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Phthalate and bisphenol A exposure among pregnant women in Canada — Results from the MIREC study

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ABSTRACT

Bisphenol A (BPA) and phthalates are endocrine disruptors possibly linked to adverse reproductive and neurodevelopmental outcomes. These chemicals have commonly been measured in urine in population surveys; however, such data are limited for large populations of pregnant women, especially for the critical first trimester of pregnancy. The aim of the study was to measure BPA and phthalate metabolites in first trimester urine samples collected in a large national-scale pregnancy cohort study and to identify major predictors of exposure. Approximately 2000 women were recruited in the first trimester of pregnancy from ten sites across Canada. A questionnaire was administered to obtain demographic and socio-economic data on participants and a spot urine sample was collected and analyzed for total BPA (GC–MS/MS) and 11 phthalate metabolites (LC–MS/MS). The geometric mean (GM) maternal urinary concentration of total BPA, uncorrected for specific gravity, was 0.80 (95% CI 0.76–0.85) μg/L. Almost 88% of the women had detectable urinary concentrations of BPA. An analysis of urinary concentrations of BPA by maternal characteristics with specific gravity as a covariate in the linear model showed that the geometric mean concentrations: (1) decreased with increasing maternal age, (2) were higher in current smokers or women who quit during pregnancy compared to never smokers, and (3) tended to be higher in women who provided a fasting urine sample and who were born in Canada, and had lower incomes and education. Several of the phthalate metabolites analyzed were not prevalent in this population (MCHP, MMP, MiNP, MOP), with percentages detectable at less than 15%. The phthalate metabolites with the highest measured concentrations were MEP (GM: 32.02 μg/L) and MnBP (GM: 11.59 μg/L). MBzP urinary concentrations decreased with maternal age but did not differ by time of urine collection; whereas the DEHP metabolites tended to be higher in older women and when the urine was collected later in the day. This study provides the first biomonitoring results for the largest population of pregnant women sampled in the first trimester of pregnancy. The results indicate that exposure among this population of pregnant women to these chemicals is comparable to or even lower than that observed in a Canadian national population-based survey.

1. Introduction

Phthalates are ubiquitous environmental contaminants resulting in widespread exposure of the human population including pregnant women. Phthalates are used in a variety of industrial, consumer and personal care products. Reported use of personal care products, particularly perfumes and fragranced products, nail polish and eye makeup, has been positively associated with urinary concentration of multiple phthalate metabolites in women of reproductive age (Buckley et al., 2012; Parlett et al., 2013) and in pregnant women (Braun et al., 2013; Cantonwine et al., 2014). Phthalates may be present in U.S. foods (Schecter et al., 2013) and in some medications and dietary supplements (Kelley et al., 2012). There is concern that at least some phthalates may be endocrine disruptors (De Coster and van Larebeke, 2012) and affect development and reproduction (Jurewicz and Hanke, 2011; Kay et al., 2013; Meeker, 2012). For example, prenatal exposure to the phthalate metabolite MEHP (mono-(2-ethylhexyl) phthalate) has been associated with higher occurrence of early first trimester pregnancy loss (Toft et al., 2012). Elevated maternal urinary concentrations

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of some phthalate metabolites have been associated with decreased child mental and motor development and increased internalizing behaviors (Whyatt et al., 2012) and decreases in the psychomotor development index (Téllez-Rojo et al., 2013), especially in girls. Reduced anogenital distances in male infants, a potential early marker of reproductive toxicity in humans, have also been observed (Suzuki et al., 2012; Swan et al., 2005, 2008). The evidence for potential effects on birth weight are conflicting with some studies noting no effects (Philippat et al., 2012; Suzuki et al., 2010; Wolff et al., 2008) and one study reporting an association between low birth weight and prenatal exposure to di-n-butyl phthalate (Zhang et al., 2009). While several studies (Adibi et al., 2009; Latini et al., 2003; Meeker et al., 2009; Weinberger et al., 2014; Whyatt et al., 2009) have examined potential risks of preterm delivery from phthalate exposure, the strongest evidence comes from a recent large case–control study which reported significant associations with MEHP, MECPP, and Σ DEHP metabolites (Ferguson et al., 2014). A number of phthalate metabolites have been identified and measured in urine, including both hydrolytic monoesters and oxidized secondary metabolites that can be conjugated with glucuronic acid and excreted in urine, with the extent of oxidation increasing with the length of the alkyl chain of the phthalate monoester (Koch and Calafat, 2009). Metabolite biomarkers for low (LMW), intermediate (IMW) and high molecular weight (HMW) phthalates have been measured (Table 1). The oxidized metabolites have a longer half-life of elimination than the simple monoesters and tend to be excreted in higher concentrations (Wittassek et al., 2011). Furthermore, identical exposures to a D*n*BP (LMW) and a DEHP (HMW) phthalate at the same time may lead to a 5- to 20-fold higher urinary excretion of MnBP compared to MEHP and therefore the relative urinary concentrations for the monoester metabolites do not necessarily correspond to the exposure level for the parent phthalate (Wittassek et al., 2011).

Similar to phthalates, the general population, including pregnant women can be exposed to bisphenol A (BPA) in their daily life. Exposure sources include dental sealants (Kloukos et al., 2013), canned foods (Cao et al., 2011) and beverages (Cao et al., 2010), polycarbonate water dispensers (Makris et al., 2013), medical devices in neonatal intensive care units (Duty et al., 2013), vinyl shower curtains and pillow protectors, dish and laundry detergents, tub and tile cleaners, soaps, lotions, shampoo, conditioners, shaving creams, nail polish, and sunscreen (Dodson et al., 2012), paper currencies (Liao and Kannan, 2011), indoor dust (Loganathan and Kannan, 2011), and thermal paper (Geens et al., 2012). The potential toxicity of BPA has been widely studied due to its ubiquitous nature (in Canada, approximately 90% of the population in a national survey had detectable concentrations of BPA in their urine (Bushnik et al., 2010)) and potential estrogenic activity (Alonso-Magdalena et al., 2012). Elevated maternal urinary concentrations of BPA have been associated with adverse effects on the infant and young child, including increased risk of preterm delivery or shortened gestational length (Cantonwine et al., 2010; Tang et al., 2013; Weinberger et al., 2014), effects on anthropometric measures at birth (Lee et al., 2014; Snijder et al., 2013) and at 4 years of age (Valvi et al., 2013), adipokine levels in 9-year-old children (Volberg et al., 2013), child wheeze (Spanier et al., 2012) and child behavior (Braun et al., 2011a; Harley et al., 2013b; Perera et al., 2012).

