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Publication Date

2022-05-01

DOI

10.1016/j.envint.2022.107235

Peer reviewed

HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2023 May 01.

Published in final edited form as:

Environ Int. 2022 May ; 163: 107235. doi:10.1016/j.envint.2022.107235.

Urinary Phthalate Metabolite Mixtures in Pregnancy and Fetal Growth: Findings from The Infant Development and the Environment Study

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Authorship Contributions: All authors contributed substantially to this study including Conceptualization (DRS, ESB, NRB, RHNN, SS, SS, KKF); Formal analysis (DRS, PAB, APK); Methodology (DRS, PAB, APK, NRB, RHNN, SS, SS, KKF); Data curation, Funding acquisition, Investigation, Project administration, Resources (NRB, RHNN, SS, SS, KKF); Software (KKF); Supervision (KKF); Validation (DRS, PAB); Visualization (DRS); Roles/Writing - original draft (DRS, PAB, KKF); Writing - review & editing (DRS, PAB, APK, TFM, LT, ESB, NRB, RHNN, SS, SS, KKF). All authors reviewed and approved the final manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abstract

Background: Prenatal phthalate exposure has been linked to reductions in fetal growth in animal and laboratory studies, but epidemiologic evidence is equivocal.

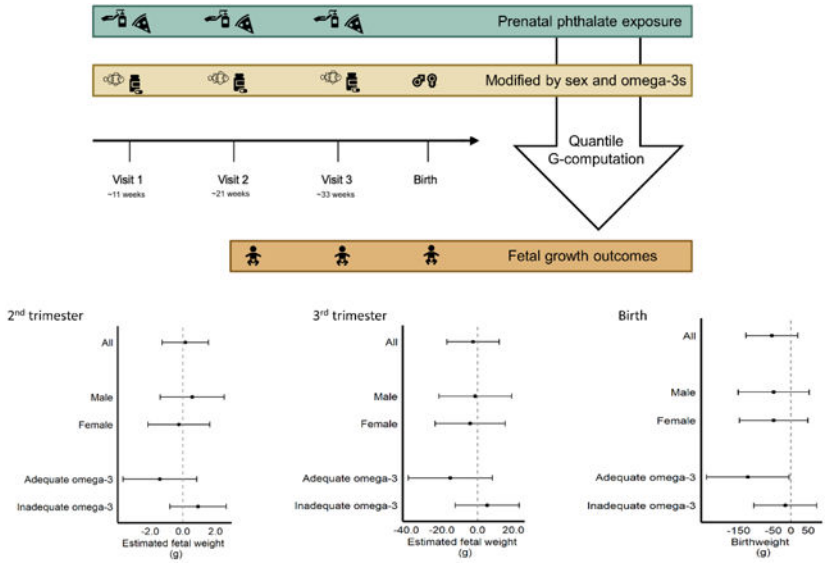
Objective: Examine the association between prenatal phthalate metabolite mixtures and fetal growth and evaluate whether that association is modified by fetal sex or omega-3 intake during pregnancy.

Methods: Analyses included 604 singleton pregnancies from TIDES, a prospective pregnancy cohort with spot urine samples and questionnaires collected in each trimester. Pregnancy-averaged phthalate exposure estimates were calculated as the geometric means of specific-gravity corrected phthalate metabolites. Fetal growth outcomes included birthweight and length, and ultrasound-derived size and velocity of estimated fetal weight, femur length, abdominal and head circumferences in the second and third trimesters. We used a novel application of quantile g-computation to estimate the joint association between pregnancy-averaged phthalate exposure and fetal growth, and to examine effect modification of that association by infant sex or omega-3 intake during pregnancy.

Results: There were few statistically significant differences in birth size and fetal growth by exposure. A one-quartile increase in the phthalate mixture was modestly associated with reduced birthweight (β [95% confidence interval)]: −54.6 [−128.9, 19.7] grams; p=0.15) and length (−0.2 [−0.6, 0.2] centimeters; p=0.40). A one-quartile increase in the phthalate mixture was associated with reduced birth length in males (−0.5 [−1.0, 0.0] centimeters) but not for females (0.1 [−0.2, 0.3] centimeters); interaction p=0.05. The phthalate metabolite mixture was inversely associated with ultrasound-derived fetal growth among those with adequate omega-3 intake. For example, a one-quartile increase in the phthalate mixture was associated with reduced abdominal circumference in the third trimesters in those with adequate omega-3 intake (−3.3 [−6.8, 0.1] millimeters) but not those with inadequate omega-3 intake (1.8 [−0.8, 4.5] millimeters); interaction p=0.01.

Conclusion: Prenatal phthalate exposure was not significantly associated with fetal growth outcomes, with some exceptions for certain subgroups.

Graphical Abstract



Keywords

Pregnancy; phthalic acid; birth weight; endocrine disruptors; fetal weight; fish oils; fatty acids; omega-3; prospective studies

1. INTRODUCTION

Phthalates are synthetic chemicals commonly used in personal care and hygiene products as well as food packaging, residential materials, and medical devices[1]. Given their widespread use, exposure to phthalates is ubiquitous in the general population including pregnant persons[2]. Prenatal phthalate exposure has been linked to adverse maternal and fetal health outcomes including pregnancy loss[3] preterm delivery[4], and abnormal fetal growth[5, 6], though epidemiologic evidence for the latter is equivocal. A 2019 review identified 19 studies examining associations between phthalates and fetal growth outcomes measured at birth, and 5 studies of phthalates and ultrasound-derived measures of fetal growth; results across studies were mixed[7]. Studies published since 2019 have also drawn inconsistent conclusions regarding this association[8–16]. Methodologic limitations in exposure or outcome assessment likely explain these mixed epidemiological findings.

Most previous investigations utilize exposure and outcome measurements assessed at a single timepoint. Outcome assessment at only one timepoint (often birthweight at delivery) may inadequately capture information regarding the pathological processes underlying potential phthalate-fetal growth association[17]. Similarly, exposure assessment at only one timepoint may inadequately capture phthalate exposure levels given their short biological half-lives[18]. It is also important to consider mixtures effects with exposure assessment, as co-exposure to multiple phthalates (e.g., mixtures) more closely resembles the human experience[19]. Methods designed to analyze mixtures are essential to address the joint effects of co-exposures[20], but are underutilized in the phthalate-fetal growth literature[21].

