Eco-Environment & Health 3 (2024) 30–44

Contents lists available at ScienceDirect

Eco-Environment & Health

journal homepage: www.journals.elsevier.com/eco-environment-and-health

Review

A review of sources, pathways, and toxic effects of human exposure to benzophenone ultraviolet light filters

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ARTICLE INFO

Keywords:
Benzophenone ultraviolet light filters
Human exposure
BP-3
Health effects
Risk assessment

ABSTRACT

Benzophenone ultraviolet light filters (BPs) are high-production-volume chemicals extensively used in personal care products, leading to widespread human exposure. Given their estrogenic properties, the potential health risks associated with exposure to BPs have become a public health concern. This review aims to summarize sources and pathways of exposure to BPs and associated health risks. Dermal exposure, primarily through the use of sunscreens, constitutes a major pathway for BP exposure. At a recommended application rate, dermal exposure of BP-3 via the application of sunscreens may reach or exceed the suggested reference dose. Other exposure pathways to BPs, such as drinking water, seafood, and packaged foods, contribute minimal to the overall dose. Inhalation is a minor pathway of exposure; however, its contribution cannot be ignored. Human exposure to BPs is an order of magnitude higher in North America than in Asia and Europe. Studies conducted on laboratory animals and cells have consistently demonstrated the toxic effects of BP exposure. BPs are estrogenic and elicit reproductive and developmental toxicities. Furthermore, neurotoxicity, hepatotoxicity, nephrotoxicity, and carcinogenicity have been reported from chronic BP exposure. In addition to animal and cell studies, epidemiological investigations have identified associations between BPs and couples' fecundity and other reproductive disorders, as well as adverse birth outcomes. Further studies are urgently needed to understand the risks posed by BPs on human health.

1. Introduction

Ultraviolet (UV) radiation from sunlight can affect human health, although sunlight is vital for maintaining circadian rhythm. The detrimental effects of UV radiation on human health include skin damage, premature aging, and increased risk of skin cancer, which are well-established [1,2]. To address these concerns, benzophenone UV light filters (BPs) are used in several products. These chemicals possess the properties required to effectively mitigate the damage caused by UV radiation.

BPs are commonly used in various consumer products, such as sunscreens, cosmetics (e.g., lipsticks and perfumes), and other personal care products (PCPs) (e.g., creams, shampoos, and toothpastes), given their capacity to absorb a broad range of wavelengths, deliver reliable performance, and remain low cost [3–5]. Among different BPs, particular emphasis has been placed on benzophenone-3 (BP-3 or oxybenzone), which is listed as a "high-production-volume chemical" [6]. However, due to mounting safety concerns, restrictions have been implemented. For instance, the European Union (EU) limited the maximum concentration of BP-3 in sunscreen products to 6% in 2017 [7]. Similarly, in China, the maximum allowable concentration of BP-3 in cosmetics was 10%, while that of BP-4 and BP-5 was 5% [8]. In addition to their use in cosmetics, BPs are not only added to other consumer products such as textiles to avoid UV radiation [9], but are also incorporated into building materials (e.g., plastics and paints) because they act as UV stabilizers, helping to prevent the degradation and discoloration of the materials caused by UV radiation exposure [10,11]. Moreover, BPs find application in the pharmaceutical industry, where they serve as intermediates in drug formulations. Consequently, some BPs are investigated as potential sources of drugs [12]. These widespread applications and utilization

Given his role as an Editor, Tao Zhang had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

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https://doi.org/10.1016/j.eehl.2023.10.001
Received 7 July 2023; Received in revised form 30 August 2023; Accepted 2 October 2023
Available online 19 October 2023

contributed to their critical role in the potential impact of human exposure.

The chemical structure of BP consists of two benzene rings connected by a carbonyl group, and various BP derivatives are synthesized by substituting different functional groups on benzene rings (Fig. 1). Whereas hundreds of naturally occurring BP derivatives have been documented, regulatory agencies have focused on commercial BPs and their metabolites, including BP, BP-1 to BP-12, 4-hydroxy-benzophenone (4-OH-BP), 4,4-dihydroxy-benzophenone (4-DHB), 2,3,4-trihydroxy-benzophenone (2,3,4-THB), 2,4,5-trihydroxy-benzophenone (2,4,5-THB), 2,4,4′-trihydroxy-benzophenone (2,4,4′-THB), and 4-methyl-benzophenone (4-MBP) (Fig. 1). To shed light on their characteristics, the physicochemical properties of specific BPs were identified by Estimation Programs Interface (EPI) Suite™ (EPIWEB 4.1, Table S1, Table S2), revealing key properties such as octanol-water partition coefficient (Log K_{ow}), air-water partition coefficient (Log K_{aw}), soil adsorption coefficient (Log K_{oc}), bioconcentration factor (BCF), bioaccumulation factor (BAF), and half-life. The distribution and fates of BPs in the environment, as well as human exposure pathways, may vary depending on their physicochemical properties and usage [6].

Biomonitoring studies have shown that BPs are present in various human specimens, including urine [13], blood [14,15], breast milk [16,17], semen [18–20], and adipose tissue [21] (Fig. 2, Table S3). Among various BPs, BP-3 was the predominant compound in human matrices, while BP-1, BP-2, 4-OH-BP, and BP-8 were also commonly detected [15,22–24]. Human exposure levels of BPs varied depending on gender [15,25], age [26], geographic [27,28], seasonal [29], and ethnic differences [30,31], which account for the differences in concentrations monitored across countries/regions. In addition, an extensive investigation into urinary concentrations over time, with a focus on the period spanning from 2003 to 2012 in the U.S., showed no significant differences in urinary BP-3 concentrations during this period [32]. Studies have also reported that BP exposure among pregnant women and their fetuses was common, with reports of detection in maternal urine [12,13], cord blood [14,15], amniotic fluid [29], and placenta [33,34]. In studies of maternal and fetal samples analyzed from the U.S., Denmark, Spain, and China, BP-1, BP-3, and 4-OH-BP were widely found [15,29,35–37]. These studies have highlighted the distribution of BPs in all different types of body tissues and fluids. Overall, human exposure to BPs is ubiquitous, and exposure levels are higher in western countries, especially in North America (Fig. 2, Table S3).

Upon topical application, BPs can be absorbed by the human body through multiple routes, including dermal absorption [38], inhalation [39], and oral ingestion [40,41]. Following human exposure, BPs undergo metabolic transformation via phase I and phase II reactions [15,38,42]. Phase I metabolism primarily occurs through enzymatic reactions such as hydroxylation, oxidation, and reduction. The resulting metabolites have different physicochemical properties and toxicity relative to the parent compounds [42]. Phase II conjugation reactions involve enzymes, including glucuronosyltransferases and sulfotransferases [42] and conjugation of metabolites with glucuronic acid and/or sulfate. For example, BP-3 can be transformed into BP-1, BP-2, BP-8, and 4-OH-BP through demethylation and hydroxylation by phase I reaction, and glucuronide and sulfate conjugation by phase II reaction (Fig. S1) [24,38,42–44]. Moreover, the phase II reactions increase the water solubility of the metabolites and facilitate their excretion from the body. BP-3 is excreted as glucuronide conjugates, accounting for 85% of the total urinary BP-3 excretion [45]. Studies have shown that BPs are estrogenic chemicals with endocrine-disrupting effects [46,47], and can elicit reproductive and developmental toxicities [48–51]. Additionally, accumulating evidence suggests that some BPs have potential neurotoxic [37,52,53] and carcinogenic properties [54–56].

The occurrence and fate of BPs in aquatic environments, coupled with their consequential impact on aquatic ecosystems, have garnered significant attention [24,57]. Notably, attention was drawn to the risks associated with organic UV filters in marine and freshwater environments [58]. Furthermore, the main ecological implications and human toxicity tied to BP-3 were reviewed [59,60]. These collective findings serve as a poignant reminder to accord due significance to the ubiquitous presence of BPs in both the environment and humans, and the potential health risks. Nevertheless, sources and pathways of human exposure to BPs and their potential risks were not reviewed in detail previously.

