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Original Contribution

Urinary Concentrations of Benzophenone-Type Ultraviolet Radiation Filters and Couples' Fecundity

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Concern has arisen about benzophenone (BP) ultraviolet (UV) radiation filters, given their use in sunscreen and personal-care products and their reported estrogenic and antiandrogenic activity. We recruited 501 couples who were discontinuing use of contraceptives in order to become pregnant for the Longitudinal Investigation of Fertility and the Environment (LIFE) Study (Michigan and Texas, 2005–2009). Couples provided urine specimens and completed daily journals until they either achieved pregnancy or had tried for 12 months. Women used fertility monitors to time sexual intercourse and digital pregnancy tests. Urinary concentrations of 5 UV filters (ng/mL) were determined using triple-quadrupole mass spectrometry: 2,4-dihydroxybenzophenone (also called BP-1); 2,2′,4,4′-tetrahydroxybenzophenone (BP-2); 2-hydroxy-4-methoxybenzophenone (BP-3); 2,2′-dihydroxy-4-methoxybenzophenone (BP-8); and 4-hydroxybenzophenone. Fecundability odds ratios were estimated for each UV filter (dichotomized at the 75th percentile) and adjusted for age, creatinine concentration, body mass index (weight (kg)/height $(m)^2$), cotinine concentration, season, and site, while accounting for time off contraception. Separate models were fitted for each UV filter and partner; final models included partners' concentrations. Male partners' concentrations of BP-2 and 4-hydroxybenzophenone were associated with reduced fecundity in adjusted models (fecundability odds ratio (FOR) = 0.69 (95% confidence interval (CI): 0.50, 0.95) and FOR = 0.74 (95% CI: 0.54, 1.00), respectively). In models adjusting for both partners' concentrations, male BP-2 concentration remained associated with reduced fecundity (FOR = 0.69, 95% CI: 0.49, 0.97). These data suggest that male exposure to select UV filters may diminish couples' fecundity, resulting in a longer time to pregnancy.

benzophenone; environment; fecundity; personal-care products; reproduction; sunscreen agents; time to pregnancy; ultraviolet light filters

Abbreviations: BMI, body mass index; BP, benzophenone; CI, confidence interval; FOR, fecundability odds ratio; ICC, intraclass correlation coefficient; LIFE, Longitudinal Investigation of Fertility and the Environment; 4-OH-BP, 4-hydroxybenzophenone; 2,4-OH-BP, 2,4-dihydroxybenzophenone [BP-1]; 2,2′4,4′-OH-BP, 2,2′,4,4′-tetrahydroxybenzophenone [BP-2]; 2-OH-4-MeO-BP, 2-hydroxy-4-methoxybenzophenone [BP-3]; 2,2′-OH-4-MeO-BP, 2,2′-dihydroxy-4-methoxybenzophenone [BP-8]; UV, ultraviolet.

Benzophenone (BP)-type ultraviolet (UV) light filters are an emerging class of environmental chemicals that may potentially impact a large segment of the population, given their use in personal-care products aimed at protecting skin and hair from UV radiation. BP-type UV filters comprise approximately 29 compounds, though the sources for some are unknown and only a few have been assessed relative to endocrine-disrupting mechanisms. Concern has arisen about the potential implications of UV filters for human health, including fecundity and fertility, given their widespread usage (including use by vulnerable population subgroups such as pregnant women and children). For example, 2-hydroxy-4-methoxybenzophenone (2-OH-4-MeO-BP), designated BP-3, is used as a sunscreen agent and is widely detected in the US population, as reflected in the biomonitoring component of the National Health and Nutrition Examination Survey (NHANES) (1), as well as in other study populations, including pregnant women, adolescents, and children (2, 3).

Approximately 10% of the dermal dose of BP-3 may be absorbed into the systematic circulation (4), serving as a route of exposure for endocrine-disrupting chemicals (5, 6).

