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Correlation and temporal variability of urinary biomarkers of chemicals among couples: Implications for reproductive epidemiological studies

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Abstract

Background: Exposure to some environmental chemicals is ubiquitous and linked to a variety of adverse outcomes, including children's health. While few studies have assessed the contribution of both male and female exposures to children's health, understanding the patterns of couple's exposure is needed to understand their joint effects.

Objective: We assessed the correlation patterns between male and female partners' concentrations of 37 environmental chemical biomarkers. We also assessed the temporal reliability of the biomarkers within couples.

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Conflicts of interest

JMB was financially compensated for serving as an expert witness for plaintiffs in litigation related to tobacco smoke exposures. Other coauthors declare no conflict of interest.

Methods: We calculated Spearman pairwise correlations between specific gravity adjusted urinary biomarker concentrations and hair mercury concentrations among 380 couples enrolled in the Environment and Reproductive Health (EARTH) study at the Massachusetts General Hospital Fertility Center (2004–2017). We calculated intra-class correlation coefficients (ICCs) for couple's biomarkers to assess the temporal variability of these exposures within a couple using multiple paired-samples from couples.

Results: All biomarkers were positively correlated within couples (range: 0.05 for *tert*-butylphenyl phenyl phosphate to 0.66 for triclosan). In general, the biomarkers with the highest within couple correlation were those of chemicals for which diet (e.g., di(2-ethylhexyl) phthalate), personal care products use (e.g., triclosan, benzophenone-3), and the indoor environment (e.g., 2,5-dichlorophenol) are considered primary exposure sources. Most other biomarkers were moderately correlated (0.3– < 0.6). Similar patterns of temporal reliability were observed across biomarkers.

Conclusions: Urinary concentrations of several biomarkers were mostly moderately correlated within couples, suggesting similar exposure sources. Future epidemiological studies should collect samples from both partners to be able to accurately determine the contribution of maternal and paternal exposures to offspring health.

Keywords

Couple; Chemicals; Phthalate; Phenol; Organophosphate flame retardants; Mercury; Correlation

1. Introduction

There is increasing concern regarding the health effects of chemical exposures. Endocrine disrupting chemicals (EDCs) have been investigated for potential health effects, including adverse reproductive health outcomes in both men and women. These chemicals include, among others, phthalates and their alternatives, phenols (Messerlian et al., 2018a), and organophosphate flame retardants (PFRs) (Carignan et al., 2017; Carignan et al., 2018). There is ubiquitous exposure to these chemicals among the general population, including men and women of reproductive age. Another exposure of concern is mercury, a neurotoxicant and potential reproductive toxicant that can pass through the placental barrier (Minguez-Alarcon et al., 2018; Wright et al., 2015).

Although studies have reported associations between biomarkers of these EDCs with adverse reproductive outcomes, a common limitation in almost all studies is that they only measure either maternal or paternal biomarkers of exposure, but not both. Only a few studies (Buck Louis et al., 2012; Buck Louis et al., 2013; Buck Louis et al., 2014; Messerlian et al., 2017; Messerlian et al., 2018a; Robledo et al., 2015; Wu et al., 2017a; Wu et al., 2017b) have considered both paternal and maternal exposures. However, limited information on the correlation patterns of the exposures within the same couple may impact the statistical analysis of associations with male and female exposures. Only one recent study has examined the correlation patterns among couples in the general population, although there was only a single sample from each partner (Chung et al., 2018). In addition, it is important to know if we can disentangle maternal from paternal contributions and determine whether

joint exposures within or across couples are important. Consequently, this will inform future studies to better assess exposure to these chemicals and how to efficiently use limited research resources.

Therefore, taking advantage of the Environment and Reproductive Health (EARTH) cohort study which evaluated urinary concentrations of a wide array of biomarkers in urine and mercury in hair, we examined the correlation patterns among biomarkers and mercury within couples. We assessed the temporal reliability of these biomarkers within couples (when both the male and female partner participated), and also within all women and men participating in the EARTH study regardless of whether their partner participated. We hypothesized that concentrations of biomarkers that are highly correlated within couples would represent chemicals with common sources among couples.

2. Methods

2.1. Study population

The EARTH study (2004–present) is an ongoing prospective cohort that has been enrolling couples seeking fertility treatment at the Massachusetts General Hospital (MGH) Fertility Center to identify determinants of fertility (Messerlian et al., 2018b). Women and men between 18–46 years and 1855 years, respectively, were eligible to participate, and approximately 50–60% of those men and women contacted by the research staff enrolled in the study. Couples were invited to participate but both men and women could participate without their partner. Upon enrollment, men and women completed questionnaires that collected information on demographics, lifestyle, and health information, and the research staff measured their height and weight. At recruitment and at subsequent visits, both men and women provided spot urine samples and one hair sample. Participants were followed from study enrollment until the female partner had a live birth or the couple discontinued treatment at MGH. Urine samples are usually collected at different times within the EARTH study for men/women. In the current analysis, men and women were eligible if they were part of a participating heterosexual couple and provided at least one urine sample on the same day as their partner. A subset of those couples also provided hair samples. All participants signed an informed consent after study procedures were explained to them by research study staff. The EARTH study was approved by institutional review boards at MGH, the Harvard T.H. Chan School of Public Health, and the Centers for Disease Control and Prevention (CDC).