Pregnant women are a unique population because of the behavioral and physiological changes to the female body during pregnancy which may potentially differentially affect their exposure to environmental chemicals (Abduljalil et al., 2012; Moya et al., 2014). To date there is a paucity of biomonitoring data on BPA and phthalate metabolites published on large cohorts of pregnant women, especially during the biologically sensitive time window for infant development of the first trimester. This paper addresses this major knowledge gap in a national-level cohort of pregnant women recruited during the first trimester in Canada.

2. Materials and methods

2.1. Study population

The Maternal-Infant Research on Environmental Chemicals (MIREC) study recruited 2000 women in the first trimester of pregnancy (<14 weeks gestation) from obstetric and prenatal clinics in ten cities across Canada. The goal was to recruit women that were generally representative of the population of pregnant women in each study area over a three year recruitment period (2008–2011). Eligibility criteria included ability to consent and to communicate in English or French, age 18 years or older, planning on delivering at a local hospital, and agreeing to participate in the cord blood collection component of the MIREC study. Women with a medical history of any of the following were excluded from the study: major chronic disease, threatened abortion, and illicit drug use. Details on the cohort have been previously reported (Arbuckle et al., 2013). One of the major objectives of the MIREC study was to obtain national-level biomonitoring data on exposure of pregnant women and their fetuses to environmental chemicals thought to potentially contribute to adverse health effects.

The study was reviewed and approved by the Health Canada Research Ethics Board and the ethics committees at the participating hospitals and research centers across Canada. Potential participants were provided with information on the objectives and design of the study and asked to sign the consent forms.

Information from questionnaires and medical charts as well as biological specimens was collected during each trimester and at delivery. Questionnaires were administered during the 1st trimester study visit to collect information on the characteristics of the participants

Table 1
Phthalate metabolites measured in the MIREC study, their limits of detection and the correction factor that was applied to compensate for inaccurate analytical standards.

Parent phthalate	Abbreviation	Metabolites	Abbreviation	Correction factor *	Limit of detection (μg/L)
Low molecular weight					
Di-n-butyl phthalate	D*n*BP	Mono-n-butyl phthalate	MnBP	0.53	0.20
Diethyl phthalate	DEP	Mono-ethyl phthalate	MEP	0.98	0.50
Butyl benzyl phthalate	BBzP	Mono-benzyl phthalate	MBzP	0.37	0.20
Dimethyl phthalate	DMP	Mono-methyl phthalate	MMP	0.75	5.0
Intermediate molecular weight					
Di-cyclo-hexyl phthalate	DCHP	Mono-cyclo-hexyl phthalate	MCHP	0.99	0.20
High molecular weight					
Di-iso-nonyl phthalate	DiNP	Mono-isononyl phthalate	MiNP	0.61	0.40
Di-n-octyl phthalate	DnOP	Mono-n-octyl phthalate	MnOP	1.12	0.70
		Mono-(3-carboxypropyl) phthalate	MCPP	0.78	0.20
Di-(2-ethylhexyl) phthalate	DEHP	Mono-(2-ethylhexyl) phthalate	MEHP	0.71	0.20
		Mono-(2-ethyl-5-oxo-hexyl) phthalate	MEOHP	0.93	0.20
		Mono-(2-ethyl-5-hydroxy-hexyl) phthalate	MEHHP	0.89	0.40

* See Langlois et al. (2012, 2014).

(e.g., maternal age and education, household income, pre-pregnancy body mass index and smoking status) and the timing of the urine collection (i.e., time of day, season, minutes since last void).

2.2. Urine collection and analysis

First trimester urine samples were collected in 125 mL Nalgene® containers (Thermo-Fisher Scientific Inc., Rochester NY, USA), aliquoted into 30 mL Nalgene® containers, frozen at −20 °C within 2 h of collection and shipped on dry ice to the MIREC coordinating center in Montreal where they were stored at −30 °C. Urine samples were shipped in batches to the Centre de Toxicologie du Québec, Institut national de Santé Publique du Québec (INSPQ) for analysis. This laboratory is accredited by the Standards Council of Canada under ISO 17025, the international standard for technical competence and quality in all areas of testing and calibration. Urine samples were analyzed for bisphenol A (BPA) and 11 phthalate metabolites: mono-n-butyl phthalate (MnBP); mono-ethyl phthalate (MEP); mono-benzyl phthalate (MBzP); mono-methyl phthalate (MMP); mono-cyclo-hexyl phthalate (MCHP); mono-isononyl phthalate (MiNP); mono-n-octyl phthalate (MnOP); mono-(3-carboxypropyl) phthalate (MCPP); mono-(2-ethylhexyl) phthalate (MEHP); mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP); and mono-(2-ethyl-5-hydroxy-hexyl) phthalate (MEHHP) (Table 1).

For the measurement of urinary total BPA (free plus conjugated) (INSPQ Method E-454), an enzymatic hydrolysis frees the conjugated compounds in urine. The samples are then derivatized at 70 °C (pentafluorobenzylation) for 2 h. Pentafluorinated benzyl derivatives are extracted with a mixture of hexane and dichloromethane and analyzed by GC–MS/MS with a GC Agilent 6890 N (Agilent Technologies; Mississauga, Ontario, Canada) coupled with a tandem mass spectrometer Quattro Micro GC (Waters; Milford, Massachusetts, USA). The measurement of ions generated was performed in MRM (multiple reaction monitoring) mode with a source in negative chemical ionization mode (NCI). The analytical column used was a HP-5MS 30 m × 0.25 mm i.d. × 0.25 μm film thickness (Agilent Technologies; Mississauga, Ontario, Canada). The limit of detection (LOD) for BPA in urine was 0.2 μg/L and was calculated by using the value equivalent to three times the standard deviation of 10 replicates of a sample at a concentration from 4 to 10 times the estimated LOD with a signal to noise (S/N) of 3.

Following an enzymatic deconjugation, the phthalate monoester compounds were extracted by solid phase extraction with anion exchange media using the Janus robotic station (PerkinElmer; Waltham, Massachusetts, USA) (INSPQ Method E-453). The extracts were brought to dryness, taken up in water and analyzed by LC–MS/MS with an Ultra Performance Liquid Chromatography (UPLC) Acquity (Waters; Milford, Massachusetts, USA) coupled with a tandem mass spectrometer Quattro Premier XE (Waters; Milford, Massachusetts, USA) in MRM mode with an electrospray ion source in negative mode. The analytical column used was an Acquity BEH Phenyl 50 mm × 2.1 mm i.d. × 1.7 μm film thickness (Waters; Milford, Massachusetts, USA). The limits of detection (LOD) for the phthalate monoester metabolites varied from 0.2 to 5.0 μg/L (Table 1) and they were estimated as a function of the signal to noise ratio (S/N) of 3 in real samples because most of the phthalate monoesters have concentrations too high in normal urine to be calculated with the standard deviation as described above with BPA.

