Urinary Concentrations of Benzophenone-Type Filters and Couple Fecundity, LIFE Study

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Benzophenone-Type UV Filters

- Emerging class of environmental chemicals that absorb UV radiation… used in sunscreen & personal care products

- 29 UV-filters, limited information on biologic activity & health effects (not all in commercial use)
  - *In vivo* & *in vitro* evidence supports estrogenic & anti-androgenic biologic activity (Fang et al. 2000; Ma et al. 2003, Schreurs et al. 2005)
  - BP-1 associated with endometriosis (Kunisue et al. 2012)
  - BP-2 & hypospadias in mice (Hsieh et al. 2007)
  - Influence sex hormone signaling (Blair et al. 2000; Suzuki et al. 2005)

- Prevalent human exposure
  - BP-3 detected in 97% of participants in NHANES (Calafat et al. 2008)

Human Reproduction - Terminology

- Fecundity
  - Biologic capacity for human reproduction irrespective of pregnancy intentions
- Fertility
  - Demonstrated fecundity as measured by live (still) births

Research Aim

- To assess the association between 5 BP-filters & couple fecundity as measured by time-to-pregnancy.
  - Male partner
  - Female partner
  - Couple

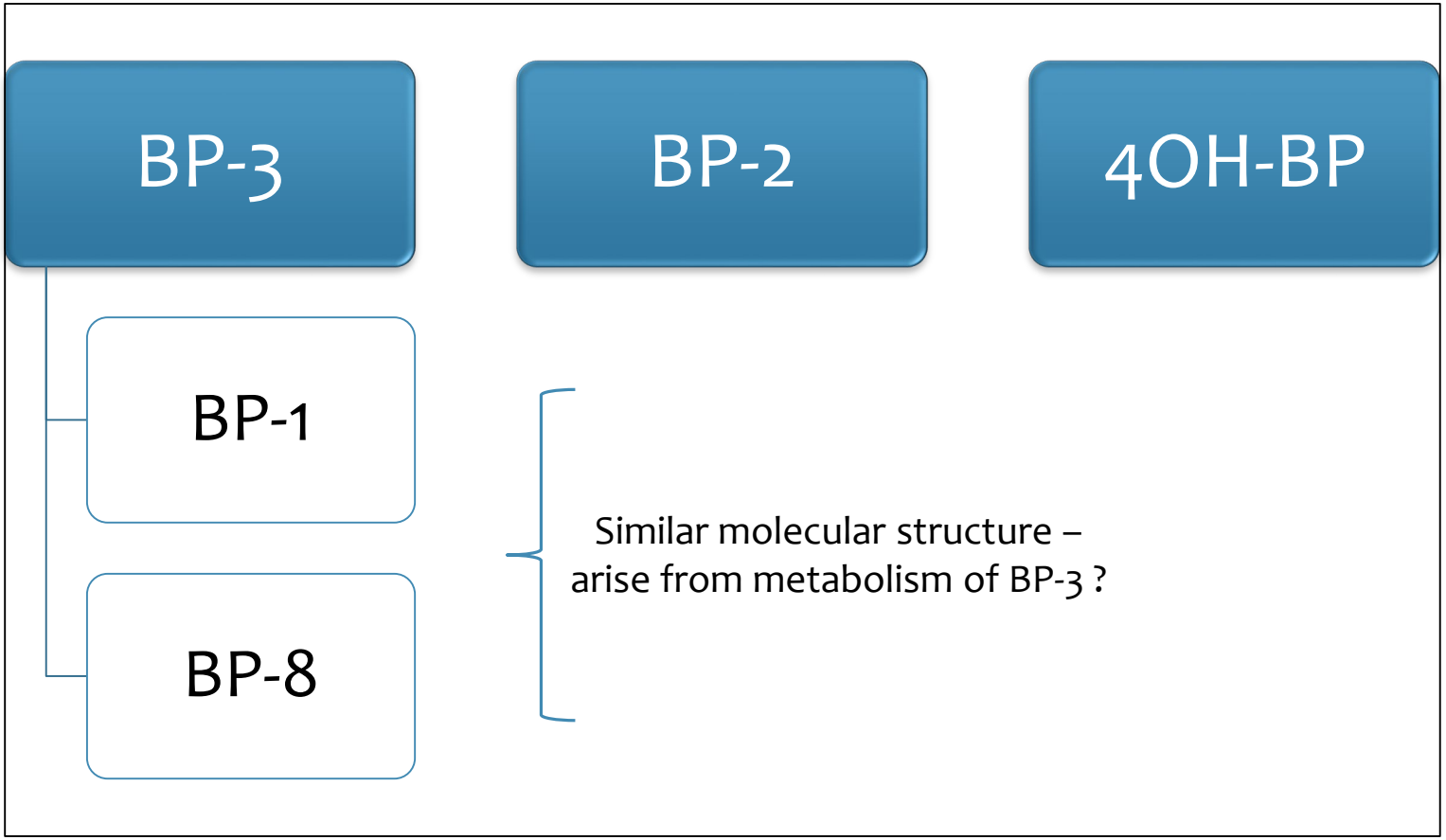
Methods

- Prospective cohort design with preconception recruitment of 501 couples
  - Population-based: 16 counties in Michigan & Texas
- Daily follow-up of couples until hCG pregnancy or 12 months of trying
  - Fertility monitor to help time intercourse
  - Digital home pregnancy tests
- Urine collection from both partners upon enrollment

Benzophenone-Type Filters

- Quantified (ng/mL) in urine using triple-quadrupole mass spectrometry*