Given these limitations in the existing literature and the mixed epidemiologic findings, further research addressing these limitations is warranted.

Laboratory evidence suggests that fetal growth reductions following prenatal phthalate exposure may occur through pathways involving hormonal disturbances, fatty acid homeostasis, placental function, oxidative stress, and/or pro-inflammatory activity[22–24]. These pathways may differ by infant sex, leading to differential effects on fetal growth outcomes[7, 25]. Evidence suggests interventions to increase omega-3 fatty acid intake may increase fetal growth and reduce the risk of low birthweight[26]. Omega-3 fatty acids compete with pro-inflammatory omega-6 fatty acids for the same enzymes and have been shown to resolve inflammation and influence placental function[22, 26, 27]. Furthermore, omega-3 fatty acids have been shown to modify the effects of phthalates on oxidative stress biomarkers[28]. Given this, omega-3 fatty acids could ameliorate the effect of phthalates on fetal growth.

We examined the joint (mixture) effect of pregnancy-averaged urinary phthalates metabolites with fetal growth outcomes measured across pregnancy and at birth. We then examined whether infant sex or prenatal omega-3 intake serve as effect modifiers of this association.

2. MATERIAL AND METHODS

2.1 Study Population

Participants were part of The Infant Development and Environment study (TIDES), a prospective pregnancy cohort with recruitment between 2010–2012 from four academic prenatal clinics: University of California, San Francisco (UCSF); University of Rochester Medical Center; University of Minnesota; and University of Washington/Seattle Children's Hospital (UW). Study design and data collection methods have been previously published[29]. Women who met inclusion criteria (<13 weeks pregnant, aged 18 years or older, able to read and write English, planned to delivery in a study hospital, and did not have a medically threatened pregnancy) were invited to participate. Data collection occurred via questionnaires and spot urine samples collected during three routine prenatal visits generally corresponding to each of the three trimesters. Study protocols were approved by the institutional review boards of each institution as well as the Icahn School of Medicine at Mount Sinai. All participants provided written informed consent prior to starting any study activities.

2.2 Maternal urinary phthalate metabolites

Spot urine samples were analyzed for specific gravity and frozen at −80 degrees[29]. Phthalate metabolites were measured via high performance liquid chromatography at the National Center for Environmental Health, Centers for Disease Control and Prevention (CDC) or UW, as described elsewhere[30]. Phthalates included in the present analyses were: mono-ethyl phthalate (MEP), mono-benzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-3-carboxy-propyl phthalate (MCPP), mono-carboxy-isononyl phthalate (MCNP), mono-carboxy-isooctyl phthalate (MCOP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP),

mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP). Due to low detection (<10%), mono-methyl phthalate was not included in the present analysis. Machine-read values or, when not available, limit of detection (LOD)/√2 were used for concentrations below the LOD[31]. We calculated the molar sum of the four di-2-ethylhexyl phthalate metabolites (ΣDEHP) from MEHP, MEOHP, MEHHP, and MECPP. Specific-gravity corrected phthalate metabolites were calculated based on Boeniger *et al*[32].

Our main exposure was the geometric mean of specific-gravity corrected phthalate metabolites was calculated from the three study visits to obtain a more stable estimate of participant's exposure during the course of pregnancy. The geometric mean was based on the total number of measurements available across pregnancy, which was three (N=134), two (N=448), or one (N=22) measurements for all phthalate metabolites except MCOP and MCNP, which were based on three (N=134), two (N=214), or one (N=256) measurements

2.3 Fetal Growth

Fetal growth was conceptualized in two ways. First, to ensure comparability to prior studies, neonatal weight (grams (g)) on the date of delivery and length (centimeters (cm)) collected within a week of birth were considered as study outcomes. We also considered gestational-age corrected birthweight and length based on the Intergrowth-21 standard[33].

Second, we assessed fetal growth measures (estimated fetal weight, abdominal circumference, biparietal diameter, femur length, head circumference) collected by up to 9 ultrasounds abstracted from medical records. If not reported in medical records, estimated fetal weight was calculated based on Hadlock's formula[34]. Ultrasounds were conducted with varying frequency (minimum of 0 and maximum of 9 ultrasounds) and timing (minimum of 14 weeks' and maximum of 38 weeks' gestation for the first ultrasound) across participants. Thus, to enable comparisons across participants, linear mixed models with restricted cubic splines were used to model log-transformed fetal growth measures[35]. Models were fit with random intercepts and slopes, and knot points were placed at the 25^{th}, 50^{th}, and 75^{th} percentiles of gestational age[35]. We assessed model fit by comparing predicted to observed values[36]. To adjust for potential bias by the number of ultrasounds (i.e., because pregnancies with more ultrasounds may be more likely to have complications or fetal growth abnormalities), we included the number of ultrasounds as a covariate in these models. These models were then used to estimate fetal size at 14 and 27 weeks (corresponding to the start of the second and third trimesters, respectively) and average fetal velocity in the second and third trimesters. Average fetal velocity was calculated as the difference in size between the first and last week of each trimester divided by the number of completed weeks per trimester.

2.4 Covariates

Covariates included confounders identified from a directed acyclic graph (Figure S1) and included self-reported maternal age, race, education, household income, pre-pregnancy body mass index (BMI, calculated as weight in kilograms divided by height in meters squared [kg/m^2]), and previous pregnancies. Race categories included White, Black, or

Other, with "Other" representing participants self-identifying as Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, more than one race, or other. Race is a social construct, and was included in models as a proxy for culturally-driven patterns of personal care product use[37], diet[38], and unmeasured social factors (e.g., stress related to racism, interpersonal discrimination) which may influence both exposure to phthalates as well as fetal growth[39, 40]. Pre-pregnancy BMI was categorized as ≤ 24.9, 25.0–29.9, and ≥ 30 kg/m^2 (only 18 participants had a BMI < 18.5 kg/m^2). All models were additionally adjusted for study center and infant sex. We did not adjust for gestational age or pregnancy complications (e.g., gestational diabetes, hypertensive disorders of pregnancy) given their potential roles as mediators[41]. However, models for ultrasound-derived fetal growth examined outcomes at the same gestational age, and models for fetal growth at birth examined gestational-age corrected birthweight and length.

