Published in final edited form as:

J Hazard Mater. 2017 February 5; 323(Pt A): 177–183. doi:10.1016/j.jhazmat.2016.03.028.

Association of birth outcomes with fetal exposure to parabens, triclosan and triclocarban in an immigrant population in Brooklyn, New York

Laura A. Geer^{a,*}, Benny F.G. Pycke^b, Joshua Waxenbaum^a, David M. Sherer^c, Ovadia Abulafia^c, and Rolf U. Halden^{b,d}

^aDepartment of Environmental and Occupational Health Sciences, State University of New York, Downstate School of Public Health, BOX 43, 450 Clarkson Ave., Brooklyn, NY, USA

^bCenter for Environmental Security, The Biodesign Institute, Global Security Initiative, and School of Sustainable Engineering and the Built Environment, Arizona State University, 781 East Terrace Mall, Tempe, AZ 85287, USA

^cDepartment of Obstetrics and Gynecology, State University of New York Downstate Medical Center, 445 Lenox Road, Brooklyn, NY, USA

^dDepartment of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, 615 North Wolfe Street, Baltimore, MD 21205, USA

Abstract

Background—Prior studies suggest associations between fetal exposure to antimicrobial and paraben compounds with adverse reproductive outcomes, mainly in animal models. We have previously reported elevated levels of these compounds for a cohort of mothers and neonates.

Objective—We examined the relationship between human exposure to parabens and antimicrobial compounds and birth outcomes including birth weight, body length and head size, and gestational age at birth.

Methods—Maternal third trimester urinary and umbilical cord blood plasma concentrations of methylparaben (MePB), ethylparaben (EtPB), propylparaben (PrPB), butylparaben (BuPB), benzylparaben (BePB), triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether or TCS) and triclocarban (1-(4-chlorophenyl)-3-(3,4-dichlorophenyl) urea or TCC), were measured in 185 mothers and 34 paired singleton neonates in New York, 2007–2009.

Results—In regression models adjusting for confounders, adverse exposure-outcome associations observed included increased odds of PTB (BuPB), decreased gestational age at birth (BuPB and TCC) and birth weight (BuPB), decreased body length (PrPB) and protective effects on

*Corresponding author at: Environmental and Occ. Health Sciences, SUNY Down-state School of Public Health, 450 Clarkson Ave Box 43, Brooklyn, NY 11203-2098, USA. laura.geer@downstate.edu (L.A. Geer).

Competing financial interests

The authors declare no competing financial interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jhazmat.2016.03.028>.

PTB (BePB) and LBW (3'-Cl-TCC) ($p < 0.05$). No associations were observed for MePB, EtPB, or TCS.

Conclusions—This study provides the first evidence of associations between antimicrobials and potential adverse birth outcomes in neonates. Findings are consistent with animal data suggesting endocrine-disrupting potential resulting in developmental and reproductive toxicity.

Keywords

Exposure; Antimicrobials; Parabens; Birth outcomes

1. Introduction

Various classes of environmental phenols including parabens, triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether; TCS), and the (non-phenolic) carbanilide triclocarban (1-(4-chlorophenyl)-3-(3,4-dichlorophenyl)urea; TCC), have the propensity to cause hormonal disturbances in both *in utero* and *ex utero* development. Exposure to these compounds occurs primarily through use of cosmetics and antimicrobial consumer products in adults and, in neonates, ingestion of breast milk containing chemical residues. Numerous studies have been conducted that examined the presence of parabens [1], TCC [2] and TCS [3] in human blood at significant levels following the use of personal care products containing these compounds. Estrogenic effects from exposure to phenols have been documented [4], including decreases in body length [5] and effects on birth weight [6] in humans, and disruptions in the reproductive endocrine system in relevant animal models, as well as early onset of puberty in sheep [7]. *In vitro* assays have allowed for the identification of antagonistic activity of androgen receptors for compounds such as TCC [8]. These data provide sufficient grounds to investigate occurrence of adverse reproductive effects on humans at typical levels of exposure.

Parabens are a class of chemicals used in cosmetics and food-stuffs as preservatives and known to affect the endocrine system. Similar to other phenols, parabens and butyl paraben (BuPB) in particular have been found to exhibit estrogenic properties [9] in both human and murine studies, directly binding to estrogen receptors, albeit at an efficacy 10,000 weaker than 17 β -estradiol and to a lower biological effect than phenols [10,12]. These compounds have been found to exhibit antiandrogenic properties *in vitro* with an androgen receptor-mediated transcriptional activity assay [20]. Parabens have also been found to promote murine adipocyte differentiation in *in vitro* assays, which may explain the increased birth weight associated with their presence in human maternal urine samples [11]. Paraben exposure has been linked to the disruption of uterine blastocyst implantation in mice [12], and decreases in sperm count as a result of maternal exposure to butylparaben in the diet of rats [13], lending evidence to the reproductive toxic potential of parabens.

The antibacterial agents TCS and TCC, commonly used in numerous products from personal care to industrial cleaning, have also been shown to exhibit endocrine-disrupting potential. For example, in a recent cohort study, Philippat et al. [6] found an inverse correlation between increases in TCS levels in maternal urine and decreases in neonate head circumference (correlation coefficient = 0.5–0.6). Various studies have revealed several other

associations, such as TCS exposure being associated with a reduction of thyroxine (T4) in female Long-Evans and Wistar rats [14,15], the sensitization of body tissue toward allergens in humans [16], and the inhibition of muscle function in mice [17]. Structural similarities between TCS and thyroid hormones may serve to explain this action [14]. In a study looking at exposure and birth outcomes, TCS was inversely associated with body length and birth weight, but this result was only seen in young males [18]. TCC is more often found as an antimicrobial in soaps and its associated metabolites have been discovered at quantifiable amounts in urine samples after exposure from soap use during even a single shower [19]. TCC is also a strong inhibitor of epoxide hydrolase [2], an enzyme involved in the process of cholesterol synthesis [20]. In rats, TCC has an effect of increasing the size of male sex accessory organs [21], likely through synergism with the androgen hormone receptor ligand [22]. Liver tumor formation has been associated with TCS exposure of mice following oral dosing [23]. In this paper, we explored the extent of human fetal exposure to the above endocrine-disrupting preservatives and antimicrobials with particular focus on associations with a range of potential adverse birth outcomes identified previously mostly in animal models.

