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Widespread Occurrence of Benzophenone-Type UV Light Filters in Personal Care Products from China and the United States: An Assessment of Human Exposure

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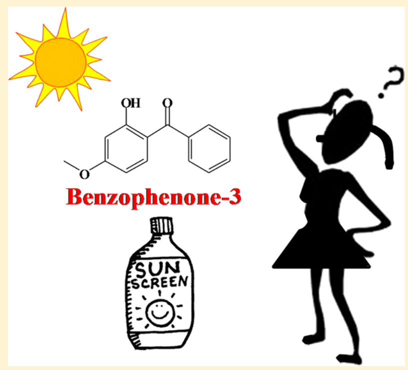
S *Supporting Information*

ABSTRACT: Benzophenone-3 (BP-3) is a sunscreen agent used in a variety of personal care products (PCPs) for the protection of human skin and hair from damage by ultraviolet (UV) radiation. Concerns have been raised over exposure of humans to BP-3, owing to the estrogenic potential of this compound. Nevertheless, the levels and profiles of BP-3 in PCPs and sources of exposure of humans to this estrogenic compound are not well-known. In this study, concentrations of BP-3 were determined in seven categories of 231 PCPs collected from several cities in China (n = 117) and the United States (U.S.) (n = 114), using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). BP-3 was found in the majority (81%) of the samples analyzed, at concentrations as high as 0.148%. The highest BP-3 concentrations (geometric mean [GM]: 548; median: 530 ng/g) were found in skin lotions (including sunscreen lotions), followed by makeup products (284; 221 ng/g). PCPs collected from the U.S. contained higher concentrations of BP-3 than those collected from China. On the basis of the concentrations measured and daily usage rates of PCPs, we estimated the daily intake of BP-3 through dermal absorption from the use of PCPs. The GM and 95th percentile exposure doses to BP-3 were 0.978 and 25.5 μg/day, respectively, for adult women in China, which were 2 orders of magnitude lower than those found for adult women in the U.S. (24.4 and 5160 μg/day). Skin lotions and face creams contributed to the preponderance of daily BP-3 exposures (>80%).



INTRODUCTION

Ultraviolet (UV) filters are a class of substances that can absorb a broad spectrum of UV radiation. UV filters have been used in a wide range of personal care products (PCPs) to protect human skin and hair from direct exposure to deleterious UV radiation.[1−3] Apart from their use as a sunscreen agent, UV filters also are used as stabilizers in cosmetics, plastics, adhesives, and rubber to prevent photolysis of polymers.[4] Benzophenone-3 (BP-3; 2-hydroxy-4-methoxybenzophenone) is a commonly used UV filter in the United States (U.S.), and the use of BP-3 in cosmetic products has been increasing in China over the past decade.[5,6]

UV filters can be introduced into the aquatic environment via wastewater discharges.[3] BP-3 has been reported to occur in surface waters in Switzerland, at a concentration range of <2 (LOQ [limit of quantitation]) to 35 ng/L,[7] and in wastewater from China, at concentrations ranging from 68 to 722 ng/L.[8] High concentrations of up to 3300 ng/L of BP-3 were found in coastal seawater near beaches in Spain.[9] BP-3 was reported in sediment from China and Spain at levels of between 0.27 and 27 ng/g dry weight (dw).[10,11] BP-3 was reported at high concentrations (3.74−3280 ng/g) in indoor dust from the U.S. and several Asian countries.[12] BP-3 was found in fish from rivers and lakes in Switzerland and in Spain at concentrations on the order of several tens to a few hundred nanograms per gram lipid.[7,13,14]

The exposure of humans to UV filters, including BP-3, is prevalent because sunscreen agents are present in many PCPs.[1−3] The major human exposure pathway for BP-3 is dermal absorption from the use of consumer products.[15−18] Studies have shown that BP-3 can readily penetrate human skin, and repeated application can increase systemic absorption of this compound.[15,16] After systemic absorption, BP-3 undergoes phase I and phase II biotransformation; BP-3 and its metabolites are excreted from the body mainly through urine.[19,20] A 2008 study by the U.S. Centers for Disease Control and Prevention (CDC) showed that BP-3 was found in 96.8% of 2517 human urine samples, collected from the U.S. general population, at concentrations in the range of 0.4−21