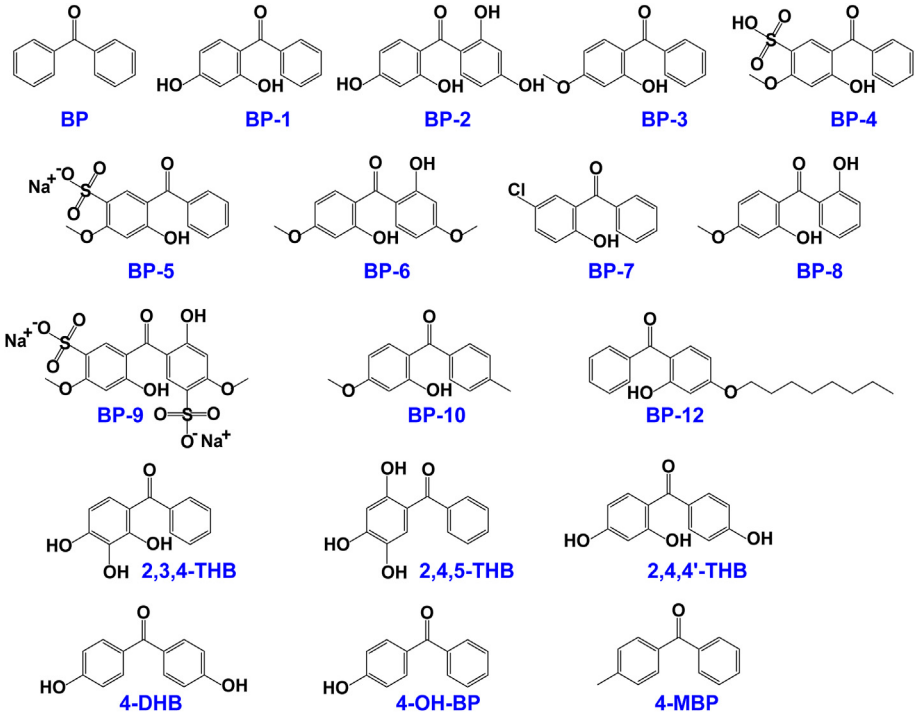

Fig. 1. Chemical structures of BPs reviewed in this study. BP-11 is a mixture of BP-2 and BP-6, so it is omitted. Full names of all BPs are given below: BP, benzophenone; BP-1, 2,4-dihydroxybenzophenone; BP-2, 2,2′,4,4′-tetrahydroxybenzophenone; BP-3, 2-hydroxy-4-methoxybenzophenone; BP-4, 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid; BP-5, 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid sodium salt; BP-6, 2,2′-dihydroxy-4,4′-dimethoxybenzophenone; BP-7, 5-chloro-2-hydroxybenzophenone; BP-8, 2,2′-hydroxy-4-methoxybenzophenone; BP-9, 2,2′-dihydroxy-4,4′-dimethoxybenzophenone-5,5′-disulfonic acid; BP-10, 2-hydroxy-4-methoxy-4′-methylbenzophenone; BP-11, 2,2′4,4′-tetrahydroxybenzophenone and 2,2′-dihydroxy-4,4′-dimethoxybenzophenone; BP-12, 2-hydroxy-4-n-octyloxybenzophenone; 2,3,4-THB, 2,3,4-trihydroxy-benzophenone; 2,4,5-THB, 2,4,5-trihydroxy-benzophenone; 2,4,4′-THB, 2,4,4′-trihydroxy-benzophenone; 4-DHB, 4,4-dihydroxy-benzophenone; 4-OH-BP, 4-hydroxy-benzophenone; 4-MBP, 4-methyl-benzophenone. More detailed information on these BPs is provided in Table S1 and Table S2 of Supporting Information.

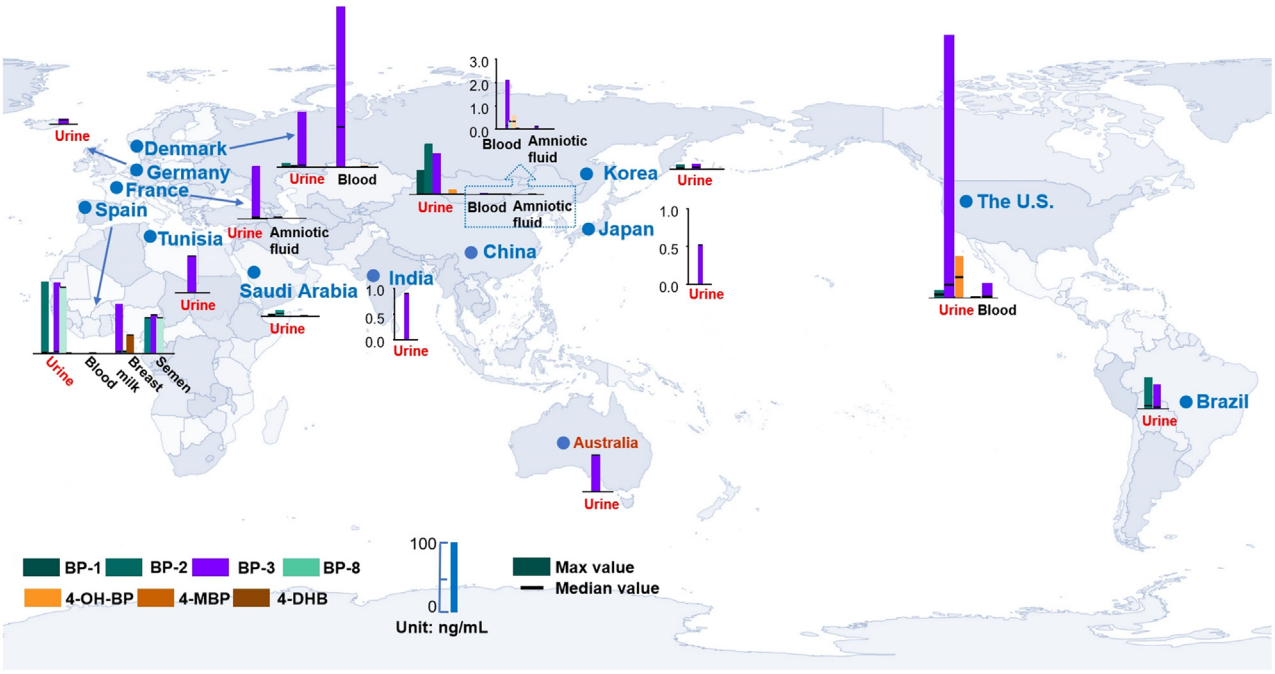

Fig. 2. Global comparison of BP concentrations in human fluids, including urine, blood, breast milk, amniotic fluid, and semen. The blood concentration values include whole blood, serum, and plasma.

Therefore, it is imperative to undertake a comprehensive literature survey to delve into the diverse aspects of exposure sources, pathways, toxicity, and health risks related to BPs. The data and related publications of this review are available in the "Web of Science" database without date restrictions. Firstly, the main search was conducted by inputting the search term "benzophenone OR benzophenone-3 OR oxybenzone OR 2-hydroxy-4-methoxybenzophenone OR benzophenone-1" into the "Web of Science" database. Subsequently, a supplementary search was designed based on the "benzophenone OR UV filter OR sunscreen AND specific outcome". The specific outcomes cover a wide spectrum of themes, including "biological monitoring", "endocrine disruption", "estrogens", "thyroid", "reproduction and development", "nervous", "hepatotoxicity", "prenatal", "fertility", and "nephrotoxicity". In addition, the safety and human exposure levels of BPs discussed in the expert committee and national reports were obtained.

The main objectives of this review are: (1) to characterize the sources and pathways via exposure to BPs and provide an assessment of exposure estimates; (2) to elucidate the toxicity and associated health risks of BPs; (3) to identify the limitations prevalent in the available information, while providing feasible recommendations for prospective studies.

2. Exposure sources and pathways

The widespread use of BPs in consumer products, especially sunscreens and other PCPs, contributes to a significant source of human exposure [9,61], in addition to their use in clothing and textiles [9]. Studies have also reported the occurrence of BPs in drinking water [40], seafood [62,63], and packaged foods [64]. Furthermore, indoor air and indoor dust can contribute to inhalation exposure of BPs [39,65]. A summary of studies that describe human exposure sources and pathways of BPs is presented in Table S4 and Fig. 3. The estimated ranges of exposure doses to BPs via each pathway are shown in Table S5 and Fig. 4.

Fig. 3. Summary of sources and pathways of human exposure to BPs [23,64,66–68].

2.1. Dermal exposure

2.1.1. Sunscreens

PCPs, such as sunscreens, cosmetics, shampoos, body washes, and lipsticks, can contribute to dermal exposure to BPs. Not all commercially available sunscreen products contain BPs, and those that contain BPs may contain 6%–10% of BP-3 and traces of other BPs [70]. A study from China reported a median BP-3 concentration of 2330 ng/g in sunscreens (n = 12) [23]. In addition, a study from the U.S. (n = 49) reported a

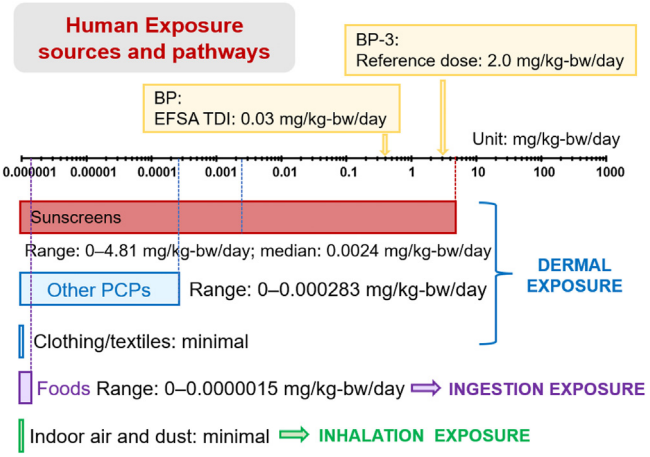

Fig. 4. Illustration of measured and estimated exposures to BPs for the general populations from various sources. Solid horizontal bars show centiles, and whiskers show minimum and maximum, where available. The European Food Safety Authority (EFSA) recommends a tolerable daily intake (TDI) of 0.03 mg/(kg-bw·day) for BP [69]. For BP-3, the reference dose of 2.0 mg/(kg-bw·day) was obtained by further dividing the no observed adverse effect level (NOAEL) value [200 mg/(kg-bw·day)] obtained from the oral teratogenicity study in rodents (Wistar rats) by a safety factor of 100 [70]. However, for other BPs, no human toxicity data are currently available.

median concentration of BP-3 at 115 ng/g in sunscreen, whereas the mean concentration was 3,730,000 ng/g [70], indicating that some brands have elevated levels of BP-3. Besides BP-3, several other BPs were also found in sunscreens [70]. Li and Kannan detected 13 BPs, including BP, BP-1, BP-2, BP-4, BP-6, BP-7, BP-8, BP-9, BP-10, BP-12, 4-OH-BP, 4-MBP, and 2,3,4-OH-BP in 50 sunscreens collected in the U.S. in 2021. The total median concentration of 14 BPs, including BP-3, was 5,930 ng/g [70], with BP having the highest median concentration (3,550 ng/g) [70]. The above evidence of measured concentrations of BPs in sunscreens emphasizes the need for vigilant scrutiny of widely used sunscreens and their health effects through the skin into the body.