Participants reported if they used fish oil supplements every day of the week prior to each study visit; we considered fish oil supplementation as any use across the three study visits. Participants also reported the number of meals with seafood per week at each study visit. We averaged these values and dichotomized seafood consumption as adequate (at least two meals/week) versus inadequate (less than two meals/week) based on dietary guidelines[42]. Benefits of seafood must be balanced against the risk of mercury exposure, especially during pregnancy[43]. As such, fish oil supplements can provide crucial omega-3s to pregnant individuals by raising omega-3 intakes[44, 45]. Thus, omega-3 intake was determined to be adequate if a participant had any fish oil supplementation or adequate seafood consumption during pregnancy; otherwise, their intake was determined to be inadequate[45].

Smoking and pre-pregnancy diabetes were rare in our study population (only 35 participants smoked or had pre-pregnancy diabetes) so we did not adjust for those factors in primary models; a sensitivity analysis assessed whether excluding individuals who smoked or had pre-pregnancy diabetes influenced our findings.

2.5 Statistical Analysis

Statistical analyses were performed using SAS 9.4 (Cary, North Carolina, US) and R version 4.0.4 (Vienna, Austria). Analyses were restricted to participants with data for urinary phthalate metabolite concentrations and fetal growth outcomes (N=604). The distribution and descriptive statistics (means ± standard deviation (SD) and N (%)) for covariates were examined for the analytic sample and full study population. Exposures were log-transformed for analyses. Exposure correlations were examined using Pearson's correlations and visualized using a heatmap.

Missing covariate data was rare (<6% of participants in analytic sample). Missing covariate data was imputed assuming missing at random using 20 multiple chained equations[46] and included all exposures, outcomes, and covariates in addition to pre-pregnancy diabetes, smoking, gestational age at each urine collection, and gestational age at delivery.

2.5.1 Multi-Pollutant Analysis—Quantile g-computation estimated the effect of simultaneously increasing all exposures by one quartile (i.e., the joint association of the pregnancy-averaged phthalate metabolite mixture) on fetal growth outcomes[47]. Models

were run separately for each fetal growth outcome in each trimester. In brief, quantile g-computation transforms the set of exposures into quantized versions by creating exposure scores $s = 0,1,2,\ldots$ which indicates which quantile-based exposure category the exposure value falls into for each individual. Non-exposure covariates are left untransformed. As described in the original paper on quantile g-computation, the approach then regresses the outcome on the quantized exposures and covariates in a generalized linear model[47].

A parametric generalized linear model regressed the outcome onto the set of quantized exposures and covariates. We report the β (95% CI) from these analyses, which represents the difference in each outcome per a one-quartile simultaneous increase in all exposures within the mixture. Positive and negative weights calculated from the regression coefficients for each quantized exposure sum to one and are interpreted as the proportion of the positive or negative partial effect attributable to a given mixture component. Weight plots from quantile g-computation can be interpreted as presenting the *relative* contributions of each mixture component to either the positive or negative partial effects and should not be interpreted as effect sizes.

A novel extension of quantile g-computation examined effect modification of the joint association by infant sex and omega-3 intake in the qgcompint package[48]. As with standard quantile g-computation, standard errors for coefficients are calculated either via standard rules for linear combinations of correlated random variables from the underlying model covariance matrix or via bootstrapping. Here, the linear combination is made from all modifier by exposure interaction terms in the underlying model. These standard errors are then used for estimating confidence intervals and constructing p-values via Wald Z-statistics. From these models, we report the β (95% CI) estimates for the phthalate metabolite mixture-fetal growth association by level of each potential effect modifier. We also assessed effect modification by each individual source of omega-3 intake separately (i.e., seafood or fish oil supplementation); these models were mutually adjusted for the other source of omega-3 intake.

2.5.2 Secondary Analysis—We ran single-pollutant analyses as a secondary analysis. Adjusted linear regression models were used to estimate the association between each pregnancy-averaged phthalate metabolite and fetal growth outcomes. Models were run separately for each fetal growth outcome in each trimester. We report the β and 95% confidence intervals (β (95% CI) from these analyses, which represent the difference in each outcome per interquartile range (IQR)-standardized increase in each exposure. The Benjamini-Hochberg false discovery rate (FDR)[49] addressed multiple comparisons; an FDR q-value < 0.10 was considered statistically significant.

2.5.3 Sensitivity Analysis—To assess the robustness of our results, we performed several sensitivity analyses. First, though pregnancy-averaged phthalates may provide a more stable estimate of exposure relative to exposure measured at a single time point, they do not ensure temporality of all analyses nor do they allow assessment of trimester-specific effects[7]. Thus, we additionally ran quantile g-computation models with the exposure mixture composed of phthalate metabolites measured at the first and third study visits. The second study visit was excluded due to small numbers of participants with measured

exposure levels for all metabolites (n=135). This allowed us to examine the contribution of exposure biomarker concentrations from the first and third visits to the overall associations observed. To ensure temporality of the exposure-outcome association, we examined these associations only for outcomes at birth.

In main analyses, participants missing any fetal growth outcomes were excluded due to variations in exposure quartile cut-offs with changes in the included sample for each outcome, which would limit the ability to draw comparisons across outcomes. However, in sensitivity analyses we re-ran multi-pollutant (quantile g-computation) analyses for birth outcomes including all participants with birthweight or length (n=754) to regain precision for those analyses. We also re-ran multi-pollutant models examining the phthalate metabolite mixture associated with fetal growth outcomes with restriction to participants who do not smoke or have pre-pregnancy diabetes (n=465).

3. RESULTS

3.1 Descriptive Analysis

Of the 966 participants with singleton pregnancies recruited for TIDES, 791 (81.9%) had data on all pregnancy-averaged phthalate metabolites. Of those, 604 (76.3%) had data collected on all fetal growth outcomes and made up the final analytic sample. Study characteristics were similar among those in the overall and analytic samples (Table S1). Study participants were predominantly White, highly educated with a higher income, a BMI ≤ 24.9 kg/m^2 and inadequate omega-3 intake (Table 1). Gestational age at birth was 38.9 ± 1.7 weeks.