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700 ng/mL, with a geometric mean value of 22.9 ng/mL.[21] Similar urinary BP-3 concentrations were reported in other U.S. studies.[22−24] Urinary concentrations of BP-3 in the U.S. general population were greater than those (<0.11−45.2 ng/mL) reported for the Chinese general population.[25,26] The occurrence of BP-3 and its metabolites has been reported in other human bodily fluids, such as breast milk and amniotic fluid, as well as in placental tissues, at concentrations on the order of a few nanograms per gram.[27−29]

Concerns have been raised over the safety of BP-3 due to this compound's potential to disrupt the endocrine system.[2] Acute toxicity of BP-3 was found to be low,[30,31] and this compound was not found to be mutagenic.[32] Other studies have shown, however, that BP-3 possesses weak estrogenic activity and weak antiandrogenic activity.[4,33−36] The estrogenic activity of BP-3 also was reported in some aquatic organisms.[31,37] In addition to its estrogenic activity, BP-3 was shown to affect hormonal activities in fish.[38] A recent epidemiologic study showed that exposure to BP-type UV filters was associated with estrogen-dependent diseases, such as endometriosis in women.[24] Only a few regulations exist with regard to allowable levels of BP-3 in PCPs. For example, the maximum allowable level for BP-3 set by the U.S. Food and Drug Administration (FDA) in sunscreen products is 6% and that by the European Commission is 10%.[39]

Although a few studies have reported on the fate of BP-3 in the environment, little is known on the occurrence of this compound in PCPs. Studies on the dermal exposure of humans to BP-3 through the use of PCPs are scarce. In this study, we measured BP-3 concentrations in 231 PCPs collected from China and the U.S., with the aim of establishing baseline concentrations of BP-3 in select consumer products and estimating potential exposure doses through dermal absorption.

■ MATERIALS AND METHODS

Sample Collection. Samples of PCPs from China (n = 117) were collected in Baoding, Beijing, Jinan, Jinchang, Liuzhou, Shanghai, and Tianjin from July to September 2012. Samples from the U.S. (n = 114) were collected in Albany, New York, during April 2012 and February to May 2013. Samples were purchased mainly from large retail stores and a few local grocery stores. Brands were chosen to represent products that are commonly consumed by the general population in both countries. The samples were divided into seven categories as toothpastes (n = 17), hair care products (shampoos and hair conditioners; n = 32), body washes (shower gels and facial cleansers; n = 31), hand soaps (n = 3), sanitation products (n = 9), skin lotions (body lotions and face creams; n = 107), and makeup products (liquid foundation and nail polishes; n = 32). Details of the PCPs analyzed are given in Table S1 (Supporting Information). All samples were stored at 4 °C until analysis.

Sample Preparation. Approximately 0.2−0.5 g of the sample was weighed (wet weight or product weight) and placed in a glass tube. Twenty nanograms of $^{13}C_{12}$-labeled bisphenol A ($^{13}C_{12}$-BPA, 99%; Cambridge Isotope Laboratories, Andover, MA) were spiked as an internal standard, and the sample was extracted with 5 mL of methyl *tert*-butyl ether (MTBE) by shaking in an orbital shaker (Eberbach, Ann Arbor, MI) at 250 oscillations/min for 30 min. After centrifugation at 3500g for 5 min (Eppendorf 5804, Hamburg, Germany), the solvent layer was transferred to another tube. The residue was extracted twice with 5 mL aliquots of MTBE by shaking. The extracts were combined, washed with 2 mL of milli-Q water (purified by an ultrapure water system; Barnstead International, Dubuque, IA), evaporated to near-dryness, and reconstituted with 3 mL of dichloromethane/hexane (1:9, v/v). A custom-made silica gel cartridge (0.9 g; 130−270 mesh silica gel; Sigma-Aldrich, St. Louis, MO), previously conditioned with 5 mL of ethyl acetate/dichloromethane (1:1, v:v) and 5 mL of hexane, was used for the purification of samples. After loading the sample, the cartridge was washed with 10 mL of hexane and eluted with 10 mL of ethyl acetate/dichloromethane (1:1, v:v). The elute was concentrated to near-dryness, reconstituted with 1 mL of methanol, filtered through a 0.2 μm nylon filter (Phenomenex, Torrance, CA), and transferred into a gas chromatographic vial for high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) analysis.