2. Materials and methods

2.1. Cohort and sampling procedure

Archived samples of third trimester maternal urine (6–9th month) and human cord blood plasma, collected at two different time points, were used in this work and originated from an urban immigrant population investigated previously for prenatal exposure to mercury [24] and to the antimicrobials triclosan and triclocarban [25]. This previous study details the sampling procedures and cohort descriptors. Pregnant women (aged 18–45 years) were recruited at the University Hospital of Brooklyn's Prenatal Clinic between October 2007 and December 2009. From the original cohort of 191, the final cohort included 185 pregnant women and singleton infants after excluding non-singleton ($n = 4$) and improbable birth weight/gestational age at birth combinations ($n = 2$) [24,25]. Random "spot" urine specimens were provided once per participant during the 6–9th month of pregnancy. A convenience subset of participants were followed to delivery, at which time an umbilical cord blood specimen was collected from the neonate for plasma isolation and storage at -80°C for subsequent lab analysis ($n = 38$). Maternal urinary concentrations were measured of each of the paraben compounds targeted, including methylparaben (MePB), ethylparaben (EtPB), propylparaben (PrPB), butylparaben (BuPB) and benzylparaben (BePB), as well as TCS and TCC (Table S1) (see Supplemental Material). Specimens from humans were collected in polypropylene vials. A random subset of umbilical blood plasma samples ($n = 21$) was analyzed for both free and total concentrations of parabens, as the sample cups had not been pre-screened for the presence of target analytes. A previously developed questionnaire was used [24] to ascertain demographic data, including maternal age, nativity, race/ethnic origin, and education level, medical history, and to assess sources of environmental exposure (*i.e.*, mercury). Neonate outcome data were collected from the patient's chart. The study and protocol were approved by the Institutional Review Boards (IRBs) of the State University of New York Downstate Medical Center, and of the New York

State Department of Health. Each participant signed an informed consent form prior to participation.

2.2. Chemical analysis

The samples were shipped on dry ice to Arizona State University and archived at -80°C . Urine aliquots of 2 mL were measured for creatinine [24]. Specimens (1 mL of material urine or 100 μL of cord blood plasma) were thawed, spiked with a solution containing six isotope-labeled standards (10 μL) as well as a solution containing two hydrolysis standards (50 μL), and diluted with a solution containing hydrolysis enzymes (1 mL). A detailed description of the standards and reagents used can be found in our prior studies [25,26]. An additional 900 μL MS-grade water was added to the umbilical cord blood samples. Target analytes were extracted using 60 mg Oasis HLB (Waters, Milford, MA) solid-phase extraction cartridges.

Extraction Procedure for TCS and TCC. To perform isotope dilution and hydrolysis of phase-II metabolites of TCS and TCC [2] for total concentration determination of TCS, TCC, 2'-OH-TCC, 3'-OH-TCC, and 3'-Cl-TCC, the biological samples (1 mL of material urine or 100 μL of cord blood plasma) were thawed, spiked with a mixed solution of isotope-labeled standards (10 μL) and a hydrolysis standard solution (50 μL), and diluted with enzyme solution (1 mL). An additional 900 μL of MS-grade water was added to the cord blood samples. Analytes were extracted using a 24-port Visiprep vacuum manifold (Supelco, St. Louis, MO) and 60 mg of Oasis HLB (Waters, Milford, MA) solid-phase extraction cartridges.

Extraction Procedure for Parabens. For parabens analysis, methanolic extracts were diluted 1 + 1 with water. Aliquots of 100 μL were injected onto a liquid chromatography triple quadrupole tandem mass spectrometer (LC-MS/MS; API 4000, ABSciex, Framingham, MA). For antimicrobials analysis, individual stock solutions of the native and isotopically labeled compounds were prepared in methanol.

All analytes and their respective labeled standards were identified using their specific retention time and two multiple reaction monitoring transitions [25,26]. All extractions were performed along with solvent blanks, reagent blanks, and instrument performance standards as reported in Pycke et al. [25,26].

2.3. Statistical analyses

Due to their non-normal distribution, urinary biomarker concentrations were log-transformed prior to analysis. Non-detect values were treated as the method detection limit (MDL) divided by the square root of two, and were imputed for all compounds except for TCS, PrPB and MePB, for which there were no non-detects. Maternal urinary biomarker levels were corrected for creatinine (micrograms per gram creatinine; $\mu\text{g/g}$) to normalize for urine dilution [18]. Covariates were selected for the final models if they achieved a $p < 0.05$ in Spearman correlations or Chi-square tests in relation to biomarker levels or birth outcomes. Predictors of birth outcomes (*i.e.*, body length, gestational age at birth, birth weight, head circumference) were analyzed using generalized linear models. We used multiple linear regression to evaluate pollutant-outcomes associations adjusted for the

possible confounders. Model confounders considered included maternal age, nativity, neonate gender, alcohol and tobacco. We adjusted for confounders that were independently associated with the outcomes variable, or which changed the magnitude of the effects size by at least 5% when included in multiple linear regression models. Co-occurring pollutants that were not highly correlated (correlation coefficient = <0.6) were adjusted for in final multi-pollutant models. The relationship between pollutant predictors and the dichotomous outcomes preterm birth (PTB), birth at <37 weeks, and low birth weight (LBW), birth weight $<2,500$ g, were analyzed using logistic regression. All statistical tests were evaluated at the significance level of $p < 0.05$, using SPSS v. 22 software (IBM, Armonk, NY).

