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Article

Exposure to Contemporary and Emerging Chemicals in Commerce among Pregnant Women in the United States: The Environmental influences on Child Health Outcome (ECHO) Program

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ABSTRACT: Prenatal chemical exposures can influence maternal and child health; however, few industrial chemicals are routinely biomonitored. We assessed an extensive panel of contemporary and emerging chemicals in 171 pregnant women across the United States (U.S.) and Puerto Rico in the Environmental influences on Child Health Outcomes (ECHO) Program. We simultaneously measured urinary concentrations of 89 analytes (103 total chemicals representing 73 parent compounds) in nine chemical groups: bactericides, benzophenones, bisphenols, fungicides and herbicides, insecticides, organophosphate esters (OPEs), parabens, phthalates/alternative plasticizers, and polycyclic aromatic hydrocarbons (PAHs). We estimated associations of creatinine-adjusted concentrations with sociodemographic and specimen characteristics. Among our diverse prenatal population (60% non-Hispanic Black or Hispanic), we detected 73 of 89 analytes in ≥1 participant and 36 in >50% of participants. Five analytes not currently included in the U.S. biomonitoring were detected in ≥90% of samples: benzophenone-1, thiamethoxam, mono-2-(propyl-6-carboxy-hexyl) phthalate, monocarboxy isooctyl phthalate, and monohydroxy-iso-decyl phthalate. Many analyte concentrations were higher among women of Hispanic ethnicity compared to those of non-Hispanic White women. Concentrations of certain chemicals decreased with the calendar year, whereas concentrations of their replacements increased. Our largest study to date identified widespread exposures to prevalent and understudied chemicals in a diverse sample of pregnant women in the U.S.

KEYWORDS: *pregnancychild health, industrial chemical, pesticides, flame retardants, phthalates, bisphenols, parabens*

INTRODUCTION

Pregnancy is a susceptible period for both mother and fetus, during which chemical exposures can contribute to numerous adverse pregnancy and child health outcomes.[1−4] Chemical exposures are ubiquitous in the United States (U.S.) due to the thousands of chemicals produced and used in numerous consumer products. Exposures can occur via food, water, air, dust, and use of consumer and personal care products.[4] During pregnancy, many chemicals to which pregnant women are exposed cross the placenta, directly exposing the fetus.[5]

Nationally representative data on chemical exposures are available from the National Health and Nutrition Examination Survey (NHANES) for approximately 350 of the more than 40,000 chemicals used in the U.S., encompassing a small proportion of potential chemical exposures.[6] A previous study of pregnant women using 2003−2004 NHANES data reported widespread simultaneous exposure to >40 chemicals.[4] The ubiquity of prenatal chemical exposures is likely underestimated because the vast majority of chemicals are not routinely surveyed in NHANES, including compounds with unknown or suspected toxicity and compounds being used as replacements for chemicals being phased out due to potential toxicity or increases in exposure (i.e., "regrettable substitutions").[7−9] Further, recent data on coexposure to multiple chemicals during pregnancy is

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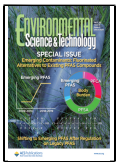

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lacking because NHANES has not oversampled pregnant participants since 2001−2006.[10] It is critical to improve methods to characterize prenatal chemical exposures more comprehensively and contemporarily.

The National Institutes of Health (NIH) Environmental influences on Child Health Outcomes (ECHO) Program provides an unparalleled opportunity for understanding environmental exposures among pregnant women in the U.S.[11] ECHO combines 69 prospectively followed pregnancy and pediatric cohorts comprising approximately 50,000 children and families from across the U.S. to understand and improve child health.[12] ECHO investigators previously recommended biomonitoring highly prevalent contemporary chemicals during pregnancy that are measured in NHANES[11] and emerging chemicals not included in NHANES but which have a high likelihood of exposure, the potential for adverse health effects, and an available biomarker of exposure.[13]

Our goal was to apply a new method for simultaneous measurement of more than 100 chemicals in nine groups of priority contemporary and emerging industrial chemicals and pesticides among pregnant women from nine ECHO cohorts representing a range of geographies and race/ethnicities. We aimed to characterize analyte detection frequencies and distributions and to assess predictors of exposure.

MATERIALS AND METHODS

Study Population. We included pregnant women from nine ECHO cohorts located in five states (California, Georgia, Illinois, New Hampshire, New York) and Puerto Rico, reflecting diverse geographic and sociodemographic populations (Table S1, Supporting Information 1). For this initial pilot study, each cohort contributed banked urine specimens from up to 20 ECHO participants (Table S1, Supporting Information 1). The only criterion for inclusion was the availability of a 6 mL of urine specimen collected during pregnancy. The study protocol was approved by the local (or central ECHO) Institutional Review Board (IRB). Written informed consent was obtained from participants in cohort-specific research and/or the ECHO-wide Cohort Data Collection Protocol. The work of the ECHO Data Analysis Center is approved through the Johns Hopkins Bloomberg School of Public Health IRB.

Chemical Analysis. We selected chemicals for analysis in collaboration with the Wadsworth Center-Human Health Exposure Analysis Resource (WC-HHEAR) at New York University. WC-HHEAR developed an analytical method for multiple chemical measurements that include both current use and emerging chemicals of concern based on laboratory capabilities as well as the biomonitoring recommendations of our prior publication.[13] This analytical method is consistent with Centers for Disease Control and Prevention (CDC) methods and was previously validated and applied in a convenience sample of 21 adult nonpregnant volunteers from Albany, NY.[14−16] Ours is the first population-based study to apply this method and the first among a diverse pregnant population. Chemical groups, parent compounds, CAS registry numbers, and environmental transformation of included analytes are provided in Data File S1, Supporting Information 2.

Briefly, urine samples were analyzed at WC-HHEAR using solid-phase extraction (SPE) coupled with high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)[14] Urine samples (0.5 mL) were incubated with β-glucuronidase/arylsulfatase (2000 units) and subjected to ABS Elut NEXUS SPE (Agilent, Santa Clara, CA) prior to analysis by HPLC-MS/MS. A Sciex HPLC system (SCIEX, Redwood City, CA) interfaced with an ABSCIEX QTRAP 5500+ triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA) with an electrospray ionization source was used in the analysis. The optimal LC-MS/MS conditions and quality assurance protocols are described in detail elsewhere.[14] Limits of detection (LODs) are presented in Data File S2, Supporting Information 2. Due to insufficient resolution to quantify 24 chemicals individually, we quantified 10 composites of multiple chemicals (e.g., we quantified a composite of 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene, and 9-hydroxyphenanthrene as a single analyte).