2.2. Quantification of urinary biomarker concentrations

At each visit, participants provided a spot urine sample in a sterile polypropylene cup using standard procedures. Study staff recorded the time of collection and measured specific gravity (SG) using a handheld refractometer (National Instrument Co. Inc.). Urine samples were divided into aliquots, frozen, and stored at –80 °C before overnight shipment on dry ice to H.M. Stapleton’s laboratory at Duke University (Durham, NC) for quantification of PFRs and to the CDC laboratory (Atlanta, GA) for quantification of all other urinary biomarkers. Each biomarker was measured by the same laboratory following the same methods consistently over the whole study period. The samples were collected from 2004 to 2017 and

were sent for chemical analysis in batches to the laboratories over years. Although time elapsed between collection and analyses ranged from months to several years, at the subfreezing temperatures used for storage of the study samples, urinary concentrations of phthalates and phenols biomarkers are known to be stable for years (Samandar et al., 2009; Ye et al., 2007).

Briefly, the analytical techniques for quantification of the urinary biomarkers of phthalates, phenols, and flame retardants involved enzymatic deconjugation of the target analytes followed by solid-phase extraction, separation by high performance liquid chromatography, and detection by isotope-dilution tandem mass spectrometry (Dwivedi et al., 2018; Silva et al., 2013; Zhou et al., 2014).

CDC staff quantified total (free plus conjugated) urinary concentrations (μg/L) of triclocarban, eleven phenols: (bisphenol F (BPF), bisphenol A (BPA), bisphenol S (BPS), methylparaben, ethylparaben, propylparaben, butylparaben, benzophenone-3, triclosan, 2,4-di-chlorophenol, and 2,5-dichlorophenol), and of twenty phthalate and phthalate alternative metabolites: cyclohexane-1 2-dicarboxylic acid monohydroxy isononyl ester (MHiNCH), cyclohexane-1 2-dicarboxylic acid monocarboxyisooctyl ester (MCOCH), mono-methyl phthalate (mMP), monoethyl phthalate (MEP), mono-*n*-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-hydroxybutyl phthalate (MHBP), mono-hydroxyisobutyl phthalate (MHiBP), mono-3-carboxypropyl phthalate (MCPP), monobenzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), monooxononyl phthalate (MONP), mono-2-ethyl-5-hydrohexyl terephthalate (MEHHTP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-isononyl phthalate (MiNP), mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP), mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono carboxyisooctyl phthalate (MCOP), and mono carboxyisononyl phthalate (MCNP).Duke staff quantified the urinary concentrations (μg/L) of five flame retardants: bis(1-chloro-2-propyl) phosphate (BCIPP), bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), diphenyl phosphate (DPHP), isopropylphenyl phenyl phosphate (ip-PPP), and tertbutyl-PPP (tb-PPP). The limits of detection (LOD) ranged from 0.01 for *tert*-butylphenyl phenyl phosphate (tb-PPP) to 2.3 μg/L for triclosan.

2.3. Hair mercury

A hair sample was collected by study staff or if the hair was not long enough, participants were instructed to collect the hair sample when they went for a haircut. Before analysis, the hair samples were cleaned by sonication for 15min in a 1% Triton X-100 solution to remove extraneous contaminants. Staff at the Trace Metals Laboratory, Harvard T. H. Chan School of Public Health rinsed the hair samples with distilled deionized water and dried 5 times at 60 °C for 48 h. Total mercury in parts per million (ppm) was measured using the proximal 2 cm of hair using a Direct Mercury Analyzer 80 (Milestone Inc., Monroe, CT) with a matrix matched calibration curve. Certified reference material GBW 07601 (human hair; Institute of Geophysical and Geochemical Exploration, China) containing 360 ppm mercury was used as the quality control standard. The LOD for mercury was 0.01 ppm with the percentage recovery for quality control standards ranging from 90 to 110%.

2.4. Statistical analysis

We calculated and compared descriptive statistics between men and women for the baseline characteristics such as age, race, body mass index (BMI), smoking, and education, and for the time varying characteristics such as season and time of the day of sample collection for both men and women among couples. We restricted our evaluation to urine samples collected on the same day for both partners due to the relatively short half-lives of the phenols, phthalates, and PFRs. Mercury concentrations in hair reflect exposure over several months (Grandjean et al., 2002) and have been shown to be correlated with mercury concentrations in blood and urine (Barbone et al., 2018; Foo et al., 1993; McDowell et al., 2004). For inclusion in the present analysis we required hair samples of couples to be measured within two months of each other to correspond with the 2 cm of the hair samples used for the measurement of mercury. We accounted for urinary dilution by adjusting for SG, using the following formula: $Pc = P\ [(SG\ mean - 1)/(SG - 1)]$, where Pc is the SG-corrected urinary concentration (μg/L), P is the measured biomarker concentration (μg/L) of the urine sample, and SG mean is the mean SG concentration in the study population (1.014 for women and 1.017 for men) (Hauser et al., 2004). We excluded BCIPP from the analyses because it was not detected in any of the measured samples. For the other biomarkers, values below the LOD were replaced with an imputed value (below the LOD), based on a single imputation conducted separately for each biomarker and sex using the fully conditional specification (FCS) method (Van Buuren, 2007). For any given value below the LOD, the predictors for imputation were race (Caucasian or not), age (continuous), ever smoking, and time of the urine sample collection.

We assessed biomarker concentrations as continuous variables, after natural-log transformation (and SG adjustment) because of skewed distributions. We assessed the pairwise correlations by calculating Spearman correlations among biomarker concentrations between partners using all samples per couple collected on the same days (paired-samples per couple collected on the same day repeated over time). We visualized the spearman correlations within and between partners as an exposome globe (Chung et al., 2018). We also assessed the between- and within-couple variability (i.e. temporal reliability) of biomarkers by calculating the intra-class correlation coefficients (ICC) of the couple's biomarkers using paired-samples from couples collected on the same days repeated over time. ICCs for couples here represent the variance explained by "the shared environment" for the couples.