3. Results

A subset of samples from the original maternal and neonate cohort were included in the antimicrobial and paraben analyses ($n = 185$ and $n = 34$, respectively) [24–26]. A number of respondents were missing data for creatinine ($n = 20$ observations) and for birth parameters ($n = 20$ observations). The prevalence of LBW was 17.2% and for PTB was 23.3% ($n = 163$). Maternal urinary and cord blood plasma pollutant levels by demographic factor can be found in Tables 1 and 2. Pollutant levels by quartile are located in Table S2. We reported creatinine-corrected urinary pollutant levels for all analyses. All creatinine values fell between >20 and <275 mg/dL. In adjusted, linear regression models (significance level $p < 0.05$), cord blood plasma PrPB was associated with decreased body length ($\beta = -1.06$ 95% CI $-2.06, -0.05$), and plasma TCC and BuPB were associated with decreased gestational age at birth, in weeks ($\beta = -2.15$ 95% CI $-3.91, -0.40$; $\beta = -3.04$ 95% CI $-5.09, -0.99$, respectively; Tables 4). Cord blood plasma BuPB was associated with increased odds of preterm birth (PTB) with an odds ratio (OR) of ($OR = 60.77$, 95% CI 2.60, 1417.93) (Table 5). Cord blood plasma BuPB was marginally associated with decreased birth weight ($\beta = -480.40$, 95% CI $-976.68, 15.89$) ($p = 0.057$). Urine BuPB was associated with decreased gestational age at birth ($\beta = -0.36$, 95% CI $-0.72, -0.01$ Table 3). We further explored these protective effects by summing urinary TCC and congeners into one parameter for the model. Results were no longer significant using the summed parameter.

In a sensitivity analysis, there was little change to parameter estimates when modeling creatinine-corrected versus for creatinine adjustment as a separate variable in the analyses. In the sensitivity analysis, urinary BuPB, PrPB and 2'-OH-TCC were marginally significantly associated with decreased body length. Cord blood plasma TCC was no longer associated with gestational age at delivery.

4. Discussion

This is the first time human fetal data for TCC and its metabolites have been assessed for prenatal exposure and potential adverse birth outcomes. In our study, pollutant levels were associated with increased odds of PTB (BuPB), decreased gestational age at birth (BuPB and TCC) and birth weight (BuPB), decreased body length (PrPB) and protective effects on PTB (BePB) and LBW (3'-CI-TCC). No associations were observed for MePB, EtPB, or TCS. Decreases in these growth parameters could serve as a precursor to additional adverse outcomes in early childhood and throughout the life course. Findings, such as for BuPB,

may be considered most robust for associations that were observed across both matrices (and in the same direction).

The ubiquitous nature of these endocrine-disrupting compounds in female-directed cosmetic and personal care products places neonates at high risk for exposure. A multitude of studies have been performed on the *in utero* effects of phenolic environmental compounds, many of which focus on bisphenol A (BPA). Research on such compounds often produced results similar to those found in this study. Tang et al. [5] found that increased exposure to BPA was associated with decreased gestational age at birth in boys, as was found with BuPB in the current study in both genders. BuPB was also associated with decreased birth weight. In contrast, BePB was protective for gestational age at birth, with similar effects seen in Philippat et al. [6] demonstrating a protective effect on weight. Parabens have been positively associated with subsequent infant weight throughout the first three years of life, suspected to be caused by the estrogenic action of these compounds [6].

In a prior study by Wolf et al. [18] TCS was associated with low birth weight and shorter body length in boys ($n = 339$), whereas in our study we found no association. In Philippat et al. [6], TCS was negatively associated with head circumference. Thus contrasting data on TCS calls for more study on the potential for adverse birth outcomes.

Various mechanisms have been proposed to account for the observed pollutant associations with birth outcomes. Watkins et al. [27] have proposed mechanisms including oxidative stress, and found associations between both levels of bisphenol A (BPA) and paraben compounds, and increased oxidative stress. Oxidative stress has been found to promote fetal growth restriction and low birth weight, along with several maternal pregnancy-related disorders, and additional adverse health effects for the child later in life [28]. Watkins et al. [27] also observed an association between TCS and elevated IL-6 levels. IL-6 is an inflammatory cytokine that has been linked to similar negative outcomes, primarily PTB [29]. Causal associations of these observations remain unproven. Various studies have explored groups of compounds known to elicit endocrine-disrupting effects in both parents and offspring. Schiffer et al. [30] examined the effects of 96 endocrine-disrupting chemicals (EDCs) on human sperm. One of the most notable EDC's from this study, TCS, activates a specific CatSper channel of principal import for regulating calcium in mammalian sperm, responsible for motility. EDCs such as TCS compete with progesterone and prostaglandins to block CatSper activation, essentially desensitizing sperm. Such effects may negatively impact fertility, highlighting concerns with reproductive outcomes in these compounds. In a recent fertility study, Dodge et al. [31] found that paternal urinary phenol (namely, methyl paraben) was associated with decreased odds of live birth. Kennedy et al. [32] exposed rats to different concentrations of TCC during lactation and documented significant post-parturition effects on offspring. These cases provide grounds for a thorough longitudinal study in which parent-child pairs would be followed from conception through early adolescence to more fully understand the effects of these compounds.