In total, we quantified 89 analytes in nine chemical groups: 79 individual and 10 composite analytes. These 89 analytes are biomarkers of 103 chemicals measured as either parent compounds or metabolites in urine depending on whether metabolites were known and analytical standards were available (Table S2, Supporting Information 1). To simplify reporting for metabolites of three parent phthalates and the phthalate alternative plasticizer DINCH, we calculated molar sums of metabolites for di-2-ethylhexyl phthalate (DEHP), di-isodecyl phthalate (DiDP), di-(2-propylheptyl) phthalate (DPHP), and di-iso-nonyl-cyclohexane-1,2-dicarboxylic acid (DINCH) (details in Data File S2, Supporting Information 2).[17,18]

Quality Control. We determined the replicability of the biomarker analysis using quality control (QC) pools and blinded duplicates.[15] Prior to this study, HHEAR collected urine from healthy adult volunteers and created two QC pools: QC Pools A and B.[15] Three aliquots each of these QC pools were run in each of the two batches (i.e., up to six QC-pooled urine samples from each of Pool A and Pool B). We calculated the overall means and coefficients of variation (CVs) for each biomarker in each pooled sample. We also analyzed 34 blinded duplicate pairs of urine sample aliquots from six cohorts and calculated the relative percent differences (RPDs) for each pair and the median of all pair RPDs. We restricted calculations of CVs to QC-pooled samples with concentrations above the LOD. We restricted calculations of RPDs to duplicate pairs, where both concentrations were >LOD and only assessed analytes with at least two sets of duplicate pairs >LOD; therefore, the median RPDs of duplicate pairs for several analytes were based on a small number of duplicates. We did not calculate CVs or RPDs for 16 analytes that were not detected in any study participant. The laboratory QC pool CVs were calculated for 32 analytes and ranged from 1 to 16%, with 91% of QC pools having a CV <10% (Table S3, Supporting Information 1). RPDs for 34 duplicate pairs from six cohorts could be calculated for 59 analytes and ranged from 7.3% (benzophenone-2) to 82.1% (imidacloprid) (Table S3, Supporting Information 1). Fifty analytes (68%) had a median RPD <50%, whereas 38 (52%) had median RPDs <30% (Table S3, Supporting Information 1).

Covariates. Sociodemographic variables included participant age (years; continuous), race/ethnicity (non-Hispanic White; non-Hispanic Black, non-Hispanic other, or non-Hispanic multiple race; Hispanic ethnicity, any race), prepregnancy or early pregnancy body mass index (BMI, measured from preconception to 16 completed weeks of gestation; continuous), highest educational attainment (high school diploma, general educational development [GED], or less; some college, Associate's degree, or trade/vocational school; Bachelor's degree or higher), and marital status (single, separated, divorced, widowed; married or partnered and living together). We

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assessed California residence since three of nine cohorts were located in California. We assessed tobacco exposure during pregnancy using $\log_2$-transformed creatinine-adjusted urinary cotinine concentrations (ng/mL). Urine specimen collection characteristics included time of day (morning [2:00 am−9:59 am], midday [10:00 am−3:59 pm], evening [4:00 pm−10:00 pm]), trimester (first, second, or third), calendar season (autumn [September−November], winter [December−February], spring [March−May], summer [June−August]), and year of collection (continuous; centered at 2008).

Statistical Analysis. *Descriptive Statistics.* We calculated the mean (SD) or geometric mean (GSD) of continuous variables and sample size (%) of categorical variables for characteristics of pregnant women in our sample. We also calculated descriptive statistics of demographic characteristics of all pregnant women in the nine participating cohorts. For each urinary analyte, we calculated the detection frequency, geometric mean (GSD), minimum and maximum, and 25th, 50th, and 75th percentiles. Sixteen analytes were not detected in any sample and excluded from further analyses (Data File S2, Supporting Information 2). We analyzed values as either dichotomous or continuous depending on the detection frequency among the participants. For analytes detected in <70% of participants, we created dichotomous variables based on each analyte's LOD and modeled the analytes as below or above the detection limit.[19] For analytes detected in ≥70% of participants, we used machine-read values (if available) or replaced values below the LOD with the analyte LOD/$\sqrt{2}$[20] and calculated $\log_2$-transformed concentrations. For six machine-read concentrations reported as zero, we added a small value (0.0001) prior to $\log_2$-transformation. Lastly, we calculated Spearman's correlations for analytes detected in at least three cohorts and ≥70% of the population.

Predictors of Chemical Exposures. We estimated univariable associations of sociodemographic and urine specimen collection characteristics with creatinine-adjusted analyte concentrations using generalized estimating equations to account for clustering of samples at the cohort level. We assumed an exchangeable working correlation matrix and used robust Huber−White sandwich estimation of variance and standard errors. For continuous concentrations, we first accounted for urinary dilution[21,22] by calculating creatinine-adjusted analyte concentrations as ($E_{corrected}$): $E_{corrected} = E_{observed} * \frac{Cr_{cohort\ median}}{Cr_{observed}}$, where we multiplied observed analyte concentrations ($E_{observed}$) by the ratio of the cohort-specific median creatinine concentration ($Cr_{cohort\ median}$) and sample-specific creatinine concentration ($Cr_{observed}$).[23,24] Then, we modeled creatinine-adjusted concentrations using an identity link and Gaussian family and reported effect estimates as % differences and 95% confidence intervals (CIs). For dichotomized concentrations, we used a log-link and Poisson family and reported prevalence ratios (PRs) and 95% CIs. To reduce the influence of individual cohorts and the potential for nonpositivity problems, we conducted predictor analyses only for analytes detected in participants from at least three cohorts and at least 10% of the overall study sample.

As a sensitivity analysis, we conducted limited multivariable models including age (continuous), race/ethnicity (non-Hispanic White; non-Hispanic Black, non-Hispanic other, or non-Hispanic multiple race; Hispanic ethnicity, any race), and educational attainment (high school diploma, GED, or less; some college, Associate's degree, or trade/vocational school; Bachelor's degree or higher). We used a complete-case approach for all analyses and did not report cell sizes less than five. We conducted statistical analyses using Stata v16.1 (StataCorp, College Station, Texas) and R v4.02 Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participant Demographics. Participants averaged 29.5 years of age at the time of urine collection were predominantly non-Hispanic White (34%) or Hispanic (40%) and married or living with a partner (68%) (Table 1). Urine specimens were collected during all trimesters and seasons, and the majority were collected from 2017 to 2020 (77%) (Table 1). Most of the urine specimens were spot samples (92%), were collected between 10:00 am and 3:59 pm (69%), and had undergone only 1 freeze−thaw cycle prior to assay (82%) (Table 1). The average age at delivery, educational attainment, and pre- or early pregnancy BMI were similar among our sample and all pregnant people from the nine participating cohorts (N = 7420) (Table S4, Supporting Information 1). Slightly fewer of our participants were non-Hispanic White and married or living with a partner (Table S4, Supporting Information 1).

