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Gestational exposure to volatile organic compounds (VOCs) in Northeastern British Columbia, Canada: A pilot study

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Élyse Caron-Beaudoin[a,b,c,d,*], Naomi Valter[a,b], Jonathan Chevrier[e], Pierre Ayotte[f,g], Katherine Frohlich[b,h], Marc-André Verner[a,b]

[a] Department of Occupational and Environmental Health, School of Public Health, Université de Montréal, 2375 chemin de la Cote-Sainte-Catherine, Montreal, QC H3T 1A8, Canada
[b] Université de Montréal Public Health Research Institute (IRSPUM), Université de Montréal, 7101, Parc Ave., Montreal, QC H3N 1X7, Canada
[c] INRS-Institut Armand-Frappier, Université du Québec, 531 boulevard des Prairies, Laval, QC H7V 1B7, Canada
[d] Center for Interdisciplinary Research on Well-Being, Health, Society and Environment (CINBIOSE), Université du Québec à Montréal, C.P. 8888, Succursale Centre-ville, Montreal, QC H3C 3P8, Canada
[e] Department of Epidemiology, Biostatistics and Occupational Health, McGill University Faculty of Medecine, 1020 Pine Avenue West, room 42, Montreal, QC H3A 1A2, Canada
[f] Centre de toxicologie du Québec, Institut National de la Santé Publique du Québec, 945 avenue Wolfe, Québec, QC G1V 5B3, Canada
[g] Axe Santé des Populations et Pratiques Optimales en Santé, Centre de Recherche du CHU de Québec-Université Laval, Hôpital du Saint-Sacrement, 1050 Chemin Ste-Foy, Québec, QC G1S 4L8, Canada
[h] Department of Social and Preventive Medicine, School of Public Health, Université de Montréal, 7101 Av du Parc, Montréal, QC H3N 1X9, Canada

ABSTRACT

Background: Northeastern British Columbia (Canada) is an area of intense hydraulic fracturing for unconventional natural gas exploitation. There have been multiple reports of air and water contamination by volatile organic compounds in the vicinity of gas wells. Although these chemicals are known developmental toxicants, no biomonitoring effort has been carried out in the region.
Objective: To evaluate gestational exposure to benzene and toluene in the Peace River Valley, Northeastern British Columbia (Canada).
Methods: Urine samples were collected over five consecutive days from 29 pregnant women. Metabolites of benzene (s-phenylmercapturic acid (S-PMA) and trans, trans-muconic acid (t,t-MA)) and toluene (s-benzyl-mercapturic acid (S-BMA)) were measured in pooled urine samples from each participant. Levels of benzene metabolites were compared to those from the general Canadian population and from a biomonitoring study of residents from an area of active gas exploitation in Pavillion, Wyoming (USA). Levels measured in participants from the two recruitment sites, and self-identifying as Indigenous or non-Indigenous, were also compared.
Results: Whereas the median S-PMA level (0.18 μg/g creatinine) in our study was similar to that in the general Canadian population, the median t,t-MA level (180 μg/g creatinine) was approximately 3.5 times higher. Five women had t,t-MA levels above the biological exposure index® proposed by the American Conference of Governmental Industrial Hygienists. The median urinary S-BMA level in our pilot study was 7.00 μg/g creatinine. Urinary metabolite levels were slightly higher in self-identifying Indigenous women, but this difference was only statistically significant for S-PMA.
Discussion: Urinary t,t-MA levels, but not S-PMA levels, measured in our study are suggestive of a higher benzene exposure in participating pregnant women from the Peace River Valley than in the general Canadian population. Given the small sample size and limitations of t,t-MA measurements (e.g., non-specificity), more extensive monitoring is warranted.

1. Introduction

Northeastern British Columbia (Canada) sits on the Montney Formation, a major source of natural gas. The Peace River Valley, located in Northeastern British Columbia, is an area of intense hydraulic fracturing (fracking) for unconventional natural gas exploitation. Indeed, > 28,000 wells of unconventional natural gas have been drilled so far in this region (Adams et al., 2016). Some communities like

Fort St-John are surrounded by > 400 active wells (Northern Health, 2007).

Communities living in the vicinity of such development have raised concerns regarding the environmental impacts and potential health effects of unconventional natural gas exploitation. Water contamination in communities near unconventional natural gas exploitation has been previously described (Alawattegama et al., 2015; Llewellyn et al., 2015; Osborn et al., 2011). In the Peace River Valley, surface and ground-water quality has steadily decreased since the natural gas boom (GWSolutions, 2016). Moreover, studies have shown that air quality can be affected by intense fracking activities (Colborn et al., 2014; Rahm, 2011; Vinciguerra et al., 2015).