Understanding the pharmacokinetics of BP filters is a formidable task, though such work is ongoing, with early findings having important implications for epidemiologic research. For example, oral administration of BP-3 in rats demonstrates that urine is a major route of excretion (7), supporting the use of urine for quantifying exposures. BP-3 is reported to be metabolized to 2,4-dihydroxybenzophenone (2,4-OH-BP), designated BP-1, which has more estrogenic activity than its parent compound, as well as 2,2′-dihydroxy-4-methoxybenzophenone (2,2′-OH-4-MeO-BP), designated BP-8 (8, 9). Other UV filters with reported estrogenic activity include 2,2′,4,4′-tetrahydroxybenzophenone (2,2′4,4′-OH-BP), designated BP-2, and 4-hydroxybenzophenone (4-OH-BP), but with even less study than other compounds. Pharmacokinetic research on BP-2 suggests that it can bind to estrogen receptors, exerting estrogen-agonistic activity in a dose-dependent manner between BP-2 exposure and increased uterine weights in rats (10). Of particular note is the recent finding that BP-1 was associated with surgically visualized endometriosis, an estrogen-dependent gynecological disease (11).

Motivated by the widespread sources of BP exposure for human populations, including couples of reproductive age, and its reported endocrine activity, we sought to explore the association between 5 BP-type UV filters and couples' fecundity, defined as the biological capacity of men and women to reproduce (12), as measured by the number of menstrual cycles required to achieve pregnancy. We selected the 5 UV filters because of their use in personal-care products and their reported endocrine activity.

METHODS

Study design and cohort

We used a prospective cohort study design to follow 501 couples in the Longitudinal Investigation of Fertility and the Environment (LIFE) Study who were discontinuing use of contraceptives in order to become pregnant. Couples were recruited from 16 counties in Michigan and Texas in 2005–2009, using marketing databases or state fishing/hunting registries, respectively. By design, eligibility criteria were minimal: couples in a committed relationship; females aged 18–44 years and males aged ≥18 years; menstrual cycle length between 21 and 42 days; no use of injectable hormonal contraceptives in the past year or current lactation; no physician-diagnosed infertility/sterility; and an ability to communicate in English or Spanish. A complete description of the methodology of the LIFE Study is available elsewhere (13).

Data and biospecimen collection

Blood and urine samples were collected from both partners in the couple during the baseline home visit. Following a brief in-person interview, couples were instructed in the completion of daily journals for reporting data on lifestyle factors and sexual intercourse, as well as menstruation and pregnancy testing results for females. Height and weight were measured in all couples, using a standardized protocol, for determination of body mass index (BMI; weight (kg)/height $(m)^2$). Research nurses instructed women in the use of the Clearblue Easy Fertility Monitor (Swiss Precision Diagnostics GmbH, Geneva, Switzerland; http://www.clearblueeasy.com), a urine-based device that tracks levels of estrone-3-glucuronide and luteinizing hormone, which are then transformed into a visual prompt to help in the timing of sexual intercourse relative to ovulation. In a validation study of the monitor, 91% of ovulations detected by ultrasonography were also detected by the monitor as the 2 peak fertility days (14). Women also were taught how to accurately use the Clearblue Digital Pregnancy Test (Swiss Precision Diagnostics), commencing on the day of expected menstruation. Approval for research in human subjects was obtained from all participating institutions, and all study participants gave full informed consent before data collection.

