intervals; BP-1: benzophenone 1; BP-3: benzophenone 3; Trad: creatinine-adjusted benzophenone concentrations (μg/g) were calculated by dividing benzophenone concentrations for urinary creatinine levels (traditional method); CAS: creatinine-adjusted benzophenone concentrations (μg/L) were calculated using the covariate-adjusted standardization method; BMI: body mass index. Circles and error bars represent linear or logistic mixed effect estimates with their corresponding 95% confidence intervals for each association explored. Models were adjusted for age, sex, active smoking, passive smoking, sampling season, and family educational level, considering the study cohort as a random effect. Numeric data corresponding to this figure can be found in Table S3.

Fig. 2. Associations between BP-1 and BP-3 concentrations in relation to obesity risk.
[1]Reference category: normal/thinness/severe thinness. β: beta coefficient; OR: odds ratio; CI: confidence intervals; BP-1: benzophenone 1; BP-3: benzophenone 3; Trad: creatinine-adjusted benzophenone concentrations (μg/g) were calculated by dividing benzophenone concentrations for urinary creatinine levels (traditional method); CAS: creatinine-adjusted benzophenone concentrations (μg/L) were calculated using the covariate-adjusted standardization method; BMI: body mass index. Circles and error bars represent linear or logistic mixed effect estimates with their corresponding 95 % confidence intervals for each association explored. Models were adjusted for age, sex, active smoking, passive smoking, sampling season, and family educational level, considering the study cohort as a random effect. Numeric data corresponding to this figure can be found in Table S3.

(Trad.) and BP-3 (CAS) concentrations (OR = 1.64; 95 % CI: 1.04–2.61, and OR = 1.72; 95 % CI: 1.08–2.73, respectively) compared to the first tertile. In females, inverse associations emerged between the second -but not third-tertile of exposure and BMI z-score, although no significant associations were observed for categorized obesity outcomes. When the molar sum of BP-1 and BP-3 concentrations was examined as a cumulative measure, associations with BMI z-scores and the odds of obesity were consistent with those observed for individual BP-1 and BP-3 concentrations analyzed separately, showing similar direction, effect magnitude and significance (Fig. S7).

4. Discussion

In this multi-country cross-sectional study, higher urinary BP-1 and BP-3 concentrations were associated with higher odds of obesity in 1339 European teenagers from six HBM4EU Aligned Studies. This association was especially observed among males. In a subsample of the population, BP-3 concentrations were also associated with higher odds of non-food allergy also in male teenagers, while an inverse association between BP-1 and adiponectin levels was observed in females. No significant associations were found for the remaining outcomes. This is one of the very first studies evaluating associations between exposure to benzophenone-type UV filters and the studied outcomes, suggesting that

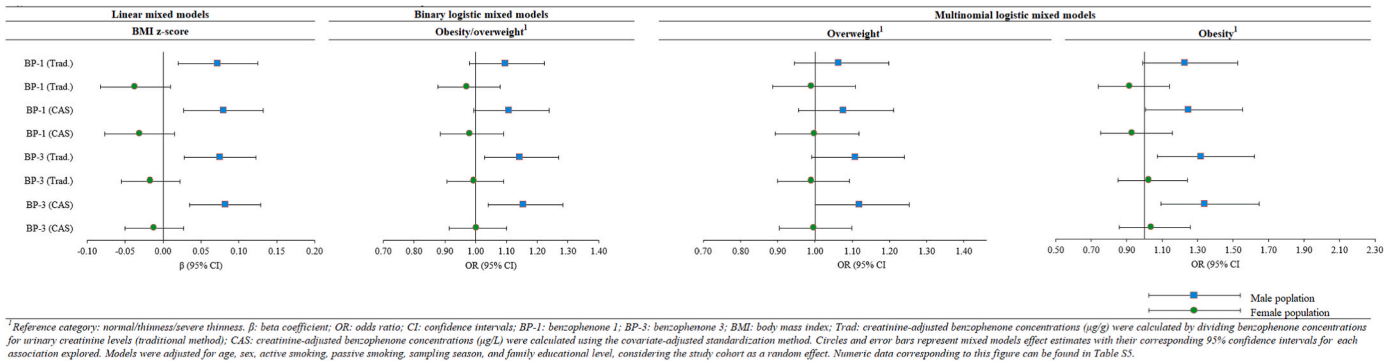


Fig. 3. Sex-stratified associations between BP-1 and BP-3 concentrations in relation to obesity risk.
[1]Reference category: normal/thinness/severe thinness. β: beta coefficient; OR: odds ratio; CI: confidence intervals; BP-1: benzophenone 1; BP-3: benzophenone 3; BMI: body mass index; Trad: creatinine-adjusted benzophenone concentrations (μg/g) were calculated by dividing benzophenone concentrations for urinary creatinine levels (traditional method); CAS: creatinine-adjusted benzophenone concentrations (μg/L) were calculated using the covariate-adjusted standardization method. Circles and error bars represent mixed models effect estimates with their corresponding 95 % confidence intervals for each association explored. Models were adjusted for age, sex, active smoking, passive smoking, sampling season, and family educational level, considering the study cohort as a random effect. Numeric data corresponding to this figure can be found in Table S5.

adolescence may be a critical window of susceptibility for potential adverse effects of endocrine-disrupting chemicals.

To our best knowledge, this is the first study applying the novel CAS approach to urinary BP-1 and BP-3 concentrations, in addition to testing traditional creatinine standardization for dilution adjustment. Urinary creatinine, a byproduct of muscle metabolism, is influenced by BMI, muscle mass, age, and sex (Barr et al., 2005). These factors can introduce several types of biases when performing traditional standardization, and collider stratification bias when creatinine is used as a covariate in relation to BMI as an outcome, potentially distorting associations between chemical exposures and health outcomes (Greenland, 2003). The CAS method helps mitigate this potential bias, offering more accurate assessments of biomarker-health risk relationships (O'Brien et al., 2016). In this study, both traditional creatinine standardization and the CAS method yielded similar results for most outcomes. However, the association between BP-3 and BMI z-score, as well as obesity/overweight, slightly differed between methods. The traditional approach showed no significant associations, while the CAS method identified positive associations. These results are in consonance with previous epidemiological studies, showing significant associations between urinary bisphenol A concentrations and obesity odds when using the CAS approach, but not the traditional method (Moon et al., 2021). For the remaining associations, both methods reported similar results, with the CAS method providing slightly more precise estimates.