A myriad of contaminants are released during fracking operations, including volatile organic compounds such as benzene (Crowe et al., 2016; Gilman et al., 2013; Macey et al., 2014; Vengosh et al., 2014), a known human carcinogen (IARC, 2012). Effects of benzene on human health, including on fetal development, have been widely studied. Prenatal exposure to low environmental levels of benzene or a mixture of organic solvents has been associated with reduced birth weight (Aguilera et al., 2009; Chen et al., 2000; Ha et al., 2002; Slama et al., 2009; Zahran et al., 2012), increased risk of childhood leukemia (Carlos-Wallace et al., 2016; Whitworth et al., 2008; Zhou et al., 2014) and birth defects such as cleft palate and spina bifida (Lupo et al., 2011; Tanner et al., 2015). *In utero* exposure to high concentrations of toluene was also associated with growth retardation, preterm birth (Wilkins-haug and Gabow, 1991), spontaneous abortion and reduced fertility (Bukowski, 2001). In other regions of unconventional natural gas exploitation, recent studies found associations between density and proximity of hydraulic fracturing wells and prevalence of birth defects as well as low birth weights (Hill, 2012; McKenzie et al., 2014). Finally, a recent study determined that 95 out of 240 chemicals (with toxicity information) present in hydraulic fracturing fluids are developmental toxicants (Elliott et al., 2016).

Because of their particular physiological state and the ongoing development of several physiological systems, pregnant women and their developing fetuses are particularly vulnerable to toxic insults. Furthermore, Indigenous communities which represent 12% of the Northeast British Columbia population (Foster et al., 2011), experience health and social inequities due to land dispossession and inadequate provision of health, social and education services (Frohlich et al., 2006; Reading and Wien, 2009). It has been suggested that exposure to environmental chemicals in socioeconomically disadvantaged children contributes to health inequities (Miranda et al., 2009).

In this pilot study we aimed to evaluate exposure to volatile organic compounds in 30 pregnant women from the Peace River Valley, Northeastern British Columbia (Canada) and to compare exposure levels with those measured in: 1) women from the general Canadian population (Canadian Health Measures Survey (CHMS)) and; 2) residents of an area of active gas exploitation in Pavillion, Wyoming (USA).

2. Material and methods

2.1. Study area and recruitment

We developed partnerships with two medical clinics located in Chetwynd and Dawson Creek (British Columbia, Canada), and pregnant women were recruited from September to November 2016 during their prenatal follow-up following approval from the physician or nurse practitioner. Chetwynd and Dawson Creek are located at 100 km from each other in the Peace River Valley, a region of intense unconventional natural gas extraction. Both communities are surrounded by between 10 and 150 active natural gas wells, at least (Northern Health, 2007) (Fig. 1). While Chetwynd is surrounded by less active wells, it is located near the Pine River Gas Plant. Medical clinics located in these cities are among the few clinics offering pregnancy follow-ups in this region.

Eligible participants (> 18 years of age, English-Speaking) were met privately, given information on the research project, and had the opportunity to ask questions. Women who agreed to participate signed a consent form and filled out a questionnaire on sociodemographic and physiologic parameters, diet, smoking habits and drinking water source. This study was approved by the Northern Health Research Review Committee and by the Université de Montréal Institutional Review Board.

2.2. Sampling and chemical analyses

Participants were asked to collect 12 mL urine samples over five consecutive days. This sampling method accounts for variability in day-to-day exposure and diet. The samples were retrieved directly at the participants' home, and were kept in the freezer at −20 °C until transported on dry ice to the Université de Montréal. For each participant, 1 mL of each of the five urine samples were pooled into a single 5 mL sample that was subsequently analyzed for two benzene metabolites (s-phenylmercapturic acid (S-PMA) and trans,trans muconic acid (t,t-MA)) and one toluene metabolite (s-benzylmercapturic acid (S-BMA)). Metabolites were extracted from urine on a solid phase extraction plate using a Perkin Elmer Janus Automated Workstation. Extracts were dried, taken up in mobile phase and analyzed by Ultra Performance Liquid Chromatography (UPLC) coupled to tandem mass spectrometry at the Centre de toxicologie du Québec laboratory in Quebec City, Canada (INSPQ, 2009). Limits of detection were 0.08 µg/L for S-PMA, 0.8 µg/L for t,t-MA and 0.07 µg/L for S-BMA. Creatinine was measured using the colorimetric end-point Jaffe method (INSPQ, 2008).