Analyte Concentrations and Correlations. We detected 73 of the 89 analytes (63 of 79 individuals and 10 of 10 composites) in at least one participant (Table 2, Figure S1, Supporting Information 1). Of these, 36 analytes (31 individuals and 5 composites) were detected in greater than 50% of participants: 3 benzophenones, 2 bisphenols, 4 fungicides and herbicides, 3 insecticides, 2 OPEs, 3 parabens, 16 phthalates/alternative plasticizers (14 individuals and 2 composites), and 4 PAHs (1 individual and 3 composites) (Table 2). Nine of these 36 analytes are not currently included in NHANES biomonitoring: 4-hydroxybenzophenone (4-OHBP), benzophenone-1 (BP1), thiamethoxam (THX), cyclohexane-1,2-dicarboxylic acid-mono(oxo-isononyl) ester (MONCH), composite of mono-2-(carboxymethyl) hexyl phthalate and mono(7 carboxyheptyl) phthalate (MCMHP/MCHPP), mono-2-(propyl-6-carboxy-hexyl) phthalate (MPCHP), mono-2-(propyl-6-oxo-heptyl) phthalate (MPOHP), monocarboxy isooctyl phthalate (MCiOP), and monohydroxy-iso-decyl phthalate (MHiDP) (Data File S2, Supporting Information 2). Notably, 19 analytes (17 individuals and 2 composites) were detected in ≥90% of the population, indicating ubiquitous exposure (Table 2). Analytes not detected in any sample included benzophenone-6, bisphenol AP, four fungicides and herbicides, four insecticides, three OPEs, heptyl paraben, and two phthalate metabolites (Data File S2, Supporting Information 2).

We observed several moderate-to-strong positive correlations and few negative correlations among analytes (Figure 1). In general, correlations were stronger within each chemical group (Figure 1). While most phthalate metabolites were moderate to highly correlated with one another (range: 0.14−0.68), correlations of phthalate metabolites with ∑DINCH (a nonphthalate plasticizer used as a replacement for phthalates, such as DEHP) were low (range: 0.08−0.21).

Predictors of Analyte Concentrations. We found higher detection frequencies or concentrations among those identifying as non-Hispanic Black, other, multiple race, or Hispanic ethnicity (n = 30 analytes); having lower educational attainment (n = 22 analytes); being unmarried/partnered (n = 11 analytes); and having higher urinary cotinine concentrations (n = 12 analytes) (Figure 2, Data File S3, Supporting Information 2). Hispanic ethnicity was associated with higher detection frequencies or concentrations of most analytes not included in

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Table 1. Demographic and Urine Specimen Collection Characteristics of 171 Pregnant Women in ECHO[a,b]

demographic characteristics	*N* (%)
age at specimen collection (years); mean (SD)	29.5 (5.3)
age category at specimen collection (years)	
<25	35 (20)
25 to <30	51 (30)
30 to <35	47 (28)
≥ 35	38 (22)
race/ethnicity (missing: *n* = 1)	
non-Hispanic White	57 (34)
non-Hispanic Black/African American	34 (20)
non-Hispanic other or multiple race	11 (6)
Hispanic	68 (40)
highest educational attainment (missing: *n* = 7)	
less than high school	16 (10)
high school degree, GED, or equivalent	28 (17)
some college, Associate's degree, or trade/vocational school	45 (27)
Bachelor's degree	36 (22)
Master's, professional, or doctorate degree	39 (24)
marital status (missing: *n* = 6)	
single, partnered, not living together	45 (27)
widowed, separated, divorced	8 (5)
married or living with a partner	112 (68)
prepregnancy or early pregnancy BMI (kg/m^2); mean (SD); (missing: *n* = 12)	26.4 (6.5)
California residence	54 (32)
urine cotinine concentration, creatinine-standardized (ng/mL); geometric mean (GSD)	0.57 (6.2)
urine specimen collection characteristics	
creatinine (mg/dL); geometric mean (GSD)	61.4 (1.7)
time of day (missing: *n* = 9)	
morning (2:00 am−9:59 am)	40 (25)
midday (10:00 am−3:59 pm)	112 (69)
evening (4:00 pm−10:00 pm)	10 (6)
trimester (missing: *n* = 2)	
1 (0−13 completed weeks)	19 (11)
2 (14−26 completed weeks)	82 (49)
3 (27+ completed weeks)	68 (40)
calendar season	
winter (december−february)	37 (22)
spring (march−may)	39 (23)
summer (june−august)	52 (30)
autumn (september−november)	43 (25)
calendar year	
2008−2015	19 (11)
2016	20 (12)
2017	40 (23)
2018	46 (27)
2019−2020	43 (25)
collection type (missing: *n* = 3)	
spot	154 (92)
first morning void	14 (8)
freeze−thaw cycles	
1	140 (82)
2	31 (18)

[a]All statistics are sample size (%) unless noted otherwise. [b]Abbreviations: BMI, body mass index; dL, deciliter; ECHO, Environmental influences on Child Health Outcomes; GED, general educational development; GSD, geometric standard deviation; kg, kilogram; m, meter; mg, milligram; mL, milliliter; ng, nanogram; and SD, standard deviation.

NHANES biomonitoring (Figure 2). For example, compared with non-Hispanic White women, Hispanic women had a 6.9 (95% CI: 1.1, 43.4) higher prevalence of bisphenol Z (BPZ) detection and a 58% (95% CI: 10, 126%) higher THX concentration (Data File S3, Supporting Information 2). In contrast, identifying as non-Hispanic Black, other, or multiple race (n = 11); having lower educational attainment (n = 14); and being unmarried/partnered (n = 6) were associated with lower detection frequencies or concentrations of other analytes such as BP1 (Figure 2, Data File S3, Supporting Information 2). We observed some notable differences in predictor associations for certain chemicals versus their increasingly utilized replacements. For example, Hispanic women had higher BPS and BPZ concentrations compared with non-Hispanic White women, whereas BPA was not associated with race or ethnicity (Data File S3, Supporting Information 2). For phthalates, Hispanic ethnicity was associated with higher concentrations of both ∑DEHP and ∑DINCH, but the magnitude was much greater for ∑DINCH: compared with non-Hispanic White women, ∑DEHP concentrations were 31% (95% CI: 7%, 61%) higher among Hispanic women, whereas ∑DINCH concentrations were 122% (95% CI: 52%, 226%) higher (Data File S3, Supporting Information 2).