Toxicological analysis

The 5 UV filters of interest were BP-3 and its metabolites (BP-1, BP-8), BP-2, and 4-OH-BP. BP-3 is the most commonly used UV filter in sunscreen and personal-care products and is readily detected in human urine (15). Urinary concentrations of all UV filters were quantified (ng/mL) by means of established procedures (16, 17) using high-performance liquid chromatography–triple-quadrupole tandem mass spectrometry with established quality control procedures. Briefly, 500 μL of urine was spiked with 10 ng of $^{13}C_{12}$-2-OH-4-MeO-BP (as an internal standard), followed by the addition of 300 μL of 1.0M ammonium acetate containing 44 units of glucuronidase and extraction with ethyl acetate. Quantification was done by isotopic dilution. The target analytes spiked into urine and passed through the entire analytical procedure, yielding a recovery of 95%–107%. Procedural blanks were analyzed with every batch of 25 samples, and concentrations of target chemicals in procedural blanks were below the limits of detection. We recorded all machine-measured concentrations without substituting for concentrations below the laboratory limits of detection, in order to minimize bias introduced by such practices when modeling human health endpoints (18, 19). Creatinine concentration was quantified (mg/dL) in 0.15 mL of urine using a Roche Hitachi 912 Chemistry Analyzer (Roche Diagnostics Corporation, Dallas, Texas) and the Creatinine Plus Assay (Roche Diagnostics Corporation, Indianapolis, Indiana). Cotinine concentration was quantified (ng/mL) in 1 mL of serum using isotope-dilution liquid chromatography–tandem mass spectrometry (20).

Statistical analysis

The data distributions of all variables, including the 5 UV filters, were fully inspected, along with estimation of geometric mean values and 95% confidence intervals and percentiles for each partner. We assessed the distributions of UV filter concentrations according to selected covariates, including BMI, serum cotinine concentration, and season of enrollment. In this exploratory analysis, statistical significance was denoted by $P < 0.05$, as tested using the χ^2 statistic, t test, or Wilcoxon nonparametric test, as appropriate. Fecundability

odds ratios (FORs) and 95% confidence intervals were estimated for each UV filter, first modeling each partner's concentrations individually and then modeling both partners' concentrations simultaneously. In the models, we dichotomized UV filter concentrations at the 75th percentile to assess more-exposed persons versus less-exposed persons relative to couple fecundity. The FOR estimates the odds of becoming pregnant for partners/couples at or above the 75th percentile for each UV filter relative to those below the 75th percentile, conditional on not achieving pregnancy during the previous menstrual cycle. Unadjusted models included concentrations of each UV filter (ng/mL) and creatinine concentration (mg/dL; continuous) to account for urinary volume, as well as age (years; continuous); adjusted models included potential confounders designated a priori (11, 21–23). These included age (years; continuous), BMI (categorized as underweight/normal (<24.9), overweight (25.0–29.9), or obese (≥30.0)) (24), smoking status as defined by measured serum cotinine concentration (no smoking (<9.99 ng/mL), passive tobacco smoke exposure (10.0–99.9 ng/mL), or active smoking (≥100.0 ng/mL)) (25), and season of enrollment (winter, spring, summer, or fall). We also included research site (Michigan or Texas) to account for any residual confounding. Given the low correlation between couples' exposures ($r \leq 0.19$, $P < 0.05$), we included both partners' UV filter concentrations in the final models to assess which partner might be more influential relative to UV filters and fecundability.

We accounted for left-truncation or time off from contraception prior to recruitment in all models (i.e., 12% and 18% of couples had been off of contraceptives for 1 month and 2 months, respectively). All couples were censored at withdrawal or after 12 months of trying to become pregnant. Cox models for discrete survival time allowing for a cycle-varying intercept were used to estimate all FORs (26), and proportional hazards and continuous covariates met linearity modeling assumptions (27). FORs less than 1 denote diminished fecundity or a longer time to pregnancy, while FORs greater than 1 denote enhanced fecundity or a shorter time to pregnancy. We did not adjust for multiple comparisons, in keeping with the exploratory nature of this work.

RESULTS

The cohort comprised mostly white couples with health insurance coverage and annual household incomes of approximately $50,000 or more (Table 1). Male partners were significantly older than female partners (median age, 31 years vs. 29 years), had higher median body mass indices (28.7 vs. 25.6), and had higher median urinary creatinine (140.1 mg/dL vs. 77.9 mg/dL) and serum cotinine (0.04 ng/mL vs. 0.02 ng/mL) concentrations, respectively.