Our study has limitations. Maternal urine was used as a proxy for fetal exposure, except where neonate cord blood plasma was available as a measure of internal dose. The timing of sampling may have biased results, as product use contributing to exposure may differ over

the course of the pregnancy, and contaminant levels may fluctuate with changing water retention profiles [18]. Though it can reasonably be assumed that levels found in our study for the third trimester were representative of exposure at other time points across the duration of pregnancy, as Mortensen et al. [33] found consistent levels of environmental phenols during different time points of pregnancy, several other studies demonstrate that multiple urine levels may be more appropriate to capture inter-individual variability and to adequately characterize longer-term exposure due to the short half-life of some of these compounds [1,3,34]. However, there is some degree of confidence in our findings of BuPB associations in both matrices (urine and cord blood plasma), indicating that similar doses were delivered to different tissue departments resulting in similar outcomes. This is less so for compounds without a matching cord blood plasma sample. Because the urine specimen collection predated the cord blood plasma collection, it can also be posited that having two determinations of exposure to a relatively short-lived compound increases our confidence that we have characterized variability in exposure at these different time points. Because we performed multiple data comparisons, we cannot rule out findings due to chance. The sample size of this study limits the ability to identify significant associations. Likewise, the homogeneity of our participant population may affect study generalizability. Additionally, our co-pollutant models did not include other pollutant compounds such as BPA and flame retardants that have been previously associated with endocrine disruption [35,36]. Findings reported here for a rather limited study cohort on both adverse (BuPB) and protective outcomes (BePB, 3'-Cl-TCC) from human exposure to antimicrobial compounds should be verified with larger, additional studies.

5. Conclusions

In summary, our study in an urban immigrant sub-population identified potential adverse birth outcomes in humans, such as reductions in birth weight, gestational age at birth and body length, as well as LBW and PTB. Such effects on reproduction were observed previously only in animal models after considerable dosing. The Endocrine Society summarizes the impact of EDCs on developmental outcomes, with an emphasis on further need for focus on effects in human epidemiological studies [35]. Similarly, the International Federation of Gynecology and Obstetrics emphasizes the need for better understanding reproductive health impacts from exposure to toxic environmental chemicals, particularly EDCs [36]. Our study found in humans, adverse effect associations that are consistent with those observed previously in tissue and animal models and human studies. Results challenge a continuation of investigations into reproductive effects and birth outcomes associated with exposure to ingredients of common consumer products of endocrine-disrupting potential.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We acknowledge Dr. Carl Rosenberg for his consultation on the statistical analyses.

Funding sources

This project was supported in part by Award Numbers R01ES015445, R01ES020889 and their supplements from the National Institute of Environmental Health Sciences (NIEHS) and by award number LTR 05/01/12 from the Virginia G. Piper Charitable Trust. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

References

1. Braun JM, Just AC, Williams PL, Smith KW, Calafat AM, Hauser R. Personal care product use and urinary phthalate metabolite and paraben concentrations during pregnancy among women from a fertility clinic. *J. Expo. Sci. Environ. Epidemiol.* 2014; 24:459–466. <http://dx.doi.org/10.1038/jes.2013.69>. [PubMed: 24149971]
2. Schebb NH, Inceoglu B, Ahn KC, Morisseau C, Gee SJ, Hammock BD. Investigation of human exposure to triclocarban after showering and preliminary evaluation of its biological effects. *Environ. Sci. Technol.* 2011; 45:3109–3115. <http://dx.doi.org/10.1021/es103650m>. [PubMed: 21381656]
3. Engel LS, Buckley JP, Yang G, Liao LM, Satagopan J, Calafat AM, et al. Predictors and variability of repeat measurements of urinary phenols and parabens in a cohort of shanghai women and men. *Environ. Health Perspect.* 2014; 122(7):733–740. <http://dx.doi.org/10.1289/ehp.1306830>. [PubMed: 24659570]
4. Fang H, Tong W, Perkins R, Soto AM, Prechti NV, Sheehan DM. Quantitative comparisons of in vitro assays for estrogenic activities. *Environ. Health Perspect.* 2000; 108(8):723–729. [PubMed: 10964792]
5. Tang R, Chen MJ, Ding GD, Chen XJ, Han XM, Zhou K, et al. Associations of prenatal exposure to phenols with birth outcomes. *Environ. Pollut.* 2013; 178:115–120. <http://dx.doi.org/10.1016/j.envpol.2013.03.023>. [PubMed: 23562958]
6. Philippat C, Botton J, Calafat AM, Ye X, Charles M, Slama R. Prenatal exposure to phenols and growth in boys. *Epidemiology.* 2014; 25:625–635. <http://dx.doi.org/10.1097/ede.000000000000132>. [PubMed: 25061923]
7. Savabieasfahani M, Kannan K, Astapova O, Evans NP, Padmanabhan V. Developmental programming: differential effects of prenatal exposure to bisphenol-A or methoxychlor on reproductive function. *Endocrinology.* 2006; 147:5956–5966. <http://dx.doi.org/10.1210/en.2006-0805>. [PubMed: 16946013]
8. Lee HJ, Chattopadhyay S, Gong EY, Ahn RS, Lee K. Antiandrogenic effects of bisphenol A and nonylphenol on function of androgen receptor. *Toxicol. Sci.* 2003; 75:40–46. <http://dx.doi.org/10.1093/toxsci/kfg150>. [PubMed: 12805653]
9. Golden R, Gandy J, Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. *Crit. Rev. Toxicol.* 2005; 35:435–458. [PubMed: 16097138]
10. Routledge EJ, Parker K, Odum J, Ashby J, Sumpter JP. Some alkyl hydroxyl benzoate preservatives (parabens) are estrogenic. *Toxicol. Appl. Pharmacol.* 1998; 153:12–19. [PubMed: 9875295]
11. Hu P, Chen X, Whitener RJ, Boder ET, Jones JO, Porollo A, et al. Effects of parabens on adipocyte differentiation. *Toxicol. Sci.* 2013; 131:56–70. <http://dx.doi.org/10.1093/toxsci/kfs262>. [PubMed: 22956630]
12. Shaw J, deCatanzaro D. Estrogenicity of parabens revisited: impact of parabens on early pregnancy and an uterotrophic assay in mice. *Reprod. Toxicol.* 2009; 28:26–31. <http://dx.doi.org/10.1016/j.reprotox.2009.03.003>. [PubMed: 19490991]
13. Oishi S. Effects of propyl paraben on the male reproductive system. *Food Chem. Toxicol.* 2002; 40:1807–1813. [PubMed: 12419695]
14. Crofton KM, Paul KB, Devito MJ, Hedge JM. Short-term in vivo exposure to the water contaminant triclosan: evidence for disruption of thyroxine. *Environ. Toxicol. Pharmacol.* 2007; 24:194–197. <http://dx.doi.org/10.1016/j.etap.2007.04.008>. [PubMed: 21783810]
15. Zorrilla LM, Gibson EK, Jeffay SC, Crofton KM, Setzer WR, Cooper RL, Stoker TE. The effects of triclosan on puberty and thyroid hormones in male wistar rats. *Toxicol. Sci.* 2009; 107:56–64. <http://dx.doi.org/10.1093/toxsci/kfn225>. [PubMed: 18940961]