Chemical Analysis. An aliquot of 10 μL of the sample extract was injected into an Agilent 1100 Series HPLC system, equipped with a binary pump and an autosampler (Agilent Technologies Inc., Santa Clara, CA). Separation was achieved on a Betasil C18 column (2.1 × 100 mm, 5 μm; Thermo Electron Corporation, Waltham, MA), which was connected to a Javelin guard column (Betasil C18, 2.1 × 20 mm, 5 μm; Thermo Electron Corporation). The mobile phase, comprising methanol and milli-Q water, was delivered at a flow rate of 300 μL/min. The gradient started at 10% methanol, followed by a 2.5 min ramp to 99% methanol, which was held for 11 min, and then reverted to the initial conditions after 5 min of stabilization time.

BP-3 was determined using an API 5500 MS/MS system (Applied Biosystems, Foster City, CA) with a turbo spray ion source operating in the negative electrospray mode. Instrumental parameters were optimized, by infusion of 100 ng/mL standard solution with a flow injection analysis, to transmit the $[M - H]^-$ ion before fragmentation into one or more product ions. The capillary voltage was maintained at −4.5 kV, and desolvation temperature was 525 °C. Cone voltage was −45 V, and collision energy was 30 eV. The nebulizing, desolvation, and cone gas was nitrogen. Data were acquired using multiple reaction monitoring (MRM) with transitions of 227 > 211 for BP-3 (98%; Sigma-Aldrich) and 239 > 224 for $^{13}C_{12}$-BPA.

Quality Assurance and Quality Control. Validity of the analytical results was verified by several quality assurance and quality control (QA/QC) measures. Because BP-3 is present in many PCPs, the analyst refrained from using skin lotions and other products that were suspected to contain this compound during the analysis. Several procedural blanks (n = 3), spiked blanks (n = 3), and spiked matrices (n = 4) were included in each analytical batch of 60 samples to evaluate the background contamination and matrix effects from sample preparation steps and instrumental analysis. Procedural blanks (0.5 mL of milli-Q water in place of samples) were processed in the same way as the samples, and no quantifiable amount of target compound was detected. The recovery of BP-3 spiked into blanks (20 ng) was 100 ± 13% (mean ± standard deviation) and that spiked into sample matrices (20 ng) was 88 ± 38%. The recovery of internal standard ($^{13}C_{12}$-BPA) spiked into all samples was 85 ± 42%. Ten samples were randomly selected for duplicate analysis, and the results showed a coefficient variation of <20% among the measured values for the target compounds. Another ten samples were randomly selected, and a third extraction was carried out with 3 mL of MTBE (after the first two extractions) to confirm that BP-3 was completely extracted from samples. In general, the residual BP-3 found in the third extraction was <2% of the total concentration in the samples. BP-3 was quantified by isotope-dilution method. The limit of

Table 1. Concentrations (ng/g Product Weight) and Detection Rates (%) of BP-3 in Personal Care Products from China and the United States[a]

	n	GM	fifth percentile	median	95th percentile	range	detection rate (%)
toothpastes	17	10.0	0.354	43.6	679	nd−786	58.8
hair care products	32	20.5	0.354	42.5	886	nd−6810	71.9
body washes	31	61.0	0.354	92.1	5440	nd−8190	80.6
toilet soaps	3	132	32.3	205	788	13.1−853	100
sanitation products	9	18.1	0.354	0.562	38 300	nd−56 100	55.6
skin lotions	107	548	0.354	530	973 000	nd−1 480 000	88.8
makeup	32	284	0.354	221	391 000	nd−1 370 000	84.4
China	117	20.1	0.354	32.7	3860	nd−1 480 000	64.1
USA	114	1200	16.9	628	923 000	nd−1 290 000	99.1
all products	231	151	0.354	184	825 000	nd−1 480 000	81.4

[a]GM = geometric mean; nd = not detected.

quantitation (LOQ) was 0.5 ng/g. Instrumental background, carry-over, and stability were checked by duplicate injections of samples and by injection of a continuing calibration check standard and pure solvent (methanol), after every 20 samples. Instrumental calibration was verified by injection of a 10-point calibration standard at concentrations ranging from 0.05 to 100 ng/mL, and the regression coefficient (r) of the calibration curve was >0.99.