4.1. BP-1/BP-3 and obesity

Despite growing concern over the potential obesogenic effects of BP-1 and BP-3, epidemiological studies remain limited and inconsistent. Our findings align with a recent study, showing a positive association between BP-3 exposure and higher BMI z-scores in teenagers (Güil-Oumrait et al., 2022). Both studies suggest that BP-3 may play a role in obesity, underscoring the importance of critical exposure windows, such as prenatal and adolescent stages.

The potential obesogenic effect of BP-3 may result from a complex interaction of estrogen-like and anti-androgenic activities (Kim and Choi, 2014; Watanabe et al., 2015), disruption of thyroid hormone balance (Lee et al., 2018), and upregulation of PPARγ (Shin et al., 2020; Wnuk et al., 2019). A previous *in vitro* study showed that BP-3 significantly enhances PPARγ gene transcription and the expression of key enzymes involved in lipid metabolism in human epidermal keratinocytes, a primary site for UV filters in the skin (Shin et al., 2020). Although evidence on mechanisms is more limited for BP-1, its structural similarity to BP-3, and similar estrogenic and anti-androgenic activity (Mustieles et al., 2023), suggest that both compounds may act through comparable pathways (Shin et al., 2020).

Previous studies using chemical mixture models have reported sex-specific associations, showing a non-monotonic relationship between BP-3 and BMI z-scores in preadolescent girls (Güil-Oumrait et al., 2022). In contrast, our study found a positive association between BP-1/BP-3 exposure and obesity odds in adolescent males. These discrepant results highlight the need for further investigation into sex-specific associations, as the influence of other compounds in mixture models may affect the observed associations. Furthermore, sex-specific associations were found between maternal prenatal urinary BP-3 concentrations and birth weight, with higher and lower levels among boys and girls, respectively (Messerlian et al., 2018; Philippat et al., 2019; Wolff et al., 2008). The trend towards higher birth weight observed in males is consistent with our current results. Sex-specific associations between BP-3 and obesity are biologically plausible based on interactions with sex hormones, such as estrogens and androgens, which differentially regulate fat metabolism and distribution in boys and girls (Philippat et al., 2019; Wolff et al., 2008).

Conversely, different epidemiological studies reported null or negative associations between BP-3 exposure and obesity outcomes. A pilot study reported a null effect, and no significant differences were found between 49 obese and 27 non-obese Indian children (2–14 years) (Xue et al., 2015). Contrary to our results, four prospective longitudinal studies indicated a potential anti-adipogenic effect of BP-3 (Berger et al., 2021; Buckley et al., 2016; Deierlein et al., 2017; Wang et al., 2022). Berger et al. (2021) found an inverse association between prenatal BP-3 exposure and BMI z-scores in five-year-old children. Another prospective birth cohort study, involving 173 US mother-child pairs, found that maternal urinary BP-3 concentrations during pregnancy were associated with a reduced fat mass percentage in girls, with no association observed in boys (Buckley et al., 2016). Similarly, a prospective study including 1017 US girls reported that BP-3 exposure was associated with lower levels of adiposity starting at age 10, with significant reductions in waist circumference observed at ages 12 and 13 (Deierlein et al., 2017). Another study, including 327 Chinese children aged 7–15 years old, reported a negative association between exposure to a mixture of UV filters, including BP-3, and different adiposity measures, such as BMI z-score, body fat percentage, subscapular skinfold thickness, waist circumference and waist-to-height ratio (Wang et al., 2022).

Discrepancies in epidemiological studies could be explained by different methodological challenges, such as exposure assessment during different critical windows including pregnancy, childhood, puberty and adolescence (Romano et al., 2014), modest sample sizes that limited

the study of sex-specific associations, exposure misclassification due to the collection of one or few urine samples to characterize exposure to these short-lived chemicals, the failure to control for some confounders such as diet and physical activity, and the anthropometric outcome evaluated (birthweight, BMI z-scores, body fat and lean mass, etc.). Additionally, as adiposity gradually increases throughout childhood and catch-up growth effects may take place (Rallis et al., 2021), it may be easier to identify associations during late childhood and adolescence than at earlier stages (Romano et al., 2014).

4.2. BP-1/BP-3 and cardiometabolic biomarkers

To our knowledge, this is the first study in adolescents addressing the associations between BP-1/BP-3 exposure and lipids such as triglycerides, cholesterol, HDL, and LDL; adipokines such as leptin, and adiponectin; glucose metabolism parameters such as glucose, insulin and HOMA-IR, and hormonal peptides such as kisspeptin 54. Of note, these markers could only be analyzed in a subsample (n = 173–471) of the total population (n = 1389), and thus a considerably lower statistical power is expected. While no significant associations were found when boys and girls were analyzed together, we observed a trend towards higher oxidative stress reflected as 8-OHdG urinary levels that is in line with previous findings (Ferguson et al., 2019; Rocha et al., 2018), together with higher serum levels of triglycerides and leptin, and lower serum adiponectin levels. A sex-specific inverse association between BP-1 and adiponectin levels was observed in females. Since low adiponectin levels have been associated with metabolic syndrome risk factors, including low-grade chronic inflammation, and BP-1/BP-3 can act through PPARγ at the adipose tissue level, potentially inhibiting adiponectin and increasing leptin (Mustieles et al., 2023; Silva et al., 2019), this potential association should be further investigated (Fantuzzi, 2008). BP-1 showed a marginal association with higher HDL levels in boys and lower levels in girls, indicating potential links to lipid metabolism. BP-3 exposure also showed a non-significant trend towards higher serum levels of the novel marker kisspeptin. Since kisspeptin is an upstream regulator of pituitary reproductive hormones, more research is needed on this topic. Despite plausible biological links, the evidence between BP-1 and BP-3 human exposure and cardiometabolic biomarkers is very limited and further research in larger sample sizes is warranted.