All biospecimen containers were provided by the laboratory to ensure conformity in the batches of supplies. Containers and field blanks were tested for possible contamination during the collection, processing, transportation and storage procedures. Water (Steril.O reagent grade deionized distilled water) was used as the sampling media. Analyses of field blanks were done at the laboratory using the same analytical procedures. Results showed that the field blanks were free of contamination for the specific tests that were investigated.

When it became necessary to purchase new lots of standards for the phthalate metabolites in early 2009, the laboratory noticed that there was a significant difference in concentration between these new lots and the previous ones. Troubled by this finding, the laboratory launched a thorough investigation which is now published (Langlois et al., 2012). The conclusion of this investigation brought to light that the phthalate metabolite standards used in the MIREC study were inaccurate. The analyses were not stopped but a correction factor was applied to all results generated (Langlois et al., 2014). The correction factors were determined on the basis of the findings of three different reliable commercial sources. The correction factors that were applied to the MIREC results are listed in Table 1.

To account for urine dilution, specific gravity was measured in thawed urine samples by a refractometer (UG-1, Atago # 3461, Atago U.S.A. Inc., Bellevue, WA).

2.3. Statistical analysis

Concentrations for each metabolite analyzed in this report were corrected by specific gravity (SG) using the following formula (adapted from Just et al., 2010):

$$P_c = P_i\left[\frac{SG_m - 1}{SG_i - 1}\right]$$

where P_c is the SG-corrected metabolite concentration, P_i is the observed metabolite concentration, SG_i is the specific gravity of the ith urine sample and SG_m is the median SG for the cohort. The statistical analysis was conducted on both the uncorrected and SG-corrected concentration levels. A third method of analysis was also considered, whereby the specific gravity was regarded as a covariate in the linear model with the effect of interest (e.g., smoking, maternal age, parity, etc.). As such, the linear model approach considered three models: i) a full model containing specific gravity, the demographic variable (effect) and an interaction term between specific gravity and the effect; ii) a reduced model with no interaction term(s); and iii) a model with the effect variable removed. Stepwise regression techniques were used to determine whether the interaction term was significant. If the interaction was not significant, then the reduced model was fit and the demographic variable was tested for significance. If the interaction term was significant, then separate regression lines were fit for each level of the main effect, since the differences between groups depended on the level of specific gravity. In the analysis presented here, when an interaction term was significant, group differences were measured at the 25th, 50th and 75th percentiles of specific gravity.

As is common in human biomonitoring studies, concentrations of environmental chemicals may be so low as to be indistinguishable from zero when measured in the laboratory and are typically reported as "<LOD", where LOD represents the limit of detection for a given contaminant and analytical method. These observations are referred to as "censored". It has been demonstrated that simple substitution with a constant such as 1/2 LOD or LOD/$\sqrt{2}$ may lead to increased bias and an underestimation of the error variance, which results in lowered power for statistical hypothesis testing (Cole et al., 2009; Helsel, 2012; May et al., 2011). To mitigate these issues, many authors have adapted techniques for survival analysis of right-censored data to the left-censored case found in environmental studies. For descriptive statistics, we implemented two popular estimation techniques for right-censored data: a) parametric maximum likelihood estimation (MLE) and b) non-parametric Kaplan–Meier (K–M) (Helsel, 2012). These methods differ in their assumptions and calculation. Furthermore, to ensure accuracy, only contaminants where 50% of the data was above the limit of detection were analyzed.

Maximum likelihood estimation assumes that the contaminant of interest follows a distribution. In particular, since many of the contaminants were right-skewed, we assumed that the data followed a lognormal distribution. In the case of the left-censored data, we must also incorporate an expression to represent whether the observation is

censored or not. Thus, the censored likelihood function becomes

$$L = \prod_{i=1}^{n} p(x_i)^{\delta_i} F(x_i)^{1-\delta_i}$$

where $\delta_i = 1$ if detected and $\delta_i = 0$ if censored. For a lognormal distribution, the probability distribution function is

$$p(x_i) = \frac{1}{x_i\sqrt{2\pi\sigma^2}} e^{\frac{(\log x_i - \mu)^2}{2\sigma^2}}.$$

Table 2
Characteristics of MIREC participants providing 1st trimester urine samples for analysis of phthalate metabolites and bisphenol A.

Maternal characteristic	N*	Percentage (%)
Maternal age (years)		
<25	120	6.7
25–29	414	23.1
30–34	643	36.0
≥35	611	34.2
Parity		
0	794	44.4
1	722	40.4
>1	270	15.1
Smoking status		
Current**	209	11.7
Former	487	27.3
Never	1087	61.0
Time of urine collection		
6:00–9:00	26	1.4
9:00–12:00	774	43.3
12:00–15:00	604	33.8
15:00–18:00	345	19.3
18:00–24:00	37	2.1
Fasting sample		
No	1725	97.8
Yes	39	2.2
Birth place		
Other	333	18.6
Canada	1455	81.4
Time since last urination (min)		
<75 min	446	26.2
76–120	560	33.0
121–170	253	14.9
>170	440	25.9
Pre-pregnancy BMI (kg/m²)		
<25	1069	64.2
25–29	363	21.8
≥30	233	14.0
Income ($)		
≤50,000	305	17.9
50,001–100,000	711	41.6
>100,000	691	40.5
Season of collection		
Fall	513	28.7
Winter	436	24.4
Spring	417	23.3
Summer	422	23.6
Education		
High school or less	154	8.6
College diploma	510	28.6
University degree	1122	62.8

* Number of women providing characteristics and urine sample for phthalate metabolites; the N for BPA maternal characteristics were slightly higher.
** Includes women who quit smoking during current pregnancy.

And the cumulative distribution function (CDF) for lognormal is

$$F(x_i) = \Phi\left(\frac{y_i - \mu}{\sigma}\right)$$

with $y_i = \log x_i \sim N(\mu, \sigma^2)$ and $\Phi(x) = P(X \le x)$ being the cumulative distribution function of a normal random variable. Geometric means and associated confidence intervals were then calculated based on the MLE.