Geometric mean concentrations of all BP-type UV filters were significantly higher for women than for men, as were percentile distributions (Table 2). Most study participants (≥94%) had detectable urinary concentrations of UV filters, except for BP-2 and BP-8; approximately one-fourth of partners' concentrations were below the limit of detection. We also assessed UV filter concentrations in relation to selected covariates. Interestingly, BP-3 and BP-1 were inversely associated with female BMI, as was BP-1 with male BMI (see Web Table 1, available at http://aje.oxfordjournals.org/). BP-1 and BP-3 concentrations were significantly higher in nonsmokers than in active smokers for both partners, as was BP-8 in males (Web Table 2). Concentrations were significantly higher for women and men enrolled during the summer months than for those enrolled during other months (Web Tables 3 and 4).

When FORs were estimated for each partner separately, 2 UV filters dichotomized at the 75th percentile of male partners' concentrations were significantly associated with FORs below 1, indicative of diminished fecundity or a longer time to pregnancy (Table 3). Specifically, BP-2 was associated with an approximately 31% reduction in fecundity (FOR = 0.69, 95% confidence interval (CI): 0.50, 0.95), and 4-OH-BP was associated with a 26% reduction (FOR = 0.74, 95% CI: 0.54, 1.00). None of the UV filters measured in females were associated with fecundability, with the exception of BP-8, but only in the creatinine- and age-adjusted model (FOR = 1.34, 95% CI: 1.02, 1.78). Since correlations between partners' UV filter concentrations were low, with the highest being observed for 4-OH-BP ($r = 0.19$; $P < 0.05$) as presented in Web Table 5, we modeled couples' joint exposures to determine whether a particular partner might be more influential relative to estimating FORs. This is important, because time to pregnancy is a couple-dependent measure of fecundity. BP-2 level in male partners remained significantly associated with diminished couple fecundity in both unadjusted and adjusted models, reflecting a 30% reduction in fecundability (FOR = 0.69, 95% CI: 0.49, 0.97) or a longer time to pregnancy (Table 4). None of the findings based upon female concentrations, modeled either individually or jointly with male partners, achieved significance. Also notable is the absence of significance when UV filter levels were modeled continuously in either individual or joint models; however, the directionality of the FORs remained consistent (data not shown).

DISCUSSION

Findings from our prospective cohort study, which involved preconception enrollment of couples who were longitudinally followed up to either pregnancy (confirmed by human chorionic gonadotropin level) or 12 months of trying, suggest that some BP-type UV filters (but not all) may be associated with diminished couple fecundity, as measured by a longer time to pregnancy. The strongest signal was for males' concentrations of BP-2, which reflected a consistent reduction in fecundability when partners' concentrations were modeled individually or jointly. In addition, when only males' 4-OH-BP concentrations were modeled, 4-OH-BP was negatively associated with fecundability. Of note is the relevance of 4-OH-BP for human fecundity, as it is a pharmaceutical intermediate of clomifene citrate (28). Only BP-8 was associated with a shorter time to pregnancy when we modeled each partner's concentrations individually, but directionality reversed when we modeled both partners together, and significance was lost.

Given our inability to identify any previous research focusing on UV filters and human fecundity or fertility, we are unable to more fully interpret our findings. The existing

Table 1. Comparison of Committed Partners According to Selected Characteristics, LIFE Study, 2005–2009