2.3. Statistical analyses

Urinary levels of volatile organic compound metabolites measured in participants from the regions of Dawson Creek and Chetwynd, and self-identifying as Indigenous or non-Indigenous, were compared using the non-parametric Mann-Whitney *U* test. The relationship between the levels of the two benzene metabolites (S-PMA and t,t-MA) was evaluated using Spearman's rank correlation analyses. All analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY).

3. Results

A total of 30 pregnant women were recruited for this pilot study, and 29 participants completed the sampling process (one participant had a miscarriage). The median sampling time was 9:00 PM, and ranged from 2:00 PM (10th percentile) to 11:00 PM (95th percentile). 50% of the participants were recruited at the Chetwynd medical clinic, and 50% at the Dawson Creek clinic. 43.3% of participants self-identified as Indigenous. 93.3% of participants had at least a high school diploma, and 20% of them worked in the industrial sector. Two participants reported smoking at the time of recruitment, and four reported being exposed to second-hand smoke during their pregnancy. Tap water was the main drinking water source for 70% of the participants (Table 1).

Participants that reported exposure to cigarette smoke (n = 12; smoking at least 100 cigarettes in their whole life (n = 7), being active smokers at the time of recruitment (n = 2) or exposed to second-hand smoke (n = 4) had median urinary S-PMA, t,t-MA and S-BMA levels of 0.21, 202 and 6.88 µg/g creatinine, respectively. Participants that reported working in an industrial field (n = 6) such as mining industry, natural gas, construction, forestry, pipeline maintenance or at hydro-electric dams, had median urinary S-PMA, t,t-MA and S-BMA levels of 0.23, 347 and 4.31 µg/g creatinine, respectively. Maximum urinary levels of S-PMA, t,t-MA and S-BMA were 1.92, 1182 and 100 µg/g creatinine, respectively.

Median urinary levels of S-PMA, t,t-MA and S-BMA in participants
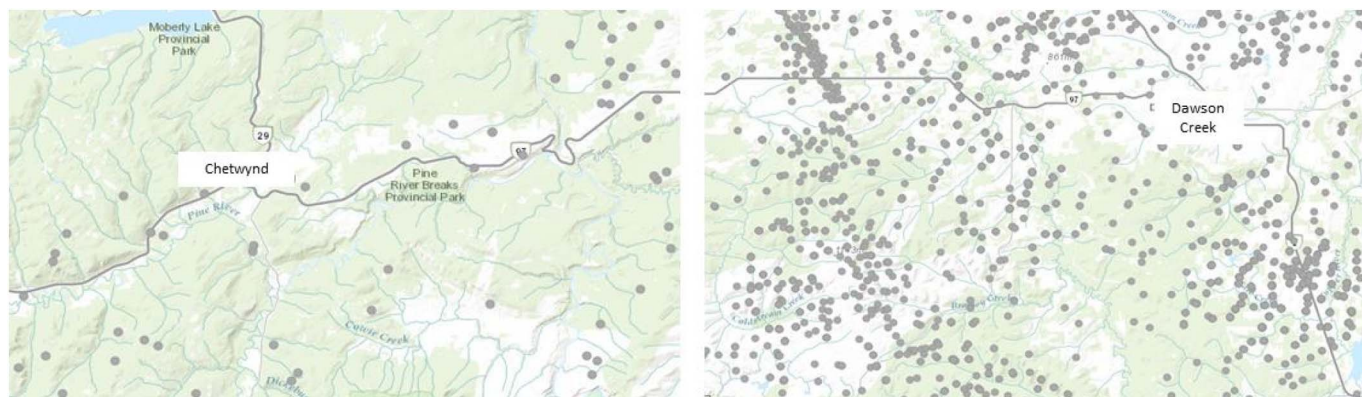
Fig. 1. Map of Chetwynd and Dawson Creek areas with hydraulic fracturing wells (circles) in 2007 (Open Data from BC Oil and Gas Commission).

with a household income less than $20,000/year were of 0.41, 319 and 7.21 µg/g creatinine, respectively. Participants reporting a household income between $50,000 and $100,000/year had median urinary levels of S-PMA, t,t-MA and S-BMA of 0.19, 182 and 5.60 µg/g creatinine, respectively, while median levels in participants with annual household income over $100,000/year were 0.17, 171 and 9.7 µg/g creatinine. S-PMA median urinary levels were statistically higher in participants with annual income less than $20,000 ($p = 0.036$).

