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Review article

Benzophenone-3: Comprehensive review of the toxicological and human evidence with meta-analysis of human biomonitoring studies

Vicente Mustieles [a,b,c,*,1], Ria K. Balogh [d,e,1], Marta Axelstad [f,1], Parisa Montazeri [c,g,h], Sandra Márquez [c,g,h], Martine Vrijheid [c,g,h], Monica K. Draskau [f], Camilla Taxvig [f], Francisco M. Peinado [a,b], Tamar Berman [i], Hanne Frederiksen [d,e], Mariana F. Fernández [a,b,c,*], Anne Marie Vinggaard [f,2], Anna-Maria Andersson [d,e,2]

[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] Department of Growth and Reproduction, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[e] International Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[f] National Food Institute, Technical University of Denmark, Kgs. Lyngby, Denmark
[g] ISGlobal, Barcelona, Spain
[h] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[i] Department of Environmental Health, Ministry of Health, Jerusalem 9101002, Israel

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ABSTRACT

Background: Benzophenone-3 (BP-3) and its major metabolite benzophenone-1 (BP-1) are widely used as UV filters in sunscreens and cosmetics to prevent sunburn and skin damage, or as stabilizers to prevent photodegradation in many commercial products. As a result, their presence is ubiquitous in the environment, wildlife and humans. Based on endocrine disruption concerns, international regulatory agencies are performing a closer evaluation.

Objective and methods: This work aimed to comprehensively review the available human relevant evidence for safety issues in MEDLINE/PubMed in order to create a structured database of studies, as well as to conduct an integrative analysis as part of the Human Biomonitoring for Europe (HBM4EU) Initiative.

Results: A total of 1,635 titles and abstracts were screened and 254 references were evaluated and tabulated in detail, and classified in different categories: i) exposure sources and predictors; ii) human biomonitoring (HBM) exposure levels to perform *a* meta-analysis; iii) toxicokinetic data in both experimental animals and humans; iv) *in vitro* and *in vivo* rodent toxicity studies; and v) human data on effect biomarkers and health outcomes. Our integrative analysis showed that internal peak BP-3 concentrations achieved after a single whole-body application of a commercially available sunscreen (4% w/w) may overlap with concentrations eliciting endocrine disrupting effects *in vitro*, and with internal concentrations causing *in vivo* adverse female reproductive effects in rodents that were supported by still limited human data. The adverse effects in rodents included prolonged estrous cycle, altered uterine estrogen receptor gene expression, endometrium hyperplasia and altered proliferation and histology of the mammary gland, while human data indicated menstrual cycle hormonal alterations and increased risk of uterine fibroids and endometriosis. Among the modes of action reported (estrogenic, antiandrogenic, thyroid, etc.), BP-3 and especially BP-1 showed estrogenic activity at human-relevant concentrations, in agreement with the observed alterations in female reproductive endpoints. The meta-analysis of HBM studies identified a higher concern for North Americans, showing urinary BP-3 concentrations on average 10 and 20 times higher than European and Asian populations, respectively.

* Corresponding authors at: University of Granada, Biomedical Research Center (CIBM), Granada, Spain.
E-mail addresses: vmustieles@ugr.es (V. Mustieles), marieta@ugr.es (M.F. Fernández).
[1] Co-first authors.
[2] Co-last authors.

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Discussion and conclusions: Our work supports that these benzophenones present endocrine disrupting properties, endorsing recent European regulatory efforts to limit human exposure. The reproducible and comprehensive database generated may constitute a point of departure in future risk assessments to support regulatory initiatives. Meanwhile, individuals should not refrain from sunscreen use. Commercially available formulations using inorganic UV filters that are practically not absorbed into systemic circulation may be recommended to susceptible populations.

1. Introduction

Excessive solar exposure is a recognized risk factor for photoaging, sunburn and skin cancer. Thus, dermatological associations recommend applying sunscreen to exposed body areas, which has been shown effective for skin cancer prevention (Green et al., 2011; Sander et al., 2020). The demand for sunscreen products has consequently increased in the last years. However, the massive production of chemical ultraviolet (UV) filters is leading to substantial release into the environment and widespread non-intentional human exposure. Growing knowledge highlights man-made chemical UV filters as emerging pollutants with deleterious effects for aquatic life and endocrine disrupting activity in living organisms (Huang et al., 2021).

Benzophenone-3 (BP-3), also named 2-hydroxy-4-methoxybenzophenone, and referred to as "oxybenzone", is the benzophenone derivative most widely used as a UV filter in sunscreens and cosmetics. The European Chemicals Agency (ECHA) also considers its potential use as a UV stabilizer to avoid photodegradation in plastic surface coatings, plastic food containers, building and electronic materials, furniture, toys and inks among many other applications (ECHA, 2021a). Benzophenone-1 (BP-1), also known as 2,4-dihydroxybenzophenone, is the major BP-3 metabolite found in both rodents and humans (Mutlu et al., 2020). Although BP-1 is thought to be used in cosmetics and plastics as a UV stabilizer (ECHA, 2021b; Park et al., 2013; Suzuki et al., 2005), data on the direct use of BP-1 in consumer products is scarce.

Benzophenone and its derivatives naturally occur in flowering plants such as mango and muscat grape (Zhang et al., 2019), but are synthesized for commercial use. BP-3 was first synthesized in 1906, and the U. S. Food and Drug Administration (FDA) approved its use in sunscreen products in the 1980s (ACS, 2018). However, recent concern about its safety has led different countries to perform a closer scrutiny. In the U.S., the FDA has prioritized BP-3 among other chemical UV filters in order to generate additional toxicological data and revisit its safety (FDA, 2019). Specific regions such as Hawaii and Key West (Florida) have even banned the use of BP-3 and other ingredients in sunscreens to protect coral reefs (Narla and Lim, 2020). In Europe, BP-3 was included in the Community Rolling Action Plan (CoRAP) list by the ECHA based on potential endocrine disruption (ECHA, 2014). Since 2017, the allowed content of BP-3 in the European Union (EU) has been reduced from 10% of product weight to a maximum of 6% in sunscreens and up to maximum 0.5% in other cosmetic products (EU, 2017). In 2018, the European Commission included BP-1 in the priority list of potential endocrine disruptors (EC, 2018). Also in 2018, the EU asked the Scientific Committee on Consumer Safety (SCCS) for a scientific opinion on the safety of BP-3, which in 2021 concluded that the use of BP-3 as a UV-filter up to a maximum concentration of 6% BP-3 in sunscreen products was not safe for consumers (SCCS, 2021).

BP-1 and BP-3 are chemicals with a short half-life (in the order of hours to days) that are rapidly excreted into urine. Both show estrogenic and anti-androgenic activity *in vitro*, and there is concern about their reproductive toxicity in rodents (Ghazipura et al., 2017; Kim and Choi, 2014). Although benzophenones constitute one of the best-known UV filter families, knowledge gaps still remain. Given the wealth of new information published in recent years, this work aimed to comprehensively review the available evidence in order to create a structured database of studies, as well as to conduct an integrative analysis as part of the Human Biomonitoring for Europe (HBM4EU) Initiative, a joint effort of 30 countries, the European Environment Agency and the European Commission, co-funded by Horizon 2020 with the aim to coordinate and advance human biomonitoring (HBM) in Europe to provide evidence for policy-making. Our work had the following *a priori* objectives: a) to identify exposure sources and predictors of exposure; b) to compare and meta-analyze HBM data for BP-3 and BP-1 worldwide; c) to summarize toxicokinetic data obtained in animals and humans; d) to evaluate relevant *in vitro* and *in vivo* toxicological data; e) to analyze all relevant human exposure-health studies available; and f) to identify research gaps and future steps.

2. Methods

2.1. Literature search methodology

This comprehensive review covered all scientific publications available in the PubMed/MEDLINE database without date restrictions, to provide a comprehensive coverage of human BP-3 and BP-1 exposure sources, levels, and adverse effects in experimental animals and humans. Given the wide scope, a multistep search strategy was performed.

First, the main search was conducted by entering the terms "Benzophenone-3 OR oxybenzone OR 2-hydroxy-4-methoxybenzophenone OR Benzophenone-1 OR 2,4-dihydroxy-benzophenone" in the MEDLINE database (no filters). By the 1st of January 2021, 957 references containing any of these exposure terms were retrieved. The keywords "benzophenone", "UV filter" or "sunscreen" could not be used in the main search given the large, unspecific and unapproachable number of references retrieved. Second, references cited by previously published reviews on BP-3 were also screened. This strategy evidenced some ancient *in vitro* references that tested several UV filter families, but without specifying "benzophenone-3" or "oxybenzone" in the title/abstract. Consequently, to identify references that escaped the main search terms, complementary searches were performed as an additional step following the algorithm "benzophenone OR UV filter OR sunscreen AND specific outcome". Specific outcomes included "puberty", "neurodevelopment OR neurocognition", "prenatal", "biomonitoring", "semen", "fertility", "thyroid" and "androgen". In these complementary searches, 678 additional titles/abstracts were screened (date: 1st of January 2021), that allowed to retrieve additional references, including those identified in previous review works. Finally, expert committee or national reports on the safety of BP-3 and human exposure levels were consulted.

2.2. Screening, classification and data extraction

All the titles and abstracts were screened by one author (VM) to determine eligibility based on exclusion criteria. A second author (MFF) screened 25% of titles/abstracts for quality assurance. Studies fitting our aims were selected and classified in the supplementary excel inventory database (INVENTORY-DB, Supplementary data 1). Fig. 1 shows a flowchart of the selection process together with the exclusion criteria. Out of 957 references screened in the main search, 209 studies were selected. Out of 678 references screened in the complementary searches, 42 additional studies were identified. Three additional reports not retrieved from PubMed were included (CDC, 2019; NTP, 2021, 2019). The resulting 254 selected references were classified in the INVENTORY-DB under the following categories: a) Exposure sources and predictors; b)

Human exposure; c) Human exposure-health associations; d) Human toxicokinetic intervention studies; e) Rodent toxicokinetic studies; f) In vitro assays and g) In vivo rodent studies (Fig. 1). These categories are indicative, which explains why the last box in Fig. 1 sums up to 335 studies, since some of the 254 selected references provided data for several categories (for example both *in vitro* and *in vivo* information, or HBM and exposure-health data).

An HBM database (see Supplementary data 2 HBM-DB) was created to retrieve and tabulate BP-3 and BP-1 HBM concentrations extracted from the available human literature. For this, the 152 references included in the first three categories (sources and predictors, human exposure and human exposure-health studies) were screened, selecting the 125 studies containing HBM data (Figure S1). Summary statistics on BP-3 and BP-1 concentrations in human biological matrices (mean, SD, minimum, maximum, median, geometric mean and percentiles) were extracted, together with study and population characteristics: year and country of sample collection, sex (male/female), age, sample size, and type of matrix and sampling method (e.g., spot urine vs. 24-h urine). When available, HBM data was extracted stratified by age and sex. Some studies/publications provided more than one data point for the evaluation of reported average BP-3 and BP-1 concentrations (e.g., one for males and one for females or for different age groups). The majority of publications (n = 108) reported BP-3 concentrations in urine. Of these, 35 publications also reported urinary BP-1 concentrations and 13 also reported urinary concentrations of BP-8, a minor BP-3 metabolite. However, only in two studies was the detection rate for urinary BP-8 higher than 50%, and therefore BP-8 was not further analyzed. A few publications reported BP-3 (and BP-1) concentrations measured in other matrices, such as blood (n = 12), cord blood (n = 1), breast milk (n = 3), amniotic fluid (n = 3), seminal plasma (n = 3), adipose tissue (n = 4), breast tissue (n = 1), nails (n = 1), brain tissue (n = 1) and placenta (n = 2). Of note, most studies measuring internal concentrations were pilot studies analyzing small sample sizes. Therefore, we focused our work and meta-analyses on biomonitoring studies using urine as the optimal exposure matrix for non-persistent chemicals (Calafat et al., 2015).

Apart from the studies tabulated in the HBM-DB, the remaining references investigating exposure sources and predictors, exposure-health associations, human toxicokinetic, *in vitro* and *in vivo* studies were synthesized and tabulated in detail, considering study quality parameters such as study design, characteristics of the population (e.g., sample/litter size and ethnicity/strain), exposure assessment or dosing (dose and route in cells/animals, timing of exposure, biological matrix in humans, number of samples analyzed, methods followed and quality measures), the effect biomarkers measured (biological matrix and the analytical method used), together with strengths and limitations of the studies. Data extraction was performed by one researcher specialized on the *in vitro*, *in vivo* or epidemiologic part, and supervised by at least one additional researcher. After the quality assessment, consistency of results across mechanistic, toxicokinetic, animal and epidemiological data was considered as the highest level of confidence in this integrative review.

2.3. Comparison and analysis of extracted HBM data

To provide an overview of reported average BP-3 (and BP-1) levels in humans, we relied on graphic presentations of the reported geometric mean or median urinary concentrations in relation to geographic region, period of sample collection, age and sex of study population (Fig. S2-4). Additionally, adjusted summary estimates of exposure levels by region, age, period and sex were meta-analyzed for the most comparable urinary BP-3 HBM datasets.

For comparison between different studies, the extracted urinary HBM BP-3 (and BP-1) data was harmonized and recoded as extensively described in the supplemental excel file (HBM-DB). In brief, studies were assigned to eight different geographic regions according to the country of sampling: North- and South-America, Northern, Southern, and Western Europe, Asia, Africa, and Australia. For the meta-analysis, all included European studies were recoded as one regional category (Europe), while South-American, African and Australian reports were omitted due to the very limited number of studies. We defined three age groups: children (0–11 years), adolescents (12–17 years), and adults (≥18 years old). For meta-analyses, year of sampling was stratified into four categories: 1996–2003, 2004–2008, 2009–2013 and 2014–2019, while in the graphic presentation of data in relation to period of sampling, data was plotted against the median year of the period (Figure S3).

Studies differed regarding mode of sampling (spot, morning and 24 h urine), whether and how urinary dilution was dealt with, and whether median, geometric mean (GM), or mean levels were reported. Based on

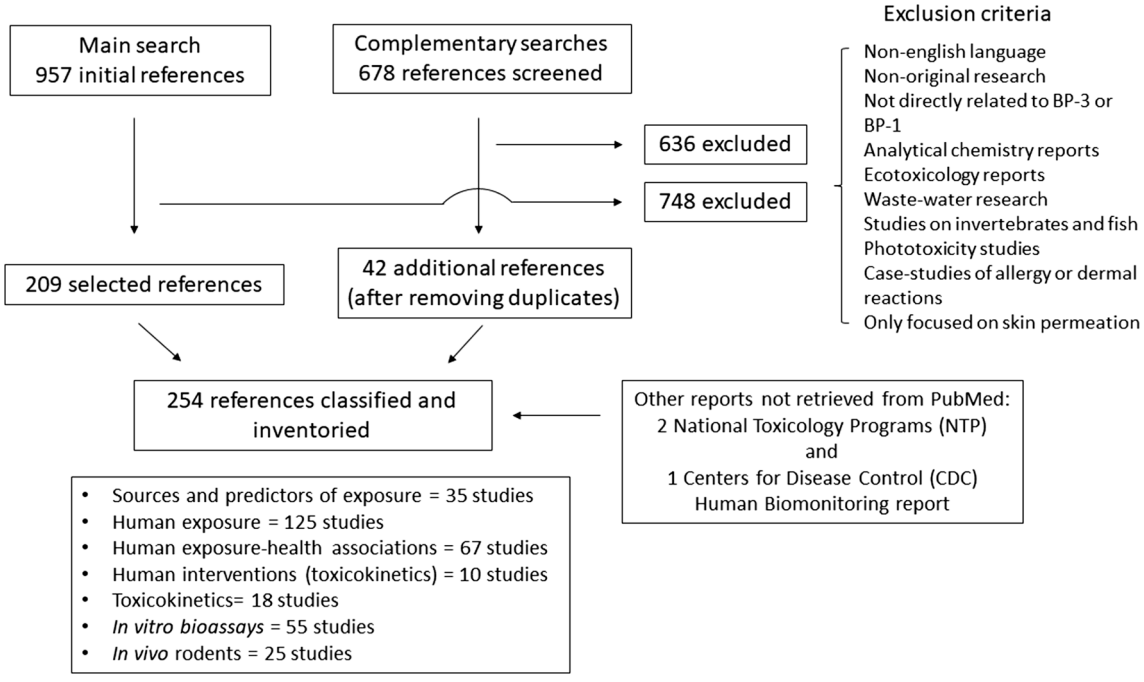

Fig. 1. Flow-chart of the literature search selection process and exclusion criteria.

the studies which reported both GM and median values or both crude and urinary dilution standardized concentrations, we observed that the reported average levels were highly correlated (R^2 ≈ 0.96, Figures S5A and S5B). Furthermore, GM and median values were assumed equivalent given that BP-3 has a log-normal distribution (Limpert et al., 2001). Therefore, we constructed a combined variable for reported BP-3 (and BP-1) GM and median levels, irrespective of sampling mode or whether crude or standardized concentrations were reported by using either the crude GM, standardized GM, crude median or standardized median, in that order. For studies reporting BP-3 HBM data in several overlapping publications, a unique publication (typically the one containing the most comprehensive/large data set from the study) was chosen to avoid duplication bias.