Characteristic	Female Partners ($n = 501$)		Male Partners ($n = 501$)	
	No.	%	No.	%
Nonwhite race/ethnicity	105	21.1	104	20.9
No health insurance	40	8.0	42	8.4
No prior pregnancy	210	41.9	215	43.0
Annual household income				
<$50,000	89	18.1	77	15.7
$50,000–$100,000	234	47.7	237	48.3
>$100,000	168	34.2	177	36.0
BMI[a] category[b]				
Underweight (<18.5)	7	1.4	2	0.4
Healthy weight (18.5–24.9)	221	44.6	82	16.9
Overweight (25.0–29.9)	136	27.4	206	42.5
Obese (≥30)	132	26.6	195	40.2
Smoking status[b] (by serum cotinine level)				
No exposure (<9.99 ng/mL)	431	88.1	387	78.5
Passive exposure (10–99.9 ng/mL)	24	4.9	22	4.5
Active smoking (≥100 ng/mL)	34	7.0	84	17.0
Season of enrollment				
Winter	131	26.1	131	26.1
Spring	151	30.1	151	30.1
Summer	110	22.0	110	22.0
Fall	109	21.8	109	21.8
Research site				
Michigan	104	20.8	104	20.8
Texas	397	79.2	397	79.2
	Median (IQR)		Median (IQR)	
Age, years[c]	29.0 (27.0–33.0)		31.0 (28.0–35.0)	
BMI[c]	25.6 (22.5–30.5)		28.7 (2.0–32.0)	
Urinary creatinine level, mg/dL[c]	77.9 (35.1–135.8)		140.1 (72.3–200.8)	
Serum cotinine level, ng/mL[c]	0.02 (0.01–0.08)		0.04 (0.02–1.49)	

Abbreviations: BMI, body mass index; IQR, interquartile range; LIFE, Longitudinal Investigation of Fertility and the Environment.

[a] Weight (kg)/height (m)^2.

[b] $P < 0.0001$ (χ^2 test).

[c] $P < 0.0001$ (t test).

literature offers some insight as to possible underlying mechanisms for the observed association between BP-2 and reduced fecundability. Similar to other metabolites of BP-3, it may possess greater estrogenic activity (10, 29–32). To this end, the underlying mechanism may involve estrogenic toxicity. Our observation that the association is largely driven by the male partner's concentration is interesting, and it may reflect antiestrogenic toxicity pathways or even possible sex-specific sensitivities, as observed in rodents (33). Schiffer et al. (34) recently reported that BP-3 may activate the cation channels of sperm, resulting in higher intracellular Ca^{2+} levels, and thereby have the ability to interfere with sperm function. While all BPs are reported to be estrogenic, their potencies are 1,000–100,000 times lower than that for 17β-estradiol, yet higher than those for other xenoestrogens such as bisphenol A (32). Pathways underlying our observed association for male BP-2 and 4-OH-BP are unknown, particularly in light of limited pharmacokinetic data for these compounds.

While our findings are strengthened by the preconception recruitment of couples and the quantification of UV filter levels at enrollment, along with the longitudinal measurement of time to pregnancy, cautious interpretation is needed in light of important study limitations. These include reliance on only 1 urinary measurement, the exploratory nature of our analysis, and potential residual confounding. Considerable variability in the concentrations of UV filters is possible, in

Table 2. Distribution of Creatinine-Adjusted Urinary Concentrations of Benzophenone-Type Ultraviolet Radiation Filters, by Partner Sex, LIFE Study, 2005–2009