We also calculated the partial Spearman correlation and the adjusted ICC as proposed by Hankinson et al. (Hankinson et al., 1995) after adjusting for different predictors of biomarker concentrations for both partners. Selection of predictors was based on previous knowledge and included men's and women's race (Caucasian or not), age (continuous), ever smoking, and time of the day of the urine sample collection. None of these covariates made a substantial difference in the correlation or ICC estimation for couples' biomarkers.

As a supplementary analysis, we calculated partner-specific ICCs for the biomarker concentrations for women and men who were part of participating couples as well as all men and women in the EARTH study to characterize the temporal reliability within each partner

over time. We conducted statistical analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC) and the Circlize R package for exposome globe generation (v 0.3.1).

3. Results

Among 474 men and 819 women participants who enrolled in the EARTH study between 2004 and 2017, there were 380 couples in which both the man and woman participated and provided at least one urine sample on the same day. These 380 couples collectively provided 1682 urine samples (average of 4 samples/couple, i.e., 2 samples/partner) (Supplementary Fig. 1). All samples were provided pre-conception. Among those 380 couples, 145 couples also had a hair sample from each partner within two months.

Most men and women were Caucasian (84%) and had never smoked cigarettes (78%). Only 3% of the women and 6% of the men were current smokers at the time of enrollment. The median age was higher in men (36.0 years) than women (34.3 years), and the median BMI was higher in men (27.6 kg/m^2) than women (24.4 kg/m^2). Only 12% of the men and 7% of the women did not have a college education (Table 1). Among the couples, 30% were diagnosed with male factor infertility, 33% with female factor infertility, and 37% with unexplained infertility at the time of enrollment. The majority (55%) of the urine samples and 76% of the hair samples were collected from 2005 through 2010. Urine collection time ranged from 7 am through 6:30 pm with 59% collected between 7 am and 10 am and only 11% collected after 12 pm. There was a fairly even breakdown of when the samples were provided throughout the year.

The percentage of samples with detectable urinary biomarker concentrations ranged from < 20% (triclocarban, MCOCH, BCIPP, tb-PPP) to 100% (MECPTP, MECPP) (Table 2). Spearman pairwise correlations between the same biomarker within a couple were all positive, with a median of 0.41 and range of 0.05 for tb-PPP to 0.66 for triclosan (Figs. 1 and 2). In general, the correlations and 95% confidence interval (95% CI) were moderate (0.3 to 0.59) to high (≥0.6) except for triclocarbon, bisphenol F, methyparaben, butylparaben, MHBP, ip-PPP, and tb-PPP (< 0.3). The most highly correlated chemicals within couples were benzophenone-3, triclosan, 2,5-dichlorophenol, MEHHTP, and MECPTP. Almost all correlations were statistically significant.

The estimated ICCs were fair (0.4–0.59) or good (0.6–0.74) for several biomarkers and poor for others (< 0.4) (Rosner, 2011). The ICCs were strongest (lower within-couple variability) for triclosan, 2,5-dichlorophenol, MEHHTP, and MECPTP and were weakest for tb-PPP and ip-PPP (Fig. 3 and Supplementary Table 1). After adjustment for potential predictors of the biomarkers concentrations in both men and women, the partial correlations and adjusted ICCs were similar to the unadjusted ones. It is worth noting that in couples, the partner-specific ICCs of the biomarkers were similar to each other and also similar to ICCs for all women and men participating in the EARTH study regardless of whether their partner participated (Supplementary Tables 2 and 3 and Supplementary Figs. 2 and 3). Among women, ICCs were highest for 2,5-dichlorophenol and triclosan and lowest for tb-PPP and DPHP. Among men, ICCs were highest for MONP, 2,5-dichlorophenol, BDCIPP, and benzophenone-3 and lowest for bisphenol S and bisphenol F.

4. Discussion

In the present study, we investigated the between and within-partner correlations and temporal variability of 37 biomarkers including urinary phenols, phthalate and phthalate alternative metabolites, PFR metabolites, and hair mercury among partners of couples where urine samples were collected on the same day and within two months for the hair samples. The distributions of the couple's biomarkers were comparable to concentrations from adults in the U.S. general population (Supplementary Table 4) (CDC, 2018). We observed moderate correlations between most biomarkers within a couple. Stronger correlations suggest similar exposure sources and weaker correlations could indicate different sources of exposure or possible differences in exposure timing even within the day of sample collection or even differences in absorption, metabolism, or excretion. Similarly, having a higher ICC for couples means that the variance between couples is higher than the within couple variance (between partners) and thus the variability for the biomarkers over time is mainly driven by between couples variance. In other words, a higher ICC means there may be shared factors that contribute to a couple's exposure, which we refer to as "shared environment".

Given the high likelihood that partners within a couple share at least some meals together, many biomarkers for which food is presumed to be the primary source of exposure were moderately to highly correlated within a couple. This included mercury, which is found in some fish, and DEHP metabolites and MHiNCH, a metabolite of di (isononyl)cyclohexane-1,2-dicarboxylate (DiNCH®) (Calafat et al., 2015), which is used in food production materials (Salvy et al., 2007; Vartanian et al., 2015). Similarly, some soaps and toothpastes, which are likely shared within couples, could be a major driver of joint exposure to triclosan. In contrast, correlations of urinary bisphenol F within couples were low. At present the primary sources of bisphenol F are unknown. Recently, mustard has been found to be a major source of bisphenol F (D and Hengstler, 2016; Zoller et al., 2016). We assumed that food might be the main source based on the known sources for bisphenol A but this low correlation may indicate that there are other possible sources other than food or differences in absorption, metabolism, or excretion.

