Characterization and quantification of endocrine disruptors in female menstrual blood samples

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ABSTRACT

Selected endocrine disrupting chemicals (EDCs) were measured in adult female menstrual blood for the first time in Ghana, Africa, taking into account the importance of non-invasive means of matrices sampling in vulnerable groups, such as pregnant women, the elderly or chronically ill people. The menstrual blood samples of twenty (20) female adults between the ages of 25–45 years were sampled. The Quick, Easy, Cheap, Effective, Rugged and Safe (QuEChERS) method was applied for the extraction and clean up, while gas chromatography-mass spectrometry (GC-MS) was used to measure the selected EDCs in adult female menstrual blood, taking into account the composition of menstrual discharge. Diethyl phthalate (DEP), Dibutyl phthalate (DBP) and Bis (2-ethylhexyl) phthalate (DEHP) were detected in all samples, whereas bisphenol A (BPA) was found in 13 participants. Dimethyl phthalate (DMP) was detected in 7 participants, Di-n-octyl phthalate (DNOP) was detected in 3 participants, Bis (2-ethylhexyl) adipate (DEHA) and pyrimidine were detected in 2 participants, while benzyl butyl phthalate (BBP) was detected in only 1 participant. The maximum concentration of DEP measured was 115.6 μg.L⁻¹, and minimum was 439 μg.L⁻¹. DEHP was the next most abundant phthalate with a maximum measured concentration of 982 μg.L⁻¹ and minimum of 95 μg.L⁻¹. The presence of parent phthalates (rather than metabolites) in menstrual blood of all participants studied suggests that bioaccumulation of selected phthalate compounds such as DEHP, DEP and DBP may be occurring with appreciable human toxicity though the carcinogenic exposure risks of DEHP via various routes were much lower than 1 × 10⁻⁶ considered to be very low.

1. Introduction

Endocrine disrupting chemicals (EDCs) consist of many natural and synthetic organic compounds that are known to interrupt normal function of the endocrine system in various ways. This class of chemicals is usually found in plastic products, most household products, as well as the environment [5,23]. Human exposure pathways to EDCs are mainly through the intake of food, water and dust, inhalation of gases and particles and dermal contact [27]. EDCs have been found in surface water, sediment, groundwater, and even drinking water in many countries [7,14]. They can interfere with the production of hormones needed for the normal functioning of the human body either through over or underproduction of hormones or by disrupting hormone production [18,23]. Since these hormones are required in small quantities and at specific moments to regulate the body’s growth.

EDC exposure is associated with changes in reproductive function and high occurrence of cancers [8]. Among females, EDCs may impair reproductive function across the life cycle, such as inducing early puberty or increasing rates of miscarriage and infertility [11,45]. EDC exposure is also associated with increased risk of reproductive cancers especially breast, ovarian, and endometrial cancers, neuro-developmental delays and abnormal growth patterns in children, and changes in immunity [10,15,23]. The impact of EDCs on female health is critical since these compounds can stimulate estrogenic responses at very low concentrations that could affect pregnant mothers and their unborn babies [15,37]. EDCs can also be transferred from a pregnant woman to the growing fetus through the placenta and to the baby through breast milk. Adult exposure to EDCs may have different consequences than exposure to a developing fetus or infant [11]. Studies show that exposures to EDCs and concomitant health effects may not

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manifest until later in life [15]. The exposure of women is heightened with the increased use of personal care products and chemical products that may contain EDCs.

In epidemiologic research, EDCs are commonly measured in human biological matrices such as blood, urine or breast milk. Other matrices, such as saliva, amniotic fluid or hair have also been used in laboratory analysis of exposure to EDCs. However, little is known about the potential use of menstrual blood in exposure analysis. Careful choice of a particular matrix is important as toxicokinetics, stability, specificity and reliability should be considered. Research based on the use of menstrual blood is scarce probably due to the difficulty in obtaining it, especially in Africa where a lot of myth is attributed to it. Nonetheless, menstrual blood, like other matrices, could be used to obtain vital information on exposure and disease.