4.3. BP-1/BP-3 and asthma/allergy outcomes

An oxidative microenvironment may disrupt immune regulation and promote systemic inflammation, increasing the odds of chronic inflammatory diseases such as asthma and allergies (Albano et al., 2022; Ioniuc et al., 2024). It is suspected that benzophenone-type UV filter exposure may heighten this risk by modulating immune or inflammatory responses, potentially via endocrine disruption (Ao et al., 2018). Our study identified a sex-specific association between BP-3 exposure and non-food allergy, with higher odds observed in males. Although we did not observe associations with asthma prevalence, previous mother-child cohort studies have reported a protective association between prenatal BP-3 exposure and wheezing symptoms in children aged 6–7 years, along with a non-significant trend toward lower asthma odds (Buckley et al., 2018; Vernet et al., 2017). No previous association was found between BP-3 and eczema (Buckley et al., 2018). Although these protective effects in specific subgroups are not currently well-understood, BP-3 has shown to have anti-inflammatory effects in certain tissues through the inhibition of PGE2, which has been linked to allergic airway diseases (Lee et al., 2020) and impaired lung function (Ye et al., 2023). These findings highlight the complexity of benzophenone UV filters and underscore the necessity for further research to better understand and clarify these unexpected associations.

4.4. Regulatory and public health implications

The widespread use of BP-1 and BP-3, particularly the frequent use of cosmetics among teenagers, and their potential health effects highlight the need for strengthened regulatory measures. Based on the latest SCCS opinion (SCCS, 2021), a provisional HBM guidance value (HBM-GV) of 340 μg of BP-3 per g of urinary creatinine was derived in relation to a reduction in the number of spermatocytes per seminiferous tubule in the offspring of experimental animals (Santonen et al., 2023). In the current dataset, only 0.94 % of adolescents surpassed this guidance value. Notwithstanding, our findings suggest that effects could take place at lower levels, supporting recommendations to reduce BP-3 concentrations in sunscreens, cosmetics and PCPs, in line with current guidelines (Matta et al., 2020; Rousselle et al., 2022; SCCS, 2021). Although research on the health effects of BP-1/BP-3 exposure still remains limited, the precautionary principle should be applied in regulatory decision-making, especially given the potential risks associated with low-level exposure. In this context, healthcare providers should guide at-risk populations, including teenagers, towards mineral-based sunscreens to minimize systemic absorption of organic UV filters while keeping high UV protection standards (Mustieles et al., 2023). Since as shown in our work and other toxicological studies BP-1 may also pose health risks, policymakers should include both BP-1 and BP-3 in risk assessments. Initiatives such as HBM4EU and PARC, which prioritize biomonitoring of these compounds, are essential for revising regulatory frameworks and supporting evidence-based policy changes (Schoeters et al., 2021).

4.5. Strengths and limitations

Strengths of this study include the large sample size for obesity measures and the pooling of data across six European surveys, which allowed us to investigate sex-stratified associations. Second, we focused on adolescence, an under-researched critical developmental period in relation to chemical exposures. Third, standardized sampling and adherence to QA/QC protocols developed inside the HBM4EU project are expected to increase the confidence in the associations observed. Finally, this is the first study to apply the novel CAS method to urinary BP-1/BP-3 concentrations.

Our findings should be interpreted with caution due to the following limitations. First, the cross-sectional design could lead to reverse causality issues. Second, exposure misclassification is possible since single-spot urine samples only capture recent exposure due to the short half-life of benzophenone-type UV filters. However, in general, this would tend to result in attenuation bias and underestimation rather than overestimation of associations (Perrier et al., 2016). Third, data on complementary obesity indicators like body fat percentage or waist-to-height ratio was not available (Güil-Oumrait et al., 2021). Fourth, the large number of comparisons increases the risk of type I errors, though our findings with BMI and obesity were consistent across statistical models and supported by toxicological data. Fifth, despite adjusting for confounders, residual confounding due to unmeasured factors remains possible. Finally, while a large sample size was available for obesity measures, the sample size was modest for assessing associations with cardiometabolic biomarkers and asthma/allergy outcomes, especially in sex-stratified analyses.

5. Conclusions

BP-1 and BP-3 UV filters exposure was associated with increased odds of obesity in a large sample of European male teenagers. In a subsample of the population, BP-3 exposure was also associated with higher odds of non-food allergy among males, while BP-1 exposure was associated with lower serum adiponectin levels in females. These findings underscore the importance of biomonitoring urinary BP-1 and BP-3 concentrations in Europe using harmonized surveys to increase the

validity and representativeness of the data, providing useful information to update risk assessments and implement strategies to reduce exposure, especially in vulnerable populations such as teenagers. Given the study's cross-sectional design and the limited evidence available, further longitudinal epidemiological studies are warranted to confirm our results.

CRediT authorship contribution statement

Francisco M. Peinado: Writing – original draft, Methodology, Investigation. **Ainhoa Pérez-Cantero:** Writing – review & editing, Formal analysis. **Alicia Olivas-Martínez:** Writing – review & editing, Formal analysis. **Lydia Espín-Moreno:** Writing – review & editing, Formal analysis. **Tomás de Haro:** Writing – review & editing, Formal analysis. **Luis D. Boada:** Writing – review & editing, Investigation. **Andrea Rodríguez-Carrillo:** Writing – review & editing, Software. **Eva Govarts:** Writing – review & editing, Software. **Susana Pedraza-Díaz:** Writing – review & editing, Data curation. **Marta Esteban-López:** Writing – review & editing, Data curation. **Ludek Blaha:** Writing – review & editing, Formal analysis. **Lucie Blahova:** Writing – review & editing, Formal analysis. **Beata Janasik:** Writing – review & editing, Data curation. **Wojciech Wasowicz:** Writing – review & editing, Data curation. **Sanna Lignell:** Writing – review & editing, Data curation. **Loïc Rambaud:** Writing – review & editing, Data curation. **Margaux Riou:** Writing – review & editing, Data curation. **Clémence Fillol:** Writing – review & editing, Data curation. **Sébastien Denys:** Writing – review & editing, Data curation. **Aline Murawski:** Writing – review & editing, Data curation. **Anne Lise Brantsæter:** Writing – review & editing, Data curation. **Amrit Kaur Sakhi:** Writing – review & editing, Data curation. **Nina Iszatt:** Writing – review & editing, Supervision, Funding acquisition. **Greet Schoeters:** Writing – review & editing, Supervision, Funding acquisition. **Marike Kolossa-Gehring:** Writing – review & editing, Supervision, Funding acquisition. **Mariana F. Fernández:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Vicente Mustieles:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Data availability

Data is available upon reasonable request to the corresponding author and the Data Request Access Committee (DRAC) of the Personal Exposure and Health Data Platform (https://hbm.vito.be/peh-data-platform) of the Partnership for the Assessment of Risks from Chemicals (PARC) European project.