Morning specimen collection; first-trimester collection; and collection during spring, summer, or autumn months were associated with higher detection frequencies or concentrations of several analytes (Data File S4, Supporting Information 2). Among analytes not included in NHANES biomonitoring, later years of specimen collection were significantly associated (p < 0.05) with lower detection frequencies of benzophenone-8 (BP8), nitenpyram, mono-2-heptyl phthalate (MHPP), the composite of mono-isopropyl phthalate (MiPP) and mono-propyl phthalate (MPrP), and 4-OHBP (Figure 2). For example, each year of specimen collection was associated with lower prevalence of MHPP detection (PR: 0.84; 95% CI: 0.79, 0.89) and lower 4-OHBP concentrations (% difference: -7%; 95% CI: −13%, −1%) (Data File S4, Supporting Information 2).

Notably, chemicals often had the opposite direction of association with year of specimen collection compared with their chemical replacements (Data File S4, Supporting Information 2). Later year of specimen collection was not associated with prevalence of BPA detection (PR: 1.0; 95% CI: 0.9, 1.1) but was associated with higher prevalence of bisphenol F (BPF) detection (PR: 1.3; 95% CI: 1.1, 1.5) and higher BPS concentrations (% difference: 18%; 95% CI: 5%, 32%) (Data File S4, Supporting Information 2). For phthalates, later year of specimen collection was associated with 12% (95% CI: −19%, −4%) lower ∑DEHP metabolite concentrations but 23% (95% CI: 13%, 33%) higher ∑DINCH metabolite concentrations (Data File S4, Supporting Information 2).

In our sensitivity analysis using multivariable models, magnitudes of association for age, race/ethnicity, and educational attainment were generally comparable to unadjusted associations though some associations became weaker (Data File S5, Supporting Information 2).

DISCUSSION

To our knowledge, this is the largest study to measure >100 contemporary and emerging chemicals in a diverse population of pregnant women in the U.S. Overall, 73 of 89 analytes were detected in at least one pregnant woman, including 30 from seven chemical groups that were not previously included in NHANES. Additionally, 19 analytes were detectable in 90−

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Table 2. Analyte Descriptive Statistics among 171 Pregnant Women in ECHO, Categorized by Prior Inclusion in National Health and Nutrition Examination Survey (NHANES) Biomonitoring[a,c]

previously not included in NHANES						previously included in NHANES					
chemical group/analyte name (abbrev	LOD	*N* (%) >LOD	GM	P25	P75	chemical group/analyte name (abbrev)	LOD	*N* (%) >LOD	GM	P25	P75
bactericide											
						triclocarban (TCS)	0.1	41 (24)	<LOD	<LOD	<LOD
benzophenones											
2,2′,4,4′-tetrahydroxyenzophenone (BP2)	0.075	13 (8)	<LOD	<LOD	0.56	benzophenone-3 (BP3)[b]	0.1	167 (98)	3.1	0.96	8.9
2,2′-dihydroxymethoxybenzophenone (BP8)	0.075	70 (41)	<LOD	<LOD	1152						
4-hydroxybenzophenone (4-OHBP)	0.075	152 (89)	0.29	0.13	0.53						
benzophenone-1 (BP1)[b]	0.075	166 (97)	1.8	0.48	6.0						
bisphenols											
bisphenol AF (BPAF)	0.02	9 (5)	<LOD	<LOD	<LOD	bisphenol A (BPA)	0.07	105 (61)	0.28	<LOD	1.1
bisphenol B (BPB)	0.1	8 (5)	<LOD	<LOD	<LOD	bisphenol F (BPF)	0.2	68 (40)	0.26	<LOD	0.65
bisphenol Z (BPZ)	0.05	24 (14)	<LOD	<LOD	<LOD	bisphenol S (BPS)	0.05	144 (84)	0.20	0.088	0.49
fungicides and herbicides											
fungicides						*fungicides*					
metalaxyl (MET)	0.075	*n* < 5	<LOD	<LOD	<LOD	2,4,5-trichlorophenoxyacetic acid (2,4,5-T)	0.05	148 (87)	0.17	0.094	0.33
pyrimethanil (PYRM)	0.1	*n* < 5	<LOD	<LOD	<LOD	4-nitrophenol (PNP)	0.1	118 (69)	0.26	<LOD	0.58
						pentachlorophenol (PCP)	0.2	110 (64)	0.59	<LOD	2.0
						herbicides					
						2,4-dichlorophenoxyacetic acid (2,4-D)	0.075	31 (18)	0.081	<LOD	<LOD
						atrazine (ATZ)	0.025	86 (50)	0.037	<LOD	0.089
insecticides											
neonicotinoid insecticides						*neonicotinoid insecticides*					
6-chloronicotinic acid (6-CNA)	0.15	17 (10)	<LOD	<LOD	<LOD	acetamiprid (ACE)	0.025	15 (9)	<LOD	<LOD	<LOD
nitenpyram (NIT)	0.05	40 (23)	<LOD	<LOD	<LOD	clothianidin (CLO)	0.1	48 (28)	<LOD	<LOD	0.15
thiamethoxam (THX)[b]	0.05	157 (92)	0.42	0.25	0.82	imidacloprid (IMI)	0.1	48 (28)	0.11	<LOD	0.13
other insecticides						*N*-desmethyl-acetamiprid (NDMA)[b]	0.03	164 (96)	0.33	0.22	0.59
sulfoxaflor (SUF)	0.01	33 (19)	<LOD	<LOD	<LOD	*organochlorine insecticides*					