Data Analysis. Statistical analyses were performed with SPSS (Version 17.0) and Origin (Version 7.5). Geometric mean (GM), median, and concentration ranges were used to describe the results. Values below the LOQ were assigned a value equal to the LOQ divided by the square root of 2 (LOQ/$\sqrt{2}$) for the calculation of GM and median. A one-way ANOVA with the Tukey test was used for the comparison of differences between groups. A one-sample Kolmogorov−Smirnov test was used to determine the normality of the data. A value of $p < 0.05$ denoted significance. All data are presented on a wet-weight (or product-weight) basis unless specified otherwise.

RESULTS AND DISCUSSION

Concentrations. The measured concentrations of BP-3 in PCPs are summarized in Table 1. Of the 231 samples analyzed, 188 (detection rate: 81%) contained BP-3 at concentrations in the range of 0.5 (LOQ) to 1 480 000 ng/g (Figure S1, Supporting Information). The GM, median, and 95th percentile concentrations of BP-3 in all samples were 151, 184, and 825 000 ng/g, respectively. The PCPs analyzed in this study were grouped into seven categories according to their usage, as described above. The highest BP-3 concentration was found in skin lotions, with respective GM and median concentrations of 548 and 530 ng/g, followed by makeup products (284 and 221 ng/g). Toothpastes (GM/median: 10.0 and 43.6 ng/g) and sanitary products (18.1 and 0.562 ng/g) contained low concentrations of BP-3 (Table 1). BP-3 concentrations in skin lotions and makeup products were 1 to 2 orders of magnitude higher than those found in toothpastes and sanitary products ($p < 0.05$, one-way ANOVA). The frequency of occurrence of BP-3 in skin lotions (89%) and makeup products (84%) were higher than that for toothpastes (59%) and sanitary products (56%). The highest concentration of BP-3 (1 480 000 ng/g, or 0.148% on a mass basis) was found in a sunscreen sample that was grouped under the category of skin lotions. Sunscreen samples contained notable BP-3 concentrations, in general, on the order of several hundreds to one thousand micrograms per gram (parts per million). A lipstick sample from the makeup product category also contained a notable concentration of BP-3 (0.137%) (Table 1).

Sunscreen products are used to protect people from damage by UV irradiation, and BP-3 is typically used as an ingredient in sunscreen products in the U.S.[1−3,5] In addition to its presence in sunscreen products, BP-3 also is incorporated into many other PCPs, including shampoos, perfumes, lipsticks, lip colors, face creams, eye creams, moisturizers, and body washes.[40] BP-3 also is used in auto care products, household products, and plastics to impart light stability.[4,40] Widespread occurrence of BP-3 (81%; Table 1) in most PCPs analyzed in this study is in accordance with the versatile applications of this compound in various commodities. The concentration of BP-3 (GM: 254 000, median: 897 000 ng/g) in sunscreen products, excluding other skin lotions (such as face creams and body lotions), was 3 orders of magnitude higher than the overall concentrations of BP-3 in all PCP samples analyzed (GM: 151, median: 184 ng/g; $p < 0.001$, Table 1).

The concentration profiles of BP-3 in various categories of PCPs were compared between China and the U.S. The concentrations of BP-3 in PCPs from China were 1 to 2 orders of magnitude lower than those from the U.S. (Table 1 and Figure 1). For example, the GM concentration of BP-3 in skin

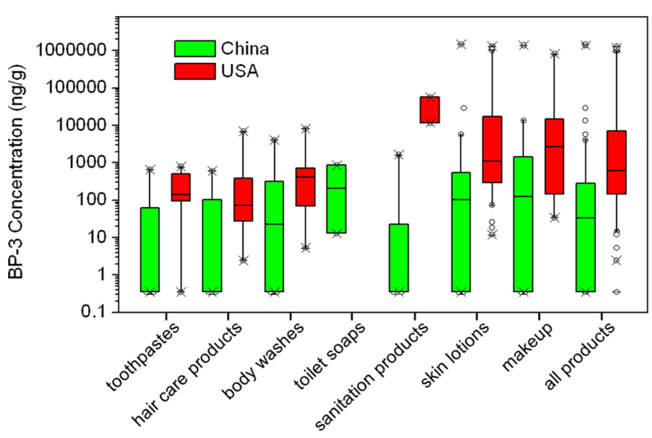

Figure 1. Comparison of concentrations of BP-3 in personal care products from China and the United States. The lower and upper stars denote the 1st and 99th percentiles, the lower and upper whiskers represent the 5th and 95th percentiles, the bottom and top edges of the box show the 25th and 75th percentiles, and the horizontal line within the box represents the median concentration, respectively. The dots are outliers.