  - **BP-1** [2,4-dihydroxybenzophenone]
  - **BP-2** [2,2',4,4'-tetrahydroxybenzophenone]
  - **BP-3** [2-hydroxy-4-methoxybenzophenone]
  - **BP-8** [2,2'-dihydroxy-4-methoxybenzophenone]
  - **4OH-BP** [4-hydroxybenzophenone]

*Zhang et al. 2011; Kunisue et al. 2010


BP-3
BP-2
4OH-BP
BP-1
BP-8
Similar molecular structure –
arise from metabolism of BP-3 ?

Statistical Analysis

- Fecundability odds ratios & 95% confidence intervals estimated for each UV filter and partner using Cox model for discrete survival time
  - BP-filters categorized at ≥75th percentile vs. lower
  - FORs <1.0 denote diminished fecundity or longer time-to-pregnancy
  - Modeling both partners' exposures, given low correlations (≤0.19)

FORs <1.0 denote diminished fecundability or a longer time-to-pregnancy

  - **serum cotinine** (no, passive, active smoking)
  - **season** (winter, spring, summer, fall)
  - **research site** (Michigan/Texas)

- Accounted for left truncation or time off contraception

- Couples censored at withdrawal or 12 months of trying

Findings

Description of Study Cohort (N=501)

Characteristic	Male Partners Median (IQR)	Female Partners Median (IQR)
Age (years)*	31 (28, 35)	29 (27, 33)
BMI (kg/m^2)*	29 (26, 32)	26 (23, 31)
Creatinine (mg/dl)*	140 (72, 201)	78 (35, 136)
Cotinine (ng/mL)*	0.04 (0.02, 1.49)	0.02 (0.01, 0.08)

* P <0.0001

Distribution of UV-Filters

BP-Filter (ng/mL)	Males (n=439) Median (IQR)	Females (n=454) Median (IQR)
BP-1*	**1.1 (0.4, 6.9)**	**4.2 (1.0, 18.1)**
BP-2	0.0 (0.0, 0.1)	0.1 (0.0, 0.2)
BP-3	2.4 (0.8, 13.9)	7.7 (1.9, 43.4)
BP-8	0.1 (0.0, 0.4)	0.1 (0.0, 0.9)
4OH-BP*	**0.1 (0.1, 0.2)**	**0.2 (0.1, 0.4)**