For the meta-analytic evaluation of BP-3, all datasets that fulfilled the following criteria were selected: 1) reported the GM with 95% CI or median urinary concentrations with quartile 1 (q1) and 3 (q3) data given from urinary concentrations above the limit of detection; 2) samples were collected within a defined period; 3) data was reported for defined age-groups; and 4) data was reported for males and females separately. This resulted in 38 data points from 25 publications included in the subsequent data modeling (Figure S1). The extended methods detail how data was further processed for meta-analyses (Supplementary data 3, page 2).

Prior to meta-analyses we calculated the SE from 95% CI. GM (or median) and SE data were natural log-transformed to achieve a more normal distribution. The meta-analysis was conducted in two parts: 1) sub-group analysis based on individual factor variables, and 2) meta-regression analysis to allow the effects of multiple factors to be investigated simultaneously. Factor variables used for sub-group analyses and meta-regression were: geographic region (Asia, Europe, North America), period of sample collection (1996–2003, 2004–2008, 2009–2013, 2014–2019), age-group (children: 0–11 years, adolescents: 12–17 years, adults: ≥18 years), and sex (female, male). Chi-square and the Higgins I^2 tests were used to assess the heterogeneity among studies. As studies had high heterogeneity (>90%), a random-effects model using the restricted maximum likelihood (REML) method was applied to pool and analyze studies (Veroniki et al., 2016). All analyses were performed in R version 4.0.3 (RStudio Team, 2020), using the "metagen" and "metafor" packages. The significance level was set at 0.05.

3. Results

3.1. Exposure sources and predictors

Tables S1 and S2 (Supplementary data 3) provide detailed information on potential or known exposure sources for BP-3 and BP-1, as well as exposure predictors. Table 1 summarize the key points of this section.

Systemic absorption of BP-3 from sunscreen formulations through skin has been demonstrated in intervention trials (Janjua et al., 2008; Matta et al., 2020), being considered the most specific and direct human exposure source. Observational studies consistently identified sunscreen use as a significant predictor of BP-3 exposure (Ashrap et al., 2018; Berger et al., 2019; Dodson et al., 2020; Ferguson et al., 2017; Mínguez-Alarcón et al., 2019; Philippat et al., 2015; Zamoiski et al., 2015). For example, Zamoiski et al., (2015) analysed more than 4,000 adult participants in the U.S. National Health and Nutrition Examination Survey (NHANES), finding significant increases in urinary geometric mean (GM) BP-3 concentrations across categories of self-reported sunscreen use from never users (9.3 ng/mL), rarely (14.8 ng/mL), sometimes (32.2 ng/mL), most of the time (74.2 ng/mL) and always users (116.8 ng/mL). Notwithstanding, sunscreen use only accounted for a limited percentage of the variability in BP-3 concentrations ($R^2 \leq 0.14$), implying the existence of other relevant sources (Zamoiski et al., 2015).

BP-3 has been quantified at varying degrees in most personal care products (PCPs) – 81% of 231 cosmetics collected in the U.S. and China - including body lotions, face creams and make-up products, among many others (Liao and Kannan, 2014). Observational studies have shown that PCP use in general predicts higher BP-3 exposure in North Americans, having identified shaving cream (Philippat et al., 2015), mouthwash/dental rinse (Ferguson et al., 2017), eye make-up/hair oil (Berger et al., 2019), and hand or body lotion/face cream/lip balm (Ashrap et al., 2018; Dodson et al., 2020) as additional cosmetic sources. PCPs collected from the U.S. contained substantially higher BP-3 concentrations (median: 628 ng/g) than those collected from China (32.7 ng/g) (Liao and Kannan, 2014), consistent with the large differences in exposure levels between North American and Asian populations. The study of benzophenone UV filters in Chinese PCPs by Lu et al., (2018) confirmed the findings by Liao and Kannan, (2014), additionally showing that BP-1 was detected at lower levels. Notably, no study has to our knowledge investigated the content of benzophenone derivatives in PCP products commercialized in Europe.

Apart from PCPs that likely constitute the major human exposure source, other potential sources exist including indoor dust (Ao et al., 2018b; Shin et al., 2020) and air (Dodson et al., 2019; Wan et al., 2015), drinking tap water (da Silva et al., 2015; Díaz-Cruz et al., 2012), textiles (Li and Kannan, 2018; Xue et al., 2017), seafood (Cunha et al., 2018) and potentially, plastic-packaged foods and beverages (Dodson et al., 2020; Kim et al., 2016). Although the relative contribution of non-PCP sources to human exposure is uncertain, these additional dietary and non-dietary sources help to explain the sustained BP-3 exposure observed in all population groups, including children, irrespectively of the year season and sunscreen use (Krause et al., 2017). Additional details for these alternative exposure sources can be consulted in the extended exposure sources section (Supplementary data 3, page 4).

BP-3 concentrations in HBM studies are influenced by season (summer) and time spent on outdoor work (Mínguez-Alarcón et al., 2019), socioeconomic status (Tyrrell et al., 2013), education, race and sex (Calafat et al., 2008; Ko et al., 2016; Mortensen et al., 2014). These variables should be considered when analyzing exposure-health associations.

Table 1
Key points of exposure sources and predictors.

✔ Sunscreen use is a clear source and predictor of BP-3 exposure, but cannot alone explain sustained BP-3 concentrations in the population including children.	(Krause et al., 2017; Matta et al., 2020; Zamoiski et al., 2015)
✔ Personal care product (PCP) use (sunscreens, skin lotions and make-up among many other products) seems the most relevant human exposure source.	(Ferguson et al., 2017; Liao and Kannan, 2014; Philippat et al., 2015)
✔ Home indoor dust and air, seafood, drinking water, packaged food and textiles likely contribute to sustained BP-3 levels in humans.	(Cunha et al., 2018; Dodson et al., 2020; Shin et al., 2020; Wan et al., 2015)
✔ BP-3 concentrations in U.S. PCPs are substantially higher compared to those from China, which is supported by home dust and HBM exposure data.	(Ao et al., 2018b; Liao and Kannan, 2014)
✔ No study has analyzed BP-3 concentrations in PCPs commercialized in Europe. The extent to which BP-1 is directly used in PCPs is unknown.	(Lu et al., 2018)
✔ Food in plastic containers and bottled water could also contribute to higher BP-3 and BP-1 levels, which should be further investigated.	(Dodson et al., 2020; Kim et al., 2016)
✔ Reading PCP ingredient labels to avoid chemicals seems effective for BP-3. Greater ingredient transparency will help consumers reduce their exposure.	(Dodson et al., 2020; Harley et al., 2016)
✔ Season, socioeconomic status, education, race/ethnicity, sex, geographical area and other predictor variables should be considered in exposure-health studies.	(Calafat et al., 2008; Mínguez-Alarcón et al., 2019; Tyrrell et al., 2013)

Recent survey data showed that reading ingredient labels is effective to avoid BP-3 (Dodson et al., 2020). Harley et al., (2016) performed a 3-day intervention study in 100 adolescent Latina girls to investigate whether using PCPs with labels stating the absence of BP-3 could lower urinary concentrations. After the intervention, urinary BP-3 concentrations decreased on average by 36% (Harley et al., 2016). Thus, regulatory actions limiting the presence of harmful chemicals in consumer products should be complemented with labeling policies to warrant ingredient transparency.

3.2. HBM levels, meta-analysis and exposure determinants

The 125 papers identified to contain BP-3 (and BP-1) HBM data were published between 2007 and 2020 and included information on human samples collected from 1992 to 2019. BP-3 HBM data were reported from all continents as shown in Fig. 2A. Most studies were based on populations from North America (54 papers) and Europe (43 papers). The identified European studies covered populations from Northern, Western and Southern Europe (Fig. 2B), while no publications reporting BP-3 HBM data for Eastern European populations were identified.

Average reported urinary BP-3 and BP-1 concentrations from individual studies are presented in Fig. 3A and 3B, respectively, plotted against year of sampling and marked by geographical region of sample collection. The earlier studies were all from North America, while BP-3 data for the other continents was available for sample collections from 2004 to 2008 and onwards. Distribution of average BP-3 levels by age and sex is shown in Figures S2 and S4.

The meta-analysis and meta-regression of BP-3 data included 38 data points from 25 studies (see Figure S1 for inclusion/exclusion strategy). Results for the random-effects sub-group meta-analyses are presented in Table 2A (data back-transformed to the original geometric mean scale). In sub-group analysis by geographical region, the overall pooled average concentration of BP-3 was highest for North American studies (22.78 ng/mL ≈ μg/g creatinine). Average pooled concentrations for Europe and Asia were, respectively, about 10-times (2.88) and 20-times (1.25) lower ($p < 0.0001$).

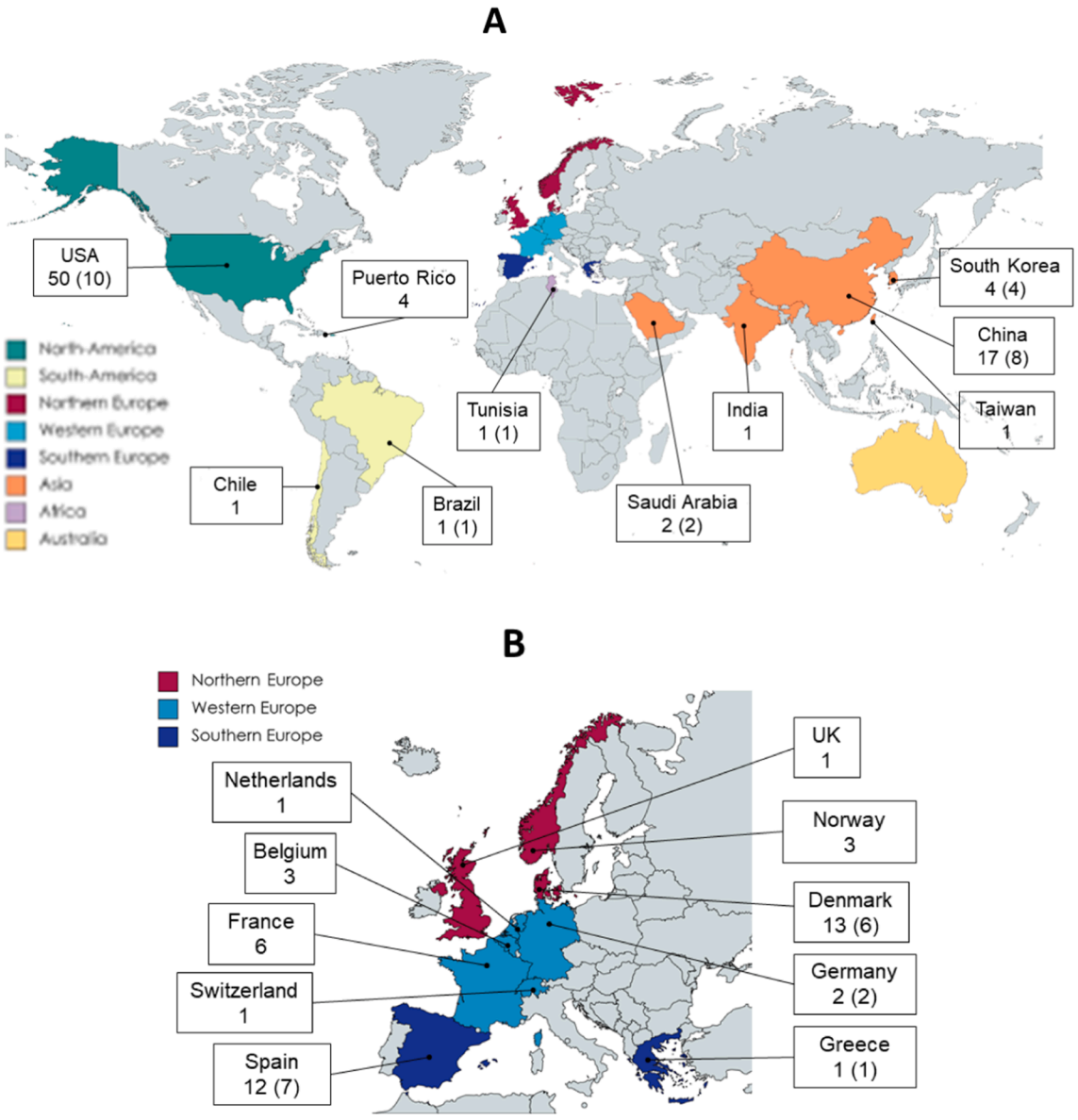

Fig. 2. Publications reporting human BP-3 exposure data according to geographical region. A) Global; B) European countries were classified into three sub-groups: Northern, Western and Southern Europe. No studies from Eastern Europe were identified. Numbers inside boxes represent the number of identified publications reporting human BP-3 biomarker data for each country. Numbers inside brackets represents the number of those publications, which also provided information on BP-1 concentrations.

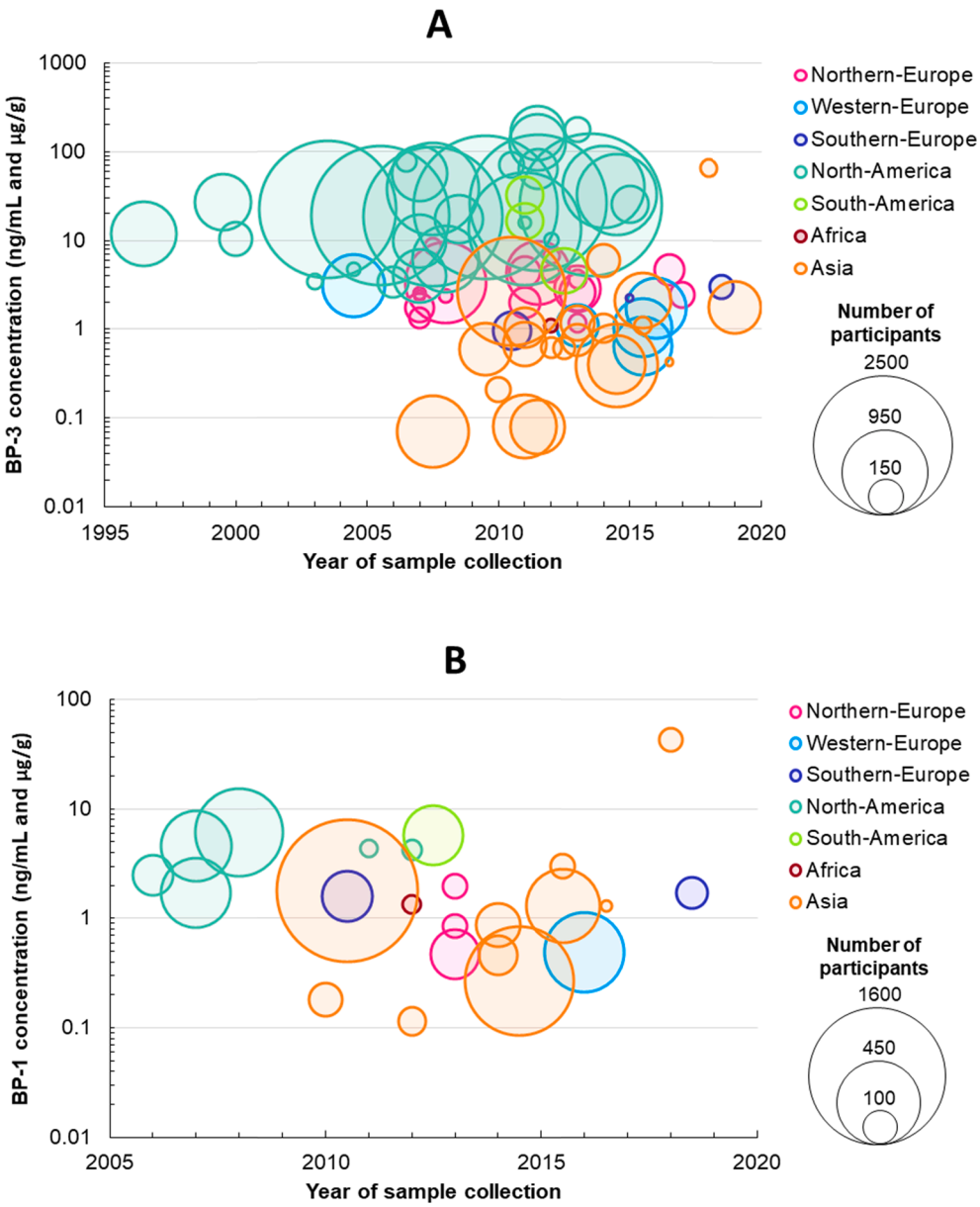

Fig. 3. A) Reported geometric mean or median urinary BP-3 concentrations according to the year of sample collection (from 1998 to 2018). B) Reported geometric mean or median urinary BP-1 concentrations according to the year of sample collection (from 2004 to 2018). The center of the circles shows the concentration value on the y-axis and the median year of sampling on the x-axis, while the size of the circles is proportional to the number of samples included in each study. Circles are colored according to the geographical location.