16. Savage JH, Matsui EC, Wood RA, Keet CA. Urinary levels of triclosan and parabens are associated with aeroallergen and food sensitization. *J. Allergy Clin. Immunol.* 2012; 130:453–460. <http://dx.doi.org/10.1016/j.jaci.2012.05.006>. [PubMed: 22704536]
17. Cherednichenko G, Zhang R, Bannister RA, Timofeyev V, Li N, Fritsch EB, et al. Triclosan impairs excitation-contraction coupling and Ca^{2+} dynamics in striated muscle. *Proc. Natl. Acad. Sci. U. S. A.* 2012; 109:14158–14163. <http://dx.doi.org/10.1073/pnas.1211314109>. [PubMed: 22891308]
18. Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, et al. Prenatal phenol and phthalate exposures and birth outcomes. *Environ. Health Perspect.* 2008; 116:1092–1097. [PubMed: 18709157]
19. Schebb NH, Ahn KC, Dong H, Gee SJ, Hammock BD. Whole blood is the sample matrix of choice for monitoring systemic triclocarban levels. *Chemosphere.* 2012; 87:825–827. <http://dx.doi.org/10.1016/j.chemosphere.2011.12.077>. [PubMed: 22273184]
20. Morisseau C, Hammock BD. Impact of soluble epoxide hydrolase and epoxyeicosanoids on human health. *Annu. Rev. Pharmacol. Toxicol.* 2013; 53:37–58. <http://dx.doi.org/10.1146/annurev-pharmtox-011112-140244>.
21. Chen J, Ahn KC, Gee NA, Ahmed MI, Duleba AJ, Zhao L, et al. Triclocarban enhances testosterone action: a new type of endocrine disruptor? *Endocrinology.* 2007; 149:1173–1179. <http://dx.doi.org/10.1210/en.2007-1057>. [PubMed: 18048496]
22. Jansen NS, Nagel SC, Miranda PJ, Lobenhofer EK, Afshari CA, McDonnell DP. Short-chain fatty acids enhance nuclear receptor activity through mitogen-activated protein kinase activation and histone deacetylase inhibition. *Proc. Natl. Acad. Sci. U. S. A.* 2004; 101:7199–7204. [PubMed: 15103026]
23. Yueh MF, Taniguchi K, Chen S, Evans RM, Hammock BD, Karin M, Tukey RH. The commonly used antimicrobial additive triclosan is a liver tumor promoter. *Proc. Natl. Acad. Sci. U. S. A.* 2014; 111:17200–17205. <http://dx.doi.org/10.1073/pnas.1419119111>. [PubMed: 25404284]
24. Geer LA, Persad MD, Palmer CD, Steuerwald AJ, Dalloul M, Abulafia O, et al. Assessment of prenatal mercury exposure in a predominately Caribbean immigrant community in Brooklyn, NY. *J. Environ. Monit.* 2012; 14:1035–1043. <http://dx.doi.org/10.1039/c2em10835f>. [PubMed: 22334237]
25. Pycke BFG, Geer LA, Dalloul M, Abulafia O, Jenck AM, Halden RU. Human fetal exposure to triclosan and triclocarban in an urban population from Brooklyn, New York. *Environ. Sci. Technol.* 2014; 48:8831–8838. <http://dx.doi.org/10.1021/es501100w>. [PubMed: 24971846]
26. Pycke BFG, Geer LA, Dalloul M, Abulafia O, Halden RU. Maternal and fetal exposure to parabens in a multiethnic urban U.S. population. *Environ. Int.* 2015; 84:193–200. <http://dx.doi.org/10.1016/j.envint.2015.08.012>. [PubMed: 26364793]
27. Watkins DJ, Ferguson KK, Anzalota Del Toro LV, Alshawabkeh AN, Cordero JF, Meeker JD. Associations between urinary phenol and paraben concentrations and markers of oxidative stress and inflammation among pregnant women in Puerto Rico. *Int. J. Hyg. Environ. Health.* 2015; 218:212–219. <http://dx.doi.org/10.1016/j.ijheh.2014.11.001>. [PubMed: 25435060]
28. Barker DJP. Maternal nutrition, fetal nutrition, and disease in later life. *Nutrition.* 1997; 13:807. [PubMed: 9290095]
29. Prins JR, Gomez-Lopez N, Robertson SA. Interleukin-6 in pregnancy and gestational disorders. *J. Reprod. Immunol.* 2012; 95:1–14. <http://dx.doi.org/10.1016/j.jri.2012.05.004>. [PubMed: 22819759]
30. Schiffer C, Müller A, Egeberg DL, Alvarez L, Brenker C, Rehfeld A, et al. Direct action of endocrine disrupting chemicals on human sperm. *EMBO Rep.* 2014; 15(7):758–765. <http://dx.doi.org/10.15252/embr.201438869>. [PubMed: 24820036]
31. Dodge LE, Williams PL, Williams MA, Missmer SA, Toth TL, Calafat AM, et al. Paternal urinary concentrations of parabens and other phenols in relation to reproductive outcomes among couples from a fertility clinic. *Environ. Health Perspect.* 2015; 123(7):665–671. [PubMed: 25767892]
32. Kennedy RC, Menn FM, Healy L, Fecteau KA, Hu P, Bae J, et al. Early life triclocarban exposure during lactation affects neonate rat survival. *Reprod. Sci.* 2015; 22:75–89. <http://dx.doi.org/10.1177/1933719114532844>. [PubMed: 24803507]