Generative AI disclosure

No Generative AI was used in the preparation of this manuscript.

Funding

This study was conducted as part of the European Human Biomonitoring Initiative (HMB4EU) project, funded by the European Union's Horizon 2020 research and innovation program under grant agreement No. 733032. It was also supported by its continuation, the European Project Partnership for the Assessment of Risks from Chemicals (PARC), No. 101057014. The views and opinions expressed are, however, those of the authors only and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.

The ESTEBAN study was funded by Santé Publique France and the French ministries of Health and the Environment. The BEA study was co-funded by the Spanish Ministry of Agriculture, Fisheries and Food and the Instituto de Salud Carlos III (SEG 1321/15). The Riksmaten Adolescents study was mainly financed by the Swedish Food Agency. Financial support was also provided from the Swedish Civil Contingencies Agency and from the Swedish Environmental Protection Agency (SEPA). The POLAES study was financially supported by Ministry of Education and Science (project no. 3764/H2020/2017/2). The NEB II study was funded by the Norwegian Institute of Public Health, and the work done as part of the HBM4EU aligned studies co-funded by two projects funded by the Research Council of Norway (references; 268465 and 275903). The GerES V study was funded by the German Ministry for Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) and the German Ministry of Education and Research (BMBF).

Vicente Mustieles was supported by a Sara Borrell postdoctoral research contract (CD22/00176), granted by the Instituto de Salud Carlos III (Spain) and Next Generation EU funds. Drs. Mustieles and Fernández acknowledge funding from the Instituto de Salud Carlos III grant No. FIS-PI23/01884, and the Biomedical Research Networking Center-CIBER de Epidemiología y Salud Pública (CIBERESP). We acknowledge the collaboration of the staff and facilities of the UGC de Laboratorios, Hospital Universitario Clínico San Cecilio (Granada, Spain). The authors also thank the Ministerio de Ciencia, Innovación y Universidades for the Programa Salvador de Madariaga awarded to MF Fernández (PRX23/00541) and the postdoctoral fellowship to Andrea Rodriguez-Carrillo granted by the Fundación Ramón Areces, Spain (ref. BEVP34P01S12928). Francisco M. Peinado was supported by a Juan de la Cierva postdoctoral contract (JDC2023-051457-I), funded by MCIN/AEI/10.13039/501100011033 and the European Union - European Social Fund Plus (FSE+). Alicia Olivas-Martínez and Ainhoa Pérez-Cantero were supported by a predoctoral contract (grants no. FI21/00236 and FI24/00299, respectively) granted by Instituto de Salud Carlos III (Spain).

Declaration of competing interest

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

Acknowledgements

We would like to thank all the study participants and families for their self-less participation and donation of biological samples in the cohorts/surveys analyzed. Funding for open access charge: Universidad de Granada / CBUA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.121912.

Data availability

Data will be made available on request.

References

Adoamnei, E., Mendiola, J., Moñino-García, M., Vela-Soria, F., Iribarne-Durán, L.M., Fernández, M.F., Olea, N., Jørgensen, N., Swan, S.H., Torres-Cantero, A.M., 2018. Urinary concentrations of benzophenone-type ultra violet light filters and reproductive parameters in young men. Int. J. Hyg Environ. Health 221, 531–540.

Albano, G.D., Gagliardo, R.P., Montalbano, A.M., Profita, M., 2022. Overview of the mechanisms of oxidative stress: impact in inflammation of the airway diseases. Antioxidants 11.

Ao, J., Yuan, T., Gao, L., Yu, X., Zhao, X., Tian, Y., Ding, W., Ma, Y., Shen, Z., 2018. Organic UV filters exposure induces the production of inflammatory cytokines in human macrophages. Sci. Total Environ. 635, 926–935.

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113, 192–200.

Berger, K., Gunier, R.B., Chevrier, J., Calafat, A.M., Ye, X., Eskenazi, B., Harley, K.G., 2018. Associations of maternal exposure to triclosan, parabens, and other phenols with prenatal maternal and neonatal thyroid hormone levels. Environ. Res. 165, 379–386.

Berger, K., Hyland, C., Ames, J.L., Mora, A.M., Huen, K., Eskenazi, B., Holland, N., Harley, K.G., 2021. Prenatal exposure to mixtures of phthalates, parabens, and other phenols and obesity in five-year-olds in the CHAMACOS cohort. Int. J. Environ. Res. Publ. Health 18.

Bláhová, L., Janoš, T., Mustieles, V., Rodríguez-Carrillo, A., Fernández, M.F., Bláha, L., 2023. Rapid extraction and analysis of oxidative stress and DNA damage biomarker 8-hydroxy-2'-deoxyguanosine (8-OHdG) in urine: application to a study with pregnant women. Int. J. Hyg Environ. Health 250, 114175.

Buckley, J.P., Herring, A.H., Wolff, M.S., Calafat, A.M., Engel, S.M., 2016. Prenatal exposure to environmental phenols and childhood fat mass in the Mount sinai Children's environmental health study. Environ. Int. 91, 350–356.

Buckley, J.P., Quirós-Alcalá, L., Teitelbaum, S.L., Calafat, A.M., Wolff, M.S., Engel, S.M., 2018. Associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic diseases among children aged 6 and 7 years. Environ. Int. 115, 79–88.

de Onis, M., Onyango, A.W., Borghi, E., Siyam, A., Nishida, C., Siekmann, J., 2007. Development of a WHO growth reference for school-aged children and adolescents. Bull. World Health Organ. 85, 660–667.