Humans may come into contact with environmental contaminants through several routes [27]. Monitoring of contaminants is essential for the determination of their effects on individuals. Though the use of pesticides and other chemicals cannot be avoided entirely, it is imperative to ensure that adverse health effects of products that contain EDCs are understood and monitored to curb the upsurge in use. Again in monitoring, there are various considerations for the selection of a suitable matrix for human biomonitoring of contaminants. These include gender, age, frequency of monitoring and the type of contaminant. Depending on the purpose, invasive or non-invasive methods of matrix sampling could be employed. Blood has been used widely due to its interaction with all tissues and organs [21]. However, blood sampling is an invasive procedure accompanied with practical constraints, particularly for children or other susceptible populations [30,36]. In addition, frequent biomonitoring is necessary for the evaluation of risk management options and effectiveness of environment and health policies [4]. For chemicals with short half-lives such as volatile organic compounds or agricultural pesticides, repeated sampling of exposure provides more insight into the true nature of these chemicals and their toxicological consequences. In these situations, non-invasive means of matrix collection is preferable, particularly in vulnerable groups, such as pregnant women, elderly or chronically ill people. Since non-invasively collected matrices need less specialized personnel for sampling, costs associated with large sampling designs may be significantly reduced compared to invasive collection of matrices [35].

Considering the advantages, there is a strong case for non-invasive collection of matrices for human biomonitoring as an ethically appropriate, cost-efficient and toxicologically relevant alternative for many of the biomarkers currently measured in invasive matrices. However, the use of menstrual discharge sampled non-invasively as a biomonitoring matrix has been minimal, likely due to the myth surrounding it in Africa. In other jurisdictions however, menstrual matrices have been used in a few instances for human biomonitoring [20,33]. Menstrual discharge is composed of three distinct body fluids including blood, vaginal secretions, and the endometrial cells of the uterine wall [19,44]. It may therefore be suitable for the monitoring of females within child bearing age and offers an advantage of early detection of contaminants before conception. In Ghana, the use of plastics in daily life as food wrappers and for storage is pervasive. Increased use of plastic products, pesticides, personal care products, pharmaceuticals and industrial chemicals has occurred during the past decade. These products contain phthalates and bisphenol A that are ubiquitous in the environment due to their wide-spread application. The high molecular weight phthalates (DEHP, DINP, DIDP), also known as phthalates in PVC polymers, plastics, food packaging, food processing materials, vinyl toys, vinyl floor coverings, and building products. The low molecular weight phthalates (DMP, DEP, and DBP), are often used in non-PVC applications, such as personal care products, paints, adhesives, and enteric-coated tablets [43]. According to UNEP [39], in Ghana, over one million tons of plastic waste is generated annually and contributes 0.29% of global plastic waste generated. Approximately, 81% of plastic waste generated are mismanaged which end up in the environment [39]. Biomonitoring is scarce and the early detection of harmful impacts of environmental contaminants is critical in the protection of neonates. Few studies in Africa have assessed levels of EDCs in biota particularly using menstrual blood as a non-invasive sampling approach. It is unclear whether adult female menstrual can be used as an indicator of EDC bioaccumulation or toxicity. The aim of the study was to measure selected EDCs in adult female menstrual blood while taking into account the composition of menstrual discharge as non-invasive method of sampling.

2. Materials and methods

2.1. Collection and storage of blood samples

Menstrual blood samples were collected by volunteers for three consecutive days from the second day of flow within the monthly cycle. Twenty (20) females from Accra and Cape Coast between the ages of 25–45 years participated in the study. Participants refrained from sex during sample collection. Since there is no standard protocol for the collection of menstrual blood, samples were collected on aluminum foil and transferred into a vacutainer tube containing anticoagulant. The collected blood samples were stored in sealed sterile containers at – 10 °C (± 2 °C) until extraction. All subjects included in the study gave their consent to participate voluntarily. Ethical approval (GHS-ERC004/ 09/19) was granted by the Ghana Health Service Ethical Review Board.