If the assumption of lognormality is not reasonable, the non-parametric Kaplan–Meier procedure is preferred. The K–M method is a well-known procedure used to estimate the survival function, $S(t)$, or time until an event occurs (e.g., failure of a component), assuming that some observations are right-censored. No distributional assumptions are made; rather an estimate of the survival function is obtained as

$$\hat{S}(t) = \prod_{t_{(i)} \le t} \frac{n_i - d_i}{n_i},$$

where $\hat{S}(t) = 1$ for $t < t_{(1)}$, and $t_{(i)}$ represents the ordered survival times $t_{(1)} < t_{(2)} < \cdots < t_{(m)}$. Then, in the context of survival analysis, n_i is the number of individuals at risk of reaching a given event at $t_{(i)}$ and d_i is the number of individuals that do reach the given event at time $t_{(i)}$.

In the left-censored case, we are interested in obtaining the median of the empirical cumulative density function (ECDF) denoted $F(t)$ which is calculated as $F(t) = 1 - \hat{S}(t)$. As suggested by other authors (Helsel, 2012; Koru-Sengul et al., 2011) the ECDF is found by "flipping" the observations after subtracting each observation from a constant larger than the maximum value, and utilizing the right-censored methods presented above. Then, the observations are re-transformed back to the original units to obtain the correct estimate of the median. Confidence intervals were calculated using Greenwood's formula, as utilized in the survival analysis (Helsel, 2012).

For hypothesis testing using the censored methods for the uncorrected and SG-corrected data, likelihood ratio tests for parametric ML estimation were used, which follow a chi-square distribution under the null hypothesis of no difference in groups. If this hypothesis was rejected, then multiple comparisons were performed using Bonferroni-adjusted confidence intervals and significantly different groups were identified. The assumptions for maximum likelihood were verified using a test for lognormality developed by Nysen et al. (2012) which accounts for left-censored observations. If the assumption of lognormality failed, then non-parametric testing was performed using the Wilcoxon rank-sum test for independent groups.

Statistical analysis was performed using SAS (Statistical Analysis System) Enterprise Guide 4.2 and R (R Core Development Team). For the censoring methods, functions from the R packages NADA and SURVIVAL were used for analysis. A 5% significance level ($\alpha = 0.05$) was implemented throughout.

3. Results

Characteristics of the women providing 1st trimester urine samples from the MIREC study for analysis of phthalate metabolites and BPA are outlined in Table 2. The majority of the women were non-smokers and of a higher socio-economic class than the general population of women giving birth in Canada (Arbuckle et al., 2013). The median gestational age of the mothers whose urine samples were collected was 12.43 weeks, with a range of 6.14 to 14.86 weeks.

One urine sample was excluded from our analysis because it was too dilute (specific gravity = 1.000, creatinine < 0.3 nmol/L) and all chemical results were below the limits of detection. There were 3 samples for whom no specific gravity results were available which were included in the uncorrected analyses but removed from the corrected analyses.

Table 3
Urinary bisphenol A and phthalate metabolite concentrations (μg/L) uncorrected and corrected for specific gravity in first trimester samples from the MIREC study.

	BPA	DnBP	DEP	BBzP	DMP	DCHP	DiNP	DnOP		DEHP		
Metabolite		MnBP	MEP	MBzP	MMP	MCHP	MiNP	MOP	MCPP	MEHP	MEOHP	MEHHP
Uncorrected												
MLE GM (95% CI)	0.80 (0.76–0.85)	11.59 (10.96–12.26)	32.02 (29.75–34.47)	5.20 (4.90–5.52)	ND	ND	ND	ND	0.86 (0.80–0.92)	2.24 (2.12–2.37)	6.39 (6.04–6.75)	9.16 (8.65–9.71)
K–M Median (95% CI)	0.82 (0.78–0.86)	12.00 (11.18–12.82)	28.00 (25.45–30.55)	5.20 (4.84–5.56)	NA	NA	NA	NA	0.92 (0.85–1.01)	2.20 (2.06–2.34)	6.50 (6.16–6.84)	9.40 (8.77–10.03)
95th percentile	5.40	69.65	530.00	41.65	10.0	0.38	NA	NA	9.26	15.00	41.00	65.65
Maximum	140.00	3100	13,000	420.00	1000	77.00	9.20	7.90	370.00	340.00	980.00	1200.00
% < LOD	12.29	0.28	0.17	0.67	85.35	92.23	98.49	97.82	17.84	2.35	0.45	0.95
N	1936	1788	1788	1788	1788	1788	1788	1788	1788	1788	1788	1788
SG-corrected												
MLE GM (95% CI)	0.90 (0.86–0.94)	13.69 (13.15–14.24)	37.73 (35.37–40.24)	6.14 (5.86–6.43)	ND	ND	ND	ND	1.02 (0.97–1.08)	2.63 (2.52–2.74)	7.54 (7.24–7.84)	10.81 (10.36–11.28)
K–M median	0.85 (0.80–0.89)	13.00 (12.51–13.49)	30.95 (28.48–33.42)	5.70 (5.38–6.02)	NA	NA	NA	NA	0.95 (0.91–1.00)	2.38 (2.28–2.48)	6.93 (6.71–7.16)	9.88 (9.52–10.24)
95th percentile	4.69	50.78	486.91	37.41	21.67	0.88	NA	NA	7.60	12.21	30.94	50.35
Maximum	204.29	1831.82	20,800	342.73	541.67	47.67	5.46	4.89	186.33	260.00	733.57	1114.29
% < LOD	12.29	0.28	0.17	0.67	85.35	92.23	98.49	97.82	17.84	2.35	0.45	0.95
N	1933	1785	1785	1785	1785	1785	1785	1785	1785	1785	1785	1785

LOD: limit of detection.
K–M median: Kaplan–Meier median, censored method.
MLE GM: maximum-likelihood estimated geometric mean, censored method.
ND: below limit of detection.
NA: not applicable due to high level of censoring.

3.1. Total BPA

Maternal urinary concentrations of total BPA ranged from non-detectable (<0.02 μg/L) to 140 μg/L, uncorrected for specific gravity, with almost 88% of the women having detectable concentrations of BPA (Table 3).

An analysis of urinary concentrations of BPA by maternal characteristics with specific gravity as a covariate in the linear model showed that the geometric mean concentrations: (1) decreased with increasing maternal age, (2) were higher in current smokers or women who quit during pregnancy compared to never smokers, and (3) tended to be higher in women who provided a fasting urine sample and who were born in Canada, and had lower incomes and education (Table 4). Parity, pre-pregnancy body mass index (BMI) and season of sample collection were not significant predictors of urinary BPA concentrations. It is noteworthy that a significant interaction with specific gravity and time of urine collection was observed indicating that the effect of time of urine collection depends on the specific gravity of the mother's urine. BPA concentrations tended to increase with time of day; however, whether the differences between times of day were significant depended on the percentile of specific gravity that was used for estimation. At the 25th percentile for specific gravity, urine collected between 9:00 and 15:00 were significantly lower in BPA than the samples collected between 15:00 and 18:00 (see Fig. 1). At the 50th percentile of specific gravity, significant differences were noted between the samples collected between 9:00 and 12:00 and those from 15:00 to 18:00; whereas at the 75th percentile of specific gravity, there were no significant differences in BPA concentrations by time of urine collection.