Although the recommended application rate of sunscreen by the American Academy of Dermatology (AAD) is 1.5–2.0 mg/cm^2, or 28 g to fully cover an adult's body [71], there are reports that the application rates are not strictly followed by consumers, and such non-compliance can result in inadequate sun protection [38]. Furthermore, it is also recommended that the sunscreens need to be applied every 2 h. It has been reported that approximately 10% of the applied dose of BP-3 is absorbed by the skin and enters the circulation [72]. One study reported that after a sunscreen product containing 4% of BP-3 was applied on the skin, 0.4% of the applied amount (median: 9.80 mg) was found in urine over a period of 48 h [38]. On the basis of the recommended usage rate of sunscreen by an individual going to a beach for a day, the daily dermal exposure dose for 14 BPs was calculated to be 2400 ng/kg-bw (body weight) per day [70]. Moreover, the estimated 95th percentile values of BP and BP-3 were 43,400 and 4,760,000 ng/(kg-bw·day), respectively, exceeding the recommended reference doses [BP: 3,000 ng/(kg-bw·day); BP-3: 2,000,000 ng/(kg-bw·day)] [69,70] by 14 and 2 times, respectively (Fig. 4). This suggests that even the recommended dose of application of sunscreens may be close to or above the reference values, suggesting the need for urgent action on this topic.

2.1.2. Other PCPs

BPs are also widely used in a variety of other PCPs. Liao and Kannan found high median concentrations of BP-3 in cosmetics such as skin lotions (530 ng/g), makeup products (221 ng/g), and toilet soaps (205 ng/g), which can also contribute to dermal exposure. BP-3 concentrations in other PCPs, such as toothpastes, hair care products, body washes, and sanitation products, were an order of magnitude lower than those in cosmetics [61]. The concentrations of BP-3 in these PCPs from the U.S. were 1–2 orders of magnitude higher than those in China [61]. Furthermore, Lu et al. reported that BP-2 was dominant in shampoos (median: 36.1 ng/g), while BP-8 was a major compound in hand sanitizers (median: 15.9 ng/g) and lipsticks (median: 7.9 ng/g) in China [23]. Among these PCPs, BP-3 was undoubtedly the dominant BPs and was one order of magnitude higher than BP-2 and two orders of magnitude higher than BP-8. Moreover, based on the data presented in Table S4 and Fig. 4, it becomes evident that the concentrations of BPs found in sunscreens, especially BP-3, were significantly higher than those found in other PCPs. Notably, the amount of BP-3 in sunscreen was at least twice as high as in other PCPs.

Furthermore, according to Lu et al., the estimated average dermal intakes (EDI) to BPs (i.e., BP-1, BP-2, BP-3, BP-8, and 4-OH-BP) from PCPs in China were as high as 283 ng/(kg-bw·day) [23], among which BP-3 was the major BP accounting for 93% of the exposure. Among PCPs, sunscreens accounted for major PCPs that contributed to 90% of exposure [23]. For average consumers who do not apply sunscreen on a daily basis, skin and hair care products and cosmetics are major sources of BP exposures [73]. In another study, the geometric mean EDI values of BP-3 were 978 ng/day for China and 24,400 ng/day for the U.S. [61], from PCPs including cosmetics, but excluding sunscreens. These EDI values of BP-3 from the daily use of cosmetics were found to be lower than the reference dose (RfD).

2.1.3. Clothing/textiles

BPs are incorporated into textiles to enhance performance and longevity (e.g., anti-fading) [9,66]. Thus, clothing and textiles are potential sources of dermal exposure to BPs. Morrison et al. conducted a study in which male participants were exposed to BP-3-contained clothing for 3 h. BP-3 and its metabolite (i.e., BP-1) were found in the urine samples of exposed participants for over 48 h following exposure, and the total mass of BP-1 and BP-3 excreted in urine in 24 h was 82.0 μg [74]. Furthermore, BPs were commonly found in intimate apparel and skin-tight active wear, e.g., BP-1, BP-2, BP-3, BP-8, and 4-OH-BP found in pantyhose with the sum median concentrations of up to 20.5 ng/g [66]. BP-3 had the highest median concentration (12.0 ng/g), followed by BP-1 (3.80 ng/g). However, a BP-1 concentration as high as 2,410,000 ng/g was found in one pantyhose sample [66], indicating that some brands have elevated levels of BP-1. Furthermore, BP-3 was found in infant clothing and textiles at median and maximum concentrations of 5.94 and 157 ng/g, respectively [9]. Despite measurable levels of BPs in textiles, the dermal exposure doses from textiles were small, falling within the range of 0.23–1.31 pg/(kg-bw·day) [66].

2.1.4. Tattoo inks

Black tattoo inks, commonly used in the art of tattooing, contain BPs. BPs are added to tattoo inks as initiators to facilitate the hardening of the printed ink when exposed to UV light (and probably as anti-fading agents). BP was found in commercially available black tattoo ink samples at concentrations ranging from 0.26 to 557 μg/g [75]. Additionally, a report documented the detection of BP-4 in black tattoo inks [76].

2.2. Ingestion exposure

2.2.1. Water

Studies have shown that BPs are present in surface water [77–79], groundwater [80,81], distilled water [40], bottled water [82], and tap water [40,83]. Surface water and groundwater can be contaminated with BPs through human activities and sewage discharges. The occurrence of BPs in surface water has been reported in several countries. The major BPs found in surface water were BP, BP-4, BP-3, and BP-1 [77,84]. In surface water from the Huangpu River, China, BP was detected at a mean concentration of 158 ng/L, accompanied with frequent detection (>80%) of BP-4 (mean: 38.2 ng/L) and BP-3 (mean: 30.0 ng/L) [77]. BP-1, BP-3, and 4-OH-BP were also frequently detected (>95%) in surface water from the Yangtze River in China, but the concentration of BP-3 (mean:

2.86 ng/L) was an order of magnitude lower than that of the Huangpu River [67]. Similarly, measurable concentrations of BPs were also observed in surface waters from the U.K., Switzerland, and Spain [77,79, 85,86]. However, studies of BPs in surface waters in other countries are limited. It is also worth noting that the main sources of BPs in surface water are sewage discharges that receive inputs from the use of PCPs and industrial activities. BPs are washed off from dermal application during swimming or bathing and eventually enter the sewerage system. In addition, BPs can also enter surface waters through direct runoff from industrial sites. Once BPs enter surface waters, they can undergo various fates and transport processes, including percolation, to reach groundwater.

Monitoring studies have detected BPs in groundwater. BP-1, BP-3, BP-4, 4-OH-BP, and 4-DHB were found in groundwater in Spain [80]. BP-3 was the most commonly detected compound, followed by BP-4 and BP-1. The mean concentrations ranged from 0.13 (4-DHB) to 2.8 ng/L (BP-4), indicating the presence of BP contamination in groundwater [80].

BPs have also been reported to occur in treated tap water and bottled distilled water [40]. BP-3 was found in all tap water and bottled water samples with geometric mean concentrations of 9.64 and 14.5 ng/L, respectively, from China [40]. This concentration was higher than that found in surface water from the Yangtze River [87]. It is possible that BPs are introduced during treatment processes. However, BP exposure via drinking water is minuscule [0.04–0.20 ng/(kg-bw·day)] [67]. Further studies are needed on the concentrations of BPs in drinking water from other countries.

2.2.2. Aquatic organisms

Some BPs can be subject to bioaccumulation in aquatic food chains, ultimately leading to their presence in higher trophic levels, including fish and other seafood that are often consumed by humans. Currently, there have been a number of articles and reviews demonstrating the bioaccumulation and trophic transfer potential of BPs in freshwater food and marine food chains [88–93], e.g., the nutrient magnification of BP-3 [92]. However, the extent of bioaccumulation is specific and depends not only on the chemical properties and lipophilicity of BPs, but also on the trophic level of the organism, which can vary due to species and individual differences [88,91]. The metabolic rate of BPs varies by species and can influence their accumulation and potential effects [93].

Aquatic organisms such as fish [62,63] and mollusks [68,94], have been reported to contain BPs. BP-3 was found in marine and freshwater biota [63]. Fish from river basins in Spain, including the Guadalquivir [median: 16.5 ng/g dry weight (d.w.); maximum: 24.3 ng/g d.w.], and Ebro (<1.2 ng/g d.w.; 2.2 ng/g d.w.) and Jucar (4.6 ng/g d.w.; 4.6 ng/g d.w.), as well as Oslofjord in Norway [<20 ng/g wet weight (w.w.); 1,037 ng/g w.w.], contained BP-3 [62, 63]. BP-3 was found in fillet of whitefish (<20 ng/g w.w.; 182 ng/g w.w.) and perch (<5 ng/g w.w.; 6.5 ng/g w.w.) from Lake Mjøsa in Norway [63]. Bivalves from the Galician coast (median: 0.5 ng/g d.w.) and mollusks from the Chinese Bohai Sea (1.25 ng/g d.w.) contained BP-3. Studies in Europe have reported the occurrence of BP-1 and BP-3 in seafood at mean concentrations of 1.3–55.7 and 2.2–49.4 ng/g d.w., respectively [41]. However, little is known about BPs in aquatic products in other countries, and further studies are needed in this regard.