UV Filter and % < LOD	Partner Sex	Total No.	UV Filter Concentration for Row Exposure, ng/mL		Percentile and UV Filter Concentration, ng/mL											
					10th		25th		50th		75th		90th		95th	
			GM	95% CI	GM	95% CI	GM	95% CI	GM	95% CI	GM	95% CI	GM	95% CI	GM	95% CI
BP-1 (2,4-OH-BP)																
<1	Female	411	4.62	3.78, 5.64	0.34	0.21, 0.41	0.98	0.68, 1.26	4.24	3.18, 5.27	18.1	14.8, 23.6	80.5	59.8, 125.0	178	115, 221
1	Male	396	1.71	1.38, 2.10	0.17	0.13, 0.21	0.35	0.30, 0.42	1.06	0.83, 1.36	6.92	4.25, 11.60	40.8	25.8, 55.9	80.6	55.9, 111.0
BP-2 (2,2′4,4′-OH-BP)																
28	Female	411	0.09	0.08, 0.11	0.01	0.00, 0.01	0.03	0.02, 0.04	0.07	0.06, 0.08	0.18	0.15, 0.23	0.65	0.45, 0.74	0.93	0.71, 1.77
28	Male	396	0.05	0.04, 0.06	0.01	0.00, 0.01	0.02	0.01, 0.02	0.04	0.04, 0.05	0.11	0.09, 0.13	0.32	0.22, 0.38	0.62	0.38, 0.97
BP-3 (2-OH-4-MeO-BP)																
<1	Female	411	9.81	7.96, 12.1	0.77	0.49, 0.94	1.94	1.51, 2.32	7.68	5.64, 10.60	43.4	31.8, 57.1	167	135, 314	429	278, 569
2	Male	396	3.97	3.24, 4.87	0.37	0.26, 0.49	0.83	0.71, 1.01	2.36	1.97, 3.09	13.9	9.0, 22.9	76.1	63.3, 118.0	164	118, 225
BP-8 (2,2′-OH-4-MeO-BP)																
29	Female	411	0.24	0.19, 0.31	0.01	0.00, 0.01	0.04	0.03, 0.05	0.14	0.11, 0.18	0.88	0.51, 1.46	9.88	5.91, 17.30	47.0	15.0, 94.1
27	Male	396	0.12	0.09, 0.15	0.00	0.00, 0.01	0.02	0.01, 0.02	0.07	0.05, 0.10	0.41	0.27, 0.62	3.32	1.81, 6.17	19.9	6.2, 49.6
4-OH-BP																
6	Female	411	0.21	0.19, 0.24	0.06	0.05, 0.07	0.10	0.09, 0.11	0.18	0.16, 0.21	0.40	0.33, 0.48	0.90	0.78, 1.33	1.79	1.29, 2.51
4	Male	396	0.13	0.11, 0.14	0.04	0.03, 0.04	0.06	0.05, 0.07	0.12	0.11, 0.13	0.24	0.20, 0.29	0.53	0.44, 0.69	0.83	0.69, 1.40

Abbreviations: CI, confidence interval; GM, geometric mean; LIFE, Longitudinal Investigation of Fertility and the Environment; LOD, limit of detection; 4-OH-BP, 4-hydroxybenzophenone; 2,4-OH-BP, 2,4-dihydroxybenzophenone; 2,2′4,4′-OH-BP, 2,2′,4,4′-tetrahydroxybenzophenone; 2-OH-4-MeO-BP, 2-hydroxy-4-methoxybenzophenone; 2,2′-OH-4-MeO-BP, 2,2′-dihydroxy-4-methoxybenzophenone; UV, ultraviolet.

Table 3. Fecundability Odds Ratios According to Urinary Concentrations of Benzophenone-Type Ultraviolet Radiation Filters, by Partner Sex and Model, LIFE Study, 2005–2009[a]

UV Filter	Female Partners ($n = 454$)						Male Partners ($n = 439$)					
	Unadjusted Model[b]		Adjusted Model 1[c]		Adjusted Model 2[d]		Unadjusted Model[b]		Adjusted Model 1[c]		Adjusted Model 2[d]	
	FOR	95% CI	FOR	95% CI	FOR	95% CI	FOR	95% CI	FOR	95% CI	FOR	95% CI
BP-1 (2,4-OH-BP)	1.06	0.80, 1.40	1.13	0.85, 1.49	1.02	0.76, 1.37	1.06	0.79, 1.42	1.06	0.79, 1.43	0.97	0.71, 1.32
BP-2 (2,2′4,4′-OH-BP)	0.77	0.57, 1.04	0.81	0.60, 1.10	0.82	0.60, 1.12	0.66[e]	0.48, 0.90	0.70[f]	0.51, 0.95	0.69[f]	0.50, 0.95
BP-3 (2-OH-4-MeO-BP)	1.11	0.83, 1.47	1.21	0.91, 1.62	1.12	0.83, 1.53	1.20	0.90, 1.59	1.20	0.90, 1.59	1.10	0.81, 1.49
BP-8 (2,2′-OH-4-MeO-BP)	1.25	0.95, 1.65	1.34[f]	1.02, 1.78	1.20	0.89, 1.63	1.39[f]	1.04, 1.86	1.43[f]	1.07, 1.91	1.34	0.98, 1.83
4-OH-BP	0.83	0.61, 1.12	0.86	0.63, 1.16	0.77	0.56, 1.06	0.84	0.64, 1.11	0.85	0.65, 1.12	0.74[f]	0.54, 1.00