33. Mortensen ME, Calafat AM, Ye X, Wong LY, Wright DJ, Pirkle JL, et al. Urinary concentrations of environmental phenols in pregnant women in a pilot study of the national children's study. *Environ. Res.* 2014; 129:32–38. <http://dx.doi.org/10.1016/j.envres.2013.12.004>. [PubMed: 24529000]
34. Meeker JD, Cantonwine DE, Rivera-González LO, Ferguson KK, Mukherjee B, Calafat AM, et al. Distribution, variability, and predictors of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico. *Environ. Sci. Technol.* 2013; 47(7):3439–3447. <http://dx.doi.org/10.1021/es400510g>. [PubMed: 23469879]
35. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. Executive summary to EDC-2: the endocrine society's second scientific statement on endocrine-disrupting chemicals. *Endocr. Rev.* 2015 <http://dx.doi.org/10.1210/er.2015-1093>.
36. Di Renzo GC, Conry JA, Blake J, DeFrancesco MS, DeNicola N, Martin JN Jr, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int. J. Gynecol. Obstet.* 2015 Sept. <http://dx.doi.org/10.1016/j.ijgo.2015.09.002>

Table 1

Geometric mean levels of biomarkers in cord blood plasma ($\mu\text{g/L}$) by maternal population characteristics and risk factors ($n = 34$).

Variable	Category	TCS	TCC	EPB	PrPB	BuPB
Age	24 Years	1.02	0.07	0.11	0.12	0.05
	25–29 Years	3.62	0.07	0.09	1.25	0.07
	30–34 Years	2.19	0.04	0.34	0.22	0.02
	35 Years	1.62	0.04	0.39	0.64	0.03
Education	Some	2.35	0.06	0.29	0.19	0.04
	High school	1.83	0.05	0.09	0.78	0.04
	Tech or more	1.46	0.07	0.12	0.27	0.05
	African American	1.70	0.08	0.12	0.29	0.04
Race/ethnicity	Caribbean	1.91	0.05	0.14	0.70	0.05
	African	3.27	0.04	1.58	0.24	0.05
	Other	9.98	0.04	0.06	0.03	0.02
	Latino	0.72	0.07	0.06	0.20	0.07
	No	1.73	0.06	0.13	0.27	0.04
Alcohol	Yes	1.29	0.04	0.40	3.03	0.05
	No	1.74	0.06	0.13	0.30	0.04
Tobacco	Yes	0.78	0.04	0.57	1.06	0.03
	Female	1.93	0.07	0.16	0.43	0.05
Gender	Male	1.67	0.05	0.13	0.21	0.04
	Yes	1.23	0.08	0.11	0.43	0.05
US Born	No	2.66	0.05	0.18	0.27	0.04

Geometric mean levels of biomarkers in maternal urine by population characteristics and risk factors (n = 184) ($\mu\text{g/g}$, creatinine corrected urine levels).

Table 2

Variable	Category	TCS	TCC	2'-OH-TCC	3'-OH-TCC	3'-Cl-TCC	EPB	PrPB	BuPB	MePB
Age	24 years	7.08	0.217	0.011	0.005	0.004	0.393	29.38	0.176	109.25
	25–29 years	11.04	0.156	0.011	0.005	0.004	0.652	47.73	0.251	191.14
	30–34 years	11.57	0.174	0.015	0.008	0.005	1.00	45.58	0.303	255.35
	35 years	19.39	0.249	0.014	0.005	0.005	0.724	89.92	0.142	362.48
Education	Some	8.14	0.217	0.011	0.005	0.004	0.554	43.91	0.123	165.01
	High school	11.13	0.160	0.013	0.006	0.005	0.453	40.36	0.240	163.32
	Tech or more	10.67	0.207	0.012	0.005	0.004	0.763	42.96	0.273	200.67
Race/ethn.	Afric. Amer.	7.33	0.151	0.010	0.005	0.004	0.505	44.32	0.164	145.16
	Caribb.	11.33	0.234	0.016	0.006	0.005	0.666	46.40	0.263	210.34
	African	9.36	0.606	0.015	0.009	0.009	1.20	54.72	0.067	341.87
	Other	46.48	0.114	0.015	0.006	0.006	4.78	34.90	2.00	281.11
	Latino	20.79	0.160	0.007	0.004	0.004	0.291	17.48	0.181	121.76
Alcohol	No	12.15	0.169	0.012	0.006	0.005	0.566	41.50	0.201	181.01
	Yes	2.46	5.82	0.134	0.027	0.011	0.557	85.41	0.141	394.28
Tobacco	No	11.94	0.171	0.012	0.006	0.005	0.573	41.52	0.205	184.78
	Yes	3.90	4.39	0.081	0.019	0.011	0.413	84.50	0.090	231.83
Gender	Female	11.49	0.248	0.014	0.006	0.005	0.547	39.00	0.166	183.92
	Male	8.28	0.172	0.012	0.006	0.005	0.555	47.85	0.206	163.28
US Born	Yes	8.63	0.173	0.011	0.005	0.004	0.540	37.52	0.178	129.03
	No	11.86	0.217	0.013	0.006	0.005	0.649	48.30	0.253	249.98

* Significance level of $p < 0.05$, bolded in text.