2.2.3. Packaged foods

In addition to direct ingestion through drinking water and seafood, BP exposure can occur via indirect routes such as packaged food products. BPs are present in food contact materials (FCMs), such as inks and coatings, or used as processing aids for polymers. Thus, the migration or leaching of BPs from FCMs into food products can occur. Many studies have reported the occurrence of BPs in foods [95,96] and packaged beverages [97,98], with notable concentrations in fatty foods [99]. In 2009, studies from Germany and Belgium reported that packaged breakfast cereals contained up to 3,730 ng/g of 4-OH-BP [95]. Similarly, BP concentrations ranging from 5.0 to 217 μg/L in packaged beverages (i.e., milk, fruit juices, and wine) were reported [97]. A study from South China found BP-1, BP-2, BP-3, BP-8, and 4-OH-BP in packaged beverages (i.e., bottled water, soft drinks, juices, and protein drinks), with the median concentration of ΣBPs at 20 ng/L [64]. In packaged milk, BP was detected at concentrations ranging from 2.84 to 18.4 ng/g [98].

Choi et al. reported the migration of BP from paper packaging to water [100]. Similarly, BP was detected in 72% of the foods packaged in cardboard boxes [101]. The highest concentration of BP (7.3 mg/kg) was found in high-fat chocolate confectionary packaged in cardboard [101]. In addition, baby teethers were reported to contain BP-1, BP-2, BP-3, BP-8, and 4-OH-BP. The amount of BPs leached from teethers into water ranged from 0.59 to 297 ng [102].

The median exposure doses of BPs (i.e., BP-1, BP-2, BP-3, BP-8, and 4-OH-BP) through the ingestion of beverages were estimated to be 0.58 ng/(kg-bw·day) for the elderly, and 1.54 ng/(kg-bw·day) for toddlers [64]. In addition, the estimated mean EDI of total BPs through the consumption of mollusks in China was 0.33 and 0.21 ng/(kg-bw·day) for toddlers and adults, respectively [68]. Overall, dietary sources contribute to exposure to BPs, but these doses were 2–3 orders of magnitude less than those from cosmetics.

2.3. Inhalation exposure

BPs occur in indoor air and dust. BP-3 concentrations in airborne particles from homes, offices, barber shops, public spaces, cars, garages, and laboratories in the U.S. (median: 2.9 ng/m^3) were in the range of 0.19–72.0 ng/m^3, with maximum median concentration found in cars at 18.3 ng/m^3 [39]. BP was detected in indoor air with a median concentration of 200 ng/m^3 in the U.S [103]. The median concentration of BP-3 in indoor dust from the U.S. (243 ng/g) was higher than those found in Korea (176 ng/g), Japan (138 ng/g), and China (78.6 ng/g) [104]. In indoor dust collected in China, a median BP-3 concentration of 242 ng/g was found in samples collected in 2016, which was three times higher than that collected in 2010 (median: 78.6 ng/g) [65,104].

Although notable concentrations of BP-3 were found in indoor air and dust samples, they accounted for approximately 5% of the total intake of BP-3 [39]. BP-1, BP-2, BP-8, and 4-OH-BP were also present in indoor dust [104]. Overall, inhalation/ingestion of dust accounted for a small fraction of the total exposure to BPs [104].

2.4. Comparison of exposure dose estimates

It is noteworthy that the highest exposure doses of BPs were found through dermal exposure from the use of cosmetics. Specifically, for those who use sunscreens, the exposure dose can be on the order of μg/(kg-bw·day), whereas the daily exposure dose from other PCPs (cosmetics) is on the order of tens to hundreds of ng/(kg-bw·day). Some brands of sunscreens have elevated concentrations of BPs, and exposure doses from those products can exceed the recommended reference doses [BP: 3,000 ng/(kg-bw·day); BP-3: 2,000,000 ng/(kg-bw·day)] (Fig. 4). Although sunscreens can protect skin from UV damage and ultimately prevent skin cancer, BP-based sunscreens may elicit other health effects that need to be carefully evaluated. Dermal exposure doses of BPs through clothing and textiles are negligible. The exposure dose through drinking water and food ingestion is on the order of a few ng/(kg-bw·day), which is 2–3 orders of magnitude lower than dermal exposure. Inhalation exposure doses via indoor air and dust are also minimal. Exposure of the general population to BPs was, in most cases, below the TDI of the European Food Safety Authority (EFSA). However, further studies are needed to critically evaluate RfDs to assess the safety of BPs in cosmetics.

3. Human health effects of BP exposure

Dermal exposure to BPs has been linked to skin irritation, allergic contact dermatitis, and photosensitivity. Furthermore, because of their

hormone-mimicking properties, BPs are associated with hormonal disruption and reproductive and developmental toxicities. Studies have also suggested that exposure to certain BPs may cause neurotoxicity, hepatotoxicity, nephrotoxicity, genotoxicity, and carcinogenicity. Table 1 lists a summary of the toxic effects of exposure to BPs. Fig. 5 demonstrates the proposed mechanisms of toxicity of BPs, including induction of apoptosis, disruptive effects on thyroid hormones and sex hormones, and oxidative stress-mediated mode of action of BPs.

3.1. Adverse dermal reactions

Dermal exposure to BPs in sunscreens has been shown to elicit irritation and sensitization, as well as anaphylactic and photosensitization reactions. Many individuals had adverse skin reactions after using various PCPs containing BP-3 [131–134]. Dermal BP-4 (5% and 10% in petrolatum) exposure led to skin irritation reactions [135], and the use of sunscreen containing BP-3 resulted in photoallergic contact dermatitis [136] and cheilitis [137]. Wearing BP-containing wristbands and swimming goggles and contact with inks containing BP-3 and BP-4 caused allergic or contact dermatitis [138,139]. When drugs containing BPs, such as ketoprofen (composed of BP moiety and propionic acid), are applied to the skin, sunlight exposure may cause photoallergic reactions and trigger dermatitis symptoms [140].

3.2. Endocrine disruption

Studies on endocrine-disrupting effects of BPs mainly focused on sex hormone and thyroid hormone disruption. The mechanisms of hormone disruption by BPs are given in Fig. 5.

3.2.1. Effect on sex hormones

BPs display estrogenic/antiestrogenic or androgenic/antiandrogenic activities both *in vitro* and *in vivo*. BP-3, in particular, was shown to exhibit estrogenic, antiestrogenic, and antiandrogenic activities in both *in vitro* and *in vivo* assays [141,142]. Several BPs exhibited estrogenic effects in fish cell lines, and human estrogen receptor (ER) expressed yeast cell lines. Although the estrogenic potency of BPs is a thousand to a hundred thousand times lower than that of 17b-estradiol (E2), it is clear that BPs exhibit estrogenic potencies in direct competition with E2 at the ER ligand binding site [143–145]. The major metabolites of BP-3, such as BP-1 and 4-OH-BP, were one or two orders of magnitude more potent estrogens than BP-3 (Table S6). The antiestrogenic and antiandrogenic activities of BP-3 and their ability to alter the expression of genes involved in hormone production pathways were demonstrated [142]. In *in vitro* assays, exposure to BP-3 (84 μg/L) led to the down-regulation of estrogen receptor α (*esr1*), androgen receptor (*ar*), and P450 aromatase B (*cyp19b*) genes in the brain of adult male zebrafish (*Danio rerio*) [142]. Furthermore, the down-regulation of 3β-hydroxysteroid dehydrogenase (*hsd3b*), 17β-hydroxysteroid dehydrogenase type 3 (*hsd17b3*), 11β-hydroxysteroid dehydrogenase type 2 (*hsd11b2*), and 11β-hydroxylase (*cyp11b2*) transcripts were also observed in human adult testes [142]. BP-3 has been shown to significantly induce the expression of vitellogenin (VTG) in rainbow trout (*Oncorhynchus mykiss*) and Japanese medaka (*Oryzias latipes*) at water concentrations of 620–749 μg/L [141]. In addition, effects on hatching rate were observed in Japanese medaka at BP-3 concentrations of 16 and 132 μg/L. Water concentration of BP-3 at 620 μg/L reduced the number of eggs produced, the proportion of fertilized eggs, egg viability, and hatching rate in medaka [141].

BP-2 exhibited estrogenic, androgenic, and antiandrogenic effects in *in vitro* assays. Moreover, *in vivo* studies confirmed the estrogenic activity of BP-2 in rats [146] and fish [147]. In rats, BP-2 was identified as an agonist of estrogen receptors α and β (ERα, ERβ), displaying effects similar to those of estrogen (i.e., E2) [146], and was shown to increase the uterine weight [146,148]. In juvenile fathead minnows, BP-2 exposure at 100 μg/L resulted in VTG induction, while exposure at 1.2 mg/L altered gonad histology in both males and females, causing feminization of male secondary sex characteristics [147]. BP-1 exhibited both estrogenic and antiandrogenic activities in *in vitro* assays [144,149]. BP-1 was shown to displace 17β-estradiol from its receptor in a competitive manner *in vitro* [150]. In addition, BP-1 at a water concentration of 981 μg/L promoted VTG expression in fish [144].

Therefore, BPs have been scrutinized for their potential effects on sex hormones. Studies suggest that BPs, such as BP-3, BP-2, and BP-1, can exhibit endocrine-disrupting properties by interfering with hormone receptors and pathways, potentially leading to disturbances in hormonal balance. While some studies reported correlations between exposure to BPs and alterations in hormone levels, the overall evidence is often derived from in *vitro* and animal studies, and the clinical significance of these findings remains uncertain.