Deierlein, A.L., Wolff, M.S., Pajak, A., Pinney, S.M., Windham, G.C., Galvez, M.P., Rybak, M., Calafat, A.M., Kushi, L.H., Biro, F.M., Teitelbaum, S.L., 2017. Phenol concentrations during childhood and subsequent measures of adiposity among young girls. Am. J. Epidemiol. 186, 581–592.

Ding, X., Gerbig, S., Spengler, B., Schulz, S., 2018. Reactive low temperature plasma ionization mass spectrometry for the determination of organic UV filters in personal care products. Talanta 178, 780–787.

Esteban López, M., Göen, T., Mol, H., Nübler, S., Haji-Abbas-Zarrabi, K., Koch, H.M., Kasper-Sonnenberg, M., Dvorakova, D., Hajslova, J., Antignac, J.P., Vaccher, V., Elbers, I., Thomsen, C., Vorkamp, K., Pedraza-Díaz, S., Kolossa-Gehring, M., Castaño, A., 2021. The European human biomonitoring platform - design and implementation of a laboratory quality assurance/quality control (QA/QC) programme for selected priority chemicals. Int. J. Hyg Environ. Health 234, 113740.

EU, 2017. Commission regulation (EU) 2017/238 - 10 February 2017 - amending annex VI to regulation (EC) no 1223. 2009 of the European Parliament and of the Council on cosmetic products. https://eur-lex.europa.eu/eli/reg/2017/238/oj/eng/pdf.

Fantuzzi, G., 2008. Adiponectin and inflammation: consensus and controversy. J. Allergy Clin. Immunol. 121, 326–330.

Ferguson, K.K., Lan, Z., Yu, Y., Mukherjee, B., McElrath, T.F., Meeker, J.D., 2019. Urinary concentrations of phenols in association with biomarkers of oxidative stress in pregnancy: assessment of effects independent of phthalates. Environ. Int. 131, 104903.

GBD 2021, 2021. Adolescent BMI Collaborators. Global, regional, and national prevalence of child and adolescent overweight and obesity, 1990-2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. Lancet. 2025 405, (10481) 785-812. .

Ghazipura, M., McGowan, R., Arslan, A., Hossain, T., 2017. Exposure to benzophenone-3 and reproductive toxicity: a systematic review of human and animal studies. Reprod. Toxicol. 73, 175–183.

Gilles, L., Govarts, E., Rambaud, L., Vogel, N., Castaño, A., Esteban López, M., Rodriguez Martin, L., Koppen, G., Remy, S., Vrijheid, M., Montazeri, P., Birks, L., Sepai, O., Stewart, L., Fiddicke, U., Loots, I., Knudsen, L.E., Kolossa-Gehring, M., Schoeters, G., 2021. HBM4EU combines and harmonises human biomonitoring data across the EU, building on existing capacity – the HBM4EU survey. Int. J. Hyg Environ. Health 237, 113809.

Gilles, L., Govarts, E., Rodriguez Martin, L., Andersson, A.M., Appenzeller, B.M.R., Barbone, F., Castaño, A., Coertjens, D., Den Hond, E., Dzhedzheia, V., Eržen, I., López, M.E., Fábelová, L., Fillol, C., Franken, C., Frederiksen, H., Gabriel, C., Haug, L.S., Horvat, M., Halldórsson, T.I., Janasik, B., Holcer, N.J., Kakucs, R., Karakitsios, S., Katsonouri, A., Klánová, J., Kold-Jensen, T., Kolossa-Gehring, M., Konstantinou, C., Koponen, J., Lignell, S., Lindroos, A.K., Makris, K.C., Mazej, D., Morrens, B., Murínová Ľ, P., Namorado, S., Pedraza-Diaz, S., Peisker, J., Probst-Hensch, N., Rambaud, L., Rosolen, V., Rucic, E., Rüther, M., Sarigiannis, D., Tratnik, J.S., Standaert, A., Stewart, L., Szigeti, T., Thomsen, C., Tolonen, H., Eiríksdóttir, Á., Van Nieuwenhuyse, A., Verheyen, V.J., Vlaanderen, J., Vogel, N., Wasowicz, W., Weber, T., Zock, J.P., Sepai, O., Schoeters, G., 2022. Harmonization of human biomonitoring studies in Europe: characteristics of the HBM4EU-Aligned studies participants. Int. J. Environ. Res. Publ. Health 19.

Govarts, E., Gilles, L., Rambaud, L., Vogel, N., Montazeri, P., Rodriguez Martin, L., Schoeters, G., Berglund, M., Tägt, J., Santonen, T., 2020. Update Statistical Analysis Plan for the Co-Funded Studies of WP8, vol. 10. Deliverable Report D.

Govarts, E., Gilles, L., Rodriguez Martin, L., Santonen, T., Apel, P., Alvito, P., Anastasi, E., Andersen, H.R., Andersson, A.M., Andryskova, L., Antignac, J.P., Appenzeller, B., Barbone, F., Barnett-Itzhaki, Z., Barouki, R., Berman, T., Bil, W., Borges, T., Buekers, J., Cañas-Portilla, A., Covaci, A., Csako, Z., Den Hond, E., Dvorakova, D., Fabelova, L., Fletcher, T., Frederiksen, H., Gabriel, C., Ganzleben, C., Göen, T., Halldorsson, T.I., Haug, L.S., Horvat, M., Huuskonen, P., Imboden, M., Jagodic Hudobivnik, M., Janasik, B., Janev Holcer, N., Karakitsios, S., Katsonouri, A., Klanova, J., Kokaraki, V., Kold Jensen, T., Koponen, J., Laeremans, M., Laguzzi, F., Lange, R., Lemke, N., Lignell, S., Lindroos, A.K., Lobo Vicente, J., Luijten, M., Makris, K.C., Mazej, D., Melymuk, L., Meslin, M., Mol, H., Montazeri, P., Murawski, A., Namorado, S., Niemann, L., Nübler, S., Nunes, B., Olafsdottir, K., Palkovicova Murinova, L., Papaioannou, N., Pedraza-Diaz, S., Piler, P., Plichta, V., Poteser, M., Probst-Hensch, N., Rambaud, L., Rauscher-Gabernig, E., Rausova, K., Remy, S., Riou, M., Rosolen, V., Rousselle, C., Rüther, M., Sarigiannis, D., Silva, M.J., Šlejkovec, Z., Snoj Tratnik, J., Stajnko, A., Szigeti, T., Tarazona, J.V., Thomsen, C., Tkalec, Ž., Tolonen, H., Trnovec, T., Uhl, M., Van Nieuwenhuyse, A., Vasco, E., Verheyen, V.J., Viegas, S., Vinggaard, A.M., Vogel, N., Vorkamp, K., Wasowicz, W., Weber, T., Wimmerova, S., Woutersen, M., Zimmermann, P., Zvonar, M., Koch, H., Kolossa-Gehring, M., Esteban López, M., Castaño, A., Stewart, L., Sepai, O., Schoeters, G., 2023. Harmonized human biomonitoring in European children, teenagers and adults: EU-wide exposure data of 11 chemical substance groups from the HBM4EU Aligned studies (2014-2021). Int. J. Hyg Environ. Health 249, 114119.