All metabolite levels were above the limits of detection. Sociodemographic characteristics were similar across regions and Indigenous/non-Indigenous status. Overall, median S-PMA concentrations in our pilot study were similar to those found in the general Canadian population (Table 2), and median S-PMA levels in pregnant women recruited in Chetwynd (0.20 µg/g creatinine) and Dawson Creek (0.18 µg/g creatinine) were not statistically different (Fig. 2).

The median S-PMA level in Indigenous women (0.24 µg/g creatinine) was higher than in Non-Indigenous women (0.14 µg/g creatinine) ($p = 0.017$) (Fig. 3). More precisely, Indigenous ($n = 9$) and Non-Indigenous women ($n = 5$) living in the Chetwynd area had median urinary S-PMA levels of 0.24 and 0.10 µg/g creatinine, respectively. Indigenous ($n = 4$) and Non-Indigenous participants ($n = 11$) from the Dawson Creek area had median urinary S-PMA levels of 0.50 and 0.15 µg/g creatinine, respectively.

The median t,t-MA levels in pregnant women recruited in Chetwynd

(271 µg/g creatinine) was 1.6 fold higher than in pregnant women recruited in Dawson Creek (171 µg/g creatinine), but this difference did not reach statistical significance ($p = 0.09$). Respectively, pregnant women from Chetwynd and Dawson had median t,t-MA levels 5.3 and 3.4 times higher than women from the general Canadian population. Moreover, 5 women out of 29 had t,t-MA levels higher than the biological exposure index (BEI®) of 500 µg/g creatinine proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACGIH, 2012) (Fig. 4).

The median t,t-MA level in Indigenous women (319 µg/g creatinine) was higher than in Non-Indigenous women (142 µg/g creatinine), although this difference was not statistically significant ($p = 0.07$) (Fig. 5). This difference was more striking when comparing the median t,t,-MA levels by ethnicity and region of residence. Indigenous women living in the Chetwynd and Dawson Creek areas had median t,t-MA levels of 319 µg/g creatinine and 251 µg/g creatinine, respectively. Median t,t-MA levels were approximately 4 and 2 times lower in Non-Indigenous women from Chetwynd (85.7 µg/g creatinine) and Dawson Creek (146 µg/g creatinine).
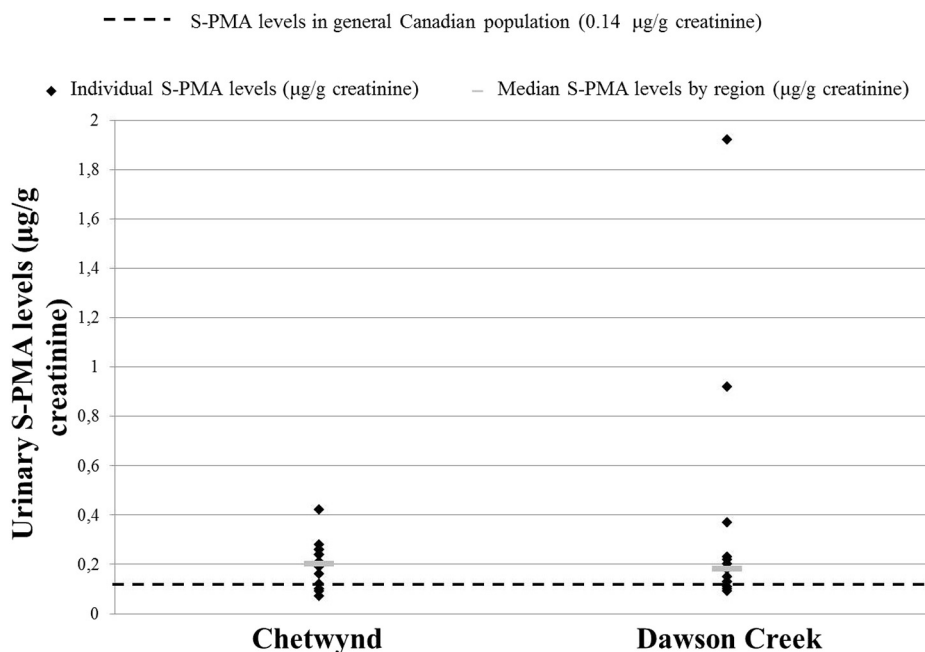

- - - - S-PMA levels in general Canadian population (0.14 µg/g creatinine)

◆ Individual S-PMA levels (µg/g creatinine)   — Median S-PMA levels by region (µg/g creatinine)