3.2.2. Effect on thyroid hormones

Exposure to BPs can disrupt thyroid function by interfering with the hypothalamic–pituitary–thyroid (HPT) axis, resulting in alterations in the regulation and metabolism of thyroid hormones. The mechanisms of thyroid hormone disruption by BPs include the down-regulation of genes involved in hormone metabolism and the central regulation of the thyroid system [106]. BP-2 was a known and most studied thyroid disruptor, and other BPs, such as BP-1, BP-3, and BP-8, were found to decrease circulating T3 and T4 levels [106,126,151,152]. Thyroid hormone metabolism genes, including deiodinase 1 (*dio1*) and uridine diphosphate glucuronosyltransferase 1 family a, b (*ugt1ab*), and central regulatory genes, including thyrotropin-releasing hormone (TRH) receptor (*Trhr*), thyroid stimulating hormone (TSH) beta (*Tshβ*), and thyroid hormone receptor beta (*Trβ*), mediate this reduction. The *Trhr* gene codes for the TRH receptor, the *Tshβ* gene codes for TSH, and the *Trβ* gene codes for the thyroid hormone receptor. Down-regulation of the TRH receptor leads to reduced signals of TRH by the pituitary and reduced levels of TSH secretion by the pituitary gland, leading to a decrease in T3 and T4 levels. This decrease in hormone levels in turn triggers an increase in TSH release by the pituitary gland via a negative feedback mechanism [151]. BP-2 can interfere with the homeostasis of the HPT axis by inhibiting or inactivating thyroid peroxidase (TPO), leading to a decrease in thyroid hormone levels [152]. A recent study reported down-regulation of the *TPO* gene from exposure to BP-1, BP-2, BP-3, and BP-8 [106]. However, a study performed with human subjects found no effect of BP-3 on the HPT axis and no changes in TSH, T3, and T4 levels [153]. Overall, studies suggest that BPs can interfere with thyroid function and may have implications for human health. However, its relevance to human exposure doses needs further investigation.

3.3. Reproductive and developmental effects

Several studies have reported that BPs are reproductive and developmental toxicants that disrupt the normal functioning of gonads and mammary glands and affect couples' fertility and birth and developmental outcomes in children. However, the reproductive toxicity studies were focused mostly on BP-3 [50].

3.3.1. Effects on reproductive outcomes

BP-3 could potentially interfere with hormonal pathways involved in ovarian function and mammary tissue development, raising concerns about their potential to contribute to reproductive issues. In rat ovary cultures *in vitro*, exposure to different doses of BP-3 had varying effects on early follicular assembly, with decreased populations of total oocytes and nests per ovary observed at a concentration of 5.8 nmol/L (1.32 μg/L) and increased populations observed at 276 nmol/L (63 μg/L) [112]. The populations of early primary follicles decreased at both exposure levels [112]. BP-3 exposure induced over-expression of Foxl2 mRNA levels through ESR2 at 5.8 nmol/L, but not at 276 nmol/L, and elevated Fst mRNA levels independently of ESR2 or Foxl2 [112]. BP-3 exposure in zebrafish (*Danio rerio*) increased the incidence of ovaries in females and testes in males at specific concentrations (female: 388 and 470 μg/L;

Table 1
Reported toxic effects of BPs in various animal models.

Health effect/toxicity	Substance	Study type	Species/cells	Exposure conditions	Effect	Reference
Endocrine disruption	BP-4	*in vivo*	Zebrafish	Aqueous exposure, 30, 3,000 μg/L, 3 d	*vtg1*, *vtg3*, *esr1*, *esr2b*, *hsd17β3*, *cyp19b*, *cyp19a*, *hhex* and *pax8* ↑.	[105]
Endocrine disruption	BP-4	*in vivo*	Zebrafish	Aqueous exposure, 30, 3,000 μg/L, 14 d	In the liver: *vtg1*, *vtg3*, *esr1* and *esr2b* ↓; in the brain: *vtg1*, *vtg3* and *cyp19b* ↑.	[105]
Endocrine disruption	BP-1, BP-3, BP-8	*in vivo*	Zebrafish	Aqueous exposure, 0–1,000 μg/L, 6 d	T4 and T3 ↓, *dio1* and *ugt1ab* ↑, thyroid hormones ↓.	[106]
Endocrine disruption	BP-2	*in vivo*	*Xenopus laevis*	Aqueous exposure, 1.6, 3.5, 6.1 mg/L, 60 d	Thyroid follicular cell hypertrophy and hyperplasia, male-to-female sex reversal, vitellogenin ↑.	[107]
Endocrine disruption	BP-2	*in vivo*	Rats	Dermal exposure, 100 mg/(kg·2d), 28 d	Proliferative activity of splenocytes ↑, metabolic activity of splenocytes and thymocytes ↑, nitric oxide production of splenocytes and thymocytes ↑, hypothalamic-pituitary-thyroid axis activity ↑.	[21]
Endocrine disruption	BP-3	*in vivo*	Rainbow trout	Aqueous exposure, 10, 100, 1,000 g/L, 14 d	Vitellogenin ↑.	[22]
Endocrine disruption	BP-3	*in vivo*	Japanese medaka	Aqueous exposure, 10, 100, 1,000 g/L, 21 d	Vitellogenin (male) ↑, fertilized egg hatching rate ↓.	[22]
Endocrine disruption	BP-1, BP-2, BP-3, BP-8	*in vitro*	GH3 cells	0–100 μmol/L, 24 h	*Tshβ* gene↓, *Trhr* gene↓, *Trβ* gene↓.	[106]
Endocrine disruption	BP, BP-1, BP-2, BP-3, BP-8	*in vitro*	FRTL-5 cells	0–320 μmol/L, 24 h	*Nis* ↑ (BP, BP-1, BP-3, and BP-8), *Tg* ↑ (BP and BP-3), *Tpo* ↓ (BP-1, BP-2, BP-3, and BP-8).	[106]
Reproductive and developmental effects	BP-3	*in vivo*	Zebrafish	Aqueous exposure, 100, 320, 500 mg/L, 12 d	The ratio of female and male (TG 234) ↑, vitellogenin concentration (male) ↑.	[23]
Reproductive and developmental effects	BP-3	*in vivo*	Rats	Oral exposure, 0, 3,000, or 30,000 ng/mL, gd6 to PND 21	*Prm1* ↓, *Prm2* ↓, *Iqcf6* ↓, *Cstl1* ↓.	[24]
Reproductive and developmental effects	BP-3	*in vivo*	Mouse	Dermal exposure, 50 mg/(kg-bw·d), 7 d	Fetal weight ↓, fetoplacenta index ↓, offspring weight ↓, placenta weights ↓, female sex ratio ↑.	[108]
Reproductive and developmental effects	BP-3	*in vivo*	Mouse	Oral exposure, 30, 212, or 3,000 μg/(kg·d), utero and lactation	Size and growth of mammary gland (male) ↓, mammary cell proliferation ↓, ERα ↓, altered mammary gland morphology.	[109]
Reproductive and developmental effects	BP-3	*in vivo*	Fish (*Carassius auratus*)	Aqueous exposure, 2, 20, 200 μg/L, 28 d	Body and intestinal weights ↓, reactive oxygen species ↓, immunoglobulin M ↓, vitellogenin ↓, 7-benzyloxy-4-trifluoromethylcoumarin-odebenzyloxylase ↓.	[110]
Reproductive and developmental effects	BP-3	*in vivo*	Zebrafish	Aqueous exposure, 0.06, 2.3, 38 μg/L, 42 d	Female sex ratio ↑, *vtg2* ↑, impair the cumulative hatching rate, heartbeats, and body length of offspring embryos.	[111]
Reproductive and developmental effects	BP-3	*in vitro*	Ovary of rats	5.8–876 nmol/L, 7 d	Total oocytes population ↓, nests per ovary number ↓, early primary follicles population ↓, *Foxl2* ↑, *Fst* ↑, p27-positive oocytes ↓.	[112]
Neurotoxicity	BP-3	*in vivo*	Rats	Dermal exposure, an area of 25 cm^2, 100 mg/(kg·2d), 23 d	In the frontal cortex: *caspase-3* and *caspase-9* activity ↑, mitochondrial apoptosis ↑, pro-apoptotic proteins *Bax* ↓ and *Bak* ↓, apoptotic DNA fragmentation ↑, *AhR* ↑, *ERβ* ↓, *GPR30* ↓; in the hippocampus: *caspase-9* ↑, anti-apoptotic proteins ↓, *ERβ* ↓, *GPR30* ↓.	[25]
Neurotoxicity	BP-3	*in vivo*	Zebrafish	Aqueous exposure, 10 μg/L, 18 h	Spontaneous movement ↑, decreased touch response ↓, hyperactivity in locomotor response ↑, shoaling behavior ↓, mirror attacks ↓; in the head region: axonal growth ↓, cell proliferation ↓, cell apoptosis ↑, *rxrgb* ↑.	[113]
Neurotoxicity	BP-3	*in vivo*	Zebrafish	Aqueous exposure, 2, 4, 6, 8, 10 mg/L, 72 d	Enteric neurons number ↓, *ret* and *hand2* ↓.	[114]
Neurotoxicity	BP-2, BP-3	*in vitro*	SH-SY5Y neuroblastoma cell line	10^{-8}–10^{-4} mol/L, 24 or 72 h	*caspase-3* ↑, apoptosis ↑.	[53]
Neurotoxicity	BP-3	*in vitro*	Mouse neuronal cells	1–100 μmol/L, 6 or 24 h	Neuronal cell apoptosis; estrogen receptor mRNAs ↓, *Pparγ* mRNA ↑, *ERα* and *Pparγ* agonists ↑.	[115]

(*continued on next page*)

Table 1 (*continued*)