Greenland, S., 2003. Quantifying biases in causal models: classical confounding vs collider-stratification bias. Epidemiology (Camb., Mass.) 14, 300–306.

Güil-Oumrait, N., Cano-Sancho, G., Montazeri, P., Stratakis, N., Warembourg, C., Lopez-Espinosa, M.J., Vioque, J., Santa-Marina, L., Jimeno-Romero, A., Ventura, R., Monfort, N., Vrijheid, M., Casas, M., 2022. Prenatal exposure to mixtures of phthalates and phenols and body mass index and blood pressure in Spanish preadolescents. Environ. Int. 169, 107527.

Güil-Oumrait, N., Valvi, D., Garcia-Esteban, R., Guxens, M., Sunyer, J., Torrent, M., Casas, M., Vrijheid, M., 2021. Prenatal exposure to persistent organic pollutants and markers of obesity and cardiometabolic risk in Spanish adolescents. Environ. Int. 151, 106469.

Harley, K.G., Berger, K.P., Kogut, K., Parra, K., Lustig, R.H., Greenspan, L.C., Calafat, A. M., Ye, X., Eskenazi, B., 2019. Association of phthalates, parabens and phenols found in personal care products with pubertal timing in girls and boys. Hum. Reprod. 34, 109–117.

Harley, K.G., Kogut, K., Madrigal, D.S., Cardenas, M., Vera, I.A., Meza-Alfaro, G., She, J., Gavin, Q., Zahedi, R., Bradman, A., Eskenazi, B., Parra, K.L., 2016. Reducing phthalate, paraben, and phenol exposure from personal care products in adolescent girls: findings from the HERMOSA intervention study. Environ. Health Perspect. 124, 1600–1607.

Ioniuc, I.K., Lupu, A., Dragan, F., Tarnita, I., Alexoae, M.M., Streanga, V., Mitrofan, C., Thet, A.A., Nedelcu, A.H., Salaru, D.L., Burlea, S.L., Mitrofan, E.C., Lupu, V.V., Azoicai, A.N., 2024. Oxidative stress and antioxidants in pediatric asthma's evolution and management. Antioxidants 13.

Kim, S., Choi, K., 2014. Occurrences, toxicities, and ecological risks of benzophenone-3, a common component of organic sunscreen products: a mini-review. Environ. Int. 70, 143–157.

Krause, M., Frederiksen, H., Sundberg, K., Jørgensen, F.S., Jensen, L.N., Nørgaard, P., Jørgensen, C., Ertberg, P., Juul, A., Drzewiecki, K.T., Skakkebaek, N.E., Andersson, A.M., 2018. Presence of benzophenones commonly used as UV filters and absorbers in paired maternal and fetal samples. Environ. Int. 110, 51–60.

Krause, M., Klit, A., Blomberg Jensen, M., Søeborg, T., Frederiksen, H., Schlumpf, M., Lichtensteiger, W., Skakkebaek, N.E., Drzewiecki, K.T., 2012. Sunscreens: are they beneficial for health? An overview of endocrine disrupting properties of UV-filters. Int. J. Androl. 35, 424–436.

Lee, J., Kim, S., Park, Y.J., Moon, H.B., Choi, K., 2018. Thyroid hormone-disrupting potentials of major benzophenones in two cell lines (GH3 and FRTL-5) and embryo-larval zebrafish. Environ. Sci. Technol. 52, 8858–8865.

Lee, K., Lee, S.H., Kim, T.H., 2020. The biology of prostaglandins and their role as a target for allergic airway disease therapy. Int. J. Mol. Sci. 21.

Li, A.J., Xue, J., Lin, S., Al-Malki, A.L., Al-Ghamdi, M.A., Kumosani, T.A., Kannan, K., 2018. Urinary concentrations of environmental phenols and their association with type 2 diabetes in a population in Jeddah, Saudi Arabia. Environ. Res. 166, 544–552.

Li, Z.M., Kannan, K., 2022. Comprehensive survey of 14 benzophenone UV filters in sunscreen products marketed in the United States: implications for human exposure. Environ. Sci. Technol. 56, 12473–12482.

Liao, C., Kannan, K., 2014. Widespread occurrence of benzophenone-type UV light filters in personal care products from China and the United States: an assessment of human exposure. Environ. Sci. Technol. 48, 4103–4109.

Lubin, J.H., Colt, J.S., Camann, D., Davis, S., Cerhan, J.R., Severson, R.K., Bernstein, L., Hartge, P., 2004. Epidemiologic evaluation of measurement data in the presence of detection limits. Environ. Health Perspect. 112, 1691–1696.

Matta, M.K., Florian, J., Zusterzeel, R., Pilli, N.R., Patel, V., Volpe, D.A., Yang, Y., Oh, L., Bashaw, E., Zineh, I., Sanabria, C., Kemp, S., Godfrey, A., Adah, S., Coelho, S., Wang, J., Furlong, L.A., Ganley, C., Michele, T., Strauss, D.G., 2020. Effect of sunscreen application on plasma concentration of sunscreen active ingredients: a randomized clinical trial. JAMA 323, 256–267.

Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., 1985. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia (Berl.) 28, 412–419.

Messerlian, C., Mustieles, V., Minguez-Alarcon, L., Ford, J.B., Calafat, A.M., Souter, I., Williams, P.L., Hauser, R., 2018. Preconception and prenatal urinary concentrations of phenols and birth size of singleton infants born to mothers and fathers from the environment and reproductive health (EARTH) study. Environ. Int. 114, 60–68.

Molina-Molina, J.M., Escande, A., Pillon, A., Gomez, E., Pakdel, F., Cavaillès, V., Olea, N., Aït-Aïssa, S., Balaguer, P., 2008. Profiling of benzophenone derivatives using fish and human estrogen receptor-specific in vitro bioassays. Toxicol. Appl. Pharmacol. 232, 384–395.

Moon, S., Seo, M.Y., Choi, K., Chang, Y.S., Kim, S.H., Park, M.J., 2021. Urinary bisphenol A concentrations and the risk of obesity in Korean adults. Sci. Rep. 11, 1603.

Morrison, G.C., Bekö, G., Weschler, C.J., Schripp, T., Salthammer, T., Hill, J., Andersson, A.M., Toftum, J., Clausen, G., Frederiksen, H., 2017. Dermal uptake of Benzophenone-3 from clothing. Environ. Sci. Technol. 51, 11371–11379.

Mustieles, V., Balogh, R.K., Axelstad, M., Montazeri, P., Márquez, S., Vrijheid, M., Draskau, M.K., Taxvig, C., Peinado, F.M., Berman, T., Frederiksen, H., Fernández, M. F., Marie Vinggaard, A., Andersson, A.M., 2023. Benzophenone-3: comprehensive