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Table 2. continued

previously not included in NHANES						previously included in NHANES					
chemical group/analyte name (abbrev	LOD	*N* (%) >LOD	GM	P25	P75	chemical group/analyte name (abbrev)	LOD	*N* (%) >LOD	GM	P25	P75
						composite of 2,4,5- and 2,4,6-trichlorophenol (2,4,5-/2,4,6-TCP)	0.2	*n* < 5	<LOD	<LOD	<LOD
						organophosphate insecticides					
						3,5,6-trichloro-2-pyridinol (TCP)[b]	0.1	154 (90)	0.5	0.25	1.1
						pyrethroid insecticides					
						composite of cis and trans-3-(2,2-di-chlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (DCCA)	0.4	69 (40)			1.2
						3-phenoxybenzoic acid (PBA)	0.7	16 (9)			<LOD
						4-fluoro-3-phenoxybenzoic acid (FPBA)	0.025	41 (24)			<LOD
organophosphate ester flame retardants											
triethyl phosphate (TEP)	0.075	73 (43)	<LOD	<LOD	0.13	bis(1,3-dichloro-2-propyl) phosphate (BDCIPP)	0.15	126 (74)	0.39	<LOD	0.87
composite of tri-*n*-butyl phosphate/tri-iso-butyl phosphate (TnBP/TiBP)	0.075	45 (26)	0.11	<LOD	0.36	composite of di-*n*-butyl phosphate and di-isobutyl phosphate (DBuP/DiBP)	0.05	10 (6)	<LOD	<LOD	<LOD
	0.2	6 (4)	<LOD	<LOD	<LOD	diphenyl phosphate (DPHP)[b]	0.05	164 (96)	0.66	0.34	1.4
parabens											
benzyl paraben (BzPB)	0.05	20 (12)	<LOD	<LOD	<LOD	butyl paraben (BuPB)	0.05	51 (30)	0.082	<LOD	0.096
						ethyl paraben (EtPB)[b]	0.01	164 (96)	0.43	0.094	1.6
						methyl paraben (MePB)[b]	0.05	168 (98)	11	3.1	52
						propyl paraben (PrPB)	0.15	150 (88)	2.8	0.52	16
phthalates and phthalate alternatives											
phthalate alternatives						*phthalate alternatives*					
cyclohexane-1,2-dicarboxylic acid-mono(oxo-isononyl) ester (MONCH)	0.025	108 (63)	0.11	<LOD	0.33	cyclohexane-1,2-dicarboxylic acid-monocarboxy isooctyl ester (MCOCH)	0.025	108 (63)	0.11	<LOD	0.33
monobenzyl terephthalate (MBzTP)	0.075	n <5	<LOD	<LOD	<LOD	cyclohexane-1,2-dicarboxyclic acid-mono(hydroxy-isononyl) ester (MHNCH)	0.05	131 (77)	0.28	0.056	0.9
monoethyl terephthalate (METP)	0.15	5 (3)	<LOD	<LOD	<LOD						
mono-*tert*-butyl terephthalate (MTBTP)	0.075	7 (4)	<LOD	<LOD	<LOD						
phthalates						*phthalates*					
composite of mono-2-(carboxymethyl) hexyl phthalate and mono(7 carboxyheptyl) phthalate (MCMHP/MCHPP)	0.1	152 (89)	0.53	0.31	1.0	mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)[b]	0.2	170 (99)	3.8	2.1	7.3
mono-2-heptyl phthalate (MHPP)	0.08	41 (24)	<LOD	<LOD	<LOD	mono (2-ethyl-5-oxohexyl) phthalate (MEOHP)[b]	0.05	166 (97)	3.2	1.9	6.7
mono-2-(propyl-6-carboxy-hexyl) phthalate (MPCHP)[b]	0.05	159 (93)	0.4	0.19	0.78	mono (5-carboxy-2-ethylpentyl) phthalate (MECPP)[b]	0.05	170 (99)	5.0	2.7	9.4
mono-2-(propyl-6-hydroxy-heptyl) phthalate (MPHHP)	0.025	44 (26)	0.048	<LOD	0.043	mono (7-COOH-2-methyloctyl) phthalate (MCOMOP)	0.025	117 (68)	0.15	<LOD	0.57

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Table 2. continued

previously not included in NHANES						previously included in NHANES					
chemical group/analyte name (abbrev	LOD	*N* (%) >LOD	GM	P25	P75	chemical group/analyte name (abbrev)	LOD	*N* (%) >LOD	GM	P25	P75
mono-2-(propyl-6-oxoheptyl) phthalate (MPOHP)	0.075	139 (81)	0.46	0.14	1.1	monobenzyl phthalate (MBzP)	0.4	52 (30)	0.96	<LOD	6.0
monocarboxy isooctyl phthalate (MCiOP)[b]	0.05	169 (99)	3.0	1.3	7.3	monocarboxy isononyl phthalate (MCiNP)[b]	0.05	158 (92)	0.37	0.18	0.69
monohydroxy-iso-decyl phthalate (MHiDP)[b]	0.05	159 (93)	0.59	0.24	1.1	monoethylhexyl phthalate (MEHP)[b]	0.1	164 (96)	1.6	0.76	3.5
composite of mono-isopropyl phthalate and mono-propyl phthalate (MiPP/MPrP)	0.1	82 (48)	0.11	<LOD	0.25	monoethyl phthalate (MEP)[b]	0.2	171 (100)	24	10	58
mono-pentyl phthalate (MPeP)	0.1	16 (9)	<LOD	<LOD	<LOD	monomethyl phthalate (MMP)	0.1	105 (61)	0.38	<LOD	1.1
						composite of mono-*n*-butyl phthalate and mono-isobutyl phthalate (MnBP/MiBP)[b]	0.05	171 (100)	11	6.0	22
						mono-*n*-octyl phthalate (MOP)	0.15	75 (44)	0.17	<LOD	0.33
polycyclic aromatic hydrocarbons											
						composite of 1- and 2 hydroxynaphthalene (NAPs)[b]	50	169 (99)	5443	2184	14480
						1-hydroxypyrene (1-OHP)	100	12 (7)	<LOD	<LOD	<LOD
						composite of 1-, 2-, 3-, 4-, 9-hydroxyphenanthrene (PHENs)	75	114 (67)	145	<LOD	314
						composite of 2-, 3-, 9-hydroxyfluorene (FLUOs)	50	118 (69)	110	<LOD	210

[a]Concentration units are ng/mL except for polycyclic aromatic hydrocarbons (ng/L). Values below the limit of detection (LOD) were set to LOD/$\sqrt{2}$ unless machine-read values were provided. [b]Detected in at least 90% of urine specimens. [c]Abbreviations: GM, geometric mean; L, liter; LOD, limit of detection; mL, milliliter; ng, nanogram; and P, percentile.