Health effect/toxicity	Substance	Study type	Species/cells	Exposure conditions	Effect	Reference
Hepatotoxicity	BP-1, BP-2, BP-3, BP-4	*in vivo*	Fish	Aqueous exposure, 0.48–4.9 mg/L, n.r.	Generates oxidative stress, liver damage.	[116]
Hepatotoxicity	BP-2	*in vivo*	*Xenopus laevis*	Aqueous exposure, 0, 1.5, 3.0 or 6.0 mg/L, 60 d	Liver pathologies	[107]
Hepatotoxicity	BP	*in vivo*	Mouse	Dietary exposure, 625, 125 ng/mL; 105 weeks	Hepatocellular neoplasms	[117]
Nephrotoxicity	BP-2	*in vivo*	*Xenopus laevis*	Aqueous exposure, 0, 1.5, 3.0 or 6.0 mg/L, 60 d	Liver and kidney pathologies	[107]
Genotoxicity	BP-3	*in vitro*	T47D, T47DKBluc, MCF-7 cells	0.5–50 μmol/L, 24 h	DNA damage ↑, R-loop formation ↑.	[118]
Carcinogenicity	BP-1	*in vivo*	Mouse	Subcutaneous injection, 200 mg/(kg-bw·2d), 56 d	BG-1 cell growth ↑, BrdUrd positive nuclei ↑, cyclin D1 protein ↑.	[19]
Carcinogenicity	BP-1	*in vitro*	MCF-7 breast cancer cells	10^{-5}–10^{-7} mol/L, 4 d	MCF-7 breast cancer cells ↑.	[119]
Carcinogenicity	BP-1	*in vitro*	BG-1 ovarian cancer cells	10^{-8}–10^{-5} mol/L, 5 d	*cyclin D1* ↑, BG-1 cell growth ↑	[120]
Carcinogenicity	BP-1	*in vitro*	LNCaP PCa cells	10^{-5}–10^{-8} mol/L, 4 d	Genes related to G1/S transition of cell cycle and metastasis ↑, *p21* protein ↓.	[55]
Carcinogenicity	BP-1	*in vitro*	LNCaP prostate cancer cells	10^{-5}–10^{-8} mol/L, 4 d	LNCaP cell proliferative activity and migration ↑, genes related with G1/S ↑, *p21* protein ↓.	[121]
Carcinogenicity	BP-3	*in vitro*	NCI-H460 and A549 lung carcinoma cells	0–300 μg/L, 24 h	Lung cancer metastasis ↑, epithelial to mesenchymal transition ↑, *caveolin-1* ↑.	[122]
Carcinogenicity	BP-3	*in vivo*	Mouse	Oral exposure, 70 mg/(kg-bw·d), n.r.	Mammary tumorigenesis in mice fed lifelong low-fat diet ↑, tumor cell proliferation ↑, tumor cell apoptosis ↓, tumor vascularity ↑.	[54]

ER, estrogen receptor; gd, gestation day; PND, postnatal day; dpf, days post-fertilization; hpf, hour post fertilization; upward arrow, increased; downward arrow, decreased.

male: 470 μg/L), indicating interference with the gonadal maturation [154].

Perinatal exposure to BP-3 at 30, 212, or 3,000 μg/(kg-bw·day) significantly affected mammary gland growth in female mice [109]. In male mice, mammary gland epithelium decreased significantly in size and growth. Conversely, in females, the proportion of ducts in mammary glands reduced, while the proportion of alveolar buds increased. Mammary gland morphology was affected by BP-3 exposure in mice [109].

3.3.2. *Effects on birth and developmental outcomes*

Several studies have investigated the effects of BPs on embryonic development and the sex ratio of offspring at birth, which result in more female offspring [111,154]. Zebrafish embryos exposed to BP-3 at concentrations of 0, 1, 10, and 100 μg/L for five days during the developmental stage, fed a normal diet for four months, did not elicit any effect on body weight and body length [155]. However, suppression of ovarian development and maturation was observed in female zebrafish [155]. At high concentrations (100 μg/L), adverse effects on the development of offspring embryos were found, resulting in reduced egg production, delayed hatching rates, altered somite counts, and increased mortality [155].

Dermal exposure of pregnant mice to BP-3 [50 mg/(kg-bw·day)] from gestation day (gd) 0 to gd 6 affected both the first and second progenies, with relatively low body weight in the first progeny and an increased proportion of females in the first and second progenies [111]. Moreover, zebrafish embryos exposed to BP-3 at concentrations of 2.3 and 38 μg/L had a significant decrease in the number of males and a significant increase in the number of females, and developmental toxicity was enhanced when both parents and offspring were exposed to BP-3 [111]. Similarly, exposure to BP-2 in *Xenopus laevis* caused a significant delay in ovary development in females, while in males, both intersex and sex-reversed gonads were observed at an exposure level of 1.5 mg/L. The sexes were completely reversed and showed only ovarian tissue at a concentration of 3.0 and 6.0 mg/L [107].

The above evidence suggests a potential association between exposure to BPs (i.e., BP-3) and embryonic development and adverse birth outcomes, including low birth weight and imbalanced sex ratio of offspring. Further epidemiological findings are provided in *Section 4.2*.

3.3.3. *Congenital defects*

Congenital defects in offspring, including Hirschsprung's disease (HSCR) and hypospadias, have been associated with prenatal exposure to BPs. HSCR is a congenital enteric nervous system developmental defect, characterized by the failure of enteric neural crest cell migration to the hindgut and the absence of enteric ganglia in the distal portion of the gut [156,157]. BP-3 exposure caused a 46% reduction in the number of enteric neurons in zebrafish embryos at water concentrations of 1.0–100 μmol/L (0.23–22.28 mg/L), and the attenuation of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling was proposed as a potential mechanism affecting enteric nervous system development [114]. A study from China showed the correlation between maternal BP-3 exposure and HSCR, and revealed that the SLIT2/ROBO1-miR-218-RET/PLAG1 pathway was the underlying mechanism behind enteric neural crest cell migration.

Hypospadias is a congenital defect in which the opening of the male urethra is abnormally positioned. Oral gavage of 6.25 mg of BP-2 to pregnant mice at 12–17 days resulted in hypospadias in male fetuses, which was related to estrogen receptor signaling pathway [158]. The effects of BPs on congenital defects have been under investigation, and although studies now suggest an association of certain BPs with HSCR and hypospadias, the evidence remains inconclusive and controversial. Moreover, these congenital defects may be related to multiple factors, and direct evidence has yet to be explored.

3.4. *Neurotoxicity*

The lipophilic nature of BPs presents a potential for crossing the blood–brain barrier and placenta. Therefore, the toxic effects of BPs on the central nervous system and infantile neurodevelopment are plausible. BP-3 exposure has been linked to increased risk of neurodegenerative diseases, as was shown to induce apoptosis by increasing oxidative stress in neuronal cells and triggering damage, as well as altering higher brain functions such as behavior and cognition [159–161].