Beyond the subgroup meta-analysis, the meta-regression model considered all factors simultaneously and indicated that the weight of the predictors in the model was significant ($p < 0.0001$), explaining a substantial proportion of the heterogeneity observed in BP-3 concentrations (R^2 = 70%). As such, we considered meta-regression estimates as our primary model, and the meta-analysis as a complementary model providing the average BP-3 concentrations for each group. *Meta*-regression estimates for BP-3 data including all factor variables are presented in Table 2B (results have been exponentiated). In line with the meta-analysis, average BP-3 concentrations reported for populations from Asia and Europe were significantly lower compared to North America BP-3 concentrations. Samples collected during the two latest time periods (2009–2013 and 2014–2019) showed significantly higher concentrations when compared to samples taken between 1996 and 2003 (this was observed in the meta-regression but not in the subgroup meta-analysis). As inferred from Fig. 3A, this increase seems to be accounted for by Asian countries, and to a lesser extent by Southern-Europe, while urinary BP-3 concentrations appeared stable in North-American and Northern- and Western-European countries. No significant differences were observed between age group or sex, although children tended to show lower concentrations than adolescents/adults and males tended to present lower concentrations than females.

For comparison among studies, we focused on the average levels as we considered these median/geometric mean levels less likely to be influenced by extreme values, which in turn are influenced by the heterogeneity of the populations and study designs. However, from a risk assessment point of view, knowing the high-end exposure levels in a population is also relevant. Urinary BP-3 levels representing high-end exposure are included in the supplementary excel database (HBM-DB) as 95-percentiles and maximum levels (if reported). Reported 95-percentiles for urinary BP-3 concentrations ranged from 0.68 to 6740 ng/mL and thus varied more between studies than medians/geometric means. Studies with the lowest reported 95-percentile were mainly from China and those with the highest were mainly from Northern American women in their mid-thirties. Notably, several of the studies reporting the highest 95-percentile urinary BP-3 concentrations were on pregnant women. In European studies of pregnant women, 95-percentiles ranged from 32.2 to 466 µg/g of creatinine. The trend in reported 95-percentiles corroborate the geographical difference between Asia, Europe and North America observed in the meta-regression analysis.

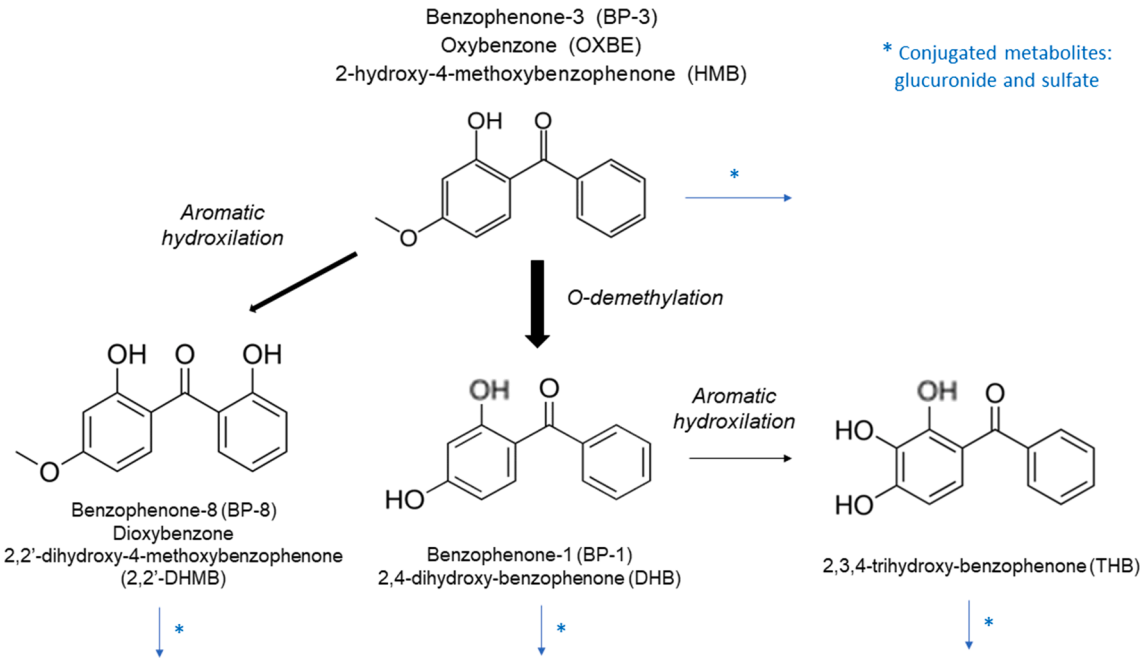

Fig. 4. BP-3 metabolites identified in rodent studies. With the exception of BP-1, the major BP-3 metabolite, other metabolites were not measured or rarely detected in human biomonitoring studies. Adapted from Jeon et al., (2008), Kim and Choi (2014) and (Mutlu et al., 2020, 2017).

Table 2
Urinary BP-3 concentrations (ng/ml ≈ μg/g creatinine) obtained by the *meta*-analysis and *meta*-regression in relation to geographical region, time period, age group, and sex (n = 38 data points from 25 studies).

Factor Variable	N	A) Meta-Analysis [a]	B) *Meta*-Regression [b]	
		Overall Average BP-3 Concentration [a]	Beta Estimate (95% CI) [b]	p-value [c]
Geographical Region				
North America	22	22.78 (14.36, 36.13)	Ref.	
Asia	9	1.25 (0.63, 2.49)	0.03 (0.01, 0.07)	<0.0001
Europe	7	2.88 (2.10, 3.96)	0.07 (0.03, 0.16)	<0.0001
Time Period				
1996–2003	3	8.86 (5.79, 13.57)	Ref.	
2004–2008	10	11.85 (6.21, 22.62)	1.93 (0.60, 6.25)	0.2729
2009–2013	17	8.46 (3.16, 22.91)	6.38 (1.81, 22.52)	0.0040
2014–2019	8	3.82 (1.54, 9.45)	7.40 (1.91, 28.56)	0.0037
Age Group				
Adults: ≥ 18yrs	28	8.22 (4.58, 14.76)	Ref.	
Children: 0-11yrs	5	2.94 (0.73, 11.84)	0.49 (0.17, 1.43)	0.1937
Adolescents: 12-17yrs	5	16.08 (3.34, 77.57)	0.82 (0.31, 2.17)	0.6931
Sex				
Female	25	9.31 (4.81, 17.99)	Ref.	
Male	13	5.63 (2.46, 12.89)	0.77 (0.40, 1.48)	0.4415

[a] Results from random effects meta-analysis by sub-group showing the exponentiated overall reported average urinary BP-3 levels (95% CI) in ng/mL ≈ μg/g creatinine by factor variable, without accounting for the influence of the remaining factor variables.
[b] Results from meta-regression results for reported average urinary BP-3 levels (exponentiated) simultaneously accounting for all factor variables. For interpretation: Values < 1 signify lower exposure and values > 1 signify higher exposure in comparison to the reference category (e.g., BP-3 concentrations in Asia are 97% lower than in North America).
[c] P-value indicates difference between groups for the meta-regression.

3.3. Toxicokinetics

3.3.1. Rodent toxicokinetic studies

Absorption, distribution, metabolism and excretion (ADME) properties of BP-3 have been studied in a number of rodent studies over the past 25 years (El Dareer et al., 1986; Jeon et al., 2008; Kadry et al., 1995; Mutlu et al., 2020, 2017; Nakagawa and Suzuki, 2002; Nakamura et al., 2015; Okereke et al., 1993). This section highlights the most important findings.

Generally, BP-3 is rapidly absorbed, peaking in plasma at 3–4 hrs post-oral exposure in rats exposed to a single gavage dose. Once in blood, BP-3 binds to plasma proteins and shows a plasma elimination half-life around 5 hrs (Jeon et al., 2008; Kadry et al., 1995).

In rodents, BP-3 is mostly metabolized to BP-1, but also to the minor metabolites 2,3,4-trihydroxybenzophenone (THB), 2,5-dihydroxy-4-methoxybenzophenone (2,5-DHMB) and 2,2′-dihydroxy-4-methoxybenzophenone (2,2′-DHMB or BP-8), and their corresponding glucuronide and sulfate conjugates (El Dareer et al., 1986; Kadry et al., 1995; Mutlu et al., 2020; Okereke et al., 1993). Similar metabolites have been observed *in vitro* following incubation of BP-3 with rat microsomes (Nakagawa and Suzuki, 2002). Fig. 4 depicts the major and minor metabolites identified for BP-3.

Total analyte concentrations in plasma after high dietary exposures (10,000 and 30,000 ppm) follow the general range of levels: BP-3 ≈ BP-

Table 3
Most relevant human and rodent toxicokinetic data, and rat to human ratios of internal plasma BP-3 concentrations.

A) Human toxicokinetic data in adult men and women after whole-body applications of sunscreen containing BP-3 at 4% w/w (Matta et al., 2020) [a]

Study design/ reference	Study population/Objective	Intervention	Analytical methods	Kinetic parameters	Main results
Randomized clinical trial conducted at a phase 1 clinical pharmacology unit (USA)/ (Matta et al., 2020)	48 healthy volunteers (Mean age: 38.7 years. 50% women). Mean (SD) BMI: 26.0 (2.9). Study period: January and February 2019 Participants remained in the clinic for 7 days and were not exposed to direct sunlight. They also had follow-up visits on days 10, 14, and 21. Objective: To determine whether the active ingredients [avobenzone, oxybenzone (BP-3), octocrylene, homosalate, octisalate, and octinoxate] of 4 commercially available sunscreens are absorbed into systemic circulation and their evolution throughout 21 days.	Participants were randomized to several groups. Oxybenzone was present at 4% and 6% in a lotion and aerosol spray, respectively. Sunscreen was applied at 2 mg/cm^2 to 75% of body surface area at 0-h on day 1, and 4 times on day 2 through day 4 at 2-h intervals. When exposure finished at day 4, participants were followed-up from day 5 to 21, and 34 blood samples per participant were collected. From day 1 to 7 participants had a shower each morning. Skin samples were collected by tape stripping (6 consecutive strippings) of the lower back on days 7 and 14.	Reverse-phase HPLC-MS/MS Valid range: 0.4–300 ng/mL	Plasma free/unconjugated BP-3 GM (range) values for the lotion: **Cmax Day 1 at 5 h (only one application): 94.2 (44.6–177.6) ng/mL – Selected value for rodent-human comparisons.** Cmax Day 4: 252.3 (131.3–498.1) ng/mL Day 5: 114.8 (64.9–244.3) ng/mL Day 6: 43.2 (28–64.7) ng/mL Day 7: 30.6 (13.7–70) ng/mL Day 10: 7.8 (3.3–24.6) ng/mL Day 14: 5.1 (1.6–32.5) ng/mL Day 21: 1.3 (0–14.4) ng/mL Terminal half-life: 75.8 h AUC Day 1: 1204 ng/mL*h AUC Day 4: 3443.7 ng/mL*h GMR (90% CI) Day 4 vs. Day 1: ≈ 2.86 (CI not provided). Skin day 7: 358.7 ng/cm2, range (40.7–5848.6) Skin day 14: 18.2 ng/cm2, range (3.9–341.3)	BP-3 maximum plasma concentrations at day 4 were 258.1 ng/mL (coefficient of variation, 53.0%) for the lotion; and 180.1 ng/mL (57.3%) for the aerosol spray. Corresponding values for the remaining UV filters were between 3.3 ng/mL and 23.1 ng/mL. A high variability in skin accumulation and absorption into blood was observed among participants. Skin absorption is the rate-limiting step, acting as a temporary accumulation site in humans. The most common adverse event was rash, which developed in 14 participants.

B) Free plasma BP-3 concentrations (ng/mL) measured in adult rats orally exposed to varying BP-3 doses through feed (Mutlu et al., 2017) [b]

Dose (ppm)	0	3000	10,000	30,000
Postnatal day 56 Males	1.63 ± 0.18	55.10 ± 5.70	188.40 ± 19.51	335.60 ± 59.85
Postnatal day 56 Females	1.38 ± 0.18	20.80 ± 3.11	98.56 ± 12.35	185.00 ± 36.17
Postnatal day 56 Males & Females [b]	1.51	37.95	143.48	260.3

C) Rat to Human ratios (RHR) at low range (LR), geometric mean (GM) and high range (HR) human absorption levels [c]

	RHR_{LR}	RHR_{GM}	RHR_{HR}	RHR_{LR}	RHR_{GM}	RHR_{HR}	RHR_{LR}	RHR_{GM}	RHR_{HR}	RHR_{LR}	RHR_{GM}	RHR_{HR}
	–	–	–	0.85	0.40	0.21	3.22	1.52	0.81	5.84	2.76	1.47

[a] The GM maximum free BP-3 concentration after one whole-body lotion application (94.2 ng/mL) was selected as a very feasible human peak-exposure scenario. Since there were 12 participants in each group, we considered the lowest (44.6 ng/mL) and highest (177.6 ng/mL) ranges to be representative, approximately, of the 10% of the population with the lowest and highest dermal absorption, respectively.

[b] To improve comparability with adult men and women, rodent internal free BP-3 concentrations were selected at postnatal day 56. The mean of male and female rodent plasma concentrations was calculated.

[c] Rat to human ratios (RHR) were calculated by dividing mean plasma free BP-3 concentrations of male and female Sprague Dawley rats at PND56 (Mutlu et al., 2017), by Cmax geomentric mean and low–high ranges of human plasma free BP-3 concentrations after one whole-body sunscreen application of lotion containing 4% of BP-3 w/w (Matta et al., 2020). **Abbreviations:** AUC (Area Under the Curve); BMI (Body Mass Index); Cmax (Maximum concentration); GM (Geometric Mean); GMR (Geometric Mean Ratio); HPLC (High-performance liquid chromatography); LOD (Limit of Detection); SD (Standard Deviation); UV (Ultra-violet).

1 > 2,5- DHMB ≫ THB, while a lower dietary exposure (3,000 ppm) results in the order: BP-1 > 2,5-DHMB ≈ BP-3 ≫ THB. The difference might be due to the saturation of metabolism at higher doses, increasing the accumulation of BP-3 in plasma and tissues (Mutlu et al., 2017).

Following a single gavage administration of BP-3 in rats, most of the administered dose is excreted in urine (53% to 58%) and feces (38% to 42%), with no observable sex difference. Similar results are seen in mice (Mutlu et al., 2020). The retention of BP-3 in tissues is very low (<1%), with the exception of the thyroids, adrenals and thymus in mice (Mutlu et al., 2020).