Table 3

Adjusted mean change and corresponding 95% confidence intervals for each birth size measure per 1-log unit increase in pollutant concentration (urine creatinine corrected, $\mu\text{g/g}$), $n = 185$.

Biomarker ^d	Maternal Urine β (95% CI)	Maternal Urine β (95% CI)
Birth weight (g)	Demographic confounders ^a	Multi-pollutant and confounders ^{a,b}
TCS		
TCC	-27 (-119.03, 64.13)	-23.78 (-115.59, 68.03)
2'-OH-TCC	14.69 (-113.14, 142.53)	17.66 (-110.52, 145.84)
3'-OH-TCC	70.17 (-87.52, 227.86)	75.52 (-84.09, 233.13)
3'-Cl-TCC	189.25 (-12.09, 390.59)	184.96 (-17.05, 386.97)
EtPB	-37.47 (-119.72, 44.78)	-36.90 (-119.66, 45.85)
PrPB	37.36 (-95.79, 170.52)	40.85 (-93.23, 174.94)
BuPB	-46.77 (-136.50, 42.96)	-50.35 (-140.93, 40.24)
MePB	59.27 (-84.96, 203.50)	61.27 (-84.72, 207.27)
BePB	NA ^c	NA
Gestational age at birth (wks)		
TCS	0.20 (-0.18, 0.58)	0.22 (-0.16, 0.60)
TCC	-0.05 (-0.40, 0.29)	-0.3 (-0.37, 0.32)
2'-OH-TCC	-0.6 (-0.55, 0.43)	-0.03 (-0.51, 0.46)
3'-OH-TCC	0.02 (-0.60, 0.63)	0.03 (-0.58, 0.65)
3'-Cl-TCC	0.42 (-0.37, 1.20)	0.39 (-0.39, 1.17)
EtPB	-0.05 (-0.36, 0.27)	-0.04 (-0.36, 0.28)
PrPB	0.1 (-0.37, 0.67)	0.17 (-0.35, 0.70)
BuPB	-0.36 (-0.72, -0.01)	-0.37 (-0.73, -0.01)
MePB	0.53 (-0.04, 1.11)	0.55 (-0.03, 1.13)
BePB	NA	NA
Body length (cm)		
TCS	0.35 (-0.29, 0.96)	0.39 (-0.24, 1.02)
TCC	-0.12 (-0.71, 0.46)	-0.10 (-0.68, 0.48)
2'-OH-TCC	-0.29 (-1.10, 0.52)	-0.28 (-1.09, 0.52)
3'-OH-TCC	-0.25 (-1.25, 0.74)	-0.23 (-1.23, 0.76)
3'-Cl-TCC	0.40 (-0.89, 1.69)	0.35 (-0.93, 1.63)
EtPB	-0.07 (-0.59, 0.44)	-0.07 (-0.59, 0.45)
PrPB	0.25 (-0.60, 1.10)	0.26 (-0.60, 1.11)
BuPB	-0.50 (-1.08, 0.07)	-0.53 (-1.11, 0.04)
MePB	0.67 (-0.22, 1.56)	0.66 (-0.24, 1.57)
BePB	NA	NA
Head circumference (cm)		
TCS	0.13 (-0.18, 0.45)	0.16 (-0.16, 0.48)
TCC	0.18 (-0.11, 0.47)	0.19 (-0.44, 0.14)
2'-OH-TCC	-0.15 (-0.25, 0.56)	-0.16 (-0.25, 0.57)

Biomarker^d	Maternal Urine β (95% CI)	Maternal Urine β (95% CI)
Birth weight (g)	Demographic confounders^a	Multi-pollutant and confounders^{a,b}
3'-OH-TCC	0.35 (−0.14, 0.85)	0.37 (−0.13, 0.87)
3'-Cl-TCC	0.55 (−0.09, 1.19)	0.54 (−0.11, 1.18)
EtPB	−0.12 (−0.38, 0.14)	−0.13 (−0.39, 0.13)
PrPB	−0.08 (−0.51, 0.35)	−0.10 (−0.53, 0.32)
BuPB	−0.13 (−0.42, 0.16)	−0.15 (−0.44, 0.14)
MePB	−0.12 (−0.35, 0.59)	0.07 (−0.40, 0.55)
BePB	NA	NA

* Significance level of $p < 0.05$, bolded in text.

^a Model covariates considered included: maternal nativity, age, alcohol use, tobacco use, and neonate gender. Final model covariates included: Birth weight = neonate gender, Gestational age at delivery = maternal age group, Length at birth = neonate gender, Head circumference = neonate gender.

^b Multi-pollutant models included TCS, TCC and BuPB. TCC was not included when modeling for TCC metabolites. BuPB was not included when modeling for any of the other parabens.

^c NA = Not available.

^d Non-detect values were treated as the method detection limit (MDL) divided by the square root of two.

Table 4

Adjusted mean change and corresponding 95% confidence intervals for each birth size measure per 1-log unit increase in cord plasma concentration (ug/L), $n = 34$.