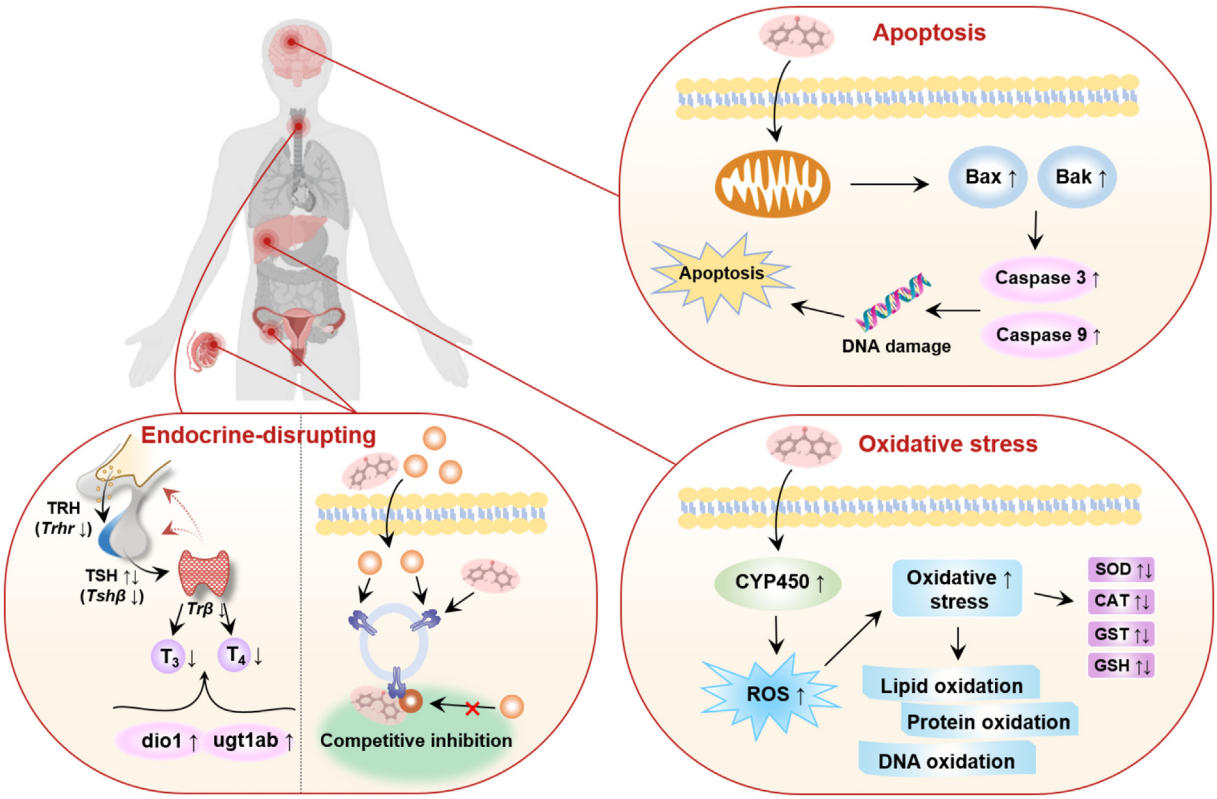

Fig. 5. Proposed mechanisms of toxicity of BPs. Apoptosis-inducing, endocrine-disrupting, and oxidative stress-mediated modes of action are proposed for BPs. The mode of action of apoptosis induction was selected from the frontal cortex of the brain [123,124]. Apoptosis was induced by increased activity of caspase-3 and caspase-9, including the pro-apoptotic proteins Bax and Bak, and increased number of cells with apoptotic DNA fragments. With regard to endocrine disruption, the first one is through action on thyroid hormone levels, as evidenced by the upregulation of *dio1* and *ugt1ab*, and the decrease of TRH and TSH receptors and their respective encoded genes *Trhr* and *Tshβ* downregulation [125]. The second is through hormonal activity, which reduces its binding by competing with the hormone receptors [126–128]. Oxidative stress-mediated mode of action is illustrated for the liver [129,130]. Increased generation of ROS, as well as an alteration in the antioxidant status, may induce lipid, protein, and DNA oxidation. CAT, catalase; CYP450, cytochrome P450; *dio1*, deiodinase 1; GSH, glutathione; GST, glutathione S-transferase; ROS, reactive oxygen species; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; *Trhr*, thyrotropin-releasing hormone receptor; *Tshβ*, thyroid stimulating hormone beta; *Trβ*, thyroid hormone receptor beta; *ugt1ab*, uridine diphosphate glucuronosyltransferase 1 family a, b.

The effects of BP-3 exposure on primary neuronal cells were demonstrated in several studies. For instance, exposure to BP-3 at 10 μg/mL for seven days led to a 36% decrease in rat primary cortical neuronal viability [162]. However, exposure to BP-3 at 25–100 μmol/L (5.75–22.3 mg/L) for only 24 h induced apoptosis of mouse neuronal cells in mouse primary neocortical cultures [115]. An *in vitro* study of the SH-SY5Y neuroblastoma cell line also showed that BP-2 and BP-3 at concentrations of 10^{-8} to 10^{-7} mol/L (2.23–22.3 mg/L) increased the activity of caspase-3 and the number of apoptotic cells [53]. The exposure affected the activity of nerve cells by enhancing apoptosis [53]. Besides *in vitro* studies, animal exposure experiments also demonstrated neuronal apoptosis of BPs. Dermal exposure of rats to BP-2 (100 mg/kg, 4 weeks) did not produce changes in apoptosis markers in the hippocampus and frontal cortex of the brain [160]. By contrast, dermal exposure to BP-3 induced mitochondrial apoptosis in the frontal cortex of rats, which was attributed to the reduced neuroprotective effects of estrogen and/or increased Ahr-mediated apoptosis [52]. This effect was observed through an increase in caspase-3 and caspase-9 activities, the induction of the pro-apoptotic proteins Bax and Bak, and an increase in the number of cells with apoptotic DNA fragments (Fig. 5) [52]. In mouse primary neocortical cells, there was also a loss of mitochondrial membrane potential and activation of the kinases p38/MAPK and GSK3β, as well as the generation of reactive oxygen species (ROS) and the upregulation of apoptosis-related genes [115]. Given that BP-3 was found to mediate the downregulation of ERα/Pparγ and the upregulation of ERβ/Gpr30 signaling, BP-3 could promote neuronal apoptosis [115]. Furthermore, prenatal exposure to BP-3 can induce apoptosis by disrupting ER signaling (especially ESR1/ESR2) while also impairing autophagy and disrupting Rxr/Pparγ signaling, thereby altering the epigenetics statuses of brain neurons [163,164]. Therefore, BP-3 can significantly affect neurodevelopment, causing behavioral changes in offspring and inducing the onset of neurological diseases, especially schizophrenia and Alzheimer's disease [164,165].

Subsequent investigations have revealed evidence regarding the impact of BP-3 exposure on cognitive and behavioral aspects [166–168]. Notably, when the BP-3 concentration was 10 μg/L, the production of ROS in the zebrafish brain was increased, and the expression of genes related to redox imbalance, including *cat* and *sod2*, was upregulated [166]. Perturbation of this oxidative balance by BP-3 has adverse effects on learning and memory processes. Such findings indicate a potential nexus between BP-3-induced brain ROS production and oxidative stress, elucidating its role in modulating cognitive functions. Moreover, notable observations were made in female rats following dermal exposure to BP-3, and the resulting diminishment in spatial memory retention was concomitant with increased extracellular glutamate levels, implying a potential cascade of neurotoxic events triggered [167]. Therefore, the disruption of cognitive processes attributed to BP-3 exposure is postulated to stem from a dual mechanism of oxidative stress and neurotoxicity. Beyond cognitive effects, BP-3 exposure at the same 10 μg/L concentration yielded discernible alterations in behavior, and

manifestations encompassed diminished locomotor activities, decreased anxiety-like responses, and attenuated development of aggressive behaviors [168]. Importantly, these behaviors affect several aquatic organisms, such as zebrafish and fighting fish [168,169]. Collectively, these behavioral shifts underscore the potential of BP-3 to encumber the social motivational framework of organisms [168]. BP-3 has both estrogenic and anti-androgenic effects, which could plausibly underpin the observed behavioral transformations by disrupting endocrine balance and perturbing sex hormone homeostasis [168,170].

3.5. Hepatotoxicity

Exposure to BPs induce oxidative damage to cellular macromolecules, such as DNA, lipids, and proteins, leading to the production of ROS and associated hepatotoxic effects. A schematic of liver oxidative damage induced by BPs is shown in Fig. 5. Exposure to BP-1, BP-2, BP-3 and BP-4 resulted in liver damage in freshwater fish *Carassius auratus* [110,116]. Lipid peroxidation and oxidative stress induced by BPs were suggested as the mechanism for liver damage [116]. Changes in the activities of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione S-transferase, as well as non-enzymatic antioxidant levels such as glutathione (GSH), were observed in aquatic organisms exposed to BPs, indicating an increase in oxidative stress. The activities of antioxidant enzymes increased dramatically at the start of BP exposure, then peaked and gradually reverted to the initial level as exposure time increased, demonstrating an adaptive response to toxic stress and a compensating strategy for oxidative stress defense to remove the excess ROS [116]. However, with prolonged exposure, the antioxidant system is unable to entirely eliminate excess ROS [116]. The GSH levels increased following exposure to BPs, showing that it is adaptable and protective against oxidative stress.

BP-2 exposure at the levels of 3.0–6.0 mg/L in *Xenopus laevis* juveniles resulted in liver pathologies such as increased prevalence of basophilia, decreased hepatocellular vacuolation and intravascular proteinaceous fluid, and hepatocyte necrosis [107]. BP exposure led to concentration- and time-dependent necrosis accompanied by a decrease in intracellular ATP and total adenine nucleotides [171]. BP is hepatotoxic and hepatocarcinogenic in mice and rats. According to the NTP Technical Report (2000), dietary exposure to BP caused liver damage in mice and rats, and associated lesions occurred at feed exposure concentrations $\geq$ 2, 500 ng/mL, including increased liver weight and hepatocyte hypertrophy, as well as concomitant cholestatic liver disease [87]. Furthermore, BP significantly increased the incidence of hepatocellular neoplasms (mostly adenomas) in mice [117].

Therefore, certain BPs have the potential to cause hepatotoxicity by disrupting cellular mechanisms and triggering oxidative stress, which could result in liver inflammation, dysfunction, and injury. Nonetheless, due to the liver's intricate metabolic functions and interactions with various compounds, there is a need for further research to establish a definite causal link between the individual or combined BPs and their effects on hepatotoxicity.

3.6. Nephrotoxicity

Kidneys are also important target organs for BP exposure. Elevated kidney weight is a distinctive feature of kidney damage caused by exposure to BPs [87]. Rats and mice fed diets containing 312, 625, and 1, 250 ng/mL of BP for 105 weeks resulted in an increased incidence of kidney nephropathy and increased occurrences of renal tubule adenoma [117]. At even higher exposure concentrations of 2,500–20,000 ng/mL, an increased incidence of foci of tubule regeneration was observed [87]. Toxic effects of BP-2 on the kidneys were also noted in *Xenopus laevis* [107]. BPs may cause nephrotoxic effects by disrupting renal cell function and triggering renal inflammation, and evidence from epidemiological investigations is presented in *Section 4.4*.

3.7. Genotoxicity

Several studies have demonstrated that BP-3 exhibits genotoxic activity by inducing chromosomal aberrations, micronucleus formation, and DNA damage. Human lymphocytes were exposed to BP-3 concentrations between 0.0125 and 0.20 g/mL in an *in vitro* study inducing chromosomal aberrations and increasing micronucleus formation [172]. Notably, the lowest exposure concentration at which these effects were observed was only one-eighth of the EU's tolerable daily intake reference dose [0.1 mg/(kg-bw·day)] [173]. The most frequently observed chromosomal aberrations include chromatid breaks, complex rearrangements, and dicentric chromosomes, but no numerical aberrations were found [172]. Furthermore, increased chromosomal aberrations and micronucleus frequencies in human peripheral blood lymphocytes are associated with a risk of cancer [174, 175]. In human breast epithelial cells, DNA damage caused by BP-3 exposure was mediated through ERα-dependent R-loop formation [118]. R-loops are a by-product of transcription that can promote genomic instability by interfering with the transcription process [176, 177]. DNA damage was linked to the dysregulation of R-loops [176]. BP-3, as a xenoestrogen similar to E2, stimulates the formation of R-loop and induces DNA double-strand breaks [118]. Nevertheless, several studies showed that BP-3 is not genotoxic *in vivo*, such as in rats, despite its teratogenic effect and genotoxicity demonstrated *in vitro* [178,179]. It is clear that BP-3 may exhibit genotoxicity by causing DNA damage and mutations, which may lead to an increased risk of cancer and other genetic diseases. This requires considerable attention, but relevant human evidence is lacking.