review of the toxicological and human evidence with meta-analysis of human biomonitoring studies. Environ. Int. 173, 107739.
Mustieles, V., Fernández, M.F., Messerlian, C., 2024. Utero metabolic Disruption-A preventable antecedent of adult disease? JAMA Netw. Open 7, e2412022.
O'Brien, K.M., Upson, K., Cook, N.R., Weinberg, C.R., 2016. Environmental chemicals in urine and blood: improving methods for creatinine and lipid adjustment. Environ. Health Perspect. 124, 220–227.
Panico, A., Serio, F., Bagordo, F., Grassi, T., Idolo, A., M, D.E.G., Guido, M., Congedo, M., A, D.E.D., 2019. Skin safety and health prevention: an overview of chemicals in cosmetic products. J Prev Med Hyg 60, E50–e57.
Perrier, F., Giorgis-Allemand, L., Slama, R., Philippat, C., 2016. Within-subject pooling of biological samples to reduce exposure misclassification in biomarker-based studies. Epidemiology (Camb., Mass.) 27, 378–388.
Philippat, C., Heude, B., Botton, J., Alfaidy, N., Calafat, A.M., Slama, R., 2019. Prenatal exposure to select phthalates and phenols and associations with fetal and placental weight among Male births in the EDEN cohort (France). Environ. Health Perspect. 127, 17002.
Pollack, A.Z., Mumford, S.L., Krall, J.R., Carmichael, A.E., Sjaarda, L.A., Perkins, N.J., Kannan, K., Schisterman, E.F., 2018. Exposure to bisphenol A, chlorophenols, benzophenones, and parabens in relation to reproductive hormones in healthy women: a chemical mixture approach. Environ. Int. 120, 137–144.
Przybyla, J., Geldhof, G.J., Smit, E., Kile, M.L., 2018. A cross sectional study of urinary phthalates, phenols and perchlorate on thyroid hormones in US adults using structural equation models (NHANES 2007-2008). Environ. Res. 163, 26–35.
Rallis, D., Balomenou, F., Tzoufi, M., Giapros, V., 2021. A systematic review indicates an association between birth weight and body fat in childhood. Acta Paediatr. 110, 2023–2039.
Rocha, B.A., Asimakopoulos, A.G., Honda, M., da Costa, N.L., Barbosa, R.M., Barbosa Jr., F., Kannan, K., 2018. Advanced data mining approaches in the assessment of urinary concentrations of bisphenols, chlorophenols, parabens and benzophenones in Brazilian children and their association to DNA damage. Environ. Int. 116, 269–277.
Romano, M.E., Savitz, D.A., Braun, J.M., 2014. Challenges and future directions to evaluating the association between prenatal exposure to endocrine disrupting chemicals and childhood obesity. Curr Epidemiol Rep 1, 57–66.
Rousselle, C., Meslin, M., Berman, T., Woutersen, M., Bil, W., Wildeman, J., Chaudhry, Q., 2022. Using human biomonitoring data to support risk assessment of cosmetic Ingredients-A case study of Benzophenone-3. Toxics 10.
Salamanca-Fernández, E., Iribarne-Durán, L.M., Rodríguez-Barranco, M., Vela-Soria, F., Olea, N., Sánchez-Pérez, M.J., Arrebola, J.P., 2020. Historical exposure to non-persistent environmental pollutants and risk of type 2 diabetes in a Spanish sub-cohort from the European prospective investigation into cancer and nutrition study. Environ. Res. 185, 109383.
Santonen, T., Mahiout, S., Alvito, P., Apel, P., Bessems, J., Bil, W., Borges, T., Bose-O'Reilly, S., Buekers, J., Cañas Portilla, A.I., Calvo, A.C., de Alba González, M., Domínguez-Morueco, N., López, M.E., Falnoga, I., Gerofke, A., Caballero, M., Horvat, M., Huuskonen, P., Kadikis, N., Kolossa-Gehring, M., Lange, R., Louro, H., Martins, C., Meslin, M., Niemann, L., Díaz, S.P., Plichta, V., Porras, S.P., Rousselle, C., Scholten, B., Silva, M.J., Šlejkovec, Z., Tratnik, J.S., Joksić, A., Tarazona, J.V., Uhl, M., Van Nieuwenhuyse, A., Viegas, S., Vinggaard, A.M., Woutersen, M., Schoeters, G., 2023. How to use human biomonitoring in chemical risk assessment: methodological aspects, recommendations, and lessons learned from HBM4EU. Int. J. Hyg Environ. Health 249, 114139.
SCCS, 2021, 2021. Scientific Committee on Consumer Safety SCCS OPINION on Benzophenone-3 3. .
SCCS. Scientific Committee on Consumer Safety SCCS OPINION on Benzophenone-3. 2021, Schmutzler, C., Gotthardt, I., Hofmann, P.J., Radovic, B., Kovacs, G., Stemmler, L., Nobis, I., Bacinski, A., Mentrup, B., Ambrugger, P., Grüters, A., Malendowicz, L.K., Christoffel, J., Jarry, H., Seidlovà-Wuttke, D., Wuttke, W., Köhrle, J., 2007. Endocrine disruptors and the thyroid gland–a combined in vitro and in vivo analysis of potential new biomarkers. Environ. Health Perspect. 115 (Suppl. 1), 77–83.
Schoeters, G., Lange, R., Kolossa, M., Barouki, R., Tarroja, E., Uhl, M., Klanova, J., Melymuk, L., Horvat, M., Bocca, B., Sarigiannis, D., Santonen, T., Mahiout, S., Luijten, M., Laguzzi, F., Kadikis, N., Wasowicz, W., Szigeti, T., Katsonouri-Sazeides, A., Alvito, P., Silva, M.J., Viegas, S., Raun Andersen, H., Berman, T., 2020. Scoping document for the first and second round HBM4EU priority substances: HBM4EU. (Accessed 24 October 2024). https://www.hbm4eu.eu/wp-content/uploads/2021/03/HBM4EU_D4.9_Scoping_Documents_HBM4EU_priority_substances_v1.0.pdf.
Scinicariello, F., Buser, M.C., 2016. Serum testosterone concentrations and urinary bisphenol A, Benzophenone-3, Triclosan, and paraben levels in Male and female children and adolescents: NHANES 2011-2012. Environ. Health Perspect. 124, 1898–1904.
Shin, J.C., Lee, E., An, S., Jin, S.H., Ha, J., Choi, W.J., Noh, M., 2020. Benzophenone-3 and benzophenone-8 exhibit obesogenic activity via peroxisome proliferator-activated receptor γ pathway. Toxicol. Vitro 67, 104886.
Silva, A.R., Gonçalves-de-Albuquerque, C.F., Pérez, A.R., Carvalho, V.F., 2019. Immune-endocrine interactions related to a high risk of infections in chronic metabolic diseases: the role of PPAR gamma. Eur. J. Pharmacol. 854, 272–281.
Song, S., He, Y., Huang, Y., Huang, X., Guo, Y., Zhu, H., Kannan, K., Zhang, T., 2020. Occurrence and transfer of benzophenone-type ultraviolet filters from the pregnant women to fetuses. Sci. Total Environ. 726, 138503.
Tschersich, C., Murawski, A., Schwedler, G., Rucic, E., Moos, R.K., Kasper-Sonnenberg, M., Koch, H.M., Brüning, T., Kolossa-Gehring, M., 2021. Bisphenol A and six other environmental phenols in urine of children and adolescents in Germany - human biomonitoring results of the German environmental survey 2014-2017 (GerES V). Sci. Total Environ. 763, 144615.
Vernet, C., Pin, I., Giorgis-Allemand, L., Philippat, C., Benmerad, M., Quentin, J., Calafat, A.M., Ye, X., Annesi-Maesano, I., Siroux, V., Slama, R., 2017. Utero exposure to select phenols and phthalates and respiratory health in five-year-old boys: a prospective study. Environ. Health Perspect. 125, 097006.
Wang, P., Huang, Y., Zhao, Y., Zhou, Y., Wang, H., Zhang, L., Shi, H., Sze-Yin Leung, K., Zhang, Y., 2022. Organic UV filters mixture exposure and childhood adiposity: a prospective follow-up study in China. Environ. Int. 158, 106912.
Wang, Z., Mínguez-Alarcón, L., Williams, P.L., Bellavia, A., Ford, J.B., Keller, M., Petrozza, J.C., Calafat, A.M., Hauser, R., James-Todd, T., 2020. Perinatal urinary benzophenone-3 concentrations and glucose levels among women from a fertility clinic. Environ. Health 19, 45.
Watanabe, Y., Kojima, H., Takeuchi, S., Uramaru, N., Sanoh, S., Sugihara, K., Kitamura, S., Ohta, S., 2015. Metabolism of UV-filter benzophenone-3 by rat and human liver microsomes and its effect on endocrine-disrupting activity. Toxicol. Appl. Pharmacol. 282, 119–128.
Wnuk, A., Rzemieniec, J., Staroń, J., Litwa, E., Lasoń, W., Bojarski, A., Kajta, M., 2019. Prenatal exposure to Benzophenone-3 impairs autophagy, disrupts RXRs/PPARγ signaling, and alters epigenetic and post-translational statuses in brain neurons. Mol. Neurobiol. 56, 4820–4837.
Wolff, M.S., Engel, S.M., Berkowitz, G.S., Ye, X., Silva, M.J., Zhu, C., Wetmur, J., Calafat, A.M., 2008. Prenatal phenol and phthalate exposures and birth outcomes. Environ. Health Perspect. 116, 1092–1097.
Xue, J., Wu, Q., Sakthivel, S., Pavithran, P.V., Vasukutty, J.R., Kannan, K., 2015. Urinary levels of endocrine-disrupting chemicals, including bisphenols, bisphenol A diglycidyl ethers, benzophenones, parabens, and triclosan in obese and Non-obese Indian children. Environ. Res. 137, 120–128.
Ye, L., Wang, B., Xu, H., Zhang, X., 2023. The emerging therapeutic role of prostaglandin E2 signaling in pulmonary hypertension. Metabolites 13.
Zhang, B., Ruan, J.J., Xie, L., Gui, M.W., Bai, X.Y., Zhang, T., 2018. Urinary benzophenone-type UV filters in people living in south China: rural versus urban areas. Environ Sci Process Impacts 20, 553–560.
ECHA, 2021. Oxybenzone - Substance Information: https://www.echa.europa.eu/substance-information/-/substanceinfo/100.004.575.