Two similar but separate developmental toxicity studies from the National Toxicology Program (NTP), using the same rat strain and exposure route, quantified BP-3 and its metabolites after repeated exposure (Mutlu et al., 2017; Nakamura et al., 2015). The most relevant results of both studies are shown in Table S3. In Mutlu et al., (2017), rat dams were exposed from gestation day (GD)6 throughout gestation and lactation to 0, 3.000, 10,000 or 30,000 ppm BP-3 in the diet. After weaning (PND28), the offspring continued exposure to the same dose levels as their dams. Blood was collected from randomly selected animals (1/sex/litter) from 5 to 6 litters per group on PND28 and PND56, and plasma concentrations were analyzed to simultaneously quantitate free/unconjugated and total concentrations of BP-3 and its metabolites. Free plasma BP-3 concentrations at postnatal day (PND)56 are reported in Table 3B. In both dams and adult offspring, BP-3 and BP-1 concentrations increased in a dose-dependent manner. Free BP-1 concentrations were higher than free BP-3 in all exposure groups (Table S3), probably because BP-1 is the major BP-3 metabolite and has shown a longer biological half-life (Jeon et al., 2008). Total plasma concentrations were ~ 60–200 times higher than free levels, demonstrating extensive conjugation of BP-3 and its metabolites. No significant sex differences were observed. In general, BP-3 and BP-1 concentrations were higher at PND56 compared to PND28, in line with a markedly increased feed consumption at PND56 (Table S3; Mutlu et al., 2017). In section 3.3.3 a species comparison of the internal BP-3 concentrations between rats and humans is shown.

3.3.2. Human toxicokinetic interventions

Nine human toxicokinetic studies were retrieved from the search, analyzed and tabulated in detail (Table S4). Three small (3–11 individuals) pilot single-application studies confirmed a substantial absorption of BP-3 into blood after dermal application and its excretion in urine together with its major metabolite BP-1 (Gustavsson Gonzalez et al., 2002; Hayden et al., 1997; Sarveiya et al., 2004). Out of the two most comparable human intervention studies (Janjua et al., 2008; Matta et al., 2020), we focus on Matta et al., (2020) that used sunscreen concentrations below the current EU limit of 6% w/w.

Matta et al., (2020) investigated repeated dermal application of BP-3 and other chemical UV-filters formulated as a lotion (4% weight/weight) or spray (6% weight/weight) (see Table 3A for study details). In brief, formulation was applied at 2 mg/cm^2 to 75% of the body surface area on day 1, and repeatedly on day 2 through day 4. When exposure finished at day 4, participants were followed-up from until day 21. Skin samples were collected by tape stripping on days 7 and 14. After just one application of the lotion, peak mean free BP-3 plasma concentrations were observed at 5 hrs post-exposure: 94.2 (range: 44.6–177.6) ng/mL. After continued maximal lotion use (4 times/day at days 2, 3 and 4), the Cmax was achieved at day 4, being 252.3 (range: 131.3–498.1) ng/mL. Similar results were observed with the aerosol spray. The Cmax led to a plasma area under the curve (AUC) 2.86 times higher at day 4 compared to day 1, indicating a moderate potential for drug accumulation (Li et al., 2013). Plasma concentrations started to decline from day 5 onwards, but were still detectable in some participants at day 21 (1.3 ng/mL range: 0–14.4). The terminal half-life (time required for plasma BP-3 to decrease by 50%) was estimated to 3 days (75.8 hrs). Skin accumulated BP-3 and acted as a reservoir.

A single sunscreen whole-body application can lead to high internal BP-3 concentrations within hours. Among all the chemical UV-filters studied, BP-3 is by far the compound showing the highest absorption into blood (Janjua et al., 2008; Matta et al., 2020). However, an important limitation of human toxicokinetic studies was the lack of plasma BP-1 data.

3.3.3. Rodent-Human exposure comparisons

Mutlu et al., (2017) and Nakamura et al., (2015) compared their internal BP-3 rodent kinetic data with human concentrations obtained from the intervention study conducted by Janjua et al., (2008). Nakamura et al., (2015) concluded that *"exposure levels of the rats dosed with 3,000–10,000 ppm of BP-3 appeared to be similar to BP-3 concentrations in humans"*. A similar conclusion was reached by Mutlu et al., (2017), reporting that free/unconjugated BP-3 plasma concentrations in their rat toxicokinetic study were within ~ 0.1–4.0-fold that of the human dermal study (Mutlu et al., 2017).

We updated this rat to human ratio (RHR), selecting the same rodent internal concentrations at PND56 (Mutlu et al., 2017; Table 3B), but selecting human data from Matta et al., (2020) that tested a sunscreen lotion containing 4% of BP-3 w/w, which is lower than the current limit of 6% in Europe (EU, 2017). The geometric mean Cmax value after just one whole-body lotion application (94.2 ng/mL) was selected, which represents a common peak-exposure scenario (e.g., sunscreen use spending one day at the beach). Additionally, the lowest and highest BP-3 concentrations of the Cmax range were considered (44.6 and 177.6 ng/mL, respectively), as an approximate representation of the 10% of the population subjected to the lowest and highest dermal absorption since a high variability exists (Table 3A). The estimated RHRs ranged from 0.21 to 5.84 depending on the dose to which rodents were exposed through feed (3000, 10,000 or 30,000 ppm), and the human concentration (low range, geometric mean or high range) chosen (Table 3C). Overall, the calculated ratios indicate that chronic oral BP-3 doses up to 10,000 ppm (corresponding to an oral dose of ≈1000 mg/kg/day) given to adult rats produce internal free BP-3 plasma concentrations that overlap with human peak concentrations of free BP-3 in blood after sunscreen use (Table 3C).

Although RHRs provide an orientation to interpret the results of *in vivo* studies, this estimation is subjected to uncertainties: 1) No human toxicokinetic data on internal BP-1 levels exist, so the comparison is incomplete; 2) While rodents are continuously dosed through the diet to constant BP-3 doses, human exposure occurs through different routes including transdermal and involves both a continuous low-dose level of exposure as demonstrated by our *meta*-analysis in population studies (Table 2), combined with intermittent peaks of exposure after sunscreen or PCPs use, among other sources.

Regarding an orientation for the interpretation of *in vitro* studies in the next section, the chosen human plasma free BP-3 concentrations after a whole-body application in Matta et al., (2020) [GM (range): 94.2 (44.6–177.6) ng/mL) in Table 3A], would correspond to an *in vitro* exposure concentration of 0.41 (0.20–0.78) μM.

3.4. In vitro biological activities of BP-3 and BP-1

BP-3 has been investigated for endocrine disrupting properties in a broad range of *in vitro* assays, and increasing amounts of data are being produced for BP-1 as well. In this section the most relevant information based on potency and data availability is commented (Table 4).

3.4.1. Estrogenic activity

Various cell-based reporter gene assays have demonstrated weak to moderate estrogenic activity of BP-3 through both ERα and ERβ nuclear receptors, in most cases showing half maximal effective concentrations (EC_{50}) exceeding 1 μM (Table 4). Of note, the studies that additionally tested BP-1 revealed more potent estrogenic effects of this compound compared to BP-3. Thus, BP-1 was found to be between 4 and 100 times more potent than BP-3 in various reporter gene assays for estrogenic

Table 4
Overview of *in vitro* effects of benzophenone 3 (BP-3) and its metabolite benzophenone-1 (BP-1).

Outcome	Model system	LOEC[a] (μM) unless otherwise specified	EC_{50} or IC_{50} (μM)	Reference
Estrogenic effects				
ER agonism	HEK-293 cell-based hERα reporter gene assay		BP-3 EC_{50}: 2.9	Schreurs et al., (2005)
	HEK-293 cell-based hERβ reporter gene assay		BP-3 EC_{50}: 25	
	HELN-based hERα and hERβ reporter gene assay	BP-3 1–10		Gomez et al., (2005)
	HEK293-based ER reporter gene assay	BP-3 10		Schreurs et al., (2002)
	MCF-7 cell-based hER reporter assay		BP-3 EC_{50}: 19.5 BP-1 EC_{50}: 1.3	Suzuki et al., (2005)
	CHO-K1 cell-based hERα reporter gene assay		BP-3 REC^{b}_{20}: 2.2 BP-1 REC^{b}_{20}: 0.099	Watanabe et al., (2015)
	CHO-K1 cell-based hERβ reporter gene assay		BP-3 REC^{b}_{20}: 3.3 BP-1 REC^{b}_{20}: 0.033	
	HeLa cell-based ERα reporter gene assay		BP-3 EC_{50}: 30 BP-1 EC_{50}: 8.5	Molina-Molina et al., (2008)
	HeLa cell-based ERβ reporter gene assay		BP-3 nd BP-1 EC_{50}: 4.0	
	Yeast two-hybrid ERα assay		BP-3 REC^{b}_{10}: 660 BP-1 REC^{b}_{10}: 1.8	Kawamura et al., (2003)
	Yeast-based (BLYES) hERα reporter gene assay		BP-3 EC_{50}: 6.44	Balázs et al., (2016)
	Yeast-based hERα reporter gene assay		BP-3 EC_{50} ~ 10 (partial agonist) BP-1 EC_{50} ~ 0.3 (full agonist)	Miller et al., (2001)
	Yeast-two-hybrid hERα reporter gene assay		BP-3 REC^{b}_{10}: 660	Ogawa et al., (2006)
	Yeast-based hERα reporter gene assay		BP-3 EC_{50}: 18.6 (partial agonist) BP-1 EC_{50}: 1.15 (full agonist)	Kunz and Fent, (2006)
	Yeast-based hERα reporter gene assay	Relative to E2: BP-3: 0.000052% BP-1: 0.0076%		Morohoshi et al., (2005)
ER antagonism	Yeast-based hERα reporter gene assay		BP-3 IC_{50}:17.8	Kunz and Fent, (2006)
ER binding	Rat uterus cytosol ER binding assay		BP-1 IC_{50}: 36.5	Blair et al., (2000)
	ERα binding assay		BP-3 nd BP-1 IC_{50}: 50	Nakagawa and Suzuki, (2002)
	ELISA-based hERα binding assay	BP-3 Suspected binding BP-1 Binding relative to DES: 1.4%		Morohoshi et al., (2005)
Cell proliferation	MCF-7 human breast cancer cells	BP-3 ≥ 1 BP-1 ≥ 1		Kerdivel et al., (2013)
Estrogen-related receptor γ (ERR γ) agonism	HepG2 cell-based ERR γ reporter gene assay	BP-3 6.25 BP-1 3.12		Zheng et al., (2020)
ER expression level	Primary mouse embryonic neocortical cells	BP-3 79% mERα decrease BP-3 86% mERβ decrease		Wnuk et al., (2018a)
Increased CXCL12 secretion	Estrogen-dependent CXCL secretion in T47D cells		BP-3 EC_{50}: 9.9 BP-1 EC_{50}: 9.5	Habauzit et al., (2017)
Increased pS2 gene transcription	MCF-7 cancer cell line		BP-3 C^{c}_{50}: 0.5 BP-1 C^{c}_{50}: 0.12	Heneweer et al., (2005)
Antiandrogenic effects				
AR antagonism	CHO-K1 cell-based AR reporter gene assay		BP-3 RIC^{b}_{20}: 5.8 BP-1 RIC^{b}_{20}: 4.5	Watanabe et al., (2015)
	HEK-293 cell-based AR reporter gene assay		BP-3 IC_{50}: 3.1 BP-1 IC_{50}: 5.7	Nashev et al., (2010)
	PC3 cell-based hAR reporter gene assay		BP-3 IC_{50} > 30 BP-1 IC_{50}: 8.6	Molina-Molina et al., (2008)
	hAR EcoScreen™ reporter gene assay		BP-3 IC_{30}: 5.5	Araki et al., (2005)
	hAR CALUX® reporter gene assay		BP-3 IC_{50}: 2.0	Schreurs et al., (2005)
	NIH3T3 cell-based AR reporter gene assay		BP-3 IC_{50} > 100 BP-1 IC_{50}: 10	Suzuki et al., (2005)
	Human breast cancer MDA-kb2 cell-based hAR reporter gene assay		BP-3 IC_{50}: 4.98	Ma et al., (2003)
	Human breast cancer MDA-kb2 cell-based hAR reporter gene assay		BP-3 IC_{50}: 17.9	Ermler et al., (2011)
	Yeast-based (BLYAS) hAR reporter gene assay		BP-3 IC_{50}: 10.2	Balázs et al., (2016)
	Yeast-based hAR reporter gene assay		BP-3 IC_{50}: 3.7 BP-1 IC_{50}: 0.69	Kunz and Fent, (2006)

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Table 4 (*continued*)

Outcome	Model system	LOEC[a] (μM) unless otherwise specified	EC_{50} or IC_{50} (μM)	Reference
Thyroid toxicity				
Altered expression of thyroid hormone regulating genes	Rat pituitary (GH3) cells	BP-3 32 BP-1 10		Lee et al., (2018)
Altered expression genes related to thyroid hormone synthesis	Thyroid follicle (FRTL-5) cells	Absolute data not given		
Inhibition of thyroid hormone synthesis	Rat thyroid microsomes	BP-3 nd < 253		Paul et al., (2014)
Activation of thyroid peroxidase activity	hTPO stably transfected into human follicular thyroid carcinoma (FTC-238) cells		BP-3 nd < 100 BP-1 0.001	Song et al., (2012)
Thyroid hormone receptor agonism	HepG2-based reporter gene assay	BP-3 Agonist		Schmutzler et al., (2007)
Thyroid hormone receptor antagonism	hTPO stably transfected into human follicular thyroid carcinoma (FTC-238) cells	BP-3 nd		
Thyroid peroxidase activity		BP-3 nd		
Iodide activity	FRTL-5 cells	BP-3 nd		
Thyroid hormone receptor agonism	hHepG2 TH-responsive luciferase-based reporter	BP-3 1		Hofmann et al., (2009)
Other endocrine effects				
Repression of progesterone receptor transcription	hPR CALUX® cells		BP-3 IC_{50}: 5.2	Schreurs et al., (2005)
Increased corticosterone levels	Primary rat adrenocortical cells	BP-3 0.0001		Ziolkowska et al., (2006a)
17β-hydroxysteroid dehydrogenase type 3 activity	Enzyme activity assay in transfected HEK-293 cells		BP-3 nd BP-1 IC_{50}: 1.05	Nashev et al., (2010)
Induced acrosome reaction and sperm penetration (progesterone-like manner)	Human sperm cells	BP-3 10		Rehfeld et al., (2018)
Induced Ca^{2+} signals through activation of CatSper	Human sperm cells	BP-3 10		Rehfeld et al., (2016)
Altered milk protein synthesis and transcriptional regulation during mammary gland differentiation	Primary murine mammary gland differentiation	BP-3 1 pM		Altamirano et al., (2020)
Affected follicular cell population and oocyte number	Rat whole ovary cultures	BP-3 0.0058		Santamaría et al., (2019)
Inhibited oocyte maturation and development to the blastocyst stage	Primary immature mouse oocytes	BP-3 0.5		Jin et al., (2020)
PPARγ agonism	Adipogenic human bone marrow mesenchymal stem cells	BP-3 30		Shin et al., (2020)
Immunomodulation				
Altered macrophage polarization	Patient-derived breast tissue explants	BP-3 30		Gregory et al., (2020)
Increased cytokine levels	Human macrophage-like cells (induced from THP-1 cell line)	BP-3 0.1		Ao et al., (2018a)
Inhibited prostaglandin E_2 (PGE_2) production	Human embryo palatal mesenchyme cells		BP-3 IC_{50}: 0.6	Jannesson et al., (2004)
Cytotoxicity				
Cytotoxicity caused by oxidative stress	Rat thymocytes	BP-3 ~ 300		Utsunomiya et al., (2019)
Induced neurotoxicity and apoptosis	Primary mouse embryonic neocortical cells	BP-3 25		Wnuk et al., (2018a)Wnuk et al., (2018b)
Cytotoxicity towards yeast and bacteria	Yeast-based BLYR strain MicroTox™ bacteria test		BP-3 IC_{50}: 47 BP-3 IC_{50}: 24	Balázs et al., (2016)
Cytotoxicity caused by apoptosis	SH-SY5Y neuroblastoma cell line	BP-3 10		Broniowska et al., (2016)
Decreased osteoblast cell proliferation	Primary rat calvarial osteoblast-like cells	BP-3 1		Ziolkowska et al., (2006b)
Cytotoxicity	Primary rat hepatocytes	BP-3 500: 33% BP-1 500: 79%		Nakagawa and Suzuki, (2002)
Genotoxicity				
Positive mutagen	Ames test: Salmonella Typhimurium strains TA97, TA98, TA100 & TA102	BP-1 0.05 μg/plate		Wang et al., (2018)
	Ames test: Salmonella Typhimurium strain TA98 & TA100	BP-3 10 μg/ml		Nakajima et al., (2006)
Increased micronuclei formation and number of chromosomal aberrations	Primary human lymphocytes	BP-3 0.0125 μg/ml		Santovito et al., (2019)
Cancer				
Increased metastatic potential	Human lung cancer cells	BP-3 50 μg/L		Phiboonchaiyanan et al., (2017)
Induced metastasis through an ER dependent pathway	Human ovarian cancer cells	BP-1 1		Shin et al., (2016)
Increased cell proliferation (and increased tumor weight in mice)	Human ovarian cancer cells	BP-1 10		Park et al., (2013)
Increased cell proliferation	Human breast cancer cells (MCF7)		BP-3 EC_{50}: 3.73	Schlumpf et al., (2001)
Increased migration and invasion	Human breast cancer cells (MCF-7 and MDA-MB-231)	BP-3 0.1 BP-1 0.1		Alamer and Darbre, (2018)
Increased cell proliferation Increased cell migration	Human breast cancer cells (MCF-7)	BP-1 0.1 BP-1 10		In et al., (2015)
Increased cell proliferation	Human breast cancer cells (MCF7)	BP-1 0.01		Nakagawa and Suzuki, (2002)