Interestingly, biomarkers whose main sources are personal care products (PCPs) were moderately to strongly correlated, such as tri-closan and benzophenone-3. However, there were exceptions, including methylparaben and MHBP, a metabolite of DBP, that were weakly correlated which may indicate that not all PCPs are shared by partners. For example, suntan/sun block, face and hand lotion, and hair spray were associated with higher urinary parabens in men from the same cohort (Nassan et al., 2017). However, among women from the same cohort, cosmetics including hair dye, foundation, blush, eye shadow, eye liner, or mascara were associated with higher paraben concentrations (Braun et al., 2014), suggesting the sources of PCP exposures are different in males and female partners and could be one reason why we observed lower correlations within couples for these chemicals. Biomarkers with potential major sources from the indoor environment such as 2,4-dichlorophenol, and 2,5-dichlorophenol were also moderately to highly correlated but not ip-PPP and tb-PPP. As virtually all our male and female participants were employed outside the home, but do not likely work in the same location as their spouse, the lower correlations between certain

chemicals derived from the indoor environment may reflect differences in occupational exposure to these chemicals.

For metabolites of phthalates and their alternatives, we observed moderate correlations within couples and fair ICCs that represent “the shared environment” for couples. This may represent some similarities in diet, PCP use, indoor environment, and other potential exposure sources within couples. Our reported correlations are similar to the phthalate metabolite correlations reported among 50 couples enrolled in the Sperm Environmental Epigenetics and Development Study (SEEDS) who were also seeking fertility treatment (Wu et al., 2017a). However, we had no negative correlations between any of the studied biomarkers among couples, which is inconsistent with the negative correlations observed before for MEHHP and MEOHP among couples in SEEDS (Wu et al., 2017b). This might be explained by the bigger sample size. In our study, we included 380 couples who contributed with 841 paired urine samples.

In a previous analysis among a subset of couples from our cohort (n = 140) (2004–2008), there were moderate positive correlations between male and female partners for all SG-corrected phthalate metabolite concentrations (Spearman coefficients ranged from 0.27 for free MEP to 0.42 for total MEHP) (Meeker et al., 2012), similar to what we observed in our current analysis. Correlation patterns of the biomarkers were similar among women and men in the EARTH study and similar to those reported by Chung et al. (Chung et al., 2018). However, the study reported by Chung et al. did not have multiple samples over time from the partners in a couple and thus used a different approach to define the “shared environment”. In our definition of the “shared environment”, we simultaneously adjusted the ICC for differences between couples.

Our study has some limitations, including the collection of spot urine samples, unknown time of last urination, and limited data to allow for the determination of exact sources, pathways and activities related to exposures. Also, although we restricted our sample to those collected on the same day from both partners, some exposure misclassification could have been introduced because of the relatively short half-lives of the target biomarkers. However, this misclassification is likely non-differential and we tried to minimize this by adjusting the ICC and the partial correlations by the time of sample collection. Finally, it is unclear whether these results are generalizable to all couples given that our study participants were recruited from a single fertility clinic in Boston, Massachusetts and mostly white and highly educated. However, biomarker concentrations for this population were similar to the rest of the U.S. (NHANES data) (CDC, 2018).

Our study had several strengths including the large sample size and the fact that couples could have repeated urine samples from each partner over time. Our study time frame ranged from 2004 through 2017 (~13 years), which allowed us to examine these biomarkers over long temporal duration. We also examined a large number of biomarkers including metabolites of phthalates and phthalate alternatives, phenols, PFRs, triclocarbon, and mercury in both partners. Finally, we addressed the lack of data on a couple’s joint exposure and thus contribution to pregnancy outcomes and offspring health.

This analysis has important implications for exposure assessment in epidemiological studies that are interested in the impact of exposures on human health. For instance, both male and female exposures may contribute to altered fecundity. However, for some exposures it may be difficult to determine if this relation is due to the male or female partner's exposure if the exposures are strongly correlated. From the causal inference standpoint, it may be difficult to disentangle maternal from paternal contributions for highly correlated biomarkers between partners. On the other hand, in cases of low correlated exposures between partners, it would be important to measure exposures in both partners if the outcome of interest is potentially related to both male and female exposures.

5. Conclusions

Urinary concentrations of biomarkers of multiple chemicals were mostly moderately correlated with fair temporal variability within couples suggesting similar exposure sources. Depending on the reproductive, perinatal, or child health outcome of interest, researchers should consider exposure correlations among couples when designing and analyzing data from their studies. Depending on the research question under study, it may be necessary to collect biological samples from both partners for exposure assessment as well as detailed temporal information related to lifestyle activities (e.g., diet, PCP use, and indoor environment exposures).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