* P <0.05

Fecundability Odds Ratios - Partners

UV-Filters	Male Partners (n=439)		Female Partners (n=454)	
	FOR (CI)[a]	FOR (CI)[b]	FOR (CI)[a]	FOR (CI)[b]
BP-1	1.06 (0.79, 1.43)	0.97 (0.71, 1.32)	1.13 (0.85, 1.49)	1.02 (0.76, 1.37)
BP-2	**0.70 (0.51, 0.95)**	**0.69 (0.50, 0.95)**	0.81 (0.60, 1.10)	0.82 (0.60, 1.12)
BP-3	1.20 (0.90, 1.59)	1.10 (0.81, 1.49)	1.21 (0.91, 1.62)	1.12 (0.83, 1.53)
BP-8	**1.43 (1.07, 1.91)**	1.34 (0.98, 1.83)	**1.34 (1.02, 1.78)**	1.20 (0.89, 1.63)
4OH-BP	0.85 (0.65, 1.12)	**0.74 (0.54, 0.99)**	0.86 (0.63, 1.16)	0.77 (0.56,1.06)

[a]Age & creatinine adjusted; [b]Fully adjusted

Fecundability Odds Ratios - Couples

UV-Filters	Male Partners (n=439)		Female Partners (n=454)	
	FOR (CI)[a]	FOR (CI)[b]	FOR (CI)[a]	FOR (CI)[b]
BP-1	1.00 (0.73, 1.38)	0.84 (0.60, 1.18)	1.16 (0.86, 1.57)	1.08 (0.78, 1.49)
BP-2	**0.70 (0.50, 0.98)**	**0.69 (0.49, 0.97)**	0.91 (0.66, 1.26)	0.89 (0.64, 1.24)
BP-3	1.13 (0.83, 1.55)	0.93 (0.66, 1.30)	1.16 (0.85, 1.59)	1.11(0.79, 1.56)
BP-8	1.23 (0.86, 1.75)	1.11(0.77, 1.60)	1.25 (0.89, 1.76)	1.20 (0.83, 1.71)
4OH-BP	0.92 (0.68, 1.25)	0.76 (0.55, 1.06)	0.81 (0.58, 1.14)	0.79 (0.56, 1.13)

[a]Age & creatinine adjusted; [b]Fully adjusted

Summary

- Male partners' urinary BP-2 & 4OH-BP concentrations associated with ≈30% reduction in fecundability
  - FOR=0.69; 95% CI=0.50, 0.95
  - FOR=0.74; 95% CI=0.54, 1.00

- Male partner's BP-2 concentration remained after accounting for female's concentration
  - FOR=0.69; 95% CI=0.49, 0.97

Summary - continued

- Findings await corroboration including longitudinal measurement of exposures
  - ICCs for BP-3 range from 0.62 to 0.80, and are higher than BPA & dichlorophenols (Meeker et al. 2013; Lassen et al. 2013; Koch et al. 2014)

- Mechanism(s) uncertain
  - Estrogenic potencies 1,000 -100,000 times lower than 17-β-estradiol, yet higher than other xenoestrogens such as BPA (Kawamura et al. 2003)
  - Sex specific vulnerabilities or differences in metabolism

Could semen quality be the pathway to diminished fecundability?

35 endpoints:
5 general, 8 motility, 6 sperm head, 14 morphology
& 2 sperm chromatin stability assay

BP-Filters & Semen Quality Endpoints

Semen Endpoint	BP-1 β (SE)	BP-2 β (SE)	BP-3 β (SE)	BP-8 β (SE)	4OH-BP β (SE)
Volume			0.15 (0.1)		
Sperm count		-0.70 (0.3)			
% Straightness		-4.71 (2.0)			
% Linear		-3.20 (1.3)			
% Immature		0.32 (0.1)*			0.26 (0.1)*
% Acrosome (area of head)				1.18 (0.5)	
% Megalo head		0.22 (0.1)*			
% Pyriform				0.30 (0.1)*	

Linear regression with fixed & random effects; BP-filters dichotomized at 75th percentile & adjusted for age, BMI, serum cotinine, research site with Box-Cox transformation of relevant semen quality endpoints (n=413). P-values <0.05 unless otherwise noted (*p ≤0.01).

Thank you….