Biomarker ^d	Neonate cord blood plasma	Neonate cord blood plasma
	β (95% CI)	β (95% CI)
Birth weight (gm)	Demographic confounders^a	Multi-pollutant and confounders^{a,b}
TCS	-89.37 (-373.83, 195.08)	-64.93 (-354.67, 224.81)
TCC	-199.80 (-670.37, 270.77)	-82.51 (-993.44, 130.81)
2'-OH-TCC	NA ^c	NA
3'-OH-TCC	NA	NA
3'-Cl-TCC	NA	NA
EtPB	-10.85 (-229.53, 207.83)	12.60 (-214.55, 239.75)
PrPB	-66.67 (-231.31, 102.97)	-42.72 (-223.40, 137.96)
BuPB	-480.40 (-976.68, 15.89)	-431.31 (-993.44, 130.81)
MePB	NA	NA
BePB	517.63 (-70.01, 1105.27)	459.16 (-263.91, 1182.23)
Gestational age at delivery (wks)		
TCS	0.58 (-0.70, 1.87)	0.37 (-0.78, 1.53)
TCC	-2.15 (-3.91, -0.40)	-0.75 (-2.74, 1.23)
2'-OH-TCC	NA	NA
3'-OH-TCC	NA	NA
3'-Cl-TCC	NA	NA
EtPB	-0.22 (-1.17, 0.73)	-0.03 (-0.96, 0.91)
PrPB	-0.54 (-1.23, 0.16)	-0.21 (-0.97, 0.54)
BuPB	-3.04 (-5.09, -0.99)	-2.35 (-4.71, 0.00)
MePB	NA	NA
BePB	2.59 (0.13, 5.04)	2.64 (-0.96, 5.38)
Length at birth (cm)		
TCS	0.46 (-1.31, 2.24)	0.65 (-1.21, 2.51)
TCC	-0.83 (-3.70, 2.04)	0.10 (-5.79, 1.25)
2'-OH-TCC	NA	NA
3'-OH-TCC	NA	NA
3'-Cl-TCC	NA	NA
EtPB	0.45 (-0.86, 1.78)	0.44 (-0.96, 1.83)
PrPB	-1.06 (-2.06, -0.05)	-1.33 (-2.49, -0.16)
BuPB	-2.06 (-5.17, 1.04)	-2.27 (-5.79, 1.25)
MePB	NA	NA
BePB	1.40 (-2.32, 5.13)	1.77 (-2.76, 6.31)
Head circumference (cm)		
TCS	-0.07 (-0.81, 0.68)	-0.09 (-0.87, 0.70)
TCC	-0.62 (-1.83, 0.60)	-0.51 (-1.89, 0.87)

Biomarker ^d	Neonate cord blood plasma	Neonate cord blood plasma
	β (95% CI)	β (95% CI)
Birth weight (gm)	Demographic confounders ^a	Multi-pollutant and confounders ^{a,b}
2'-OH-TCC	NA	NA
3'-OH-TCC	NA	NA
3'-Cl-TCC	NA	NA
EtPB	0.20 (-0.37, 0.76)	0.24 (-0.34, 0.83)
PrPB	-0.07 (-0.52, 0.37)	-0.01 (-1.94, 1.10)
BuPB	-0.64 (-2.0, 0.70)	-0.42 (-1.94, 1.10)
MePB	NA	NA
BePB	0.49 (-1.10, 2.09)	0.10 (-1.84, 2.04)

* Significance level of $p < 0.05$, bolded in text.

^a Model covariates considered included: maternal nativity, age, alcohol use, tobacco use, and neonate gender. Final model covariates included: Birth weight = neonate gender, Gestational age at delivery=maternal age group, Length at birth = neonate gender, Head circumference = neonate gender.

^b Multi-pollutant models included TCS, TCC and BuPB. TCC was not included when modeling for TCC metabolites. BuPB was not included when modeling for any of the other parabens.

^c NA = Not available.

^d Non-detect values were treated as the method detection limit (MDL) divided by the square root of two.

Table 5

Odds ratios and corresponding 95% confidence intervals per 1-log unit increase in biomarker concentration against birth size measure (ug/g, urine creatinine corrected levels, $n = 185$; ug/L cord blood plasma levels, $n = 34$).

Outcome	Maternal Urine Odds ratio ^{**} (95% CI)	Cord Blood Plasma ^{**} Odds ratio (95% CI)
LBW (y/n)		
TCS	0.72 (0.39, 1.32)	1.32 (0.33, 5.32)
TCC	1.22 (0.74, 2.01)	0.60 (0.04, 8.02)
2'-OH-TCC	0.97 (0.47, 1.99)	NA
3'-OH-TCC	0.58 (0.19, 1.79)	NA
3'-Cl-TCC	0.10 (0.01, 0.76)	NA
EtPB	1.18 (0.74, 1.89)	1.89 (0.62, 5.81)
PrPB	0.92 (0.44, 1.94)	1.52 (0.66, 3.45)
BuPB	1.45 (0.88, 2.39)	10.27 (0.68, 156.07)
MePB	0.83 (0.37, 1.87)	NA
BePB	NA ^a	0.18 (0.01, 2.63)
PTB (y/n)		
TCS	0.95 (0.60, 1.50)	1.40 (0.41, 4.77)
TCC	1.03 (0.67, 1.57)	4.59 (0.68, 31.17)
2'-OH-TCC	0.96 (0.53, 1.74)	NA
3'-OH-TCC	0.90 (0.42, 1.94)	NA
3'-Cl-TCC	0.70 (0.26, 1.91)	NA
EtPB	1.15 (0.78, 1.69)	2.65 (0.83, 8.48)
PrPB	1.27 (0.67, 2.43)	1.86 (0.84, 4.08)
BuPB	1.42 (0.93, 2.16)	60.77 (2.60, 1417.93)
MePB	0.78 (0.40, 1.54)	NA
BePB	NA	0.03 (0.01, 0.44)

* $p < 0.05$, bolded in text.

^aNA = Not available.

** Adjusted for neonate gender.