3.2. Phthalates

Several of the phthalate metabolites analyzed were not prevalent in this population (MCHP, MMP, MiNP, MOP), with percentages detectable at less than 15% (Table 3). The phthalate metabolites with the highest measured concentrations were MEP (geometric mean (GM): 32.02, maximum: 13,000 μg/L, >99% detected) and MnBP (GM: 11.59, maximum: 3100 μg/L, >99% detected); and the DEHP metabolites (MEHP, MEOHP, MEHHP) were detected in over 95% of the urine samples.

For the phthalate metabolites, maternal age was a significant predictor of MBzP (highest in women <30 compared to women ≥35 years), MEHHP (lower in women <25 compared to women 25–29 or ≥35 years), and MEHP and MEOHP (higher in women 25–29 than in those <25 years). Parity was only a significant predictor of MEP, with first pregnancies having the higher concentrations. Women who were current smokers at the time of the urine collection or who had quit during the pregnancy tended to have lower urinary concentrations of MEHHP and MEOHP.

As with BPA, a significant interaction was found between specific gravity and time of urine collection for some of the phthalate metabolites (MnBP, MCPP, MEHHP, MEHP, MEOHP, and MEP). For MnBP, concentrations increased with time of day with significant differences between specific time periods noted only at the 25th or 50th percentile of specific gravity (data not shown).

MCPP concentrations also increased with time of day, with urines collected between 9:00 and 12:00 significantly lower than those collected between 15:00 and 18:00; however, at the 75th percentile of specific gravity only urines collected between 9:00 and 12:00 were significantly lower from those collected between 18:00 and 24:00 (data not shown).

Fig. 2 displays the MEOHP urinary concentrations by time of day of collection and specific gravity, showing that the differences between sampling times depend on the specific gravity of the urine. For example, only at the 75th percentile of specific gravity are MEOHP concentrations collected in urine between 6:00 and 9:00 significantly higher than those collected between 9:00 and 15:00.

Women who had fasted prior to the urine collection had higher concentrations of MBzP and MEP. Foreign born women had lower

Table 4
Geometric mean maternal urinary concentrations of prevalent phthalates and BPA in the first trimester by characteristics of the woman, including specific gravity as a covariate.

Parent		BPA	DnBP	DEP	BBzP	DnOP	DEHP		
Metabolite		BPA	MnBP	MEP	MBzP	MCPP	MEHP	MEOHP	MEHHP
Maternal age (years)	N*	p = 0.009	p = 0.25	p = 0.075	p < 0.0001	p = 0.82	p = 0.0086	p = 0.0033	p = 0.0003
<25	120	1.02	12.43	40.85	6.75	0.80	1.84	4.94	6.60
25–29	414	0.83	12.30	34.21	6.21	0.85	2.49	6.83	9.75
30–34	643	0.82	11.18	31.64	5.01	0.86	2.17	6.26	9.01
≥35	611	0.74	11.40	29.35	4.57	0.89	2.24	6.54	9.51
Parity		p = 0.095	p = 0.62	p < 0.0001	p = 0.061	p = 0.50	p = 0.22	p = 0.39	p = 0.42
0	794	0.85	11.41	37.65	4.99	0.84	2.28	6.43	9.06
1	722	0.78	11.51	28.71	5.19	0.90	2.27	6.48	9.44
>1	270	0.75	12.09	26.15	5.91	0.85	2.04	5.97	8.71
Smoking status		p = 0.0014	p = 0.19	p = 0.054	p = 0.12	p = 0.054	p = 0.067	p = 0.012	p = 0.0052
Current**	209	1.01	10.47	39.67	5.91	0.76	1.97	5.46	7.62
Former	487	0.81	11.82	31.37	5.20	0.94	2.36	6.76	9.71
Never	1087	0.77	11.70	30.79	5.06	0.85	2.24	6.40	9.21
Time of urine collection		p = 0.032 ***	p = 0.0001 ***	p = 0.040 ***	p = 0.22	p = 0.014 ***	p < 0.0001 ***	p = 0.0003 ***	p < 0.0001 ***
6:00–9:00	26	0.60	7.88	33.37	4.76	0.52	2.34	6.68	8.64
9:00–12:00	774	0.67	8.96	29.05	4.90	0.62	1.62	4.55	6.32
12:00–15:00	604	0.72	10.02	27.26	5.40	0.73	1.98	5.59	8.08
15:00–18:00	345	0.94	12.40	27.12	5.60	1.01	2.81	7.93	11.79
18:00–24:00	37	1.08	16.34	26.16	5.67	1.46	2.22	7.32	10.41
Fasting sample		p = 0.036	p = 0.19	p = 0.02	p = 0.011	p = 0.72	p = 0.36	p = 0.47	p = 0.44
No	1725	0.80	11.51	31.38	5.14	0.86	2.25	6.39	9.18
Yes	39	1.13	13.82	53.00	7.79	0.81	1.96	5.77	8.19
Birth place		p = 0.035	p = 0.22	p = 0.0003	p = 0.0004	p = 0.59	p < 0.0001	p = 0.0056	p = 0.0039
Other	333	0.73	12.21	41.10	4.36	0.84	2.72	7.18	10.43
Canada	1455	0.83	11.45	30.15	5.42	0.87	2.14	6.21	8.89
Time since last urination		p = 0.047	p = 0.0049 ***	p = 0.014	p = 0.0004 ***	p = 0.65	p = 0.071	p = 0.0056	p = 0.0025
<75 min.	446	0.77	8.77	27.08	3.86	0.82	2.02	5.63	7.95
76–120	560	0.77	10.56	32.84	4.67	0.86	2.28	6.55	9.38
121–170	253	0.91	10.16	35.08	4.39	0.87	2.35	6.79	9.81
>170	440	0.86	10.67	36.16	5.60	0.91	2.34	6.73	9.72
Pre-pregnancy BMI (kg/m^2)		p = 0.052	p = 0.94	p = 0.80	p = 0.0068	p = 0.65	p < 0.0001	p = 0.23	p = 0.44
<25	1069	0.77	11.53	31.15	4.99	0.85	2.37	6.44	9.18
25–29	363	0.87	11.75	31.39	5.08	0.91	2.13	6.31	9.16
≥30	233	0.86	11.51	33.37	6.28	0.87	1.77	5.78	8.43
Income ($)		p = 0.021	p = 0.014	p = 0.049	p < 0.0001	p = 0.39	p = 0.21	p = 0.016	p = 0.0042
≤50,000	305	0.92	13.27	37.97	6.71	0.83	2.21	5.88	8.28
50,001–100,000	711	0.81	11.25	30.69	5.16	0.85	2.17	6.26	8.95
>100,000	691	0.76	11.36	30.43	4.75	0.91	2.36	6.89	10.04
Season of collection		p = 0.53	p = 0.22	p = 0.13	p = 0.70	p = 0.032 ***	p = 0.50	p = 0.93	p = 0.68
Fall	513	0.78	11.84	28.33	5.11	0.66	2.19	6.36	9.07
Winter	436	0.84	11.96	32.70	5.37	0.70	2.28	6.47	9.06
Spring	417	0.79	10.72	34.45	5.34	0.78	2.35	6.46	9.59
Summer	422	0.84	11.81	33.50	5.02	0.78	2.15	6.25	8.95
Education		p = 0.027	p = 0.0010 ***	p = 0.10	p = 0.0059 ***	p = 0.57	p = 0.014	p = 0.0006	p = 0.0002
High school	154	0.96	10.20	35.21	6.08	0.79	1.96	5.20	7.19
College diploma	510	0.83	9.24	35.06	4.57	0.87	2.10	6.03	8.62
University degree	1122	0.78	10.14	30.26	4.31	0.87	2.35	6.73	9.72