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Table 4 (*continued*)

Outcome	Model system	LOEC[a] (μM) unless otherwise specified	EC_{50} or IC_{50} (μM)	Reference
Carcinogenic potential	Yeast-based UMU test	BP-3 1–10 μg/well		Nakajima et al., (2006)
Increased cell proliferation and metastasis	Human prostate cancer cells	BP-1 1		Kim et al., (2015)

a) LOEC: Lowest Observed Effect Concentration.
b) REC_{10}: The concentration of the chemical showing 10 % of the agonistic activity of the highest activity level of the standard E2 (1 μM).
REC_{30}: The concentration of the chemical showing 30 % of agonistic activity of the standard DHT (5E-4 μM).
c) C_{50}: 50% induction of pS2 gene transcription above background levels.
nd: Not detectable.

activity (Kunz and Fent, 2006; Miller et al., 2001; Molina-Molina et al., 2008; Suzuki et al., 2005; Watanabe et al., 2015). An increase in estrogen-regulated pS2 gene transcription in MCF-7 cells at low concentrations, was also reported for both BP-3 and BP-1, presenting EC_{50} values of 0.5 and 0.12 μM, respectively (Heneweer et al., 2005).

3.4.2. Anti-androgenic activity

BP-3 has shown antagonism of the androgen receptor (AR) in several cell-based reporter gene assays at moderate as well as high concentrations, showing EC_{50} values between 2 and 10 μM (Table 4). BP-1 also exhibits AR antagonism, in most cases with a higher potency than BP-3 (Kunz and Fent, 2006; Molina-Molina et al., 2008; Suzuki et al., 2005), showing half-maximal inhibitory concentrations (IC_{50}) as low as 0.69 μM (Kunz and Fent, 2006).

3.4.3. Thyroid hormone disruption

BP-3 has been identified as a thyroid receptor agonist (Schmutzler et al., 2007), showing slight agonistic effects at 1 μM (Hofmann et al., 2009), which is supported by a concomitant effect on expression of thyroid hormone regulated genes at 10 μM in rat pituitary (GH3) cells (Lee et al., 2018). No effects of BP-3 on neither thyroid hormone synthesis nor thyroid peroxidase (TPO) activity was found (Paul et al., 2014; Schmutzler et al., 2007; Song et al., 2012). In contrast, BP-1 was shown to activate TPO at a very low concentration (0.001 μM) in human follicular thyroid carcinoma cells (Song et al., 2012), which needs to be confirmed in future studies. Moreover, BP-1 altered thyroid hormone regulated gene expression in a rat cell line at the high concentration of 32 μM (Lee et al., 2018). In addition to a confirmation of the potent TPO activity of BP-1, more studies comparing BP-3 and BP-1 on thyroid hormone disrupting endpoints are needed.

3.4.4. Other endocrine effects

BP-3 has been reported to directly affect the motility of human sperm cells *in vitro*, showing an EC_{50} of 4.7 μM (Rehfeld et al., 2018,2016). This effect is likely linked to a mechanism involving binding to and displacement of progesterone from a membrane bound progesterone receptor and agrees with the BP-3-induced repression of progesterone receptor transcription found by Schreurs et al., (2005).

Notably, BP-3 showed potent adverse effects on *in vitro* endpoints related to female reproduction. Thus, BP-3 inhibited mouse oocyte maturation and development to the blastocyst stage at 0.5 μM (Jin et al., 2020), disrupted rat follicular cell population and oocyte number at a lowest observed effect concentration (LOEC) of 6 nM (Santamaría et al., 2019), as well as altered milk protein synthesis and transcriptional regulation during mammary gland differentiation at 1 pM (Altamirano et al., 2020). These effects may be related to the estrogenic and/or antiandrogenic characteristics of BP-3, although it cannot be excluded that potential anti-progesterone and thyroid actions are involved.

Finally, Nashev et al., (2010) showed that BP-1 – but not BP-3 – could inhibit human 17β-hydroxysteroid dehydrogenase 3 activity (IC_{50} = 1.05 μM), the enzyme that converts androstenedione to testosterone in Leydig cells, which may be an additional antiandrogenic or testosterone reducing effect of BP-1.

3.4.5. Immunomodulation

Following exposure of human macrophages to 0.1 μM BP-3, an increased production of inflammatory cytokines was observed (Ao et al., 2018a). Moreover, BP-3 seems to have a weak effect (at 30 μM) on macrophage polarization in human mammary tissue explants (Gregory et al., 2020).

Interestingly, Jannesson et al., (2004) showed that BP-3 inhibited prostaglandin E2 (PGE2) production at 0.6 μM in human embryo palatal mesenchymal cells. In parallel, a human clinical trial indicated that the use of BP-3 (in addition to fluoride) in toothpaste reduced gingival inflammation, which might be explained by the inhibitory effect of BP-3 on PGE2 production (Jannesson et al., 2004).

3.4.6. Cytotoxicity, genotoxicity and cancer

Cytotoxicity was observed, in general, at higher BP-3 concentrations (≥10 μM). However, a more specific inhibition of rat osteoblast cell proliferation was observed at 1 μM (Ziolkowska et al., 2006b). Limited studies have indicated the potential genotoxic effects of both BP-3 and BP-1. Thus, positive mutagenic responses in the Ames test were observed for BP-3 and especially BP-1 (Nakajima et al., 2006; Wang et al., 2018). Moreover, BP-3 also increased micronuclei formation in human lymphocytes providing further evidence for a genotoxic effect of BP-3 (Santovito et al., 2019).

Most cancer *in vitro* endpoints were detected in hormone-sensitive cell models, in which BP-3 and BP-1 caused relatively potent effects. BP-3 promoted breast cancer cell proliferation (EC_{50} = 3.7 μM), as well as increased invasion and migration of cells at 0.1 μM (Alamer and Darbre, 2018; Schlumpf et al., 2001). Several studies support the ability of BP-1 to induce cell proliferation, invasion, migration and metastasis in breast cancer cells at low concentrations (from 0.01 to 1 μM) (Alamer and Darbre, 2018; Nakagawa and Suzuki, 2002). BP-1 also stimulated cell proliferation of human ovarian cancer cells at 1–10 μM (Park et al., 2013; Shin et al., 2016), and proliferation of human prostate cancer cells at 1 μM (Kim et al., 2015).

3.4.7. In vitro summary

Both BP-3 and its metabolite BP-1 show clear estrogenic and anti-androgenic effects *in vitro,* in most cases BP-1 being more potent. BP-1 is clearly estrogenic at concentrations below 1 μM. This concentration overlaps with mean peak concentrations in human plasma after sunscreen use (Table 3, Matta et al., 2020). Moreover, both compounds show potential to induce carcinogenic effects in hormone-sensitive tissues. A few studies also indicate possible thyroid hormone disrupting effects of BP-3 and BP-1, and inhibitory effects on immune defense and sperm motility by BP-3. Based on available *in vitro* studies, it seems plausible from a mechanistic point of view that BP-3, especially when metabolized to BP-1, may be able to exert adverse effects *in vivo* at current human exposure peak scenarios.

3.5. In vivo BP-3 and BP-1 adverse effects

We identified 23 peer-reviewed *in vivo* studies that were reviewed and tabulated, together with two recent NTP reports describing additional *in vivo* BP-3 data. All findings in female and male rodents are

presented in Table S5 and S6, respectively. The most relevant results are presented in Table 5 and discussed below.

3.5.1. Female reproductive endpoints

The *in vivo* estrogenicity of BP-3 has been investigated in 7 uterotrophic assays, but only one included a dose high enough to elicit a statistically significant increase in uterine weight (Table 5). In immature rats treated for three days with 1525 mg/kg bw/day in the feed, a statistically significant 23% increase in uterine weight was seen (Schlumpf et al., 2001), whereas all other uterotrophic studies tested BP-3 doses of 1000 mg/kg/day or lower, and found no significant effects on uterine weights (Schlecht et al., 2004; Suzuki et al., 2005; Ohta et al., 2012; Laplante et al 2018; NTP 2019; Majhi et al 2020). Three uterotrophic studies also tested the effects of BP-1, and in line with its higher estrogenic *in vitro* potential (Table 4), BP-1 elicited a potent estrogenic response *in vivo* (Table 5). In all BP-1 studies, statistically significant increases in uterine weights were seen at doses between 300 and 1000 mg/kg bw/day (Koda et al., 2005; Suzuki et al., 2005; Ohta et al., 2012).

While most of the uterotrophic studies with BP-3 did not find statistically significant increases in uterine weights, consistent with the known relatively low sensitivity of this assay, other estrogen-sensitive endpoints were sometimes affected (Table 5). In adult female ovariectomized (OVX) rats orally exposed to BP-3 doses of 250 or 1000 mg/kg bw/day for 5 days, altered gene expression of ERβ in the uterus and ERα in pituitary was observed in both dose groups (Schlecht et al., 2004). In OVX mice, exposure to a low oral dose of 3 mg/kg bw/day during four consecutive days altered ER-dependent gene expression in the uterus (LaPlante et al. 2018) and in mammary glands (Majhi et al., 2020). Together, these data indicate that short-term exposure to relatively low doses of BP-3 may cause significant effects on gene expression, whereas doses above 1000 mg/kg bw/day are needed to elicit a uterotrophic response (Table 5).

Several developmental repeated-dose toxicity studies have investigated the effects of BP-3 on female reproduction, often focusing on estrous cyclicity and the mammary glands (Table 5). In a 90-day study with adult female rats receiving doses of 3125, 12,500 and 50,000 ppm in the feed (corresponding to ≈ 196, 780 and 3261 mg/kg bw/day), a statistically significantly increase in estrous cycle length was seen in the two highest dose groups (French, 1992). In female mice, an oral BP-3 dose of 50000 ppm also significantly increased estrous cycle length, whereas lower oral doses showed no significant effects. Dermal studies in both species, using lower doses (up to 364 mg/kg bw/day), did not affect estrous cyclicity (French, 1992). In a study examining reproductive assessment by continuous breeding (RACB), mice given up to 50000 ppm of BP-3 in feed showed no changes in estrous cycle length, when this endpoint was assessed in adult F1 females (Chapin 1997). In a more recent developmental study with rats, using the modified one generation (MOG) design, estrous cyclicity was assessed in animals receiving 3000, 10,000 or 30000 ppm in the feed, corresponding to 200–300; 700–1000 and 2600–3500 mg/kg bw/day (NTP, 2021). At the two highest doses, statistically significant but not very marked effects on estrous cyclicity were observed in the adult F1 offspring, corroborating the earlier findings that high doses of BP-3 (>700 mg/kg bw/day) may adversely affect estrous cyclicity. Additionally, a chronic exposure academic study using Trp53 null mammary transplanted mice reported a significant change in the proportion of mice in the different estrous stages, using a much lower oral dose of 70 mg/kg/day (Kariagina et al., 2020). This study also found that the combination of this BP-3 dose with a high fat diet increased mammary tumor cell proliferation and decreased tumor cell apoptosis.

Mammary gland development has been investigated in low-dose developmental toxicity studies in mice, testing oral BP-3 doses of 0.03, 0.212 or 3 mg/kg/day. The highest dose induced permanent changes to ductal density and proliferation in the mammary glands of female offspring, five weeks after weaning. At this time point no changes in ERα-mediated gene- and protein expression were seen, while progesterone receptor (PR) protein expression was increased in mid and high dose groups (LaPlante et al., 2018). At weaning, female offspring from all exposure groups had larger ductal areas; at puberty the highest dose showed an increased number of terminal end buds; and in adulthood, females at the highest dose had a decreased fraction of the mammary gland comprised of ducts. Mammary gland histology was also affected in the male offspring at weaning (Matouskova et al., 2020). These studies indicate that mammary gland development may be very sensitive to BP-3 exposure.

Effects of BP-3 exposure on general developmental toxicity have also been reviewed (Table S6). A recent study investigated how BP-3 exposure through drinking water (50 nM) for 28 days affected meiotic maturation, embryo development and oocyte quality in female mice. This exposure did not affect body or ovary weights in the dams, but the percentage of mouse embryos that reached the blastocyst stage was significantly lower, and the rate of early apoptosis in the oocytes was markedly increased after BP-3 exposure (Jin et al., 2020). Another recent study investigated developmental toxicity after a dermal dose of 50 mg/kg bw/day given to rat dams from GD0-6. This exposure caused no effect on the number of implantations or abortions, whereas small reductions on fetal and neonatal body weights were observed in the absence of maternal toxicity (Santamaria et al., 2020). In contrast, regulatory studies have only found adverse developmental effects at doses also causing some degree of maternal toxicity. In the RACB study (Chapin 1997), decreased pup survival was seen at the highest dose (50000 ppm) but only together with significant reductions in dam body weight. In the preliminary MOG study, the highest tested dose (50000 ppm) resulted in significantly decreased body weights in dams from GD10-21, whereas no significant differences were observed in the number of live fetuses, implantation sites or offspring body weights (Nakamura et al., 2015). And in the full MOG study, the intermediate and the high doses of 10,000 and 30000 ppm caused lower gravid uterine weights, fewer implants, and fewer live fetuses, but dam body weights were also significantly decreased (NTP, 2021).

3.5.2. Male reproductive endpoints

Adverse reproductive effects of BP-3 have also been reported in male rodents, usually on sperm parameters (Table 5). In a 90-day oral toxicity study (French, 1992), adult male rats dosed with the highest concentration (50,000 ppm ≈3656 mg/kg bw/day) had a significant ≈30% decrease in epididymal sperm concentration. This was, however, observed at a dose where marked body weight reductions were also seen. The lower dose of 12500 ppm (corresponding to 875 mg/kg) caused a non-significant 14% decrease in sperm concentration and no adverse effects on body weight. In male rats treated dermally with doses up to 200 mg/kg bw/day, semen parameters were not significantly affected.

In orally exposed mice, the highest dose (50000 ppm) significantly decreased sperm concentrations by 27%, and all three tested doses caused a significant increase in sperm cell abnormalities, an effect not seen in the rat studies. In dermally treated mice, BP-3 doses of 23, 91 and 364 mg/kg bw/day all showed significant dose-related decreases in sperm concentrations (by 9%, 16% and 34% respectively) in the absence of systemic toxicity. In an industry-funded study, Daston et al., (1993) re-investigated these effects by dosing male mice topically with BP-3 (10, 20, 100 or 400 mg/kg/day) for 13 weeks. They found suggestive non-significant reductions in sperm concentrations of approximately 15% at the lower dose levels and of 20% at 400 mg/kg/day, but concluded that BP-3 exposure did not affect male reproductive function.