Fig. 2. Individual and median urinary levels of *S*-phenylmercapturic acid (S-PMA) (µg/g creatinine) in our pilot study, by region. Five urine samples were obtained from each participant over five consecutive days. These urine samples were pooled prior to chemical analysis. The dotted line represents the S-PMA median level in the general Canadian population (as measured in the CHMS cycle 3).
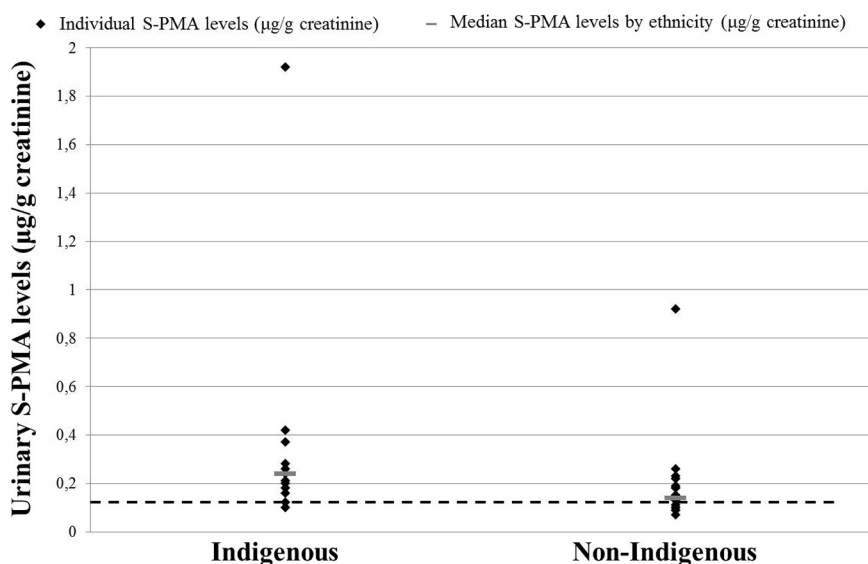
Fig. 3. Individual and median urinary levels of *S*-phenylmercapturic acid (S-PMA) (µg/g creatinine) in our pilot study, by ethnicity. Five urine samples were obtained from each participant over five consecutive days. These urine samples were pooled prior to chemical analysis. The dotted line represents the S-PMA median level in the general Canadian population (as measured in the CHMS cycle 3).

4. Discussion

4.1. Comparison with the general Canadian population

In this pilot study we analyzed two benzene metabolites (S-PMA and t,t,-MA) and one toluene metabolite (S-BMA) in urine samples of pregnant women living in Northeastern British Columbia. In 2012, the median urinary level of S-BMA in females from the general American population that participated in the National Health and Nutrition Examination Survey (NHANES) was 7.2 µg/g creatinine (CDC, 2015). A study conducted by Schettgen et al. (2008) measured toluene metabolite S-BMA in urine of 30 participants from the German general population. In non-smokers and smokers, median urinary S-BMA levels were 8.2 µg/L and 11.5 µg/L, respectively. We reported a similar median urinary S-BMA level of 8.6 µg/L in this pilot study. Urinary S-PMA levels were similar to those from women who participated in the Canadian Health Measure Survey (CHMS). However, the median urinary t,t,-MA level (180 µg/g creatinine) was approximately 3.5 times higher in our pilot study compared to that from CHMS (51 µg/g creatinine) (Health Canada, 2015). Moreover, 8 participating women out of 29

(28%) showed t,t,-MA levels above the 95th percentile measured in the CHMS (460 µg/g creatinine) (Health Canada, 2015). In Pavillion (Wyoming, USA), a region of intense hydraulic fracturing activity, Crowe et al. (2016) also reported elevated benzene concentrations in ambient air near residences located close to well pads (between 8.7 and 780 ppb) and higher median urinary t,t-MA level in residents close to hydraulic fracturing wells (369 µg/g creatinine), compared to the general American population (76.9 µg/g creatinine).