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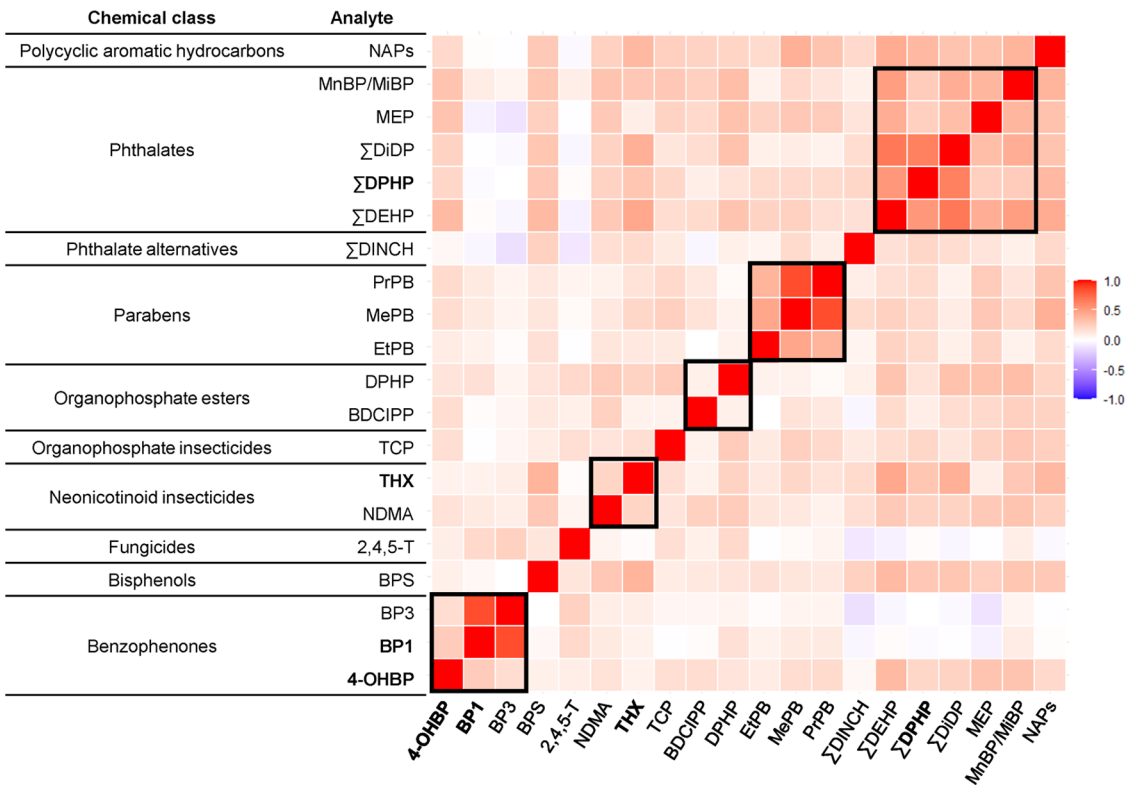

Figure 1. Spearman correlation heat map of urinary analyte concentrations measured among 171 pregnant women in ECHO. It includes analytes detected in at least three cohorts and ≥70% of the overall study sample. Values below the limit of detection (LOD) were set to LOD/$\sqrt{2}$ unless machine-read values were provided. Bold indicates analytes not previously included in NHANES biomonitoring. Boxes indicate within class correlations.

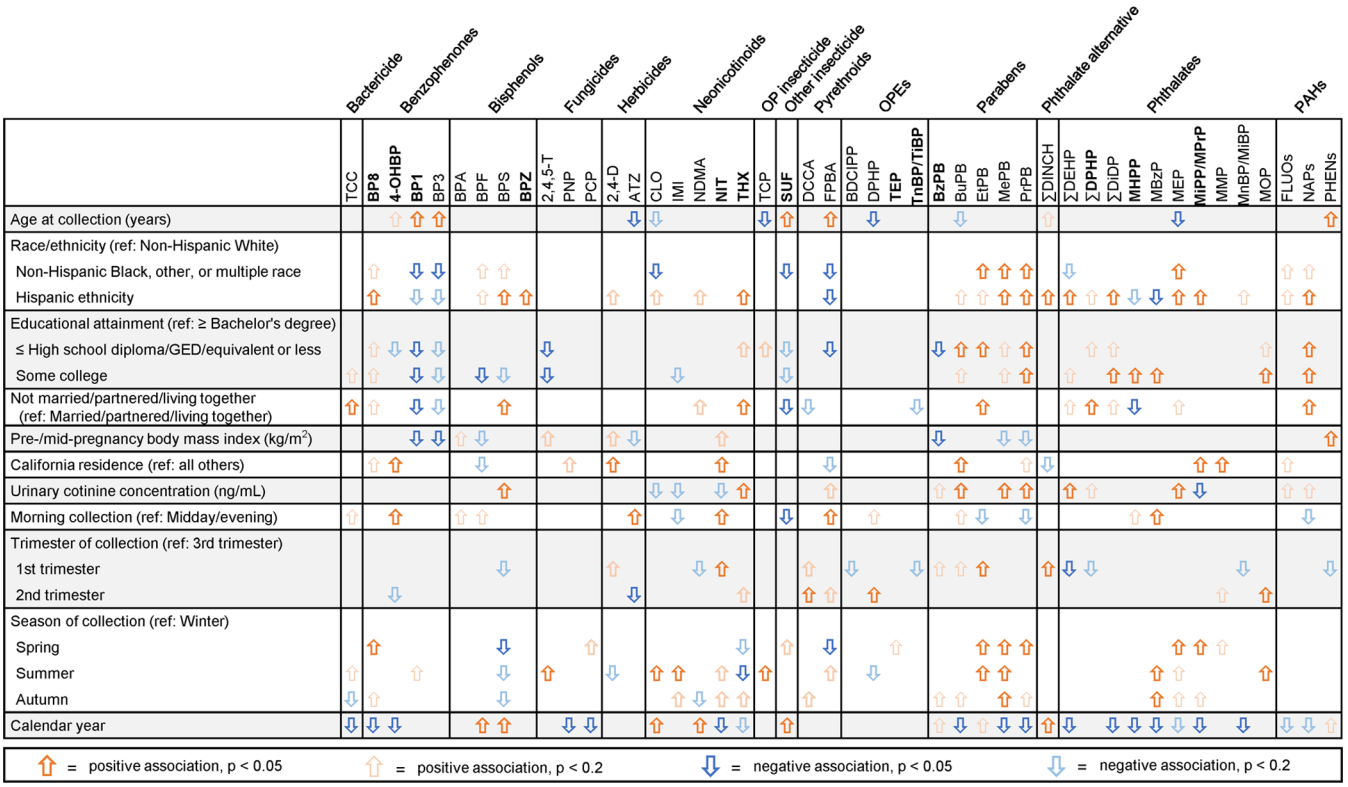

Figure 2. Univariable associations of maternal sociodemographic and specimen collection characteristics with creatinine-adjusted analyte concentrations. Bold indicates analytes not previously included in NHANES biomonitoring. OP, organophosphate; OPE, organophosphate ester; and PAH, polycyclic aromatic hydrocarbon.