Specific-gravity adjusted phthalate metabolites at the three study visits (Table S2) were averaged for analyses (Table 2). We observed positive correlations between most phthalate metabolites (Figure 1). MCOP and MCPP were moderately correlated (Pearson’s correlation > 0.60) with one another, as were MnBP with both MBzP and MiBP. Given strong correlations between DEHP metabolites (average Pearson’s correlation 0.78), the ΣDEHP was used in analyses.

3.2 Multi-Pollutant Analysis

A one-quartile increase in the pregnancy-averaged phthalate metabolite mixture was inversely associated with birthweight (−54.6 [−128.9, 19.7] grams; p=0.15) and length (−0.1 [−0.2, 0.0] centimeters; p=0.14) (Figure 2, Table S3).

Significance was similar with the use of gestational-age corrected z-scores. MBzP contributed the most to the inverse association between the phthalate metabolite mixture and birthweight (Figure S1) and length (Figure S2) relative to other metabolites included in the mixture. Ultrasound-derived fetal size (Figure 3) and velocity (Figure 4) were not significantly different for a one-quartile increase in pregnancy-averaged exposure. At birth, male infants were 0.5 centimeters shorter (−1.0, 0.0) for each one-quartile increase in the phthalate metabolite mixture, whereas the association was null for females (0.1 [−0.2, 0.3]; p for interaction = 0.05). Few other sex-based differences were observed (Table S4).

The phthalate metabolite mixture was inversely associated with fetal growth outcomes among those with adequate omega-3 intake but not those with inadequate omega-3 intake; estimates were greater in magnitude for abdominal circumference and femur length during pregnancy (Table S5). For example, a one-quartile increase in the phthalate metabolite mixture was associated with a 1.8 (−0.8, 4.5) millimeter difference in abdominal circumference in the third trimester among those with inadequate omega-3 intake, and a −3.3 (−6.8, 0.1) millimeter difference in abdominal circumference in the third trimester among those with adequate omega-3 intake (p for interaction = 0.02). This association appeared to be driven by fish oil supplementation, as the phthalate metabolite mixture was strongly inversely associated with almost all fetal growth outcomes among those with fish oil supplementation but not associated with fetal growth outcomes among those without fish oil supplementation (Table S6). Conversely, the phthalate metabolite mixture was positively associated with some fetal growth outcomes among those with adequate seafood consumption and not associated with fetal growth outcomes among those with inadequate seafood consumption (Tables S7).

3.3 Single Pollutant Analysis

All phthalate metabolites were modestly inversely associated with in birth size (range - 3.0 to −58.8 grams in birthweight, and 0.1 to −0.4 centimeters in birth length) in single-pollutant analyses (Table S8); findings were similar for birthweight and length z-scores. Most individual phthalate metabolites were not significantly associated with fetal size (Table S9) or velocity (Table S10). MCPP was positively associated with biparietal diameter size in the second and third trimesters, and velocity of biparietal diameter, abdominal circumference, and head circumference in the second trimester. However, no comparisons were statistically significant when using FDR q-values.

3.4 Sensitivity Analysis

When first and third trimester phthalate metabolite measurements were included separately in the quantile g-computation model, the mixture was inversely associated with birthweight (−31.8 [−146.0, 82.4] grams) and length (−0.1 [−0.8, 0.5] centimeters). Measurements from the third trimester, and specifically DEHP and MCNP, contributed the most to the inverse effect of the phthalate metabolite mixture on birthweight (Figure S3). MBzP in the third trimester contributed most strongly to the inverse effect of the phthalate metabolite mixture on birth length (Figure S4).

Quartiles of pregnancy-averaged specific-gravity adjusted phthalate metabolites were similar in sensitivity analyses including all participants with measured birth outcomes (Table 11). These analyses found associations of lesser magnitude and significance than our main analysis, but in similar directions (Table S12). Quartiles of pregnancy-averaged specific-gravity adjusted phthalate metabolites were similar in sensitivity analyses among those who did not smoke or have diabetes (Table 13). These analyses found associations similar to our main analysis (Table S14).

4. DISCUSSION

In this prospective pregnancy cohort, we observed that a mixture of prenatal phthalate exposures was modestly associated with reduced infant size at birth and with reduced fetal growth in certain subgroups. Findings were imprecise and included the null, but direction of the association was consistent across outcomes (i.e., original units versus z-scores), single and multiple pollutant analyses, and in sensitivity analyses. We identified MBzP as a major contributor to the inverse association between phthalate metabolites and fetal growth outcomes. Phthalate exposure was associated with reduced birth length in male infants relative to female infants, but no other sex-based differences in the phthalate-fetal growth association were observed. Unexpectedly, the association between the phthalate metabolite mixture and fetal growth was significantly modified by omega-3 intake, with inverse associations of large magnitude among participants with adequate intake compared to those with inadequate intake. These differences were driven primarily by fish oil supplementation as opposed to seafood intake. Finally, inverse associations between phthalates and birth size were of greater magnitude for exposures in the third trimester as opposed to the first trimester in this cohort.

Birthweight is an important indicator of short- and long-term health[50, 51]. Whether phthalate exposure during pregnancy influences size at birth including birthweight has been examined in numerous prior studies with inconsistent results likely attributable to methodologic heterogeneity in exposure and outcome assessment[7]. In fact, a prior analysis in this study population found that first trimester MCOP and DEHP were associated with increased birthweight[52]. We observed consistent associations between pregnancy-averaged phthalate metabolites and smaller sizes at birth, but confidence intervals were imprecise and included the null. The use of exposure and outcome assessment at one timepoint likely impacted the difference in findings between the prior and current study. Further, a novel component of the current analysis is the use of a multi-pollutant mixtures approach. Mixtures modelling approaches allow researchers to better mimic real life exposure circumstances[19]. Few prior studies have examined whether environmental mixtures including phthalates influence size at birth. Phthalate exposure in these studies has been generally modestly inversely associated with birth size[9, 10, 15, 21, 53, 54], though the significance and strength of associations has varied. Phthalate exposure levels in these studies have been comparable or higher than in the current study, but statistical methods have varied widely and include cluster-based methods[9, 21], multivariable regression[53, 54], Bayesian kernel machine regression[15, 21], and quantile g-computation[10]. Two of these studies included other (i.e., non-phthalate) environmental exposures when estimating mixture effects[9, 10]. These methodologic discrepancies make direct comparisons of results difficult despite similarities in exposure. However, Van den Dries et al. employed similar methodology and reported similar effect sizes for birthweight comparisons between the highest to lowest quartiles of exposure (−142 grams in Van den Dries and −164 grams in the current study); phthalate metabolite concentrations in the current study were generally lower[10]. Quantile g-computation is a relatively new mixtures method that possesses many advantages including interpretability, computational ease, non-linearity and non-additivity of individual mixture components, and minimal bias under various exposure scenarios[47].