4.2. Sources of benzene in Northeastern British Columbia

Benzene exposure can occur from active and passive smoking, filling gas tanks and automobile driving (Wallace, 1990). Benzene in products such as paints and adhesives can contribute to exposure, but concentrations in these materials are relatively low (Wallace, 1990). A potential benzene exposure source in our group of pregnant women might include the intense fracking activity in the region. In Northeastern British Columbia around 28,000 wells were drilled to extract natural gas (Adams et al., 2016). Natural gas' main constituent is methane, but it also contains other chemicals including benzene (Hendler
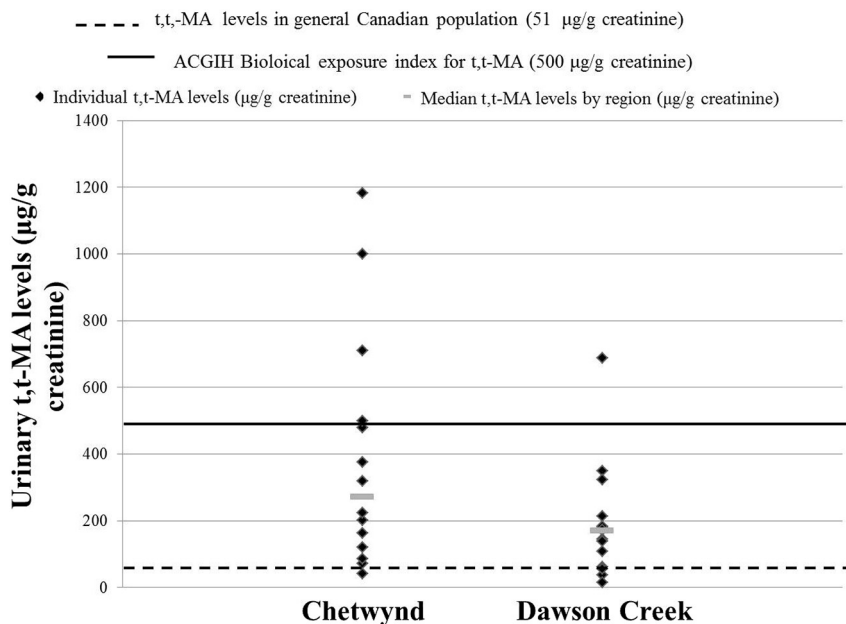

Fig. 4. Individual and median urinary levels of trans,trans muconic acid (t,t-MA) (µg/g creatinine) in our pilot study, by region. Five urine samples were obtained from each participant over five consecutive days. These urine samples were pooled prior to chemical analysis. The dotted line represents the median t,t-MA level in the general Canadian population (as measured in the CHMS cycle 3). The bold black line represents the biological exposure index (BEI®) of 500 µg/g creatinine for urinary t,t-MA levels adopted by the ACGIH.
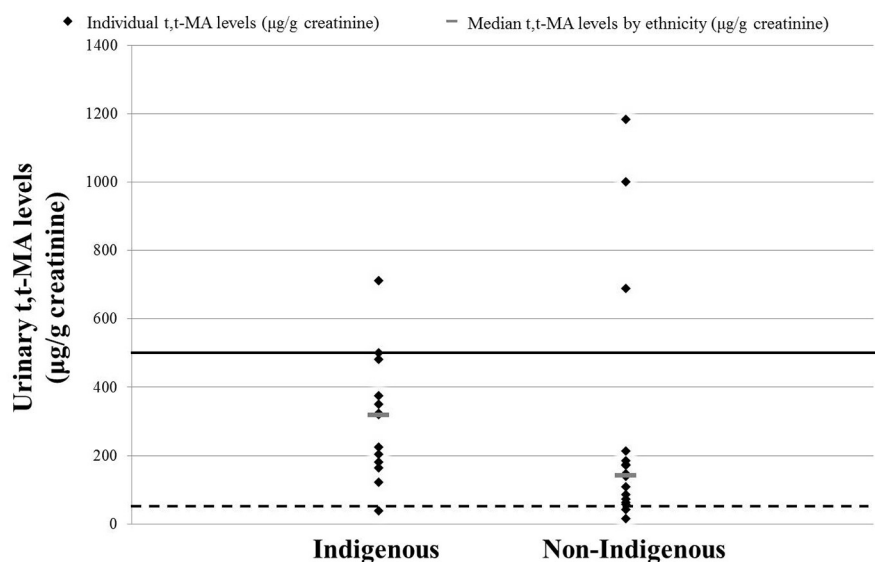
Table 1
Characteristics of pregnant women from Dawson Creek and Chetwynd, BC ($n = 30$).