Abbreviations: CI, confidence interval; FOR, fecundability odds ratio; LIFE, Longitudinal Investigation of Fertility and the Environment; 4-OH-BP, 4-hydroxybenzophenone; 2,4-OH-BP, 2,4-dihydroxybenzophenone; 2,2′4,4′-OH-BP, 2,2′,4,4′-tetrahydroxybenzophenone; 2-OH-4-MeO-BP, 2-hydroxy-4-methoxybenzophenone; 2,2′-OH-4-MeO-BP, 2,2′-dihydroxy-4-methoxybenzophenone; UV, ultraviolet.

[a] Separate models were fitted for each UV filter and partner. Concentrations of UV filters were dichotomized at the 75th percentile, with the group corresponding to lower values serving as the referent. All models accounted for left-truncation or time off contraception.

[b] Adjusted for each partner's UV filter concentration (ng/mL; dichotomized) and urinary creatinine concentration (mg/dL; continuous).

[c] Adjusted for each partner's UV filter concentration (ng/mL; dichotomized), urinary creatinine concentration (mg/dL; continuous), and age (years; continuous).

[d] Adjusted for each partner's UV filter concentration (ng/mL; dichotomized), urinary creatinine concentration (mg/dL; continuous), age (years; continuous), body mass index (categorical; see Table 1), smoking status as defined by serum cotinine level (active exposure, passive exposure, or no exposure; see Table 1), season (winter, spring, summer, or fall), and research site (Michigan or Texas).

[e] $P < 0.01$ (*t* test).

[f] $P < 0.05$.

light of their short half-lives, which range in hours (35). As such, misclassification of exposure cannot be entirely eliminated from consideration. However, a recent Danish study assessing the temporal variability in nonpersistent chemicals in urine specimens (36) showed that the intraclass correlation coefficients (ICCs) for BP-3 (ICC = 0.69–0.80) were higher than those for bisphenol A (ICC = 0.10–0.42) or the sum of dichlorophenols (ICC = 0.39–0.72). A similar ICC for BP-3 (ICC = 0.62) was observed among pregnant women in Puerto Rico (37), though both ICCs were lower than that reported for

Table 4. Fecundability Odds Ratios According to Couples' Urinary Concentrations of Benzophenone-Type Ultraviolet Radiation Filters, by Model, LIFE Study, 2005–2009[a]