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Table 2. Dermal Intake (ng/day) of BP-3 from the Use of Personal Care Products by Adult Females in China and the United States

			China		USA	
category	daily usage (g/day)	retention factor	GM	95th percentile	GM	95th percentile
shampoos	12.8	0.01	0.244	6.79	25.6	586
hair conditioners	13.8	0.01	1.12	60.9	6.96	36.9
body shower	14.5	0.001	0.035	5.29	1.30	9.55
facial cleanser	4.06	0.001	0.136	10.5	1.97	30.4
toilet soaps	4.80	0.01	6.32	37.8	6.32	37.8
body lotions	8.69	1.00	868	9130	18 100	4 400 000
face creams	2.05	1.00	61.1	13 900	2200	54 700
liquid foundations	0.67	1.00	40.7	2330	4060	705 000
total exposure			978	25 500	24 400	5 160 000

lotions from China was 43.6 ng/g, which was 69 times lower than the concentrations found in samples from the U.S. (3000 ng/g). Similarly, the GM concentration of BP-3 in makeup products from China was 81.1 ng/g, which was 28 times lower than that found in corresponding samples from the U.S. (2300 ng/g) ($p < 0.05$, Figure 1). The overall GM concentration of BP-3 (20.1 ng/g) in all Chinese samples was 60 times lower than the concentrations (1200 ng/g) determined for the U.S. samples ($p < 0.05$, Table 1). Further, BP-3 was detected more frequently in the U.S. samples (99%) than in the Chinese samples (64%) (Table 1).

BP-3 has been approved for use at recommended concentrations in sunscreen products sold in many countries, including the U.S., Canada, China, and Korea.[1,2,4,39,40] It is worthwhile to note that BP-3 is not a major UV filter in sunscreen products in China. Methoxy ethylhexyl acrylate and butyl methoxy dibenzoylmethane are the major UV filters in cosmetics in China.[5,6] A survey on the frequency of use of sunscreen agents in 414 sunblock products in Chinese markets showed that BP-3 was used in 15% of the products, which was considerably below the values reported for methoxy ethylhexyl acrylate (≥90%) and butyl methoxy dibenzoylmethane (30%).[41] These results may explain the lower detection rates and concentrations of BP-3 in Chinese cosmetic products analyzed in the present study. Further, the U.S. general population uses sunscreen and other PCPs on a daily basis,[42] which may explain higher concentrations of BP-3 found in American urine samples than the concentrations reported in Chinese urine samples.[21−26]

Dermal Exposures. Several parameters, such as daily usage rate and modes of use of PCPs, and retention characteristics of BP-3 on the skin should be considered when evaluating human exposure to BP-3 through dermal application of PCPs.[43] For the purpose of dermal exposure estimation, PCPs analyzed in this study were grouped into 11 categories (Table S1, Supporting Information), on the basis of mode and amount of usage. We estimated the exposure dose of BP-3 through dermal application of PCPs using eq 1:[44]

$$\mathrm{EDI} = \sum_{i=1}^{n} C_i R_i f_i \tag{1}$$

where EDI is the estimated daily intake (ng/day), C is the concentration of BP-3 in the PCP analyzed (ng/g), R is the daily usage rate (g/day), and f is the retention factor of products on the skin (coefficient). For the purpose of estimation of average and worst-case exposure scenarios, the GM and 95th percentile concentrations, respectively, of BP-3 measured in PCPs were used. Hand soap samples from the U.S. were not analyzed, and therefore, BP-3 concentrations determined for hand soap samples from China were substituted for the U.S. The daily usage rates of PCPs by adult women in the U.S. and Europe were: 12.8 g/day for shampoos, 13.8 g/day for hair conditioners, 14.5 g/day for shower gels, 4.06 g/day for facial cleansers, 4.80 g/day for hand soaps, 8.69 g/day for body lotions, 2.05 g/day for face creams, and 0.67 g/day for liquid foundations (Table 2).[43,45−48] The usage rates of PCPs for adult women in China were not available, and therefore, we adopted the values reported for adult women in the U.S. and Europe.[43,45−48] The retention factors for BP-3 on the skin were in the range of 0.001−1 (Table 2), depending on the mode of application.[44]