Our mixtures approach also allowed us to examine exposure biomarkers from individual study visits for the investigation of periods of susceptibility to exposure. We identified the third trimester as a potentially vulnerable window for the relationship between phthalate exposure and birth size. However, prior studies have identified the first[12] and second[10, 12, 53] trimesters as potential periods of susceptibility. Adipogenesis initiates in the second trimester[55] and may be disrupted by exposure to phthalates[56, 57]. As birthweight is composed of 12–15% fat mass (adipose)[58], these overall consistent findings for trimester-specific associations may suggest adipogenesis as a potential pathway whereby fetal growth is compromised by phthalate exposure. Further research examining periods of susceptibility and mechanisms whereby fetal development may influenced by phthalates is clearly needed.

Birth size is a proxy for the fetal growth patterns which contribute to it. Ultrasound-derived measures of fetal growth can provide additional information regarding the etiology and prognosis for the infant as well as periods of fetal vulnerability to phthalate exposure[17]. Few prior studies have examined ultrasound-derived measures of fetal growth in relation to phthalate exposure[7]. Four studies[10, 12, 59, 60] have reported that phthalates were associated with lower fetal weight during pregnancy and one study[54] reported phthalates were associated with intrauterine growth restriction; not all studies have confirmed these findings[61]. We found little evidence for an association between phthalates and ultrasound-derived measures of fetal growth. The inconsistency of our study in relation to prior reports may be explained by differences in study populations or methodology. Prior studies have examined associations between phthalates and fetal growth indices in the Netherlands[10, 12], Spain[61], China[54], United States[59], and among males in France[60]; these studies have generally had comparable or higher phthalate exposure levels. Prior studies have primarily involved single pollutant methods[12, 54, 59–61] with a recent study using quantile g-computation[10]. We observed no effect modification by infant sex. There is little consistency in the literature regarding effect modification of the phthalate-fetal growth association by infant sex[7].

Phthalates may influence fetal growth through several biologic pathways. Phthalates may have pro-inflammatory effects operating through peroxisome proliferator-activated receptors (PPARs) and/or the induction of cyclooxygenase-2 expression[23]. Operating through PPARs, phthalates may influence essential fatty acid homeostasis, which is essential for normal placental function[23]. Inflammation and placental function have been tied to fetal growth restriction[7]. Omega-3 fatty acids have anti-inflammatory effects and can aid in regulating placental transport[22, 27]. Thus, omega-3 intake has been hypothesized to protect against the adverse effects of phthalate exposure on fetal growth outcomes[22]. Contrary to this hypothesis, in this analysis, phthalate exposure was associated with reduced fetal growth in participants with adequate omega-3 intake as compared to those with inadequate omega-3 intake. Notably, this appeared to be driven by fish oil supplementation in models where omega-3 intake was separated by source (fish oil supplementation or seafood consumption). These discrepancies in findings by source of omega-3s suggest that the factor driving observed differences in the phthalate-fetal growth relationship may not be omega-3 itself. In this cohort, fish oil supplementation was double that of the general population (25% versus 12%)[44], potentially due to cohort characteristics (i.e., highly educated, healthy, predominantly White population). Further, fish oil supplementation

is multifactorial, and frequently co-occurs with other behaviors (e.g., increased physical activity, dietary deficiencies)[62]. Unfortunately, we did not have detailed ascertainment of participant behaviors which may have driven fish oil supplementation in this population. These unmeasured behaviors may have influenced our findings, resulting in the effect of phthalates on reduced fetal growth appearing pronounced among supplementers. For example, supplementers tend to have higher rates of physical activity[62], and physical activity is associated with smaller size at birth[63]. We were unable to control for physical activity in analyses; thus, the compounding effects of increased physical activity and phthalate exposure may have contributed to our findings among supplementers. If not an artifact of uncontrolled confounding, our findings may have an underlying biological explanation. However, prior literature does not provide a persuasive biological explanation for our findings at this time. Importantly, despite our contrary results for omega-3s overall – and fish oil more specifically – a diet including adequate seafood intake may ameliorate the adverse effects of phthalate exposure on fetal growth outcomes. Given the biologic plausibility of omega-3 as a nutritional intervention against the adverse effects of phthalates on fetal growth, and our encouraging findings among those with adequate seafood intake, further study is needed.

The results of this study should be considered in light of its strengths and limitations. This is one of the first studies to comprehensively examine the mixtures association between phthalate exposure and fetal growth outcomes from multiple timepoints during pregnancy. We implemented a novel application of quantile g-computation to examine effect modification of this association by infant sex and omega-3 intake. Our primary modelling approach considered exposure averaged across pregnancy, which accounts for variation in exposure levels over time but ignores temporality of the exposure-outcome relationship in models examining ultrasound measures of fetal growth during early pregnancy. However, a sensitivity analysis accounted for this lack of temporality. Results of our analyses for omega-3 intake may be subject to measurement error, as participants only reported seafood intake and fish oil supplementation in general as opposed to the specific types of seafood and fish oil supplements. We were also unable to assess all dietary sources of omega-3 intake (e.g., walnuts, chia seeds) or supplementation (e.g., flax, prenatal vitamins with DHA). Sensitivity analyses sought to confirm robustness of results, but findings may still be due to uncontrolled confounding, in particular by factors that are associated with fish oil supplementation. Alternate reference or standards for fetal growth specific to the US population might have been used in place of Intergrowth-21 population standard. US professional societies do not currently recognize a national reference or standard for fetal growth outcomes[33, 64]. Given our interest in comparisons of rank rather than absolute differences, we do not anticipate our choice of reference or standard to substantially influence study conclusions.