2.2. Extraction and clean up

The modified method described by [41] was used for extraction and clean up. About 0.5 ml of blood serum was diluted with 1.5 ml of distilled water. Samples were placed in a 5 ml centrifuge tube containing 6 g of magnesium sulfate and 1.5 g sodium chloride with 1 ml of 1% acetic acid in acetonitrile (v/v). The mixture was vigorously vortexed for 30 s, shaken up and down for 5 min, vortexed again for 30 s and centrifuged at 4400 rpm for 15 min at 4 °C. For sample clean up, 600 µl supernatant of each sample was transferred into a 1.5 ml tube containing the solid phase extraction sorbent (25 mg of primary-secondary amine, 25 mg of end-capped octadecysilane (C18) and 150 mg of magnesium sulfate). The tube was mixed by hand (up and down) for 10 mins, vortexed for 30 s and centrifuged at 4400 rpm for 10 min at 4 °C. Supernatant were collected and filtered through 0.22µPTFE filter into vials.

2.3. Analysis of selected EDCs

The blood samples were analyzed for selected EDCs with a GC-MS QP 2020 Shimadzu equipped with an RT-MS trace analysis column (30 m × 0.25 mm × 0.25 µm). Helium gas of high purity (99.99%) was used as the carrier gas at a flow rate was 1 ml min⁻¹ at a pressure of 83.1 kP. Sample volume of 1 µl was injected in pulsed splitless mode with an inlet temperature of 265 °C.

To quantify phthalates, the column temperature was programmed as follows: initial oven temperature was set at 70 °C for 2 min, then increased to 200 °C at 15 °C/min. It was further ramped up at 6 °C/min to 310 °C and held for 1 min. The interface and ion source temperatures were set at 265 °C and 220 °C respectively. For bisphenol A, the column temperature program was as follows: 50 °C for 1 min, ramped up at 15 °C/min to 180 °C, further ramped up at 8 °C/min. to 300 °C and held for 1 min. The interface and ion source temperatures were set to 270 °C and 220 °C, respectively. Quantifications were all carried out in the selected ion monitoring mode (SIM), selecting two characteristics fragments ions for each.

2.4. Quality control

All glassware used was thoroughly washed with hexane and...
acetonitrile, then heated at 140 °C for 1 h to ensure that contamination of glassware was reduced. The EDC extraction solvent and matrix adsorbent were studied using blank samples spiked with standards. The blank values of the analytical procedure were determined by extracting the spiked sample by the same method as the real blood sample with recovery of spiked sample in the range of 86–116%. The estimation of the limit of detection (LOD) for the selected EDCs in the blood samples was conducted based on U.S. EPA guidelines [40] with a confidence level of 95%. An LOD of 3 × (detection peak/blank peak + standard deviation) was observed. Instrumental detection limits were calculated by a signal-to-noise ratio of 3 times the sample concentration and ranged from 100 to 310 µg L⁻¹. Method detection limits of the selected EDCs including DMP, DEP, BBP, DEHP, DBP, DnOP, DEHA and BPA were 5, 7, 10, 5, 15, 10, 7 and 40 µg L⁻¹, respectively. Surrogate standards and internal standards concentrations of 20 µl of 5 ppm and 50 µl of 20 ppm in 1 ml, respectively, were added to all the samples to monitor the matrix effects, calibration and quantification. A calibration curve was made by serial dilutions of calibration standards with at least five concentrations for each selected EDC compound monitored. Linear regression with coefficient of (R²) > 0.99 was accepted.

2.5. Human exposure and health risk assessment

The cancer risks (CR) of the endocrine disrupting chemicals in the menstrual blood samples were estimated according to the US EPA recommendation. The formulas with modification from the US EPA, [38] which have been widely employed in previous studies ([6]; [25]; [42,47]) were used to assess the average daily dosage (ADD, mg kg⁻¹ d⁻¹) and cancer risk of the selected EDCs via different exposure pathways, namely ingestion (ADDing), dermal absorption (ADDder) and inhalation (ADDinh) as Eqs. (1)–(4):

\[
ADD_{ing} = \frac{C_d \times I_d \times EF \times ED}{BW \times AT} \times CF
\]