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100% of pregnant women, including 2 benzophenones, 3 insecticides, 1 OPE, 2 parabens, 10 phthalate metabolites, and 1 PAH. Our study adds to the growing literature documenting multiple chemical exposures that occur during pregnancy, a critical and vulnerable period of human development.[4,5]

This analysis is based on a multiyear effort to identify priority chemicals for biomonitoring in the ECHO Program. Previously, ECHO investigators recommended novel chemicals for biomonitoring based on three criteria: (1) prevalence in environmental or human biospecimens, (2) preliminary evidence of their toxicity for health outcomes of interest to ECHO (i.e., adverse perinatal outcomes, neurodevelopmental outcomes, respiratory outcomes, and obesity/diabetes), and (3) a biomarker was reported for measurement in human biospecimens.[13] In this initial study, we measured eight biomarkers of chemicals not included in NHANES that were identified in our prioritization of novel chemicals:[13] bisphenol AF (BPAF), bisphenol B (BPB), azoxystrobin, cyprodinil, metalaxyl, pyrimethanil, tebuconazole, and tetraconazole. Although these eight chemicals were infrequently or not detected in our sample, six were pesticides measured as the parent compounds and not the anticipated metabolites that would be present in urine because some pesticide metabolite standards were not available for our study. We recommend future studies measure the parent compounds in plasma or hair to assess exposure if standards for the metabolites remain unavailable. We also measured 41 analytes that were included on the list for future prioritization (Data File S1, Supporting Information 2), many of which needed biomarker development or demonstration of human exposure.[13] Of these 41 analytes, 35 were detected in at least one sample and 21 were detected in >50% of samples suggesting widespread exposures (Data File S2, Supporting Information 2).

Nine analytes detected in more than half of our samples are not currently included in NHANES biomonitoring, including the neonicotinoid pesticide thiamethoxam (92%), the benzophenones 4-OHBP (89%) and BP1 (97%), and metabolites of the phthalate DPHP (MPCHP/MPOHP, 89%). We also measured additional metabolites of the phthalate alternative plasticizer DINCH (MONCH) and the phthalates DEHP (composite of MCMHP/MCHPP) and DiDP (MCiOP and MHiDP) that may help to characterize exposures to these parent compounds in addition to metabolites already included in NHANES. In addition, our method included 44 analytes currently measured in NHANES, many of which have been identified by authoritative bodies as likely or known carcinogens or as developmental or reproductive toxicants.[25−35] NHANES does not oversample pregnant participants, and chemical classes are measured in biospecimens from nonoverlapping random subsamples of NHANES participants. Therefore, our novel findings demonstrate substantial coexposure to multiple contemporary chemicals across nine chemical groups in a large number of pregnant women.

We observed neonicotinoid insecticides were highly detected (six detected and thiamethoxam and *N*-desmethyl-acetamiprid in more than 90%), increasing temporally, and generally more highly detected among Hispanic women. Four of these neonicotinoids have been previously measured in NHANES. We found generally higher detection frequencies and concentrations compared with the four measured in NHANES (collection period 2015−2016).[36] This may, in part, be due to our later study collection period (primarily 2017−2020). The most frequently detected neonicotinoid in NHANES was N-desmethyl-acetamiprid (35% overall, 38% in females),[36] which we detected in 96% of our participants. While this difference in detection frequencies is expected due to a higher LOD in NHANES (0.2 ng/mL) compared with this method (0.03 ng/mL), our participants also appear to have higher exposures. For example, our 75th percentile for *N*-desmethyl-acetamiprid was 0.59 ng/mL compared with 0.36 ng/mL in NHANES. We also found more universal detection of several neonicotinoids with no or low detection frequencies (<10%) in NHANES.[36] Finally, we found higher concentrations or detection frequencies in later years of collection for several neonicotinoids (acetamiprid and clothianidin), which have been increasingly used in the U.S. as a replacement for organophosphate pesticides and other pyrethroids.[36,37] Neonicotinoids are used in a variety of applications, including agricultural uses,[38−41] flea control in pets,[42] and residential landscaping pest control.[43,44] In agricultural settings, neonicotinoids are primarily used as seed treatments and readily taken up by the plant leading to their presence in all components of the plant (e.g., roots, stems, flowers, and leaves) and cannot be washed off; thus, food has been identified as an important source of exposure.[45,46]

We also documented widespread detection of several chemicals that are replacements for chemicals with declining use due to regulatory or market-based activities. For example, we found higher concentrations in the later calendar years for BPA replacements (BPF and BPS) and phthalate alternatives (DINCH metabolites). Concurrently, we found an indication of decreasing or stable levels of certain chemicals that have been the focus of bans and market-based campaigns to reduce their use in consumer products, such as certain phthalates, some parabens and benzophenones, and BPA.[47−50] Notably, geometric mean levels of BPS and BPF were similar to BPA, and BPS was more frequently detected (84%) than BPA (61%). These exposures may be cases of "regrettable substitution" given bisphenols are structurally homologous and may have similar hormonal activity and endocrine-disrupting effects to BPA.[9,51,52] Similarly, the alternative plasticizer DINCH is being used as a replacement for DEHP and other high-molecular-weight phthalates.[53−56] We also observed widespread exposures to OPEs, which may have adverse reproductive and child development outcomes[57] and have been increasing in use as a replacement for polybrominated diphenyl ether (PBDE) flame-retardant chemicals. PBDEs have been banned and/or phased out due to concerns about bioaccumulation, long half-lives, and toxicity since the early 2000s, leading to increased use of replacement OPE flame retardants in fabric, electronics, and other consumer product materials.[58,59] More recently, OPEs have been used as phthalate replacements in nail polish and perfumes.[60,61] One potential reason for increases in exposure to replacements is the lack of a legal requirement in the U.S. to provide a minimum set of data on the potential health harms of chemicals currently on the market, such as in Europe.[62]

We identified demographic differences in several exposures, with Hispanic ethnicity being associated with higher concentrations of multiple pesticides, phthalates, bisphenols, and parabens, consistent with prior evidence that chemical exposures (including certain phthalates, pesticides, and phenols) are frequently higher among women of color.[63−65] Racial and ethnic differences in diet and consumer product use, due in part to structural racism, may contribute to these disparities.[66−69] Many chemicals associated with race and ethnicity were also observed to be higher among women with lower educational attainment (high school or less). Our multivariable modeling results suggest race and ethnicity remain important predictors after accounting

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for age and education. Still, these associations may be partly explained by features of our sample or cohort geography as some cohorts have a higher percentage of certain racial/ethnic participants and the sample size was modest from individual cohorts. An important limitation of our study is the lack of consideration of country or region of origin, acculturation, and immigration status for women identifying as Hispanic ethnicity. Given the wide geographic range of our study, grouping all Hispanic women together obfuscates the potential for notable differences in chemical exposures occurring within this diverse group of pregnant women. Prioritizing opportunities to collect and incorporate the necessary data to fully characterize and understand differences among unique racial and ethnic groups will be critical for future research, especially as we expand chemical biomonitoring to additional ECHO participants.