3.8. Carcinogenicity

Several BPs have been linked to cancers in the liver and kidneys. The effects of carcinogenicity on the liver and the kidney were discussed in *Sections 3.5* and *3.6*, respectively.

Sex hormones are known to play a crucial role in the development of breast cancer, ovarian cancer, and prostate cancer. Certain BPs, specifically BP-1 and BP-3, promote the growth and proliferation of these types of cancer cells. *In vitro* studies have shown that BP-1 can stimulate concentration-dependent proliferation and migration of MCF-7 human breast cancer cells similar to E2 [150, 119]. This effect is enhanced by increasing the expression of cyclin D1 and cathepsin D while decreasing the expression of p21 (regulator of cell cycle progression) [119]. Thus, BP-1 may accelerate cancer metastasis by regulating cell cycle-related genes [119]. BP-3-fed adult mice in a high-fat diet showed breast tumor cell growth promotion and reduced apoptosis [54]. Studies on BG-1 human ovarian cancer cells showed that BP-1 stimulated proliferation via the estrogen receptor signaling pathway and promoted tumor formation in xenograft mouse models transplanted with BG-1 cells [120]. BP-1 promoted the growth of BG-1 cells, which was related to the upregulation of cyclin D1 but had no significant effect on p21 [158]. The agonistic effect of BP-1 on ERα showed activation of the Wnt/β-catenin signaling pathway in human SKOV3 ovarian cancer cells [56]. Moreover, BP-1 was found to promote the migration of BG-1 cells by regulating the expression of epithelial–mesenchymal transition (EMT) markers (E-cadherin, snail, slug, and N-cadherin) [180]. Increased cyclin E expression and decreased p21 expression were observed in LNCaP human prostate cancer cells treated with BP-1, suggesting that BP-1 enhanced cell viability and promoted cell proliferation and migration through the AR signaling pathway [55].

BP-3 was shown to exert carcinogenic effects on lung cancer cells. At concentrations of 50, 100, and 150 μg/L, BP-3 was shown to significantly increase the size and number of NCI-H460 lung cancer cells [122]. It was demonstrated that the increase in cancer cell proliferation was through the EMT process and an increase in caveolin-1 (Cav-1) expression. This, in turn, increased the number of anoikis-resistant cells and increased the proliferation of cancer cells. BP-3 exposure led to upregulation of ERK

and increased levels of anti-apoptotic Bcl-2 and Mcl-1 proteins, further supporting its carcinogenic potential [122].

4. Epidemiological studies

4.1. Couples' fecundity

Epidemiological studies have shown a significant association between urinary concentrations of BPs and reported couples' fertility. BP-2 and 4-OH-BP were significantly associated with reduced fertility, whereas BP-1, BP-3, and BP-8 were not [181]. BP-2 was related to a 31% decrease in fertility, and 4-OH-BP was related to a 26% decrease in fertility, both of which may have resulted in a longer time to achieve pregnancy [181]. The concentrations of BP-1, BP-2, BP-3, BP-8, and 4-OH-BP in seminal plasma were associated with reduced fecundity in males, although not statistically significant [51]. Another study found that urinary concentrations of BP-2 and BP-8 were significant factors in male semen quality, although no association was observed for BP-1, BP-3, or 4-OH-BP [20]. A study of 295 couples in China found no association between urinary BP-3 concentrations and spontaneous abortion [182].

4.2. Birth outcomes

Maternal exposure to BPs has been shown to affect fetal birth outcomes, including gestational age, birth weight, length, head circumference, and the sex ratio of offspring. An association between maternal BP-3 exposure and gestational age was observed to be negative and gender-specific, with no correlation found for girls [49]. The effect on birth weight was also gender-specific, with increasing maternal urinary BP-3 increasing birth weight for boys and decreasing for girls [183,184]. It was found that for every 1-unit increase in ln-transformed BP-3 urinary levels, the birth weight of boys increased by 26 g [183]. Another study found that boys were about 44 g heavier per ln-unit increase in urinary BP-3 concentration, while girls were 21 g lighter [184]. There was also a positive association between BP-3 exposure and head circumference at birth, with an increase of 0.1 cm per ln-unit of urinary BP-3 concentration [183].

In animal studies, BP exposure resulted in an altered sex ratio in offspring, similar to that demonstrated in epidemiological studies. High levels of BP-3 in the urine of pregnant women were associated with lower birth weight in girls and higher birth weight in boys [184]. Another study showed that sex-biased birth outcomes in offspring were not associated with BP-3 exposure but were associated with BP-2 and 4-OH-BP [48]. Notably, maternal and paternal urinary BP-2 concentrations were associated with an excess of female births, while maternal 4-OH-BP concentrations were associated with an excess of male births [48].

4.3. Endometriosis

Exposure to BPs may be associated with the development of endometriosis. Elevated urinary levels of BP-1, rather than BP-3, were associated with increased odds of endometriosis diagnosis [28]. However, a recent study showed that females exposed to BP-3 presented a significantly elevated risk of endometriosis [185]. Moreover, a study investigating gene expression levels in endometriotic tissues in relation to urinary BP levels revealed that exposure to BP-3 and 4-OH-BP was associated with the overexpression of genes involved in lipid metabolism disruption [186]. In females with higher urinary 4-OH-BP concentrations, an increased odds of *APOE* gene expression associated with lipid metabolism was found in endometriosis tissue [186]. In addition, exposure to BP-3 was associated with elevated levels of expression of the *PLCG2* gene, which encodes an important enzyme in the phosphatidylinositol signaling system [186].

4.4. Kidney disease

A study of the relationship between the urinary concentrations of BPs and chronic kidney function markers was conducted in 441 healthy Korean women aged 20–45 years, and found significant positive association between urinary BP-1 and kidney function biomarker, albumin-to-creatinine ratio, in healthy adult females [121]. Another study showed a significant association between BP-3 concentration and lower estimated glomerular filtration rate and decreased kidney function [187].

5. Conclusions

The widespread occurrence of BPs in human tissues and body fluids indicates ubiquitous exposure to these chemicals in human populations. Limited information is available with regard to the occurrence of BPs in foods and tap water. Despite high levels of BPs present in indoor air and indoor dust, inhalation exposure and dust ingestion doses were negligible. Importantly, dermal exposure through the use of sunscreens and other PCPs is the dominant pathway of exposure to BPs. Exposure from the use of sunscreens may exceed reference values for individuals using certain products that contain elevated levels of BPs. Moreover, daily use of various types of cosmetics that contain BPs can augment exposure.

BPs are estrogenic chemicals recognized for their reproductive toxicity, as well as their potential to disrupt thyroid hormones. Most toxic effects stem from endocrine-disrupting effects, which are primarily manifested in reproductive and developmental impairments. Notably, epidemiological studies suggest that these effects include decreased semen quality, impaired couple's fertility, and altered sex ratios. In addition, the consequences of human exposure to BPs extend to neurotoxicity, evidenced by harmful influence on neuronal cells, cognition, and behavior. Hepatotoxicity, nephrotoxicity, and genotoxicity also characterize adverse outcomes, often caused by oxidative stress. In severe cases, BPs were associated with carcinogenicity. Therefore, it is imperative to recognize the potential hazards caused by BP contamination.

Going forward, the assessment of health toxicity induced by BPs will merit great attention. As BPs become more widely utilized and awareness of their health toxicity increases, the existing research is limited by factors such as reliance on animal and *in vitro* studies, as well as variations in exposure levels and study methodologies. Further research efforts are needed to reveal additional human health effects and refine our understanding of their mechanisms of action. In addition, current literature focuses on individual BPs, lacking sufficient understanding of the potential risks associated with cumulative exposure to multiple BPs. Considering the potential synergistic or additive effects, we need a comprehensive assessment of the combined effects of different BPs. Although studies on the toxicity of BPs have been reported, the long-term health effects of BPs for humans lack comprehensive knowledge. Further research is warranted to explore the potential associations between long-term exposure to BPs and chronic health problems, such as endocrine disruption, reproductive disorders, and cancer. Furthermore, based on the disclosure of these toxic effects, regulatory measures are expected to evolve as evidence continues to accumulate with the aim of reducing human exposure and preventing potential health hazards, effectively minimizing the risks caused by BPs.

Author contributions

Y.N.Y.: conceptualization, investigation, writing–original draft, writing–original revise. Y.W.: investigation, writing–review & editing. H.L.Z. and Y.X.G: supervision, writing–review & editing. T.Z. and K.K.: conceptualization, investigation, supervision, writing–review & editing, funding acquisition.

Declaration of competing interests

The authors declare no competing financial interest.

Acknowledgments

This work was supported by the Natural Science Foundation of China (No. 22022612, and No. 21677184), Natural Science Foundation of

Guangdong Province, China (No. 2020A0104006 and No. 2021A1515010243), and the Fundamental Research Funds for the Central Universities. The work was supported, in part, by the National Institute of Environmental Health Sciences (NIEHS) under award number U2CES026542 (KK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIEHS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eehl.2023.10.001.

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