(1)

\[
ADD_{der} = \frac{C_d \times SA \times AF \times ABS \times EF \times ED}{BW \times AT} \times CF
\]

(2)

\[
ADD_{inh} = \frac{C_d \times I_d \times EF \times ED}{PEF \times AT \times BW}
\]

(3)

\[
CR = \sum (ADD \times CFS)
\]

(4)

Where C_d is the individual concentration of selected EDCs measured in blood (µg L⁻¹); I_d is the daily intake rate; (d) is the ingestion rate (mg d⁻¹); I_d is the inhalation rate (m³ d⁻¹). SA is the dermal exposure area (cm²). ABS is the dermal absorption factor (mg cm⁻² d⁻¹). BW is the body weight (kg). AT is the averaging time (Days): for non-cancer risks, AT = ED \times 365; for carcinogens risks, AT = average lifetime \times 365. ED is the exposure duration. EF is the exposure frequency (days/year⁻¹). C_d is the conversion factor (1.0 × 10⁻⁶ kg mg⁻¹). PEF is the particle emission factor (1.36 × 10⁷ m³ kg⁻¹). CSF represents the cancer slope factor. The carcinogenic risk of selected EDC was determined from Eq. (4). The estimated carcinogenic risks may be considered very low if the value of risk is less than 1 × 10⁻⁶; low in the range of 1 × 10⁻⁶ to 1 × 10⁻⁴, moderate from 1 × 10⁻⁴ to 1 × 10⁻², high from 1 × 10⁻² to 1 × 10⁻¹ and very high if the value is greater than 1 × 10⁻¹ [29]. (Table 1).

3. Results

Assessment of organic contaminants in the menstrual blood samples of 20 female adults between the ages of 25–45 indicated the presence of both phthalates and bisphenol A; phthalates were more abundant across samples. Three contaminants: diethyl phthalate, dibutyl phthalate, and bis (2-ethyl hexyl) phthalate were detected in samples of all participants. BPA was present in blood samples of thirteen participants while DMP was detected in 7 participants. Table 2 indicates that only one participant had detectable levels of benzyl butyl phthalate, two participants had detectable levels of bis (2-ethyl hexyl) adipate and pyrimidine, and three participants had detectable levels of di-n-octyl phthalate and progesterone.

Three participants had detectable levels of six of the various contaminants, six participants had five contaminants, four participants had four contaminants, and one of the participants had three contaminants as shown in Fig. 1.

Higher concentrations of DMP, DEP, DEHP, DBP and BPA were present in menstrual blood compared with BBP, DEHA, and DnOP that had negligible concentrations as indicated in Table 2. Among the phthalates, DEP had the highest concentration followed by DEHP, DBP and then DMP. DEP, DEHP, and DBP were present in higher concentrations than BPA.

We observed that pyrimidine and DEHP showed much variability with a standard deviation of 0.532 and 0.288, respectively (Table 3). DEP and progesterone showed similar deviation from the mean, while the other contaminants had standard deviations of less than 0.1. DEP had the highest mean concentration of 824.8 µg L⁻¹, whereas DnOP had the lowest mean concentration of 0.65 µg L⁻¹. The maximum concentration of DEHP recorded from one of the subjects was 115.6 µg L⁻¹ and the minimum was 439 µg L⁻¹. DEHP, the next most abundant phthalate had a maximum recorded concentration of 982 µg L⁻¹ and minimum recorded concentration of 95 µg L⁻¹.

3.1. Human exposure and health risk assessment

This study evaluated the CR of DEHP using a cancer slope factor of 0.014 via ingestion, inhalation and dermal contact based on the concentrations of the selected EDCs of the individual menstrual blood sample. Reference was made to the acceptable risk level recommended by the US EPA (1 × 10⁻⁶) when estimating the lifetime excess CR of phthalate esters. The assessment of cancer risks via all the routes showed that none of the routes exceeded the recommended allowable level. The