* Number of women for phthalate metabolites; the N for BPA maternal characteristics were slightly higher.
** Includes women who quit smoking during current pregnancy.
*** Significant interaction between specific gravity (SG) and characteristic; GM for 50th percentile of SG reported.

concentrations of MBzP, but higher concentrations of MEHHP, MEHP, MEOHP and MEP. The length of time since the last urination was a significant predictor of MnBP, MBzP, MEHHP, MEOHP and MEP. Pre-pregnancy BMI was associated with urinary concentrations of MBzP and MEHP (with BMI < 25 having higher levels than those with BMI ≥ 30). Income was a significant predictor for MnBP, MBzP (highest in those with ≤$50,000), MEHHP, MEOHP and MEP. A significant interaction with specific gravity was observed with season of collection for MCPP. Higher maternal education was significantly associated with elevated concentrations of MEHHP and MEOHP, except for MBzP, where the reverse was true at the 25th and 50th percentiles of specific gravity.

3.3. Correction for specific gravity

In addition to considering specific gravity as a covariate, statistical analysis and hypothesis testing were also performed using specific gravity-corrected data. The results for the specific gravity correction are provided in Supplementary material Table S1. For variables such as smoking status, fasting and maternal birth place, similar conclusions of statistical significance were obtained regardless of the specific gravity correction method. For other variables however, some slight differences were noted. In particular, for MEP, time of urine collection was significant ($p = 0.04$) when specific gravity was considered as a covariate, while no significant difference ($p = 0.4924$) was found when the specific gravity correction was used.

3.4. Censored versus substitution methods

While not the primary objective of our study, we have also compared results of hypothesis testing using censored methods (likelihood ratio and Wilcoxon) with results using substitution of half the detection limit. Supplementary Tables S2 and S3 display p-values for the various methods for contaminants BPA and MEOHP respectively. From both tables, it is evident that conclusions were similar among the statistical

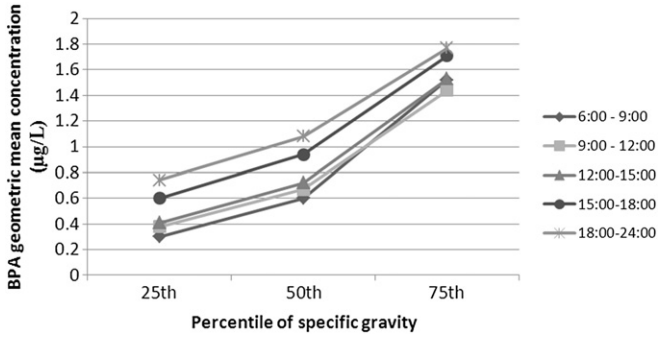

Fig. 1. BPA urinary 1st trimester concentrations (geometric mean) by time of urine collection and specific gravity.

methods used, however some differences were noted. For instance, considering specific gravity as a covariate, parity was a significant predictor for BPA using the substitution methods ($p = 0.0442$), however it is not significant when considering the maximum likelihood method ($p = 0.0946$). Nevertheless, given that censored methods are based upon sound statistical theory and have demonstrated improved efficiency in many empirical studies (Cole et al., 2009; Helsel, 2012; May et al., 2011), we implemented censored methods in the present analysis.

4. Discussion

This paper reports urinary BPA and phthalate metabolite concentrations in a larger population of pregnant women than has ever been reported in the literature and expressly for the first trimester, a critical window of exposure for the development of the infant. It also represents a diverse geographical distribution of pregnant women from across Canada with some participation of women from varied ethnic and socio-demographic strata. The prevalent urinary exposures for this population were: BPA (87.7% detected), MnBP (99.7% detected), MEP (99.8% detected), MBzP (99.3% detected), MCPP (82.2% detected), MEHP (97.6% detected), MEOHP (99.6% detected), and MEHHP (99.0% detected).

Based on a spot urine sample, the first trimester geometric mean concentration of total BPA (uncorrected for specific gravity) in MIREC (0.80 µg/L; 95% CI 0.76–0.85 µg/L) tended to be lower than those reported in the Generation R (1.3 µg/L) (Snijder et al., 2013), CHAMACOS (1.0 µg/L) (Harley et al., 2013a), and INMA (2.1 µg/L) (Casas et al., 2013) cohorts and also lower than those reported in the Canadian Health Measures Surveys (CHMS) of 2007–2009 (1.26 µg/L) (Health Canada, 2010a) and 2009–2011 (1.2 µg/L) for women 20–39 years of age (Health Canada, 2013a). While 97.4% of the women 20–39 in the CHMS 2009–2011 sample had detectable levels of BPA in their urine, the figure for MIREC participants was somewhat lower at 88%. It should be noted that the same laboratory and analytical methods were used in both the CHMS and MIREC analyses, so the results should be comparable. It is possible that there are population differences between studies (e.g., consumer product formulations) which account for the lower urinary BPA concentrations observed in MIREC. Methodological differences were not a factor in explaining significantly lower urinary levels of BPA in a Canadian national survey compared to an American (Lakind et al., 2012). Women in the MIREC study, who were younger, smoked, had fasted, were born in Canada, had lower income and education level and provided their urine sample later in the day had significantly higher urinary concentrations of BPA. Similar results were reported in the Spanish birth cohort study, where women who were younger, less-educated, smoked, and who were exposed to second-hand tobacco smoke (SHS) had higher BPA concentrations than others (Casas et al., 2013). In contrast, maternal age, education, and smoking status were not significant predictors in the CHAMACOS study of predominantly low income Mexican-Americans or Mexican immigrants in California (Quirós-Alcalá et al., 2013). In the Cincinnati HOME study where the median BPA concentration at 16 weeks was 2.0 ng/mL (compared to 0.82 ng/mL in MIREC), creatinine-standardized BPA concentrations were also higher among women with lower education than among women with higher education and were the highest between 1500 and 1659 h (Braun et al., 2011b).