Characteristic	n (%)	Median (range)
Age (years)		*31* (21–41)
Region of residence		
Chetwynd	15 (50.0)	
Dawson Creek	15 (50.0)	
Self-identify as Indigenous		
Yes	13 (43.3)	
No	17 (56.7)	
Highest education degree obtained		
High school unfinished	2 (6.7)	
High school diploma	8 (26.7)	
Certificate, diploma or associate degree	10 (33.3)	
University degree (Bachelor, Master, Doctorate)	10 (33.3)	
Participants working in industrial field		
Yes	6 (20)	
No	24 (80)	
Smoker at time of recruitment		
Yes	2 (6.7)	
No	28 (93.3)	
Second-hand smoke during pregnancy		
Yes	4 (13.3)	
No	26 (86.7)	
Gestational age (weeks)		*18.5* (6.0–39.0)
Drinking water source		
Tap water	21 (70.0)	
Bottled water	8 (26.7)	
Other	1 (3.3)	
Pre-pregnancy BMI		*23.9* (19.1–36.3)
< 24.9	17 (56.7)	
25.0–29.9	4 (13.3)	
30.0–34.9	3 (10.0)	
35.0–39.9	2 (6.7)	

et al., 2009). It has been demonstrated that workers from the natural gas industry are exposed to volatile organic compounds such as benzene and toluene during well development and production (Hendler et al., 2009). Several studies conducted in the United States found that the oil and gas industry is an important source of benzene exposure, and systematically reported higher levels of organic volatile compounds in ambient air from these regions compared to regional samples (Adgate et al., 2014; Colborn et al., 2014; Gilman et al., 2013; Pétron et al., 2012; Zielinska et al., 2011). Moreover, fracking activities are a risk for water resources (Vengosh et al., 2014), and water contamination may be a potential pathway for benzene exposure. Indeed, it has been demonstrated that following surface spills from natural gas facilities in Colorado, elevated levels of benzene were detected in the groundwater

system (Gross et al., 2013). In Pennsylvania, inadequate disposal of hydraulic fracturing wastewater contaminated surface waters with benzene, barium and radium (Ferrar et al., 2013; Warner et al., 2013).

In Northeastern British Columbia, the recent approval of the Liquefied Natural Gas Plants could lead to the drilling of 50,000 new hydraulic fracturing wells in the region (Hughes, 2014). Therefore, monitoring initiatives in human populations, air and water are needed.

4.3. Environmental justice

In our pilot study, the median urinary t,t-MA level in Indigenous women was 2.3 times higher than in Non-Indigenous women, although this difference was non statistically significant ($p = 0.07$) (Fig. 5). This difference in t,t-MA levels would need to be confirmed in a subsequent study with a larger sample size. Nonetheless, these preliminary results raise concerns regarding environmental racism which is "the intentional or unintentional racial discrimination in the enforcement of environmental rules and regulations, which leads to the singling-out of minority and low-income communities for the siting of noxious facilities" (Bullard, 2000). For instance, it has been demonstrated that hazardous waste facilities are disproportionately located in low income areas and communities of color (Bullard, 1983; Chavis and Lee, 1987; Gould, 1986; Mohai and Bryant, 1992; Norton et al., 2007; White, 1992). In Texas, Johnston et al. (2016) showed that the proportion of people of color living in the vicinity of hydraulic fracturing disposal wells was significantly higher than the proportion of non-Hispanic Whites. In Pennsylvania, a recent study showed that farmers with small operations face increased environmental risks from hydraulic fracturing activities (Malin and DeMaster, 2015). Environmental injustice is a great concern, especially for Indigenous communities already facing health inequalities. Close contact between Indigenous people and their environment through spiritual practices and traditional lifestyle may increase their exposure to contaminants from industrial activities (Hoover et al., 2012), and such disproportionate environmental burden has already been demonstrated in Canada (Mackenzie et al., 2005; Van Larebeke et al., 2008).

4.4. Limitations

Our pilot study has limitations, and therefore, caution should be exerted when interpreting biomarker levels in participating pregnant women from Northeastern British Columbia. First, the small number of participants prevents us from drawing conclusions on the sources of benzene and the potential need for exposure mitigation strategies.

Table 2

Urinary levels of benzene and toluene metabolites in Dawson Creek and Chetwynd (BC), in the general Canadian population (CHMS), and in the Pavillion Wyoming Study.

	Benzene metabolites		Toluene metabolite
	S-PMA (µg/g creatinine)	**t,t-MA** (µg/g creatinine)	**S-BMA** (µg/g creatinine)
Dawson Creek and Chetwynd, BC (this study)	Median: 0.18 10th percentile: 0.09 95th percentile: 0.74 *n* = 29	Median: 180 10th percentile: 53.3 95th percentile: 899 *n* = 29	Median: 7.00 10th percentile: 3.1 95th percentile: 106.8 *n* = 29
CHMS cycle 3[a]	Median: 0.14 10th percentile: < LOD 95th percentile: 5.10 *n* = 1248	Median: 51.0 10th percentile: 19.0 95th percentile: 460 *n* = 1260	Not measured
Pavillion, Wyoming study[b]	Median: < LOD Maximum: 0.80 *n* = 11	Median: 369 Maximum: 2050 n = 11	Not measured

[a] Measured levels in females aged from 3 to 79 years old (Health Canada, 2015).
[b] Only the median and maximum levels were available for the Pavillion, Wyoming study (Crowe et al., 2016).