5. CONCLUSIONS

In this prospective pregnancy cohort, prenatal exposure to a mixture of phthalates was modestly inversely associated with birth size and, in certain subgroups, fetal growth. Further research is needed to identify and understand potential factors that may modify this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge all study staff and participants, in particular the study coordinators who performed the chart reviews: Garry Alcedo, Sarah Caveglia, Alana Cordeiro, and Stacey Moe.

Funding Acknowledgements:

This work was supported by the Intramural Research Program, National Institutes of Health, National Institute of Environmental Health Sciences (ZIA103313) and the extramural NIEHS grants R01 ES016863-04 and P30 ES005022. Funding sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

ABBREVIATIONS

CI	confidence interval
cm	centimeter
DEHP	di-2-ethylhexyl phthalate
DHA	docosahexaenoic acid
FDR	false discovery rate
g	grams
IQR	interquartile range
kg	kilograms
LOD	limit of detection
MBzP	mono-benzyl phthalate
MCNP	mono-carboxy-isononyl phthalate
MCOP	mono-carboxy-isooctyl phthalate
MCPP	mono-3-carboxy-propyl phthalate
MEP	mono-ethyl phthalate
MiBP	mono-isobutyl phthalate
MnBP	mono-n-butyl phthalate
TIDES	The Infant Development and Environment Study
UCSF	University of California, San Francisco
UW	University of Washington/Seattle Children’s Hospital
wk	week

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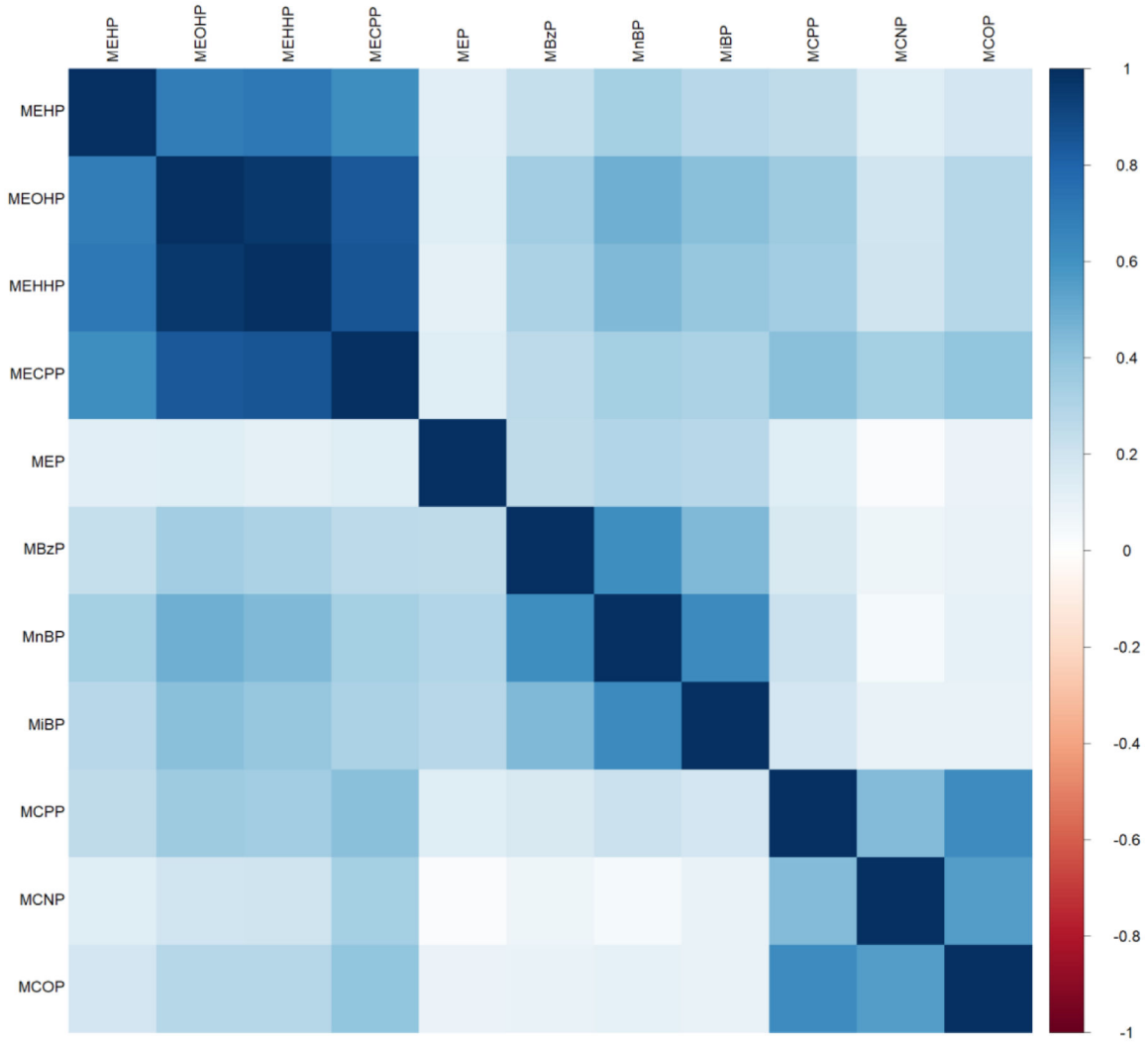

Figure 1.

Correlation matrix of pregnancy-averaged specific-gravity adjusted phthalate metabolites in analytic sample (N=604), TIDES, 2010–2012. Abbreviations: MEHP, mono-2-ethylhexyl; MEOHP, mono-2-ethyl-5-oxohexyl; MEHHP, mono-2-ethyl-5-hydroxyhexyl; MECPP, mono-2-ethyl-5-carboxypentyl; MBzP, mono-benzyl phthalate; MCNP, mono-carboxy-isononyl phthalate; MCOP, mono-carboxy-isooctyl phthalate; MCPP, mono-3-carboxy-propyl phthalate; MEP, mono-ethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-n-butyl phthalate