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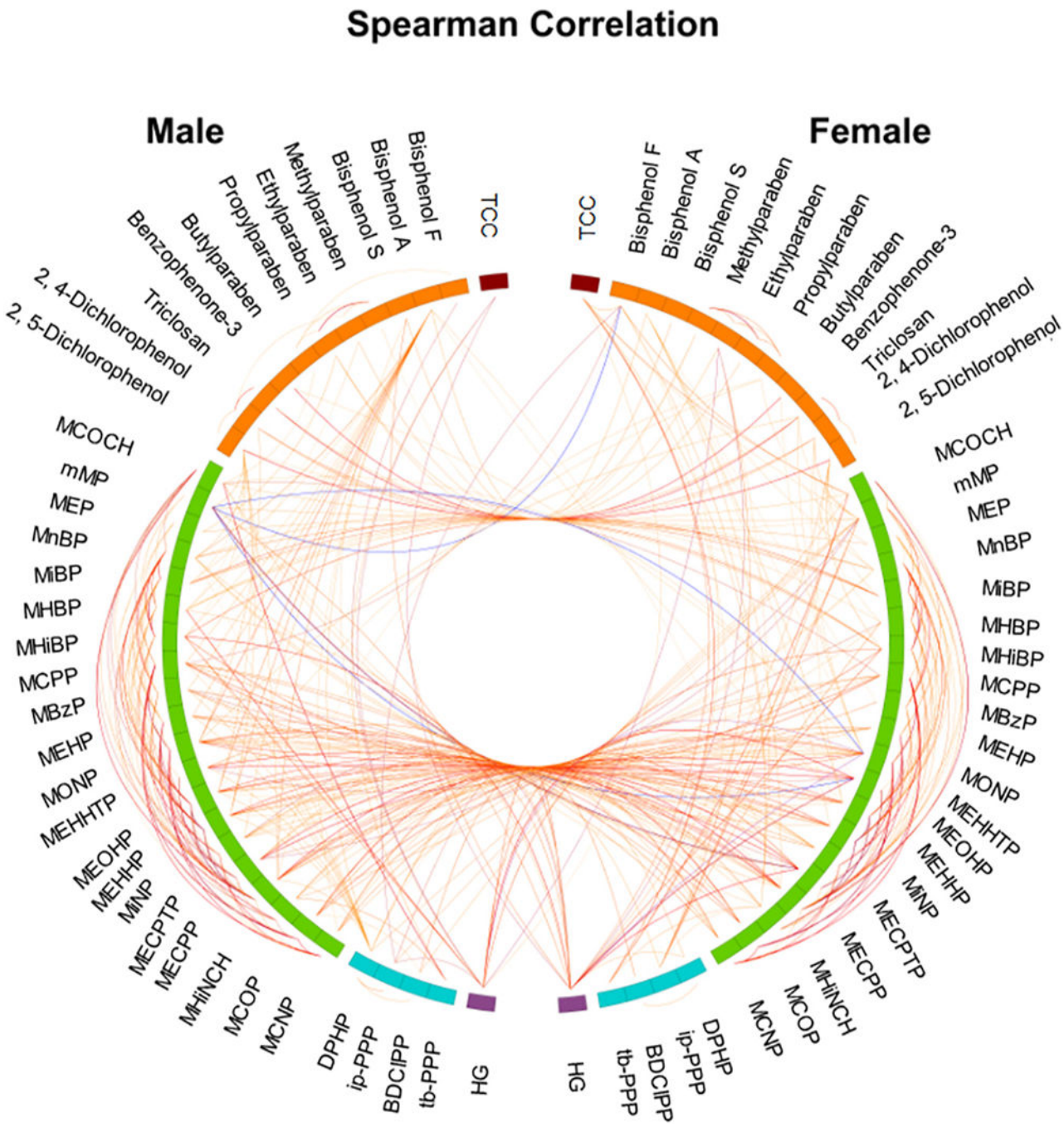

Fig. 1.

Exposome Spearman pairwise correlation globe among the couples in the Environment and Reproductive Health (EARTH) study.[a] Exposome correlation globe showing the Spearman pairwise correlation of biomarkers within women, within men, and within couples. [b] Right-half represents biomarkers in women and left-half represents biomarkers in men. [c] All biomarkers are ordered according to the molecular weights within the same biomarker family (pheonls, phthalates and alternatives, and PFRs) from above to below. [d] Only Spearman's rank correlations > 0.25 and <−0.25 were shown as connections in the globe. [e]

Color intensity and line width are proportional to the magnitude of the correlation. [f] Red lines denote positive correlations and blue lines denote negative correlations. Abbreviations: EARTH; the Environment and Reproductive Health Study; PFR; organophosphate flame retardants. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