| Contaminant               | Percentage (n = 20) |
|---------------------------|---------------------|
| Bisphenol A               | 65                  |
| Dimethyl phthalate        | 35                  |
| Diethyl phthalate         | 100                 |
| Dibutyl Phthalate         | 100                 |
| Benzyl Butyl Phthalate    | 5                   |
| Bis (2-ethyl hexyl) adipate| 10                  |
| Bis (2-ethyl hexyl) phthalate| 100             |
| Di-n-octyl Phthalate      | 15                  |
| Progesterone              | 15                  |
| Pyrimidine                | 10                  |
than 1 carcinogenic exposure risks of DEHP via various routes were much lower than 0.208 ng/ml were detected. In neonates and infants, exposure to selected phthalate compounds such as DEHP, DEP and DBP may be occurring with appreciable human toxicity. A similar observation of possible phthalate retention and bioaccumulation was made in a clinical study of phthalate elimination in blood, urine and sweat [12,13]. Studies on EDCs in blood are few and even more scare are studies on EDCs in menstrual blood within the sub-Saharan African context. The identification of phthalate esters (instead of metabolites) in menstrual blood among all participants studied suggests that bioaccumulation of phthalate esters of DEP, DBP and DEHP identified were the most abundant compounds measured. A study carried out by Wang et al. [43] reported corresponding abundant compounds of phthalate metabolites of urine samples in a review of phthalate exposures. Human exposure to phthalates is based mainly on the measurement of urinary monoester metabolites, although several secondary and oxidative metabolites have been reported to occur in human specimens [34]. Studies on EDCs in blood are few and even more scare are studies on EDCs in menstrual blood within the sub-Saharan African context. The identification of phthalate esters (instead of metabolites) in menstrual blood among all participants studied suggests that bioaccumulation of selected phthalate compounds such as DEHP, DEP and DBP may be occurring with appreciable human toxicity. A similar observation of possible phthalate retention and bioaccumulation was made in a clinical study of phthalate elimination in blood, urine and sweat [12,13]. Progesterone is an essential hormone that affects reproductive health. The low detectable levels of progesterone among participants could indicate health effect of EDCs. Guo et al. [17]; Li et al. [24] indicated that there is ample evidence to suggest that endocrine disruptors may affect progesterone production in females.

4. Discussion

Human exposure pathways to EDCs vary and obtaining information pertaining to exposure effects and diseases is mainly done by analyzing compounds in human biological matrices. In total, ten different compounds were detected in menstrual blood samples. Studies conducted on BPA in human biological matrices in Africa mostly measured urinary BPA [32]. The maximum concentration of BPA found in menstrual blood in this study was similar to the maximum concentrations found in urine samples reported by [1]. However, Gounden et al. [16] conducted a study on maternal and cord blood in which BPA concentrations lower than 0.208 ng/ml were detected. In neonates and infants, exposure to EDCs may occur through the placenta or via breast-feeding [28]. Lower blood BPA levels than those in this study were found in children and pregnant women in China [46]. The identified concentrations could be attributed to the cumulative effect of three distinct body fluids that consist of blood, vaginal secretions and the endometrial cells of the uterine wall. It could also be attributed to the widespread use of plastics for both domestic and commercial purposes with over one million tons of plastic waste is generated annually which contributes 0.29% of global plastic waste generated [39], considering the increased desire for the consumption of processed and packaged foods. The main sources of BPA and phthalates in blood are dietary sources such as food and drinks packaged in cans and polycarbonate bottles, as well as paper and plastic films [9]. These chemicals could leach from polycarbonate plastics and plastic films used for food packaging and storage containers [2].

Table 3

| Contaminant (µg.L⁻¹) | Minimum | Maximum | Mean  | Std. Deviation |
|----------------------|---------|---------|-------|----------------|
| BPA                  | .000    | 208     | 96    | .074           |
| DMP                  | .000    | 187     | 40    | .067           |
| DEP                  | 439     | 1156    | 825   | .173           |
| DBP                  | .081    | 244     | 127   | .035           |
| BBP                  | .000    | 60      | 3     | .013           |
| DEHA                 | .000    | 47      | 4     | .010           |
| DEHP                 | 95      | 982     | 565   | .288           |
| DNOP                 | .000    | 7       | 1     | .002           |
| PROG                 | .000    | 555     | 68    | .170           |
| PBI                  | .000    | 2149    | 164   | .532           |

carcinogenic exposure risks of DEHP via various routes were much lower than $1 \times 10^{-6}$. The results of the risk assessment are summarized in Table 4.