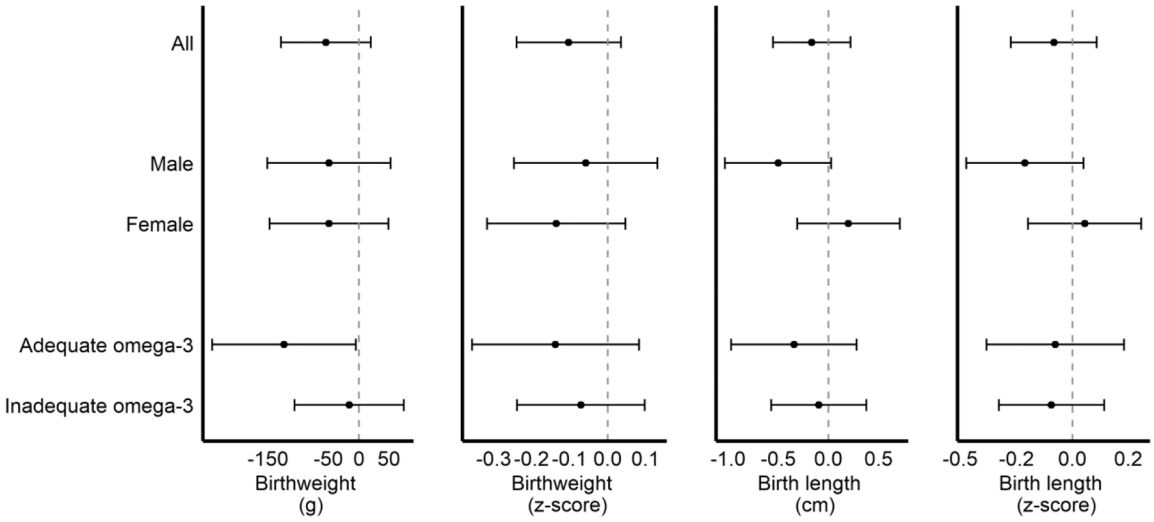

Figure 2.

Multi-pollutant model results (β and 95% confidence intervals) for the association between the pregnancy-averaged phthalate metabolite mixture and fetal growth outcomes at delivery in analytic sample (N=604), TIDES, 2010–2012. β represents the difference in outcome for a one-quartile increase in the phthalate mixture. Models were adjusted for maternal age, BMI, race, education, income, parity, infant sex, and study site. Abbreviations: cm, centimeters; g, grams

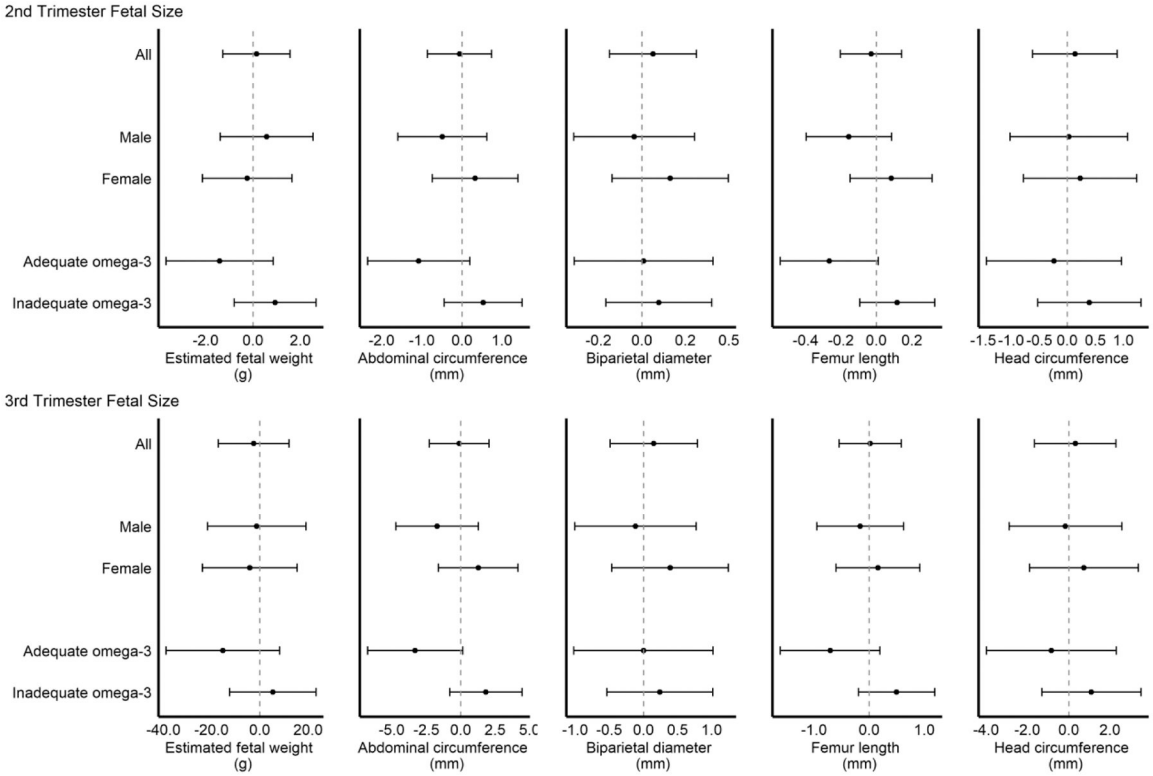

Figure 3.

Multi-pollutant model results (β and 95% confidence intervals) for the association between the pregnancy-averaged phthalate metabolite mixture and fetal size in the 2nd trimester (14 weeks) and 3rd trimester (27 weeks) in analytic sample (N=604), TIDES, 2010–2012. β represents the difference in outcome for a one-quartile increase in the phthalate mixture. Models were adjusted for maternal age, BMI, race, education, income, parity, infant sex, and study site. Abbreviations: g, grams; mm, millimeters