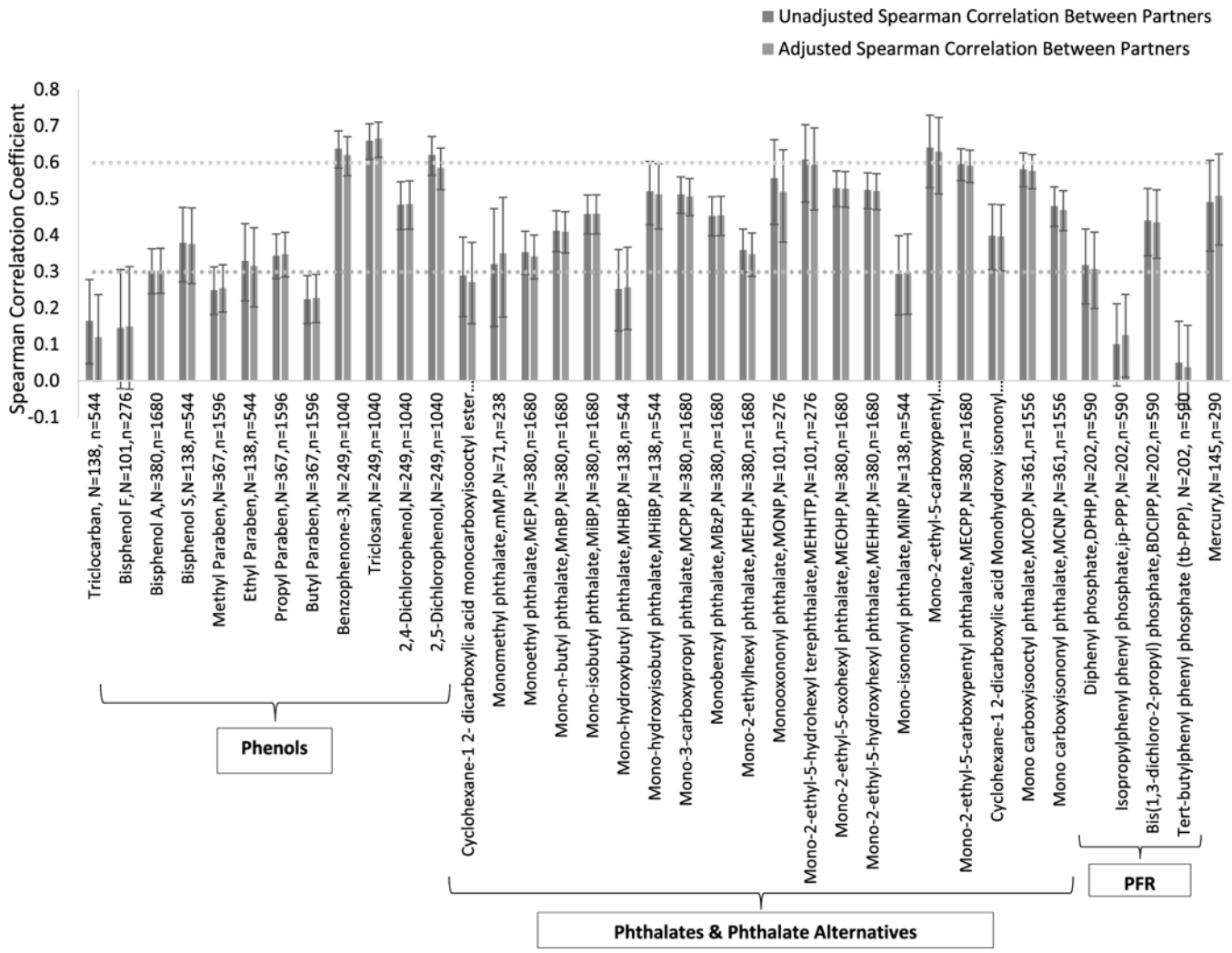

Fig. 2.

Spearman pairwise correlation coefficients and 95% confidence intervals of biomarkers between the partners among couples in the Environment and Reproductive Health (EARTH) study. [a] All urinary biomarkers were adjusted for specific gravity. [b] All biomarkers concentrations were in μg/L, except part-per million (ppm) for hair mercury. [c] All biomarkers are ordered according to the molecular weights within the same biomarker family. [d] Partial correlation coefficients are adjusted for men's and women's race (Caucasian or not), age (continuous), ever smoking, and time the sample collection. Abbreviations: EARTH; the Environment and Reproductive Health Study; N, number of couples; n, number of the samples provided by couples; Correlation, Spearman correlation coefficient; SG, specific gravity adjusted; PFR; organophosphate flame retardants.