UV Filter	Unadjusted Model[b]				Adjusted Model 1[c]				Adjusted Model 2[d]			
	Females ($n = 424$)		Males ($n = 424$)		Females ($n = 424$)		Males ($n = 424$)		Females ($n = 424$)		Males ($n = 424$)	
	FOR	95% CI	FOR	95% CI	FOR	95% CI	FOR	95% CI	FOR	95% CI	FOR	95% CI
BP-1 (2,4-OH-BP)	1.10	0.81, 1.48	0.98	0.72, 1.34	1.16	0.86, 1.57	1.00	0.73, 1.38	1.08	0.78, 1.49	0.84	0.60, 1.18
BP-2 (2,2′4,4′-OH-BP)	0.88	0.64, 1.21	0.67[e]	0.48, 0.94	0.91	0.66, 1.26	0.70[e]	0.50, 0.98	0.89	0.64, 1.24	0.69[e]	0.49, 0.97
BP-3 (2-OH-4-MeO-BP)	1.07	0.78, 1.46	1.13	0.83, 1.54	1.16	0.85, 1.59	1.13	0.83, 1.55	1.11	0.79, 1.56	0.93	0.66, 1.30
BP-8 (2,2′-OH-4-MeO-BP)	0.80	0.57, 1.12	0.90	0.66, 1.22	0.81	0.58, 1.14	0.92	0.68, 1.25	0.79	0.56, 1.13	0.76	0.55, 1.06
4-OH-BP	1.18	0.85, 1.66	1.20	0.85, 1.70	1.25	0.89, 1.76	1.23	0.86, 1.75	1.20	0.83, 1.71	1.11	0.77, 1.60

Abbreviations: CI, confidence interval; FOR, fecundability odds ratio; LIFE, Longitudinal Investigation of Fertility and the Environment; 4-OH-BP, 4-hydroxybenzophenone; 2,4-OH-BP, 2,4-dihydroxybenzophenone; 2,2′4,4′-OH-BP, 2,2′,4,4′-tetrahydroxybenzophenone; 2-OH-4-MeO-BP, 2-hydroxy-4-methoxybenzophenone; 2,2′-OH-4-MeO-BP, 2,2′-dihydroxy-4-methoxybenzophenone; UV, ultraviolet.

[a] Concentrations of UV filters for both partners were dichotomized at the 75th percentile, with the group corresponding to lower values serving as the referent. All models accounted for left-truncation or time off contraception.

[b] Adjusted for both partners' UV filter concentrations (ng/mL; continuous) and urinary creatinine concentration (mg/dL; continuous).

[c] Adjusted for both partners' UV filter concentrations (ng/mL; continuous), urinary creatinine concentration (mg/dL; continuous), female partner's age (years; continuous), and difference between the partners' ages.

[d] Adjusted for both partners' UV filter concentrations (ng/mL; continuous), urinary creatinine concentration (mg/dL; continuous), female partner's age (years; continuous), difference between the partners' ages, couples' body mass index (categorical; see Table 1), season (winter, spring, summer, or fall), smoking status as defined by serum cotinine level (active exposure, passive exposure, or no exposure; see Table 1), and research site (Michigan or Texas).

[e] $P < 0.05$ (*t* test).

BP-3 (ICC = 0.81) in a study involving 4 Flemish couples (38). These data offer promise for the use of a single urine sample in epidemiologic research, but efforts utilizing longitudinal biospecimen collection for repeated measurements are needed. Finally, our findings are consistent with results from previous cohort studies focusing on other nonpersistent environmental chemicals, such as bisphenol A and phthalates, and various couple fecundity endpoints (39, 40). Previously, we reported diminished couple fecundity or a longer time to pregnancy in the LIFE Study for male concentrations of monomethyl, mono-*n*-butyl, and monobenzl phthalates but not female concentrations (41), and similarly so for both partners' exposures to persistent compounds (42). In future work, we will focus on trying to delineate signals from chemical mixtures, as methods for the analysis of complex chemical mixtures continue to evolve.

Other important study findings include our observed associations between BMI and cotinine and concentrations of BP-type UV filters, with the exception of a previously reported inverse relationship between urinary BP-3 levels and BMI (11). One possible explanation for a relationship between BP-type UV filters and BMI may be BMI's role as a proxy marker for outdoor activity and the use of sunscreen products, since active people have been reported to use more sunscreens than inactive people (43). As yet, we do not have an explanation for the association between UV filters and cotinine.

In sum, we found initial evidence that a higher male BP-2 concentration is associated with diminished couple fecundity, even when accounting for both partners' concentrations. Exposure of male partners to this BP-type filter may have implications for human fecundity, as reflected in a longer time to pregnancy.

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