We evaluated chemicals from a wide range of uses and applications, including agricultural and home use pesticides, personal care products, and multiple plastic-related applications, including food packaging materials, home construction materials, home use products, and furniture- and foam-related materials.[13] As such, people come into contact with these chemicals via air, food, drinking water, and dermal contact.[11,13,70−73] Many of these chemicals migrate from their original source and have been found in intermediary exposure media, such as dust, often at higher concentrations, supporting their use as an important source of exposure monitoring.[74,75] In addition, we observed higher concentrations of some parabens, phthalates, and pesticides in summer and spring compared with winter, which could be due to seasonal variation in exposure sources, such as personal care product use, diet, or time spent indoors.

A major strength of our study is the rigorous, literature-based approach we used to identify candidate chemicals, many not included in NHANES biomonitoring.[13] We simultaneously quantified compounds from multiple chemical groups that have not been previously included together in prior studies, including fungicides and herbicides, OPEs, parabens, and emerging phthalate and alternative plasticizers. We used a validated, high-throughput method to simultaneously quantify concentrations of analytes in multiple chemical groups using a small volume of urine (<1 mL), which will facilitate larger future ECHO studies. Additionally, we included cohorts with diverse sociodemographic characteristics and broad geographical coverage and assessed associations with a variety of demographic and specimen characteristics to identify potentially vulnerable populations and inform the design of future studies.

Because our study focused on urinary analytes, we did not include compounds such as perfluoroalkyl substances, PBDEs, and polychlorinated biphenyls, which have been previously documented to have widespread exposures among pregnant women and the general U.S. population.[11,76] Some RPDs of duplicate pairs were high, which may reflect a lack of sample homogeneity or analytical variance. Many of the analytes had CVs <30%, similar to our prior methods paper,[14] and higher RPDs may suggest sample inhomogeneity. Because of limited power, we were unable to fully assess independent predictors in multivariable analyses, and we did not have information on specific sources of exposure, such as diet or personal care product use. While urine is the preferred biological matrix for measurement of nonpersistent chemicals,[77] a limitation of our study design for evaluating predictors of exposure is the measurement of analytes in a single urine sample. Many of these chemicals are rapidly metabolized and eliminated in urine with short biological half-lives and/or are better measured in serum or hair. Future ECHO studies will measure analytes in repeated samples during pregnancy to assess intraindividual variability and include a sufficient sample size to reduce exposure measurement error for studies of predictors and health outcomes.

Our study sample was similar to participants of the parent ECHO cohorts with respect to several sociodemographic characteristics. Although our sample may not be fully representative of the U.S. population, we were able to assess exposures within diverse racial, ethnic, geographic, and socioeconomic subgroups. While we were unable to evaluate the potential health risks of these exposures given the pilot nature of our study, our results both document widespread exposures during pregnancy across the U.S. and demonstrate the feasibility of this multiclass assay. Our findings provide a foundation for a larger ECHO study to evaluate the relationships of these exposures to adverse health outcomes.

Our data support the importance of temporal biomonitoring of multiple chemicals to identify how policies and related activities have successfully reduced exposures, and where future interventions should focus. This study also reinforces the need to identify systematic solutions to avoid potential "regrettable substitutions" and prevent future harmful exposures, including improvements to chemical alternative assessments and approaches that address chemical classes instead of individual chemicals.[7,78,79] Finally, ECHO has collected rich information on exposure sources and health outcomes that can be used to identify potential individual- and policy-level interventions and evaluate the health impacts of these exposures.[11] Illuminating contemporary and emerging chemical exposures during pregnancy is critical to identify common sources of potentially modifiable exposures and inform interventions aimed at exposure reduction on the individual, clinical, and population levels, with implications for maternal, child, and lifelong health.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c08942.

Additional descriptive information and quality control analysis results (PDF)

Additional chemical information and statistical analysis results (XLSX)

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Notes

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.
The authors declare no competing financial interest.
The data sets for this manuscript are not publicly available because, per the NIH-approved ECHO Data Sharing Policy, ECHO-wide data have not yet been made available to the public for review/analysis. Requests to access the data sets should be directed to the ECHO Data Analysis Center, ECHO-DAC@rti.org.

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■ ABBREVIATIONS

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
4-OHBP	4-hydroxybenzophenone
ATZ	atrazine
BDCIPP	bis(1,3-dichloro-2-propyl) phosphate
BP1	benzophenone-1
BP3	benzophenone-3
BP8	2,2'-dihydroxy-methoxybenzophenone
BPA	bisphenol A
BPF	bisphenol F
BPS	bisphenol S
BPZ	bisphenol Z
BuPB	butyl paraben
BzPB	benzyl paraben
CDC	Centers for Disease Control and Prevention
CLO	clothianidin
DCCA	3-(2,-di-chlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid
∑DEHP	molar sum of di-2-ethylhexyl phthalate metabolites
∑DiDP	molar sum of di-iso-decyl phthalate metabolites
∑DINCH	molar sum of di-iso-nonyl-cyclohexane-1,2-dicarboxylic acid metabolites
∑DPHP	molar sum of di-(2-propylheptyl) phthalate metabolites
DPHP	diphenyl phosphate
ECHO	Environmental influences on Child Health Outcome
EtPB	ethyl paraben
FLUOs	composite of 2-, 3-, and 9-hydroxyfluorene

FPBA	4-fluoro-3-phenoxybenzoic acid
IMI	imidacloprid
LOD	limit of detection
MBzP	monobenzyl phthalate
MEP	monoethyl phthalate
MePB	methyl paraben
MHPP	mono-2-heptyl phthalate
MiPP/MPrP	composite of mono-isopropyl phthalate and mono-propyl phthalate
MMP	monomethyl phthalate
MnBP/MiBP	composite of mono-*n*-butyl phthalate and mono-iso-butyl phthalate
MOP	mono-*n*-octyl phthalate
NAPs	composite of 1- and 2-hydroxynaphthalene
NDMA	*N*-desmethyl acetamiprid
NIH	National Institutes of Health
NIT	nitenpyram
NHANES	National Health and Nutrition Examination Survey
PCP	pentachlorophenol
PHENs	composite of 1-, 2-, 3-, 4-, and 9-hydroxyphenanthrene
PNP	4-nitrophenol
PrPB	propyl paraben
SUF	sulfoxaflor
TCC	triclocarban
TCP	3,5,6-trichloro-2-pyridinol
TEP	triethyl phosphate
THX	thiamethoxam
TnBP/TiBP	composite of tri-*n*-butyl phosphate and tri-iso-butyl phosphate

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