Median phthalate metabolite concentrations in maternal urine in MIREC were comparable to those reported for women 20–39 years of age in Cycle 2 of the CHMS (2009–2011) (Health Canada, 2013a) but tended to be lower than in an American (Engel et al., 2009) or Spanish pregnancy cohort (Casas et al., 2011) (Fig. 3). The availability of consumer products containing certain phthalates may be declining, as levels of several phthalate metabolites are decreasing over time in Canada (Fig. 3), which may explain differences observed with earlier cohorts. An interesting observation was the vastly different median urinary concentrations of MEP reported in the Spanish (324 µg/L) and American cohorts (386 µg/L) compared to the Canadian studies (48 µg/L in the CHMS survey and 28 µg/L in MIREC). The American cohort (Engel et al., 2009) was of lower socio-economic status than the MIREC cohort and their samples were collected in 1999–2001 and were affected by approximately 40% by the correction in the MEP phthalate standard (CDC, 2012) which may explain the differences. It is noteworthy that a maximum urinary MEP concentration of 13,000 µg/L was measured in MIREC and a significant association between urinary MEP and lower income was observed.

Although the limit of detection for MMP in MIREC was higher (5 µg/L) than that for NHANES (0.5 µg/L), the proportion of NHANES 2009–2010 results below the LOD was too high to calculate a geometric mean (CDC, 2013), indicating that exposure to this phthalate is not prevalent in either country. The percentage of non-detects for MMP in Canadian women 20–39 years of age ranged from 87% (2007–2009) to 76% (2009–2011),

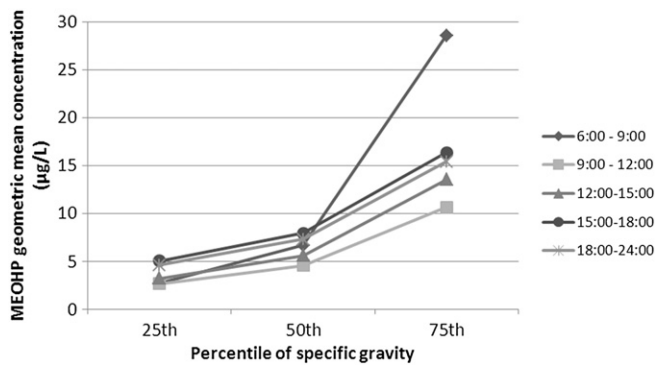

Fig. 2. MEOHP urinary 1st trimester concentrations (geometric mean) by time of urine collection and specific gravity.

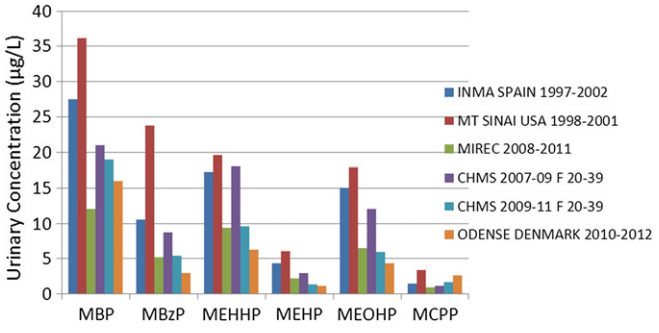

Fig. 3. Comparison of uncorrected median phthalate metabolite concentrations (µg/L) in urine from various international studies: INMA Spain (n = 118; Casas et al., 2011), Mt Sinai (n = 295; Engel et al., 2009), MIREC (n = 1788), CHMS 2007–2009 (n = 364; Health Canada, 2013a); CHMS 2009–2011 (n = 190; Health Canada, 2013a) and Denmark (Tefre de Renzy-Martin et al., 2014).

comparable with MIREC data (85%) with the same LOD (Health Canada, 2010a, 2013a).

Maternal age was a significant predictor of MBzP (highest in women <30 compared to women ≥35 years), MEHHP (lower in women <25 compared to women 25–29 or ≥35 years), and MEHP and MEOHP (higher in women 25–29 than in those <25 years). A small study of Puerto Rican women also reported that MBzP urinary levels were higher in younger women, but also reported higher concentrations of MnBP in the youngest women (Cantonwine et al., 2014). In MIREC, the only phthalate metabolites significantly associated with parity was MEP, with first pregnancies having the higher concentration.

In MIREC, although the numbers were small, women who fasted (n = 39) had significantly higher urinary concentrations of the low molecular weight phthalate metabolites MBzP and MEP and lower (although not statistically significant) levels for the DEHP metabolites. In the Canadian Health Measures Survey, concentrations of the DEHP metabolites were significantly lower and no different for MEP and MBzP in the fasted as compared to the non-fasted groups (Saravanabhavan et al., 2013). A fasting study of 5 volunteers has provided support for the hypothesis that exposure to high molecular weight phthalates is driven by food consumption as they reported a trend of declining urinary concentrations during the fast for the metabolites of the high molecular weight phthalates (DEHP, DiNP, DiDP/DPHP); in contrast, for most of the low molecular weight phthalates, only a weak association with fasting was observed (Koch et al., 2013). Not considering whether subjects fasted prior to urine collection may underestimate exposure to some phthalates (Wittassek et al., 2011).

PBPK modeling has shown that the ratio between MEHP and the oxidized metabolite MEHHP can vary between 2.89 and 5.4 (Lorber et al., 2010). This range of ratios is somewhat higher than the ratio of uncorrected geometric means found in MIREC of 1.43, but within the range for the specific gravity corrected geometric mean ratios of 4.1.

Given the ubiquitous presence of phthalates in the environment, one of the major concerns in measuring phthalate metabolite concentrations in urine is possible external contamination, including during collection (urine cups, aliquot tubes, etc.) and laboratory analysis (laboratory reagents, sampling equipment, and analytical apparatus) (Koch and Calafat, 2009). Simple monoester metabolites are prone to external contamination during the analytical procedure; whereas the secondary oxidized phthalate metabolites are not susceptible (Wittassek et al., 2011). Based on the results of the field blanks and testing of collection materials, there is no evidence that external contamination was a concern in this study.