The average exposure dose of BP-3 (calculated from GM concentrations) through dermal absorption, from application of PCPs, by adult women in China was 0.978 μg/day. The worst-case exposure dose, calculated from 95th percentile concentrations, was 25.5 μg/day for adult women in China. The GM and 95th percentile EDI values for adult women in the U.S. were 24.4 and 5160 μg/day, respectively, which were 25 and 200 times higher than those calculated for adult women in China (Table 2). Body lotions were the predominant contributors to dermal exposure, accounting for 89% for Chinese women and 74% for U.S. women to the total exposure dose of BP-3 (calculated from the GM EDIs). The next major sources of BP-3 exposure were face cream (6% and 9% of the total dose for Chinese and Americans, respectively) and liquid foundation (4% and 17% of the total dose for Chinese and Americans, respectively). Contributions of the other five categories of PCPs to the total BP-3 exposure were minor (<1% each) (Figure 2).

Following dermal absorption, BP-3 can be biotransformed and excreted as metabolites, such as 2,4-dihydroxylbenzophe-

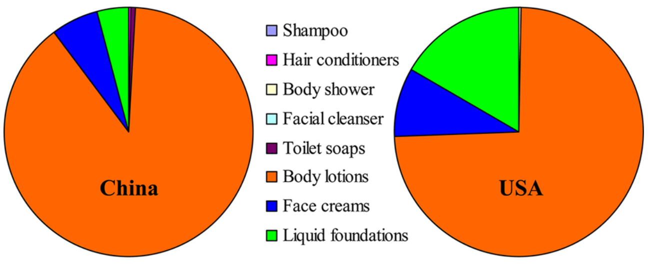

Figure 2. Contributions of different categories of personal care products to total BP-3 exposure dose through dermal absorption in China and the United States.

none, 2,2′-dihydroxy-4-methoxybenzophenone, and 2,3,4-trihydroxybenzophenone, in urine.[15−21] Urinary concentrations of BP-3 and its metabolites have been used in the estimation of human exposure doses [21] using the following eq 2:

$$\mathrm{EDI}_{\mathrm{tot}} = C_{\mathrm{u}}R_{\mathrm{u}} \quad (2)$$

where $\mathrm{EDI}_{\mathrm{tot}}$ is the cumulative daily intake (μg/day), C_u is the concentration of BP-3 in urine (μg/L), and R_u is the urine excretion rate (L/day). The GM urinary BP-3 concentrations reported for adult Chinese and U.S. women were 0.977 and 30.7 μg/L, respectively.[21,26] The daily urine excretion rate was approximately 1.5 L for adult women.[49] On the basis of urinary BP-3 concentrations, $\mathrm{EDI}_{\mathrm{tot}}$ values estimated for BP-3 were 1.47 and 46.1 μg/day for adult women in China and the U.S., respectively. The dermal intake calculated from GM concentrations of PCPs analyzed in this study was 0.978 and 24.4 μg/day for adult Chinese and U.S. women, respectively (Table 2). Taken together, the contribution of PCPs to total BP-3 exposure was 67% and 53% for adult women in China and the U.S., respectively. Our results suggest that the majority of BP-3 exposure in adult women is from the use of PCPs.

It should be noted that several uncertainties exist in our estimation of BP-3 exposures from PCPs. The number and type of PCPs analyzed in this study are limited. Several cosmetics, such as spray perfume, moisturizer, antiperspirant, and hair spray, were not included in our analysis. Inhalation exposure from ambient air during the application of cosmetics was not evaluated, which can be a pathway of exposure. Sunscreens are probably used in large amounts and more frequently during summertime. Therefore, our exposure estimate from PCPs is an underestimation of the actual exposure dose.

Our previous studies have reported widespread occurrence of several types of estrogenic chemicals, including parabens, phthalates, siloxanes, and polycyclic musks, in a variety of PCPs.[50−53] This study shows frequent occurrence and high concentrations of BP-3 in PCPs (Table 1). Although these chemicals are added to PCPs for specific reasons, risk assessment should be considered in the context of potential benefits as well. For example, application of sunscreen products to protect against deleterious effects of UV irradiation is important, but the frequency and quantity of usage should be taken into consideration while making decisions regarding the safety of the products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional information as noted in the text (one table and one figure). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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