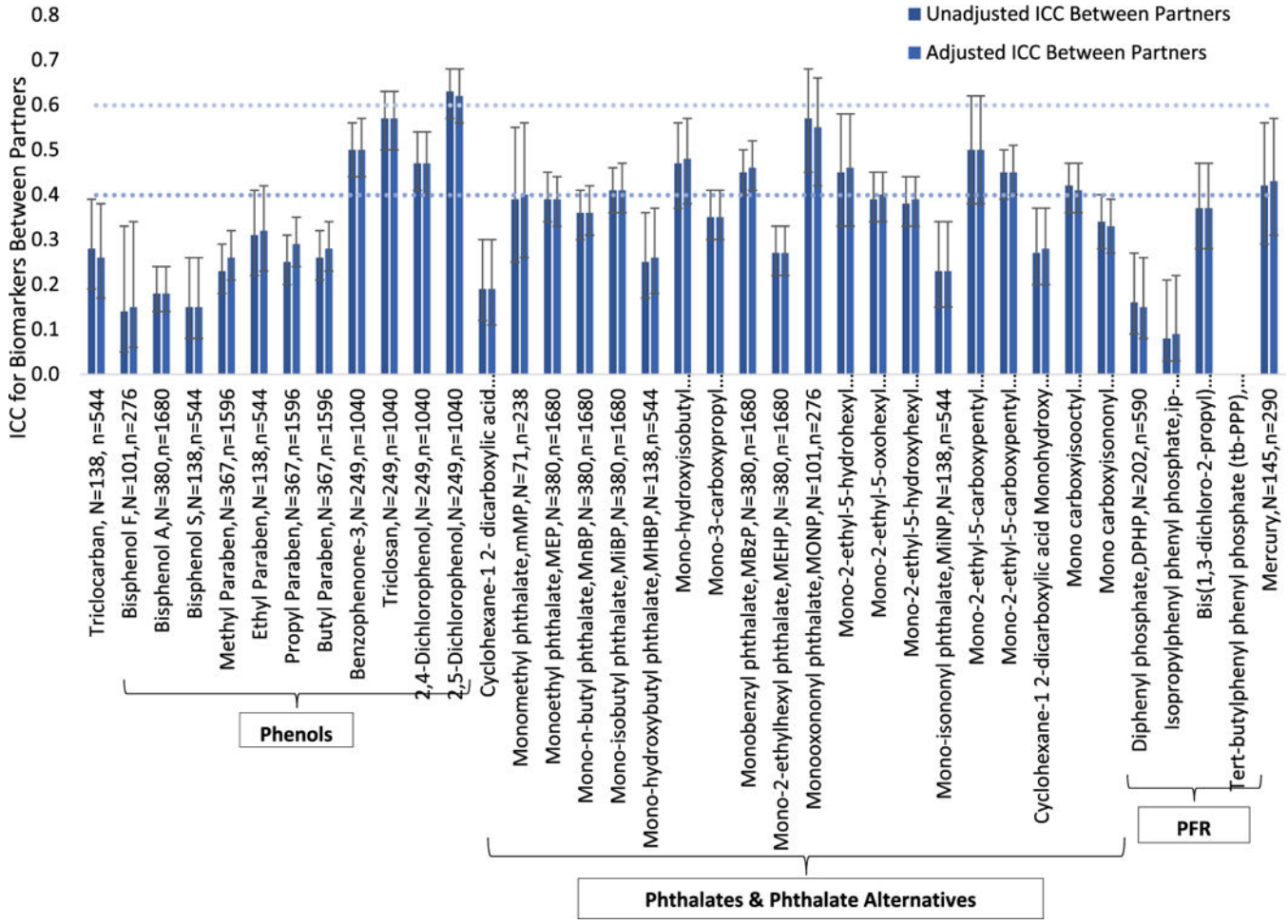

Fig. 3.

Intra-class correlation coefficients (ICCs) and 95% confidence intervals for biomarkers among the couples in the Environment and Reproductive Health (EARTH) study. [a] All biomarkers concentrations were in μg/L, except part-per million (ppm) for hair mercury. [b] All biomarkers are ordered according to the molecular weights within the same biomarker family. [c] ICC represents ICCs for SG-adjusted biomarkers in multiple paired from couple's samples. [d] Adjusted ICCs are adjusted for men's and women's race (Caucasian or not), age (continuous), ever smoking, and time of the sample collection. Abbreviations: EARTH; the Environment and Reproductive Health Study; N, number of couples; n, number of the samples provided by couples; ICC, intra-class correlation coefficient; SG, specific gravity adjusted.

Table 1

Demographic characteristics for 380 couples in the Environment and Reproductive Health (EARTH) study.

Baseline characteristics	Female partner (*N*=380)[a]	Male partner (*N*=380)[a]
Age (years)	34.3 ± 4.25	36.0 ± 5.58
Race		
Caucasian	310 (82)	327 (86)
Black/African American	12 (3)	12 (3)
Asian	40 (11)	27 (7)
Other	18 (5)	14 (4)
BMI (Kg/m^2)[a]	24.4 ± 4.93	27.6 ± 5.33
BMI categories		
Underweight	10 (3)	3 (1)
Normal weight	244 (64)	115 (30)
Overweight	79 (21)	172 (45)
Obese	47(12)	90 (24)
Education categories		
Less than college graduate	27(7)	47 (12)
College graduate	115 (30)	101 (27)
Graduate degree	195 (51)	152 (40)
Missing	43 (11)	80 (21)
Smoking status		
Never	283 (74)	261 (69)
Past	87 (23)	94 (25)
Current	10 (3)	25 (7)
Ever smokers	97 (26)	119 (31)
Time varying characteristics for urine sample collection	*n*=841	*n*=841
Time of the day		
<7 am and ≤9 am	248 (29)	425 (51)
<9 am and ≤12 pm	499 (59)	322 (38)
Afternoon: >12 pm	94 (11)	94 (11)
Collected in April through September	401 (48)	401 (48)

Data are presented as N or n (%) for categorical/binary variables and mean ± SD for continuous variables. Abbreviations: EARTH; the Environment and Reproductive Health Study; N, number of participant; n, number of urine samples; SD, standard deviation; BMI, body mass index; Kg, Kilogram; m, meter.

Table 2

Summary of the distributions of the biomarkers measured among couples in the Environment and Reproductive Health (EARTH) study.