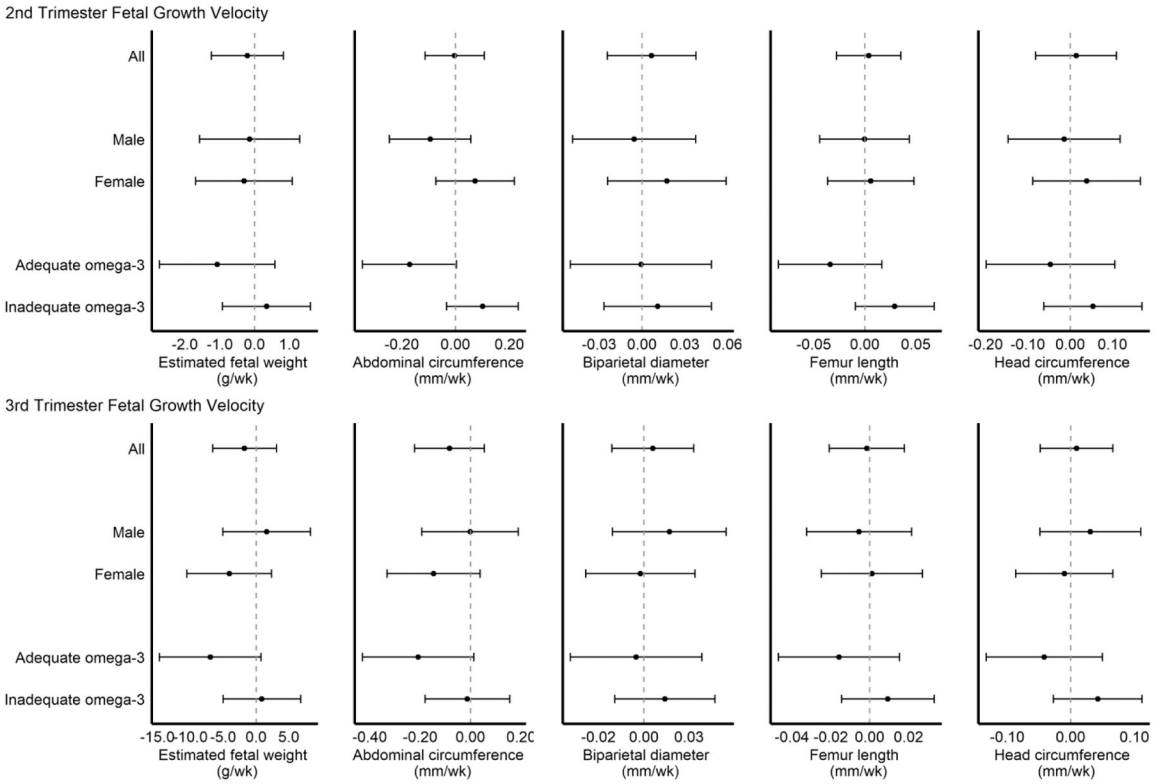

Figure 4.

Multi-pollutant model results (β and 95% confidence intervals) for the association between the pregnancy-averaged phthalate metabolite mixture and fetal growth velocity in the 2nd and 3rd trimesters in analytic sample (N=604), TIDES, 2010–2012. β represents the difference in outcome for a one-quartile increase in the phthalate mixture. Models were adjusted for maternal age, BMI, race, education, income, parity, infant sex, and study site. Abbreviations: g, grams; mm, millimeters; wk, gestational week

Table 1.

Study sample characteristics in analytic sample (N=604), TIDES, 2010–2012

Participant characteristics	Mean ± SD or N (%)
Age (years)	30.5 ± 5.7
Race	
White	404 (66.9%)
Black	87 (14.4%)
Others[a]	113 (18.7%)
Education	
High school degree or less	95 (15.8%)
Any technical school/college	261 (43.5%)
Graduate degree	244 (40.7%)
Income	
< $25K	151 (25.9%)
$25K – $65K	112 (19.2%)
> $65K	319 (54.8%)
Pre-pregnancy BMI (kg/m^2)	
BMI ≤ 24.9	351 (58.7%)
BMI 25.0–29.9	123 (20.6%)
BMI ≥ 30	124 (20.7%)
Any prior pregnancies	
Yes	365 (62.1%)
No	223 (37.9%)
Center	
University of California San Francisco	158 (26.2%)
University of Minnesota	104 (17.2%)
University of Rochester Medical Center	204 (33.8%)
University of Washington	138 (22.8%)
Infant sex	
Male	287 (47.5%)
Female	317 (52.5%)
Omega-3 intake during pregnancy	
Adequate[b]	238 (39.4%)
Inadequate	364 (60.3%)
Any smoking during pregnancy	
No	503 (83.3%)
Yes	29 (4.8%)
Pre-pregnancy diabetes	
No	557 (92.2%)
Yes	30 (5.0%)
Gestational age at birth (weeks)	38.9 ± 1.7
Birthweight (grams)	3350.5 ± 557.2

Participant characteristics	Mean ± SD or N (%)
Birth Length (centimeters)	50.2 ± 2.9

Missingness included education (n=4), income (n=22), parity (n=16), pre-pregnancy BMI (n=6), omega-3 intake (n=2), smoking (n=72), pre-pregnancy diabetes (n=17)

[a]Other category refers to participants self-identifying as Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, more than one race, or other

[b]Adeauate omega-3 intake defined as meeting recommend intakes of seafood (at least two meals/week) or fish oil supplementation during pregnancy

Table 2.

Distributions of specific-gravity pregnancy-averaged adjusted phthalate metabolites (ng/mL) in analytic sample (N=604), TIDES, 2010–2012

Phthalate	Metabolite	Percentiles				
		Minimum	25th	50th	75th	Maximum
Diethylhexyl (DEHP)	Mono-2-ethylhexyl	0.3	1.4	2.2	3.4	26.6
	Mono-2-ethyl-5-oxohexyl	0.6	3.6	5.4	8.1	105.7
	Mono-2-ethyl-5-hydroxyhexyl	0.9	4.8	7.2	11.0	119.2
	Mono-2-ethyl-5-carboxypentyl	2.5	7.5	11.1	16.9	120.3
	ΣDEHP[a]	0.02	0.06	0.09	0.13	1.34
Diethyl	Mono-ethyl (MEP)	2.2	17.1	37.7	84.5	3925.4
Benzylbutyl	Mono-benzyl (MBzP)	0.4	2.3	4.4	8.5	484.6
Dibutyl	Mono-n-butyl (MnBP)	0.8	5.6	8.8	14.5	1228.7
Di-isobutyl	Mono-isobutyl (MiBP)	0.6	3.7	6.0	10.0	62.3
Di-n-octyl	Mono-3-carboxy-propyl (MCPP)	0.2	1.2	2.2	4.5	187.7
Di-isodecyl	Mono-carboxy-isononyl (MCNP)	0.2	1.6	2.5	4.4	320.9
Di-isononyl	Mono-carboxy-isooctyl (MCOP)	1.2	7.6	16.4	34.9	508.1

[a]Molar sum in nmol/mL