In the developmental RACB study in mice (Chapin 1997), oral doses of up to 50000 ppm did not cause changes in sperm number, motility or morphology in the F_1 offspring. In the preliminary MOG study (Nakamura et al. 2015), BP-3 doses of 0, 1000, 3000, 10000, 25,000 and 50000 ppm, (corresponding to 0, 68, 200, 680, 1700 and 3400 mg/kg bw/day) were given to rat dams from GD6 – PND23. Despite a low group size (n = 4 in the high dose group, and 5–8 in the other dose groups),

Table 5
Overview of selected *in vivo* effects of benzophenone-3 (BP-3) and its metabolite benzophenone-1 (BP-1).

Effect Target	Observed effect	Study design	Species	Exposure	Dose: mg/kg bw/day*	LOEL	Reference
Uterus weight	No effect of BP-3 on uterine weight. No effects on body weight.	Uterotrophic assay	Balb/C mice, OVX	4 days	3		LaPlante et al., (2018)
	No effect of BP-3 on uterine weight. No effects on body weight.	Uterotrophic assay	Balb/C mice, OVX	4 days	3		Majhi et al., (2020)
	No effects of BP-3 on wet or blotted uterus weights. Lower bw gain in the high dose group.	Uterotrophic assay	SD rats, OVX	3 days	320, 1000		NTP (2019)
	No effect of BP-3 on absolute or relative wet and blotted uterine weight. No clinical signs or bw reductions.	Uterotrophic assay	C57BL/6J mice, OVX	7 days	30, 100, 300, 1000		Ohta et al., (2012)
	No effect of BP-3 on uterine weight. No effects on bw.	Uterotrophic assay	SD rats, OVX	5 days	250, 1000		Schlecht et al., (2004)
	The high dose (1525 mg/kg/day) BP-3 caused a significant increase (23%) in the uterine wet weight. No effects on bw.	Uterotrophic assay	LE rats, immature	4 days	611, 937, 1525	1525	Schlumpf et al., (2001)
	No effect of BP-3. Bw was monitored and no effects reported.	Uterotrophic assay	F344 rats, OVX	3 days	20, 100, 500		Suzuki et al., (2005)
	High dose BP-1 increased wet and blotted uterine weight (~13%). No effects on bw.	Uterotrophic assay	SD rats, OVX	3 days **(BP-1)**	100, 250, 625	625	Koda et al., (2005)
	High dose BP-1 increased abs. and rel. wet and blotted uterine weights, by oral (25–28%) and sc dosing (178–204%). Uterine weight was higher (55%) after 300 mg BP-1 sc. No effects on bw were seen.	Uterotrophic assay	C57BL/6J mice	7 days **(BP-1)**	30, 100, 300, 1000	1000 (oral), 300 (sc)	Ohta et al., (2012)
	High dose BP-1 exposure significantly, but only slightly increased uterine weight. Bw unaffected.	Uterotrophic assay	F344 rats	3 days **(BP-1)**	20, 100, 500	500	Suzuki et al., (2005)
	At PND23, dams (N = 5–8) in the 1000 ppm group had increased absolute and relative uterus weights.	Gestational and lactational	SD rats	GD6-PND23	1000, 3000, 10000, 25000, 50,000 (**ppm**)	1000	Nakamura et al., (2015)
Uterus gene expression	ERα mRNA was significantly increased (70%) in BP-3 exposed mice compared to controls.	Uterotrophic assay	Balb/C mice, OVX	4 days	3	3	LaPlante et al., (2018)
	BP-3 exposure significantly decreased ERβ mRNA expression in the uterus but only at the 250 mg/kg dose (N = 11).	Uterotrophic assay	SD rats, OVX	5 days	250, 1000	250	Schlecht et al., (2004)
Uterus histopathology	In the uterus, the incidence of stromal polyp in 3000 ppm females was significantly increased (18 vs 8 in controls). A significantly increased incidence of atypical endometrium hyperplasia of the uterus also occurred at 3000 ppm (19 vs 9 in controls); however, the incidence of adenocarcinoma was significantly decreased in this group (N = 50).	2-year carcinogenicity study	SD rats	2 years	1000, 3000, 10,000 (**ppm**)	3000	NTP (2019)
Estrous cycle	Estrous cycle length was dose-dependently increased in the mid and high dose groups (14–19%). In high dose females % diestrus and metestrus stage were also increased (16 and 40% but not significant), while bw was decreased by 11%.	Repeated dose	F344/N Rats	13 weeks. Adults	3125,12500, 50,000 **(ppm)**	12500 ~ 780 mg/kg bw/d	French, (1992)
	Estrous cycle length was significantly increased in the high dose group (11%). Body weights were significantly reduced in the high dose group (13%).	Repeated dose	B6C3F1 mice	13 weeks. Adults	3125, 12500, 50,000 **(ppm)**	50000 ~ 3260 mg /kg bw/d	French, (1992)
	No effect after dermal exposure (N = 10).	Repeated dose	F344/N rats	13 weeks. Adults	12.5, 50, 200		French, (1992)
	No effect after dermal exposure (N = 10).	Repeated dose	B6C3F1 mice	13 weeks. Adults	22.75, 91, 364		French, (1992)
	In mice fed LFD + BP-3, there was a statistically significant increase in the proportion of mice in diestrus/metestrus with a complementary decrease in the proportion of mice in proestrus/estrus.	Chronic exposure and high or low fat diets	BALB/c Trp53-null mammary transplanted mice	Exposure periods unclear	70	70	Kariagina et al., (2020)
Estrous cycle in F1 females	No change in estrous cycle length. Bw was reduced in mid and high dose groups (13 and 18%).	RACB (Continuous Breeding)	CD-1 mice	Until five produced litters.	~1800, 4000, 9000		Chapin, (1997)

(*continued on next page*)

Table 5 (*continued*)

Effect Target	Observed effect	Study design	Species	Exposure	Dose: mg/kg bw/day*	LOEL	Reference
	Mid- and high dose females spent approximately 5% more time in estrus than did the control females. A significant decrease in the length of proestrus (approximately 2 h) was observed in the 10000 ppm group. High dose group bw was decreased (14%).	MOG Gestational, lactational and adult.	SD rats	GD6-PND150	3000, 10000, 30,000 **(ppm)**	10000 ~ 983 mg/kg bw/d	NTP (2021)
Mammary gland proliferation	HFD + BP-3 for 5 days gave higher proliferation in response to E2 than did mice fed HFD alone. No BP-3 effects were observed in the absence of E2, and no BP-3 effects were observed in mice fed LFD or in adults.	Pubertal or adult	BALB/c mice, OVX	5 days. 7 or 14 weeks old.	0.7, 7, 70	7	Kariagina et al., (2020)
Mammary tumorigenesis	In adult mice fed a high fat diet (HFD), BP-3 increased tumor cell proliferation, decreased tumor cell apoptosis and increased tumor vascularity.	Chronic, with high or low fat diet	BALB/c Trp53-null mammary transplanted mice	Exposure periods unclear	70	70	Kariagina et al., (2020)
	In the high dose group, ductal density at 5 weeks after weaning (and exposure) was significantly lower and Ki67 expression (used as a marker of proliferation) was significantly increased.	Prenatal and lactational exposure	Balb/C mice	6 weeks. GD0-LD21	0.03, 0.212, 3	3	LaPlante et al., (2018)
Mammary gland histology	At PND 21, females had larger ductal areas compared to controls. At puberty, the females exposed to low and high dose had a significant increase in the extent of growth into the mammary fat pad. There was also a significant increase in the number of terminal end buds in high dose females. In adulthood, there was a decreased fraction of the mammary gland comprised of ducts as the dose of BP-3 increased. This effect was statistically significant in the high dose group	Prenatal and lactational exposure	Balb/C mice	6 weeks. GD0-LD21	0.03, 0.212, 3	0.03	Matouskova et al., (2020)
Mammary gland ER and PR expression	At puberty, a significant decrease in PR-positive epithelial cells was observed in the mid dose females. In adult females from low and mid dose groups, there was a decreased fraction of ERα-positive cells.	Perinatal exposure	Balb/C mice	6 weeks. GD0-LD21	0.03, 0.212, 3	0.03	Matouskova et al., (2020)
Adrenal histopathology	In the adrenal cortex, the incidences of focal hypertrophy were significantly increased in 1000 and 3000 ppm females at the end of the 2-year study (42 and 39 vs 25 in controls). (N = 50).	2-year carcinogenicity study	SD rats	2 years	1000, 3000, 10,000 **(ppm)**	1000	NTP (2019)
Sperm parameters	No statistically significant effect on % motile sperm, abnormal sperm, testicular spermatid concentration, and epididymis sperm concentration was seen. However, a nominal (non-significant) decrease in epididymal sperm concentration (8–30%) was reported in the higher dose group throughout the study period and on day 91. No effects on bw.	Chronic	B6C3F1 mice	91 days. 5 days/week from 8 to 9 weeks old.	10, 20, 100, 400		Daston et al. (1993)
	Sperm concentration was, significantly decreased (27%) in the high dose group. No significant differences in % sperm motility and % abnormalities was seen (though a nominal increase in the high dose group in abnormalities of 21%). The lower dose of 12500 ppm (~875 mg/kg) caused a non-significant 14% decrease in sperm concentration. Bw was reduced (31%) in high dose group.	Repeated dose	F344/N rats	13 weeks. Adults	3125, 12500, 50,000 **(ppm)**	50000 ~ 3656 mg/kg bw/d	French, (1992)
	Sperm concentration was decreasing with dose and significantly decreased in the high dose group (9, 17, and 27%	Repeated dose	B6C3F1 mice	13 weeks. Adults	3125, 12500, 50,000 **(ppm)**	3125 ~ 480 mg/kg bw/d	French, (1992)

(*continued on next page*)

Table 5 (*continued*)

Effect Target	Observed effect	Study design	Species	Exposure	Dose: mg/kg bw/day*	LOEL	Reference
	from low to high dose) and % abnormalities was significantly increased from 3125 ppm (55–107%). No significant differences were seen in % sperm motility. Body weights were reduced in the two highest dose groups (9–16%).						
	No effect of dermal exposure.	Repeated dose	F344/N rats	13 weeks. Adults	12.5, 50, 200		French, (1992)
	A significant dose-related decrease in epididymal sperm concentration was seen at all doses following dermal exposure (9%, 16% and 34%).	Repeated dose	B6C3F1 mice	13 weeks. Adults	22.75, 91, 364	22.75	French, (1992)
	No effects on epididymal sperm number, motility, and morphology in high dose group. Bw reduced in high dose group (8%).	RACB (Continuous Breeding)	CD-1 mice	Until five produced litters.	~1800, 4000, 9000		Chapin, (1997)
Sperm parameters F1 males	No effects on motile sperm, progressively motile sperm, or testis spermatid head concentration. Males in the 30000 ppm group displayed lower cauda epididymal sperm counts (approximately 14%). Mid and high dose bw's were decreased (~5% and 16%).	MOG Gestational, lactational and adult.	SD rats	GD6-PND150	3000, 10000, 30,000 **(ppm)**	30000 ~ 3003 mg/kg bw/d	NTP (2021)
Testis histopathology	In the testes, the incidence of fibrinoid necrosis of the arterioles was significantly increased in 10000 ppm males at the end of the 2-year study (16 in control vs 25 in high dose group), and the incidence of interstitial cell hyperplasia occurred with a positive trend (1 in control vs 5 in high dose). (N = 50).	2-year carcinogenicity study	SD rats	2 years.	1000, 3000, 10,000 **(ppm)**	10,000	NTP (2019)

* Doses shown in mg/kg bw/day, unless otherwise specified. Oral dosing unless otherwise specified. Bw (body weight); PND (postnatal day); sc (subcuntanous); ER (estrogen receptor); PR (progesterone receptor); GD (gestational day); LD (lactational day); LFD (low fat diet); HFD (high fat diet); OVX (ovariectomized); SD (Sprague Dawley); LE = (Long Evans); abs (absolute); rel (relative); MOG (Modified one-generation); RACB (reproductive assessment by continuous breeding); Supplementary tables S5 and S6 contains all evidence for *in vivo* endocrine activity.

some statistically significant effects on male reproductive endpoints were observed. On PND23, the number of spermatocytes per seminiferous tubule was significantly reduced at 3000 ppm and higher, and an increase in apoptotic germ cells was seen from 10000 ppm and higher. Testosterone levels were significantly decreased in the groups exposed to 3000 and 25000 ppm but were also nominally lower in males exposed to 1000, 10,000 and 50,000 ppm.

In a follow-up investigation of the male offspring from the full MOG study, transcriptomic profiling of testes on PND 30 was performed using non-retained rat pups. Alteration in gene expression patterns were observed in testes of high dose animals (30000 ppm) and included decreased expression of ERα and ERβ mRNA as well as a decreased expression of several genes related to sperm motility. Serum testosterone levels were significantly reduced (by 28%) at the high dose group (Nakamura et al. 2018). Similar effects were seen in another developmental study, where rat dams were dermally exposed to 100 mg/kg during gestation. After weaning, male offspring were exposed again from PND43-56, and gene expression was measured in the brain on PND57. In cortex and hippocampus, expression of ERβ was decreased, as were serum testosterone levels (Krzyżanowska et al. 2018) (Table S6). In the full MOG study, which included doses of 3000, 10,000 or 30,000 ppm (corresponding to 200–300, 700–950 and 2600–3000 mg/kg bw/day), very few endocrine-related endpoints were significantly affected. However, epididymal sperm counts were significantly decreased (by 14%) in high dose males, corroborating results from previous studies. No significant effects were seen on other sperm parameters, anogenital distance (AGD), nipple retention, sexual maturation or development/function of male reproductive organs (NTP, 2021). In a recently performed Hershberger assay in rats, BP-3 doses of 320 & 1000 mg/kg/day did not exhibit any androgenic or antiandrogenic activity *in vivo* (NTP, 2019).

3.5.3. Other in vivo endpoints

A few *in vivo* studies have also investigated other effects of BP-3 exposure, including carcinogenic, thyroid hormone disrupting and neurodevelopmental effects. For all three areas, there are indications that BP-3 exposure may cause some effects, but clear signs of dose-response and of adversity are missing (Tables S5 and S6).

In a genotoxicity study in SD rats, chromosomal aberrations in bone marrow cells were investigated after 1 or 5 days of BP-3 oral exposure and no effects were seen (Robison et al., 1994). A recent and much larger carcinogenicity study with two-year exposure (n = 50/sex) found that BP-3 exposure affected the uterus and caused a significant increase in the incidence of stromal polyps and endometrial hyperplasia in the mid-dose group (3000 ppm), but that the incidence of uterine adenocarcinomas was significantly decreased in these animals, indicating that the observed histopathological changes were not causing uterine cancer (NTP, 2019). In the same NTP study, the testes were affected in the high dose group (10000 ppm), with increased incidence of interstitial cell hyperplasia and fibrinoid necrosis of the arterioles in exposed males. Again, no increase in testes cancer was observed. In the adrenal cortex, the incidences of focal hypertrophy were significantly increased in low (1000 ppm) and mid (3000 ppm) dose females (NTP, 2019), an effect that may be related to the fact that the adrenals seem to be one of the few organ systems where BP-3 tends to accumulate (Mutlu et al., 2020).

Another organ system in which BP-3 tends to accumulate in rodents is the thyroid gland. The 2-year carcinogenicity study (NTP, 2019) showed an increased incidence of C-cell adenoma in thyroid glands from

mid-dose females (3000 ppm), whereas no significant changes were seen in the follicular (hormone-producing) cells of the thyroid. Other results showed mixed findings for the influence of BP-3 on thyroid hormones. Krzyżanowska et al., (2018) measured thyroid hormones in developmentally exposed animals and found no effects on TSH, free T3 or free T4 plasma concentrations. Nakamura et al., (2015) observed a non-significant reduction in serum T3 levels in high-dose males. Finally, Skórkowska et al., (2020) found that BP-3 exposure increased free T3 and T4 levels, while TSH levels were decreased, i.e. an opposite direction of effects than normally seen by thyroid hormone disrupting chemicals in rodent studies.