Biomarker (μg/L)[a,b]	Female partner						Male partner		
	Couple (N)	Sample (n)	LOD	Detection %	Geometric mean	25–75th percentile	Detection %	Geometric mean	25–75th percentile
Triclocarban	138	544	0.10	12	< LOD	< LOD	15	< LOD	< LOD
Phenols									
Bisphenol F	101	276	0.20	43	0.33	(0.14, 0.60)	26	0.21	(0.14, 0.30)
Bisphenol A	380	1680	0.10–0.40	80	0.90	(0.30, 2.00)	89	1.28	(0.60, 2.70)
Bisphenol S	138	544	0.10	73	0.35	(0.07, 0.85)	76	0.38	(0.20, 0.90)
Methylparaben	367	1596	1.00	99	80.6	(26.5, 272)	99	27.4	(9, 82.8.00)
Ethylparaben	138	544	1.00	57	2.97	(0.70, 9.60)	46	1.62	(0.70, 3.00)
Propylparaben	367	1596	0.10–0.20	97	13.9	(3.00, 69.5)	89	2.61	(0.50, 12.2)
Butylparaben	367	1596	0.10–0.20	55	0.61	(0.14, 2.90)	29	0.23	(0.07, 0.30)
Benzophenone-3	249	1040	0.20–0.40	99	93.7	(25.3, 398)	99	45.2	(14.8, 141)
Triclosan	249	1040	1.0–2.30	79	10.4	(1.80, 32.6)	74	11.5	(1.63, 51.7)
2, 4-Dichlorophenol	249	1040	0.10–0.20	75	0.41	(0.14, 0.90)	82	0.49	(0.20, 1.00)
2, 5-Dichlorophenol	249	1040	0.10–0.20	87	1.03	(0.40, 2.40)	93	1.60	(0.50, 4.15)
Phthalates and phthalate alternatives									
Cyclohexane-1 2-dicarboxylic acid monocarboxyisooctyl ester (MCOCH)	138	544	0.50	22	< LOD	< LOD	19	< LOD	< LOD
Monomethyl phthalate (mMP)	71	238	0.50	67	1.08	(0.35, 2.30)	66	1.19	(0.35, 2.80)
Monoethyl phthalate (MEP)	380	1680	0.60–1.20	99	38.1	(12.4, 118)	99	43.8	(15.0, 126)
Mono-n-butyl phthalate (MnBP)	380	1680	0.40–0.60	94	7.03	(2.60, 20.7)	97	9.97	(4.75, 24.1)
Mono-isobutyl phthalate (MiBP)	380	1680	0.20–0.80	96	4.48	(1.60, 12.6)	96	6.75	(3.20, 15.2)
Mono-hydroxybutyl phthalate (MHBP)	138	544	0.40	55	0.73	(0.28, 1.55)	53	0.61	(0.28, 1.10)
Mono-hydroxyisobutyl phthalate (MHiBP)	138	544	0.40	83	2.01	(0.80, 4.90)	89	2.05	(0.90, 4.35)
Mono-3-carboxypropyl phthalate (MCPP)	380	1680	0.18–0.40	88	2.08	(0.70, 5.45)	94	3.42	(1.30, 8.55)
Monobenzyl phthalate (MBzP)	380	1680	0.20–0.30	88	2.23	(0.70, 6.90)	94	3.13	(1.26, 8.21)
Mono-2-ethylhexyl phthalate (MEHP)	380	1680	0.50–1.20	65	1.99	(0.60, 4.60)	75	2.72	(0.85, 6.60)
Monooxononyl phthalate (MONP)	101	276	0.40	86	3.06	(1.10, 7.60)	84	2.86	(0.80, 7.80)

Biomarker (μg/L)[a,b]	Female partner						Male partner		
	Couple (N)	Sample (n)	LOD	Detection %	Geometric mean	25–75th percentile	Detection %	Geometric mean	25–75th percentile
Mono-2-ethyl-5-hydrohexyl terephthalate (MEHHTP)	101	276	0.50	96	5.87	(1.90, 15.5)	93	6.11	(2.10, 17.9)
Mono-2-ethyl-5-oxohexyl phthalate (MEOHP)	380	1680	0.20–0.70	98	5.87	(1.90, 15.8)	97	8.00	(2.70, 20.9)
Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP)	380	1680	0.20–0.70	98	9.03	(2.90, 24.4)	98	13.9	(4.80, 36.4)
Mono-isononyl phthalate (MiNP)	138	544	0.50–0.90	50	1.25	(0.64, 2.10)	53	1.51	(0.64, 3.00)
Mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP)	101	276	–	100	24.0	(6.20, 83.8)	100	23.1	(6.60, 82.1)
Mono-2-ethyl-5-carboxypentyl phthalate (MECPP)	380	1680	0.40	99	15.8	(5.20, 40.0)	99	22.0	(7.55, 53.0)
Cyclohexane-1 2- dicarboxylic acid Monohydroxy isononyl ester (MHiNCH)	175	678	0.40	26	0.42	(0.28, 0.50)	30	0.45	(0.28, 0.60)
Mono carboxyisooctyl phthalate (MCOP)	361	1556	0.30–0.70	98	14.9	(4.70, 47.5)	99	22.4	(6.90, 76.7)
Mono carboxyisononyl phthalate (MCNP)	361	1556	0.20–0.60	93	2.89	(1.20, 6.50)	96	3.53	(1.70, 8.00)
Organophosphate flame retardants (PFR)									
Diphenyl phosphate (DPHP)	202	590	0.03–0.18	89	0.70	(0.35, 1.39)	86	0.60	(0.29, 1.26)
Isopropylphenyl phenyl phosphate (ip-PPP)	202	590	0.02–0.12	75	0.21	(0.07, 0.48)	66	0.20	(0.09, 0.47)
Bis(1, 3-dichloro-2-propyl) phosphate (BDCIPP)	202	590	0.02–0.13	84	0.61	(0.24, 1.71)	84	0.41	(0.15, 1.10)
Bis(1-chloro-2-propyl) phosphate (BCIPP)	202	590	0.07–0.18	0	< LOD	< LOD	0	< LOD	< LOD
Tert-butylphenyl phenyl phosphate (tb-PPP)	202	590	0.01–0.15	14	< LOD	< LOD	11	< LOD	< LOD
Mercury	145	290	0.01	100	0.52	(0.32, 1.17)	100	0.62	(0.40, 1.25)

Abbreviations: EARTH; the Environment and Reproductive Health Study; N, number of couples; n, number of the samples provided by couples; LOD, limit of detection.

[a] All biomarkers concentrations are in μg/L, except part-per million (ppm) for hair mercury.

[b] All biomarkers are ordered according to the molecular weights within the same biomarker family.