Table 4

| Sample ID | Ingestion | DEHP | Inhalation | Total |
|-----------|-----------|------|------------|-------|
| 1         | 2.532E-09 | 1.010E-10 | 3.723E-13 | 2.633E-09 |
| 2         | 5.786E-09 | 2.309E-10 | 8.509E-13 | 6.018E-09 |
| 3         | 1.159E-09 | 4.624E-11 | 1.704E-12 | 1.205E-09 |
| 4         | 8.005E-09 | 3.194E-10 | 1.177E-12 | 8.326E-09 |
| 5         | 3.929E-09 | 1.568E-10 | 5.778E-13 | 4.086E-09 |
| 6         | 1.093E-09 | 4.362E-11 | 1.608E-13 | 1.137E-09 |
| 7         | 6.542E-09 | 2.610E-10 | 9.621E-13 | 6.804E-09 |
| 8         | 1.068E-09 | 4.263E-11 | 1.571E-13 | 1.111E-09 |
| 9         | 3.616E-09 | 1.443E-10 | 5.318E-13 | 3.761E-09 |
| 10        | 6.649E-09 | 2.653E-10 | 9.778E-13 | 6.916E-09 |
| 11        | 5.995E-09 | 2.578E-10 | 8.765E-13 | 6.198E-09 |
| 12        | 3.460E-09 | 1.381E-10 | 5.098E-13 | 3.599E-09 |
| 13        | 6.625E-09 | 2.643E-10 | 9.742E-13 | 6.890E-09 |
| 14        | 3.616E-09 | 1.443E-10 | 5.318E-13 | 3.761E-09 |
| 15        | 5.926E-09 | 2.364E-10 | 8.715E-13 | 6.163E-09 |
| 16        | 5.326E-09 | 2.125E-10 | 7.832E-13 | 5.539E-09 |
| 17        | 7.808E-10 | 3.115E-11 | 1.148E-13 | 8.121E-10 |
| 18        | 6.625E-09 | 2.643E-10 | 9.742E-13 | 6.890E-09 |
| 19        | 8.071E-09 | 3.220E-10 | 1.187E-12 | 8.394E-09 |
| 20        | 6.049E-09 | 2.414E-10 | 8.896E-13 | 6.292E-09 |

5. Conclusion

The study set out to measure selected EDCs in adult female menstrual blood as non-invasive method of sampling. Menstrual blood is an easily

![Fig. 1. Participants with number of distinct contaminants in menstrual blood sample.](image1)

![Fig. 2. Mean level of selected EDCs in menstrual blood sample of participants.](image2)
obtainable body fluid and collected through non-invasive means. Bisphenol A, Dimethyl phthalate, Diethyl phthalate, Dibutyl Phthalate, Benzyl Butyl Phthalate, Bis (2-ethyl hexyl) adipate, Bis (2-ethyl hexyl) phthalate, Di-n- octyl Phthalate, and Pyrimidine were detected in female menstrual blood. Continuous human exposure to organic compounds that are endocrine disrupting in nature is an important issue that requires frequent monitoring. Hence, the use of menstrual discharge sample collected through non-invasive means provides an alternative biomonitoring matrix critical to the protection of vulnerable groups, such as chronically ill participants. The detection of phthalates in the menstrual blood of all study participants suggests that bioaccumulation of phthalate may be occurring with appreciable human toxicity.

CRediT authorship contribution statement

Benjamin Ason: Conceptualization, Methodology, Original draft preparation, Formal Analysis, Writing Frederick Ato Armah: Software, Data curation, Formal Analysis Reviewing and Editing David Kofi Essumang: Supervision, Reviewing and Editing.

Declaration of Competing Interest

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.

Data availability

Data will be made available on request.

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