A few studies have investigated the effects of BP-3 exposure on neuronal development (Table S6). Pomierny et al., (2019) performed a developmental toxicity study in SD rats with gestational and pubertal exposure. The tested BP-3 dose (100 mg/kg applied dermally) reduced the anti-oxidant capacity, increased lipid peroxidation, altered glutamate regulation and increased apoptosis in frontal cortex and hippocampus in the adult offspring. Behavioral effects were also analyzed, and the study showed that while BP-3 did not disrupt short-term memory, the exposure did weaken offspring's spatial memory (Table S6).

Two *ex vivo* studies investigated the effects of gestational BP-3 exposure in mice on neuronal gene and protein expression and epigenetics in offspring, followed by a 7-day exposure of neocortical primary cultures. BP-3 induced apoptosis, caused neurotoxicity and decreased ERα and ERβ expression levels in neocortical cells of embryonic offspring (Table S5). BP-3 also caused hypermethylation of the estrogenic genes possibly explaining the reduced mRNA and protein levels of the estrogen receptors (Wnuk et al., 2018c). In the same test system, Wnuk et al., (2019) confirmed that BP-3 impaired autophagy and disrupted the expression and epigenetic regulation of several neurogenesis- and neurotransmitter-related genes.

3.5.4. *In vivo summary*

Overall, regulatory studies identified decreases in sperm concentration in males at dose levels of 700–1000 mg/kg bw/day or higher. The exception was a dermal repeated-dose toxicity study in mice, showing significant decreases in sperm concentration at doses of 23 mg/kg bw/ and above (French, 1992). In females, regulatory studies indicate endocrine-mediated effects on estrous cyclicity in response to mid-high BP-3 doses (≈700 mg/kg bw/day) together with short-term altered ER gene expression in reproductive tissues at lower doses (≈250 mg/kg bw/day). One academic study (i.e., independent research and/or university-based setting) supported the effect on altered estrous cyclicity at a ten times lower dose of 70 mg/kg bw/day (Kariagina et al., 2020), while other academic studies also identified short-term changes in ER regulated gene expression in uterus, mammary glands, pituitary, hippocampus and cortex at low doses (LaPlante et al., 2018; Majhi et al., 2020; Matouskova et al., 2020). Additionally, new adverse effects have been identified by academic studies, with the mammary gland showing exquisite sensitivity. In low-dose developmental studies, adverse histopathological effects have been observed at doses between 0.3 and 3 mg/kg bw/day (LaPlante et al., 2018; Matouskova et al., 2020). Also neurodevelopmental effects have been identified (Pomierny et al., 2019; Wnuk et al., 2018c). Altogether, it cannot be ruled out that adverse reproductive or neurodevelopmental effects could occur at lower BP-3 doses than those identified as safe in regulatory studies. Future studies must consider testing lower doses and performing a comprehensive assessment of female reproductive outcomes including mammary gland endpoints (Table 5).

3.6. *Human exposure-health association studies*

The search retrieved 67 publications exploring exposure-health relationships that were analyzed and tabulated in detail (Supplementary data 3, Tables S7-12). This section provides a summary of the most important epidemiological findings.

3.6.1. *Birth outcomes*

Eight mother-child cohorts have studied the relationship between maternal prenatal urinary BP-3 concentrations and birth outcomes, finding a possible sex-specific association towards higher birth weight (BW) among boys, and lower BW among girls, especially when exposure was measured in the third trimester (Table S7). Wolff et al. (2008) reported higher and lower BW among boys and girls, respectively, in response to higher third trimester urinary BP-3 concentrations among 404 US mother-child pairs. The French EDEN cohort only included boys, reporting positive associations between third trimester urinary BP-3 and offspring BW and head circumference (HC), in addition to higher placental weight among 473 pregnant women (Philippat et al., 2019, 2011). Aker et al. (2019) estimated average prenatal BP-3 concentrations measured in three urine samples collected from 749 Mexican pregnant women. They reported positive associations with gestational age (GA), and suggestive positive associations with BW z-scores and a higher risk of being large for GA, being these results not modified by child sex. The EARTH study, a preconception cohort of sub-fertile couples, found that paternal preconception BP-3 exposure - but not maternal preconception or prenatal exposure – was associated with higher offspring BW, being this association stronger in boys (Messerlian et al., 2018). In the same cohort, Mustieles et al. (2020) did not observe associations between paternal or maternal preconception BP-3 exposure and preterm birth risk, but Zhang et al. (2021) reported an inverse association between first trimester urinary BP-3 concentrations and prematurity, mainly among boys. Long et al. (2019) studied 847 Chinese mother-child pairs, reporting that third trimester urinary BP-3 and BP-1 concentrations were inversely associated with BW in girls but not boys. In line with the usually higher biological activity of BP-1, the magnitude of effect estimates was higher for BP-1 compared to BP-3. The sum of all benzophenones investigated showed a trend towards higher BW in boys but not girls (Long et al., 2019). Interestingly, only exposure at third trimester - but not first and second trimesters – was associated with BW.

Other studies found null associations with BW, such as a small study performed in 157 Danish mother-child pairs (Krause et al., 2018), or an inverse association with gestational age (Tang et al., 2013), although the later study measured BP-3 in a urine sample collected just after hospital admission for labor, so reverse causality cannot be excluded. The LIFECODES cohort studied 482 US women, reporting a null association between average prenatal urinary BP-3 concentrations and BW, in either boys or girls, only finding among boys an inverse association with fetal abdominal circumference measured by ultrasound (Ferguson et al., 2018). The discrepancy of this study with previous ones is not known, but could be influenced by the study design: a nested case-control study over-representing preterm birth cases.

3.6.2. *Fertility and reproductive outcomes*

The eight epidemiological studies that investigated reproductive hormones, fertility and female-related reproductive endpoints are presented in Table S8. Pollack et al. (2018) recruited 143 US healthy premenopausal women not using hormonal contraception, who provided repeated urine and blood samples up to 8 times for a total of two menstrual cycles. BP-1, BP-3 and other phenolic EDCs were measured in 509 spot urine samples, and reproductive hormones (estradiol (E2), progesterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH)) in serum samples collected at early follicular phase, ovulation and mid-luteal phase. BP-1 and BP-3 were associated with increased progesterone and with decreased E2, FSH, and LH serum levels (Pollack et al., 2018). If confirmed in subsequent studies, these findings may have implications for fertility and other hormonally-mediated chronic diseases. A cross-sectional study of 789 premenopausal women from the NHANES survey found that the cluster represented by BP-3, triclosan and bisphenol A - but not these compounds in isolation - was associated with a history of infertility (Arya et al., 2020). Notwithstanding, two longitudinal preconception cohorts did not support the association between couple's BP-3/BP-1 exposure and fecundity

(Buck Louis et al., 2014; Mínguez-Alarcón et al., 2019). Regarding female reproductive diseases, the ENDO study reported that urinary BP-1 concentrations were associated with increased odds of endometriosis, with women in the highest BP-1 quartile presenting a 65% higher odds of endometriosis compared to the three lower quartiles (Kunisue et al., 2012). BP-3 exposure also tended to be associated with increased endometriosis risk, but associations were more evident with BP-1. Although not significant, an association between higher urinary BP-3 and BP-1 concentrations and a suggestive higher risk of uterine fibroids was also reported in a subsequent analysis of the cohort (Pollack et al., 2015). The Spanish ENDEA Study compared 35 endometriosis cases to 89 controls, finding that the odds of endometriosis were significantly higher in women in the second tertile of urinary BP-1 and BP-3 concentrations (Peinado et al., 2020). On the contrary, two case-control studies assessing BP-3 in one urine sample after diagnosis, reported null associations with the risk of polycystic ovary syndrome in a very low-exposed Chinese population (Gu et al., 2019), and with breast cancer among North American women (Parada et al., 2019).

Five studies/cohorts investigated male reproductive health. Scinicariello and Buser (2016) analyzed cross-sectional data from the US NHANES survey, finding that higher urinary BP-3 concentrations were associated with lower serum total testosterone (TT) levels in male adolescents. Adoamnei et al. (2018) recruited 215 Spanish male university students aged 18–23 years, reporting positive associations between urinary BP-1 and BP-3 concentrations and serum FSH levels. Additionally, BP-1 concentrations were associated positively with the TT/E2 ratio and negatively with the inhibin B/FSH ratio. Notwithstanding, no associations were observed with sperm quality parameters. Joensen et al. (2018) studied 65 male participants with Filaggrin gene (FLG) loss-of-function mutations and 130 controls without FLG mutations. Filaggrin is a protein involved in skin barrier functions, and FLG mutation carriers are subjected to increased transdermal penetration of personal care products. Within the group of FLG mutation carriers, higher urinary BP-1 and BP-3 concentrations were associated with higher TT and E2 serum levels and lower FSH, although no association was observed with sperm parameters. None of these associations were evident in the control group. The preconception LIFE cohort did not find associations with semen quality parameters when BP-1 or BP-3 were measured in either urine samples (Buck Louis et al., 2015), or seminal plasma (Smarr et al., 2018). Although without reaching statistical significance, suggestive inverse associations between paternal preconception seminal plasma BP-1 and BP-3 concentrations and fecundity were reported in the LIFE study (Buck Louis et al., 2018). A study in Chinese males with idiopathic infertility did not find associations between urinary BP-3 concentrations and sperm quality (Chen et al., 2013).

3.6.3. Child anthropometry and puberty

Six studies analyzed anthropometric outcomes and puberty in girls (Table S9). Buckley et al. (2016) observed that third trimester urinary BP-3 concentrations were inversely associated with body fat mass among North American girls, but not boys at 4–9 years of age, in line with the previous prenatal association in the same cohort between BP-3 and lower BW among girls (Wolff et al., 2008). Deierlein et al. (2017) studied 1017 girls recruited at three US sites, assessing BP-3 in urine samples collected at 7 years, and evaluating anthropometric parameters yearly until the age of 15. Baseline BP-3 exposure was inversely associated with waist circumference (but not BMI) from the age of 10 onwards, achieving statistical significance at 12 and 13 years. In this same cohort, Wolff et al. (2015) observed that girls in the fifth quintile of BP-3 concentrations showed a significantly delayed breast development: a mean of 5–6 months later compared to those in the lowest quintile. This delay is consistent with a lower adiposity among girls in response to BP-3 exposure. On the contrary, Binder et al. (2018) reported that urinary BP-3 concentrations at 8 - but not 11 - years of age were associated with an earlier age at menarche among 200 Chilean girls; while Harley et al. (2019) reported non-significant trends between higher prenatal and peripubertal urinary BP-3 concentrations, and an earlier age at menarche among 179 Latina girls. Buttke et al. (2012) did not find cross-sectional associations with age at menarche in 440 pubertal girls from NHANES.

Regarding boys, Huang et al. (2020) recruited 521 children aged 7–15 years (Table S9). Baseline urinary BP-3 concentrations were inversely and longitudinally associated with stages of testicular volume in boys. This study is consistent with the inverse association between urinary BP-3 and serum testosterone observed in NHANES adolescent males (Scinicariello and Buser, 2016). Other possible mechanisms may include alterations in DNA methylation, as shown by a small pilot study among Danish peripubertal children, that found 73 differentially regulated regions longitudinally associated with urinary BP-3 exposure. One interesting marker identified was thyroid hormone receptor interactor 6 gene (TRIP6), mainly induced in testicular Leydig cells during puberty. In this study, BP-3 exposure was associated with higher TRIP6 DNA methylation, and lower TRIP6 serum protein levels (Almstrup et al., 2020).

3.6.4. Thyroid hormones biomarkers

Seven studies reported associations between BP-3 and thyroid hormone levels (Table S10). The LIFECODES cohort (USA) investigated 439 pregnant women who provided urine and blood samples at four times throughout pregnancy, reporting that urinary BP-3 concentrations were associated with all serum thyroid hormones at least at one prenatal visit (Aker et al., 2018). BP-3 was inversely associated with total triiodothyronine (TT3) levels at all visits except the second one, and with free thyroxine (FT4) levels at all visits except the fourth one. BP-3 was also inversely associated with the T3/T4 ratio at the last visit. BP-3 tended to be positively associated with thyroid stimulating hormone (TSH), especially at the second and third prenatal visits. Berger et al. (2018) studied a cohort of 454 pregnant women (Mexico), finding that average prenatal urinary BP-3 concentrations were inversely associated with serum FT4 and TT4 levels in women, and with lower TSH among neonates. Associations were slightly attenuated after covariate adjustment. Aker et al. (2016) reported an inverse association between the prenatal average of urinary BP-3 concentrations and serum FT3 levels in 106 pregnant women from Puerto Rico. Among 1829 adult participants of the NHANES survey (USA), urinary BP-3 concentrations were cross-sectionally and inversely associated with serum TT4 and FT4 levels. BP-3 concentrations also tended to be associated with decreased TT3 and FT3 levels, but higher TSH serum levels (Kim et al., 2017). In the same NHANES population, Przybyla et al. (2018) revealed that BP-3 concentrations were inversely associated with TT4 in males, while a non-significant but positive direction of association was observed with TT3 serum levels in females. Two low-exposed mother-child cohorts found null associations between maternal urinary concentrations of BP-3 or BP-1 and thyroid hormones levels in 183 Danish (Krause et al. 2018) and 386 Chinese (Guo et al. 2020) pregnant women. Overall, the associations between urinary BP-3 concentrations and thyroid hormone levels observed in human studies support an inhibitory effect of BP-3 and/or BP-1 on thyroid hormone synthesis.

3.6.5. Neurodevelopment

Few studies explored associations with children's neurodevelopment (Table S6). No associations were reported between prenatal BP-3 exposure and cognitive function (Jiang et al., 2019; Nakiwala et al., 2018). While Philippat et al. (2017) did not observe any association with behavior among 529 French boys at either 3 or 5 years, Guo et al. (2020) reported that prenatal BP-3 exposure was associated with an increased risk of prosocial problems among 386 Chinese children aged 10 years. Since preliminary data in rodents suggest that BP-3 is able to cross the blood-brain barrier and exert neurological effects including neuronal apoptosis (Krzyżanowska et al., 2018), future studies will help to confirm or rule out BP-3-related neurodevelopmental effects.

3.6.6. Metabolic health

Four epidemiological studies have revealed an unexpected and apparently protective relationship between BP-3 and BP-1 and the risk of type 2 diabetes (Table S11). Using data from the NHANES survey, Ward et al. (2020) reported an inverse cross-sectional association between urinary BP-3 concentrations and diabetes risk among 8,498 US adults. A small case-control study performed in Saudi Arabia reported that participants in the third and fourth quartiles of both BP-1 and BP-3 concentrations showed a significantly reduced risk of diabetes (Li et al., 2018b). Salamanca-Fernández et al. (2020) studied 670 Spanish adults observing a borderline longitudinal association between serum BP-1 concentrations and lower diabetes risk. Among 217 pregnant women from the EARTH Study, Wang et al. (2020) found that first trimester BP-3 concentrations were associated with lower glucose levels, and that women with higher second trimester BP-3 concentrations had lower odds of an abnormal glucose load test. This association was modified by several factors: women with female-factor infertility, carrying female fetuses, presenting older age or lower BMI and those women whose urine samples were collected during summer showed the strongest inverse associations between BP-3 and glucose levels, whereas no associations were observed in the remaining subgroups. With the exception of Wang et al., most previous studies did not consider season or outdoor activities as potential confounders or effect modifiers. More studies are needed to clarify whether these protective associations are explained by residual confounding (Mínguez-Alarcón et al., 2019) or by a true biological effect.

3.6.7. Oxidative stress and inflammation

Several studies investigated oxidative stress and inflammatory markers in relation to BP-3 exposure (Table S12). Urinary BP-3 concentrations were positively associated with higher urinary concentrations of 8-hydroxy-deoxy-guanosine (8OHdG) and 8-isoprostane among pregnant women (Ferguson et al., 2019; Watkins et al., 2015) and children (Rocha et al., 2018). A hospital-based cohort of adults undergoing non-cancer-related surgery measured BP-3 and oxidative stress markers in adipose tissue samples, reporting associations with reduced glutathione (GSH) and increased glutathione peroxidase (GPx) levels (Artacho-Cordón et al., 2019). Notwithstanding, one prenatal study reported an apparently contradictory finding: urinary BP-3 concentrations were associated with higher 8OHdG concentrations measured in urine, but with lower systemic inflammation estimated through C-reactive protein levels measured in serum (Watkins et al., 2015).