4.1. Health Canada regulations and primary prevention

Despite the many sources of exposures to BPA, dietary intake due to migration from food packaging and use of BPA-containing polycarbonate storage containers is considered as the primary route of exposure for the general, non-occupationally exposed population (Health Canada, 2008). The Government of Canada, through scientific assessment, determined that BPA is toxic to human health (Canada, 2010) and a provisional tolerable daily intake of 25 μg/kg body weight from food packaging has been established (Health Canada, 2008, 2012). There is currently no biomonitoring-based guidance value to allow interpretation of urinary levels measured in the MIREC study. Current dietary exposure to BPA through food packaging uses was determined not to pose a health risk to the general population, including newborns and young children (Health Canada, 2008, 2012). Due to laboratory and experimental uncertainty and potential low dose effects reported in developmental and neurobehavioral studies (Environment Canada and Health Canada, 2008), Health Canada heightened its risk management measures with focus on minimizing exposure from products consumed by newborns and infants. As of 2010, Health Canada has prohibited the manufacturing, advertisement, sale, or import of BPA-containing polycarbonate baby bottles (Health Canada, 2010b). Health Canada has also committed to facilitating the assessment of proposed industry alternatives to BPA for use in infant-formula and other can coatings, as well as targets for BPA in infant-formula cans (Health Canada, 2012). BPA is also included on Health Canada's list of prohibited and restricted cosmetic ingredients (Health Canada, 2011a). Canadians are encouraged to read labels ensuring containers are BPA-free, and avoiding products with the number "7 PC" in the center of the recycling symbol. If consumers opt to continue using older bottles that may contain BPA, these should not be heated while containing liquid. It is recommended that water or other liquids be boiled and allowed to cool to lukewarm in a non-polycarbonate container before transferring.

For phthalates, food and the use of consumer products made from polyvinyl chloride (PVC) plastics are the primary sources of exposure to phthalates to the general population. As with BPA, the weight of evidence is presently insufficient for developing health-based biomonitoring guidance values to interpret urinary levels measured in the MIREC study. Nevertheless, Health Canada has assessed several phthalates as priority substances, including DEHP, D*n*BP, DOP and BBP. Based on these assessments, only DEHP was declared toxic and now included on Health Canada's list of prohibited and restricted cosmetic ingredients (Health Canada, 2011a). In 2011, Health Canada has also restricted the use of six phthalates (DEHP, D*n*BP, BBP, DiNP, DiDP, and DOP) to no more than 1000 mg/kg (0.1%) in soft vinyl children's toys and childcare articles whether imported, sold or advertised in Canada (Health Canada, 2011b). On July 13, 2013, Health Canada announced a high-priority assessment under the Chemicals Management Plan for 14 substances which are part of the Phthalate Substance Grouping and 14 additional substances which are under consideration for inclusion in the grouping (Health Canada, 2013b). For individual primary prevention, consumers are encouraged to read labels on personal care products and vinyl clothing, avoiding products with the number "3" in the center of the recycling symbol, and if unsure, the manufacturer may be called for content clarification. Further, "Health Canada advises parents and caregivers to monitor their children's use of soft vinyl (PVC) toys not specifically designed for sucking and chewing (such as vinyl bibs and bath, squeeze or inflatable toys), and to remove these products from the child's environment if they observe the child sucking or chewing on them for extended periods" (Health Canada, 2011b).

4.2. Strengths and limitations

A major limitation of the study is that at the time the study was designed, we were limited to measuring the phthalate metabolites for which the laboratory had methods and therefore were missing some of the major oxidative metabolites for the longer chain phthalates. For example, we did not measure mono(2-ethyl-5-carboxy-pentyl)phthalate (MECPP), which has been identified as the most prominent oxidative DEHP metabolite in urine and exhibits the longest half-live of elimination (>15 h) in urine (Fromme et al., 2007).

Another significant limitation in assessing an individual's exposure is that only one spot urine sample was collected per woman during the 1st trimester. As these chemicals have a short half-life (hours) and there are multiple sources and routes of exposure, intra-individual variability in results are expected. The extent of the variability depends on the phthalate metabolite with DEHP metabolites often displaying more variability than other metabolites (Braun et al., 2012; Frederiksen et al., 2013; Peck et al., 2010; Preau et al., 2010). The study population, interval between sample collections and frequency of collections can also impact variability as measured by the intraclass correlation coefficients (ICCs) as illustrated for MEP where the ICC has ranged from <0.3 (Adibi et al., 2003; Teitelbaum et al., 2008) to >0.5 (Braun et al., 2012; Frederiksen et al., 2013; Peck et al., 2010).

The ability of a single spot urine to accurately reflect an individual's exposure over a period of time has generally been poor for BPA with ICCs ranging from 0.12 (Braun et al., 2011b) to 0.24 (Meeker et al., 2013). As collecting and analyzing multiple urine samples from an

individual in a large prospective cohort study would substantially increase the costs and participant burden, one recommendation has been to note the time of urine collection and the time since the last void (Preau et al., 2010). Although this information was collected in MIREC, it was not included in the univariate models for identifying other predictors of exposure and should be considered for any models examining potential health risks from the exposure.

This study has several strengths. This diversity and large sample size enable a more accurate estimate of the potential distribution and range of exposures (extremes) in the Canadian population and will facilitate the assessment and management of potential risks associated with these ubiquitous chemicals by the regulatory agencies. The finding that urinary BPA levels are higher in smokers, who are already at higher risk of adverse pregnancy outcomes (Nieuwenhuijsen et al., 2013) and in younger women of lower education and income, suggests that this population sub-group warrants further research and education to reduce their risks. In regard to phthalates, there was no common population sub-group with elevated exposure; however, given the multiple phthalates and various sources of exposure, this may not be surprising. As the MIREC study was not designed to identify major sources of exposure for these chemicals, it did not have the data on diet, food packaging and use of consumer products to correlate with urinary levels. One of the strengths of the MIREC study is that it does fill a major data gap by providing data on the range of urinary concentrations of these chemicals, measured in the same laboratory, in a large diverse population of pregnant women that can be compared to both the general population of Canada and to women of reproductive age. Thus providing direct measures of exposure in this vulnerable population in order to improve decisions for protecting health and preventing disease and can serve as the basis for future monitoring and research activities.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/j.ijheh.2012.12.002/j.envint.2014.02.010.

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