4. Discussion and gaps in knowledge

This work comprehensively analyzed the different evidence mainstreams available (*in vitro*, *in vivo* and humans), to address the potential influence of BP-3 and BP-1 exposure on human health. Below we discuss the most relevant aspects and highlight knowledge gaps.

4.1. Human exposure patterns

The review confirms that virtually all humans present detectable BP-3 and BP-1 concentrations, with evidence of internal exposure in a variety of biological matrices including urine, serum, amniotic fluid, cord blood, placenta, breast milk, seminal plasma and adipose tissue among other human matrices (Supplemental Excel File HBM-DB). Several studies have shown correlations between urinary BP-3 concentrations and those found in other matrices, supporting the use of urinary BP-3 as a valid proxy for internal exposure (Artacho-Cordón et al., 2017; Frederiksen et al., 2021; Philippat et al., 2013). The *meta*-analysis of HBM studies revealed significant geographical differences, with North Americans presenting about 10 and 20 times higher urinary BP-3 concentrations than European and Asian populations, respectively (Table 2). Although mean urinary BP-3 concentrations among Europeans were in the low-dose range (2.88 ng/mL ≈ μg/g creatinine – Table 2), levels can be quite high in the top exposure percentiles (range 32.2 to 466 μg/g in pregnant women). While strengths of our *meta*-analysis include the structured selection of the studies together with the quality checks performed, we also acknowledge some limitations to the post-harmonization of international HBM data, including differences in analytical methods (e.g., liquid vs. gas chromatography), limits of detection and time frame of sampling among others. This work also highlights the need for a more precise reporting in HBM studies, including medians and percentiles 90 and 95, to facilitate the pooling of data.

Regarding sources, dermal exposure through sunscreen and cosmetics is linked to peak-exposures, while food, textiles, indoor air and dust more likely contribute to a continuous low-dose exposure (Table 1). Therefore, human BP-3 exposure is anticipated to be the result of a continuous background exposure, combined with intermittent exposure peaks that can reach high levels after sunscreen (Matta et al., 2020; Janjua et al., 2008) and probably cosmetic use. Notwithstanding, the contribution of PCPs (different from sunscreen) to internal BP-3 and BP-1 concentrations has not been investigated to date with intervention studies. Future HBM studies must generalize the assessment of BP-1 together with BP-3.

4.2. Toxicokinetic characteristics

BP-3 is rapidly metabolized to BP-1 (and other minor metabolites such as BP-8) and excreted in urine in both rodents and humans, supporting its classification as a non-persistent chemical. However, data also supports the possibility of a temporal accumulation in certain tissues. Thus, rodent studies showed that, although less than 1% of the oral dose of BP-3 remained in the body 72 h post-exposure, tissue to blood ratios were disproportionately higher for thymus, thyroid and adrenal glands (Mutlu et al., 2020). Adipose tissue also appeared as a temporary depot in rodents and humans (Artacho-Cordón et al., 2019; Mutlu et al., 2020; Wang et al., 2015), and BP-3 also accumulates in skin after sunscreen application, constituting a reservoir for the following days after exposure cessation (Matta et al., 2020). This temporary tissue accumulation may be in line with BP-3′s lipophilic nature (Kim and Choi, 2014), which could have implications for specific adverse effects. Whether BP-1 shows a temporal accumulation in specific tissues in unknown. Another data gap is the longer half-life reported for BP-1 compared to BP-3 (Jeon et al., 2008), that should be confirmed by other rodent and human toxicokinetic studies.

The intervention study by Matta et al., (2020) demonstrated that a unique whole-body application of a sunscreen containing BP-3 at levels below those allowed by the latest European regulation (max. 6% of product weight in sunscreens; EU, 2017), produces an internal peak plasma concentration of 94.2 ng/mL of BP-3 (0.41 μM). Additionally, up to three weeks are needed to clear plasma BP-3 concentrations after repeated sunscreen application during 4 days (Matta et al., 2020). Our comparison of rodent and human internal BP-3 concentrations showed that peak-exposure concentrations after human dermal sunscreen application may overlap with low and intermediate (up to 10000 ppm) chronic oral doses tested in rodent studies (Table 3). A possible limitation of our toxicokinetic comparison is that data from the rodents was obtained following oral exposure, while human data was obtained following dermal exposure (the most relevant for humans). Since biotransformation of BP-3 to BP-1 and half-lives may change between dermal and oral (first pass metabolism) exposure routes, future studies should also assess internal BP-1 levels in human toxicokinetic studies to enable refinement of the comparison of rodent and human internal exposure levels. Regarding *in vivo* toxicity studies, most were performed using oral exposure. However, since the few studies using subcutaneous/dermal exposure showed coherent results with oral exposure studies for altered expression of ERs, uterotrophic and sperm effects (Daston et al., 1993; French, 1992; Krzyżanowska et al., 2018; Nakamura et al., 2018; Ohta et al., 2012; Skórkowska et al., 2020; Suzuki et al., 2005), the

performed oral studies were considered valid for identifying the intrinsic toxicological properties of both BP-3 and BP-1.

Another important aspect is the wide variability in dermal absorption (Matta et al., 2020). Thus, in 12 adult participants evaluated, internal BP-3 levels after a unique whole-body sunscreen application ranged from 44.6 to 177.6 ng/mL (4-fold difference). This is consistent with the relatively frequent genetic variations in skin barrier permeation, such as filaggrin gene loss-of-function mutations present in about 10% of persons of European ancestry (Irvine et al., 2011), that have been linked to increased BP-3 absorption and higher likelihood to observe adverse reproductive effects in adult males (Joensen et al., 2018). This wide individual variability in dermal absorption should be taken into account in future risk assessments in order to protect the highest exposed segment of the population.

4.3. Adverse effects of highest concern

BP-3 and particularly BP-1 are estrogenic at concentrations below 1 μM, which overlaps with peak concentrations achieved in human plasma after sunscreen use. This mode of action is compatible with female endocrine disrupting effects reported by *in vivo* studies. Short-term exposure during 4–5 days to BP-3 at low (3 mg/kg/d) and moderate (250 mg/kg/d) oral doses (that overlap with human peak-exposure after sunscreen use) caused alterations in the gene expression of estrogen receptors in the uterus of mice and rats, respectively (LaPlante et al., 2018; Schlecht et al., 2004). Additionally, chronic studies have shown prolonged estrous cyclicity and mammary gland proliferation/altered histology in rodents at low to moderate doses (French, 1992; Kariagina et al., 2020; LaPlante et al., 2018; Matouskova et al., 2020). Moreover, human observational studies have linked BP-3 and BP-1 exposure to disrupted female hormone regulation (Pollack et al., 2018), uterine fibroids (Pollack et al., 2015) and endometriosis (Peinado et al., 2020). Additionally, BP-3 and BP-1 also show potential to induce *in vitro* carcinogenic effects in hormone-sensitive tissues at low doses. Indeed, the latest National Toxicology Program observed a higher incidence of stromal polyps and atypical endometrium hyperplasia at the lowest dose tested of 3000 ppm (NTP, 2019; SCCS, 2021). Overall, although the previous NTP and SCCS panels expressed “equivocal evidence for BP-3 related adverse effects”, this comprehensive review supports that a possible mid- and long-term contribution to female reproductive problems should be seriously considered, especially for heavy users of sunscreen and cosmetics.

Although there is some concern for BP-3 effects on the male reproductive system, including reduced sperm quality and lower testosterone levels, these effects were mostly observed at high doses in animal studies, with the exception of a low dose dermal study in mice (French, 1992). Human observational studies have not found clear associations between BP-3/BP-1 exposure and semen quality parameters, with some exceptions (Joensen et al., 2018). The association between BP-3 and reduced testosterone in adolescent boys from the NHANES needs to be replicated in future studies (Scinicariello and Buser, 2016). Regarding possible effects in the testes, the latest NTP study reported a significantly higher incidence of fibrinoid necrosis of the arterioles in males (10,000 ppm), together with an increasing trend of testis interstitial cell hyperplasia, both effects observed at the end of the 2-year study (NTP, 2019; SCCS, 2021).

The human literature showed a consistent pattern of associations in pregnant women, children and adults linking higher BP-3 exposure to lower thyroid hormone levels. Although a few *in vitro* studies support possible actions of BP-3 and BP-1 on thyroid regulation, more evidence is needed to better delineate this possible mode of action. Of note, the thyroid gland was shown to accumulate BP-3 concentrations in rats and especially in mice (Mutlu et al., 2020). Indeed, the latest NTP report showed a significantly higher incidence of thyroid C-cell adenoma at 3,000 ppm in females at the end of the 2-year study (NTP, 2019; SCCS, 2021). Future studies should clarify whether the possible accumulation of BP-3 in the thyroid gland, even if temporal, can interfere with thyroid gland structure and/or function.

Evidence from mother-child cohorts also highlights a possible association between maternal urinary BP-3 concentrations and higher birth weight among boys but lower birth weight among girls. This association was more evident when exposure was measured in the third trimester. A possible explanation could be the efficient anti-PGE2 activity shown by BP-3 in humans (Jannesson et al., 2004) that may mediate increased pregnancy length or delayed cervical ripening (Chatterjee et al., 1991), consequently increasing birth weight. Notwithstanding, we are not aware of a mechanism that could explain the opposing association between boys and girls, which could also be explained in terms of altered estrogen-androgen balance (Ghazipura et al., 2017). Comparison with rodent studies is complex, since they are not considered an optimal model for birth outcomes (Ferguson and Chin, 2017).

4.4. Regulatory and policy implications

The integration of the different evidence mainstreams shows concern of possible adverse effects in humans, especially at high internal doses, compatible with a frequent use of sunscreens and personal care products.

This work highlights the need for risk mitigation measures in the U.S., the geographical region showing the highest exposure levels measured to date. Although BP-3 exposure among Europeans and Asians is considerably lower, concern still exists under high-exposure scenarios. Our current results show that the previous decision of the European Commission to limit BP-3 from 10% to 6% w/w in sunscreens may not be sufficiently protective in light of a recent high-quality human toxicokinetic study (Matta et al., 2020). Indeed, the last report of the SCCS has opined that the use of BP-3 as a UV filter is sunscreen formulations is only safe at a maximum of 2.2% w/w in body creams, propellant and pump sprays, although not in face creams, hand creams and lipsticks (SCCS, 2021). Moreover, a recent study performed a risk assessment using urinary BP-3 concentrations in European HBM studies concluding that, although there is no concern for the general population, a risk to human health exists under reasonable worst-case exposure scenarios (Rousselle et al., 2022). Our work fully supports the SCCS opinion to further reduce the use of BP-3 in sunscreen formulations in Europe, together with a call for regulatory action in the U.S.

The regulation of UV filters should also consider environmental implications. Indeed, BP-3, together with other organic UV filters, represents a concern for aquatic life (DiNardo and Downs, 2018; Huang et al., 2021). A recent work elaborated this holistic view arguing that decision-making must include ethical principles including sustainability, beneficence, non-maleficence, justice, community, and precautionary substitution. The application of these criteria to the case of BP-3 reinforced the need for more stringent regulations (Matouskova and Vandenberg, 2022).

The latest SCCS opinion expressed that, although there are indications to suggest that BP-3 may have endocrine effects, the overall evidence is not conclusive enough at present, after consideration of both *in vitro* and *in vivo* studies, either individually or taken together (SCCS, 2021). Our current work differs from this view, finding substantial *in vitro* evidence to identify BP-3 as a chemical with endocrine disruption potential (Table 4), and moderate evidence from *in vivo* studies, in which endocrine-related outcomes were found at low and moderate doses (Table 5; French, 1992; Kariagina et al., 2020; LaPlante et al., 2018; Matouskova et al., 2020; Santamaria et al., 2020). Future regulatory studies should consider testing lower BP-3 doses based on findings from academic studies, because effects occurring at moderate to high doses may differ from those observed at lower doses. Another need would be to include more sensitive endpoints such as for example mammary gland development.

Another regulatory gap is the absence of mixture risk assessments for co-occurring UV filters and other compounds with similar adverse

effects. Since most chemical UV filters have a limited spectral band of UV absorption, their use in combination is common (DiNardo and Downs, 2018; Jansen et al., 2013; Latha et al., 2013), complicating the evaluation of potential adverse effects in humans. Case studies co-administering BP-3 with other frequently used sunscreen agents (e.g., other benzophenones, cinnamates, salicylates, camphor derivatives, etc.), as well as other chemicals triggering similar pathways or exerting similar adverse effects, are needed to evaluate mixture effects (Heneweer et al., 2005; Kunz and Fent, 2009, 2006; Li et al., 2018a).

Regarding prevention, people should be encouraged to practice proper photoprotection including photoprotective clothing, staying in the shade while outdoors, and applying sunscreen to exposed areas (Narla and Lim, 2020). Beyond regulatory actions, citizens should also be informed about ways to reduce chemical exposure. Studies have demonstrated that it is possible to reduce the exposure to BP-3 and other EDCs present in personal care products, just by reading labels (Dodson et al., 2020; Harley et al., 2016). Educational campaigns together with greater ingredient transparency are recommended. Finally, healthcare providers and the public, should be informed about alternative formulations also recommended by dermatologists, such as sunscreens using mineral filters (e.g., zinc oxide and titanium dioxide) that are not dermally absorbed into blood (or only in trace amounts) and may provide the same or even better UV protection than BP-3-based formulations (DiNardo and Downs, 2018; Narla and Lim, 2020). This recommendation may be especially relevant in the case of susceptible populations like pregnant women and children.

5. Conclusions

This work supports the identification of BP-3 and BP-1 as chemicals with endocrine-disrupting potential. Peak-internal BP-3 concentrations achieved after a single whole-body application of commercially available sunscreens (4% w/w) overlap with concentrations eliciting endocrine disrupting effects *in vitro*, with short-term effects on estrogen receptor gene expression, as well as with chronic concentrations causing *in vivo* adverse female reproductive effects in both regulatory and academic rodent studies, and with some but still limited observational studies. Human biomonitoring data highlights a higher concern for North Americans, exposed to significantly higher urinary BP-3 concentrations compared to European and Asian populations. Although our *meta*-analysis showed that Europeans are exposed to a seemingly low urinary BP-3 mean concentration, the fraction of the population in the top exposure percentiles may be at risk. There is a need to revisit the latest European regulation, since our integrative analysis together with other recent works show compelling evidence that it may not be sufficiently protective. More research is needed for BP-1 in both HBM and toxicological fields. BP-1 should also be considered in risk assessment and policy-making together with BP-3. This work should accelerate new policies worldwide and may be considered as a point of departure for future risk assessments. Meanwhile, healthcare practitioners may inform susceptible populations including pregnant women and children about alternative sunscreen formulations using mineral UV filters (which are not absorbed into blood), among other measures to avoid excessive solar radiation.

Data availability

Beyond data published as Supplementary Material, additional literature search data and analytic code are available from the corresponding authors upon reasonable request.

CRediT authorship contribution statement

Vicente Mustieles: Conceptualization, Methodology, Investigation, Writing – original draft. **Ria K. Balogh:** Investigation, Data curation, Visualization, Writing – original draft. **Marta Axelstad:** Investigation, Methodology, Writing – original draft. **Parisa Montazeri:** Formal analysis, Writing – review & editing. **Sandra Márquez:** Software, Writing – review & editing. **Martine Vrijheid:** Supervision, Writing – review & editing. **Monica K. Draskau:** Investigation, Writing – review & editing. **Camilla Taxvig:** Investigation, Writing – review & editing. **Francisco M. Peinado:** Investigation, Writing – review & editing. **Tamar Berman:** Supervision, Writing – review & editing. **Hanne Frederiksen:** Supervision, Writing – review & editing. **Mariana F. Fernández:** Funding acquisition, Project administration, Supervision, Writing – review & editing. **Anne Marie Vinggaard:** Supervision, Methodology, Funding acquisition, Writing – review & editing. **Anna-Maria Andersson:** Supervision, Methodology, Funding acquisition, Writing – review & editing.

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.

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Appendix A. Supplementary data

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