Metabolic polymorphism could be a factor influencing urinary levels of benzene and toluene metabolites. A study conducted by Verdina et al. (2001) suggests that metabolic polymorphism affect the urinary levels of t,t-MA and S-PMA to a limited extent. Other factors to consider include the influence of sorbic acid on t,t-MA levels, exposure to cigarette smoke, and variations in urinary creatinine during pregnancy.

4.4.1. Interference with sorbic acid

Urinary t,t-MA levels can be influenced by factors other than benzene exposure, including the intake of sorbic acid, a food preservative partially metabolized into t,t-MA. Estimates of the intake of sorbic acid are in the range of 1–2 mg/kg/day (60–120 mg/day for a 60 kg woman), which results in an average of 78–114 µg/g creatinine of urinary t,t-MA levels (Mischek and Krapfenbauer-Cermak, 2012; Pezzagno and Maestri, 1997). To reach an average urinary t,t-MA level above 500 µg/g creatinine in pooled samples solely based on sorbic acid intake, large doses of sorbic acid would need to be ingested in the hours preceding urine sampling. We cannot rule out the possibility of higher sorbic acid consumption in participating pregnant women from the Peace River Valley compared to women included in CHMS.

4.4.2. Smoking and second hand smoke

It is well established that t,t-MA levels are influenced by smoking and second hand smoke exposure. Active and passive smoking were evaluated in the questionnaire and only four participants (13%) reported smoking or being exposed to second hand smoke (Table 1). These participants did not exhibit urinary t,t-MA levels above the 500 µg/g creatinine biological exposure indices. It should be noted that this guideline is used in the context of industrial hygiene and may not be appropriate to evaluate risks for the general population, especially pregnant women that are in a more vulnerable physiological state. Only two participants (7%) were smokers at the time of recruitment, compared to 11% in CHMS; the difference in t,t-MA levels between our pilot study and CHMS is therefore unlikely to be due to smoking.

4.4.3. Creatinine adjustment during pregnancy

Another factor that was taken into consideration is the creatinine levels that might change during pregnancy. These changes in creatinine levels could influence t,t-MA levels expressed in µg/g creatinine, and consequently bias our comparisons with levels from CHMS. However, Melikian et al. (1994) compared urinary t,t-MA levels expressed in µg/g creatinine in non-pregnant and pregnant non-smokers and found no significant differences. In addition, the median urinary t,t-MA level from our study in µg/L (190 µg/L) was also higher than that from CHMS (46 µg/L). These findings suggest that differences in urinary t,t-MA levels between our study and CHMS are probably not due to variations in urinary creatinine levels.

4.5. Correlation between S-PMA and t,t-MA

To ensure that the use of t,t-MA as an indicator of potentially higher benzene exposure is adequate, we tested the strength of the correlation between urinary S-PMA and t,t-MA levels (µg/L) using Spearman rank correlation. A moderate, statistically-significant correlation was found (r = 0.47). Other studies also reported similar correlation coefficients between the same urinary metabolites in environmentally exposed adults (Melikian et al., 1999) and in children (Fang et al., 2000). A number of studies also positively evaluated the accuracy of using urinary t,t-MA as a biomarker of benzene exposure at environmental and mostly occupational levels (Cocco et al., 2003; Hoet et al., 2009; Scherer et al., 1998). Finally, studies of occupational and environmental exposures showed correlations between benzene concentration in air and urinary t,t-MA levels (Ducos et al., 1992; Inoue et al., 1989; Kang et al., 2005; Lovreglio et al., 2010). Urinary levels of benzene and other volatile organic compounds have proven to be excellent markers for environmental exposure (Fustinoni et al., 2010; Tsangari et al., 2017; Waidyanatha et al., 2001) and should be considered in future research efforts.

5. Conclusion

Results from our pilot study, although limited because of the small sample size and limitations related to our exposure biomarker (*e.g.*, non-specificity), are suggestive of a potential higher benzene exposure in participating pregnant women than in the general Canadian population. Whether the high urinary t,t-MA levels measured in this study are related to hydraulic fracking remains unknown. Given the documented health effects of benzene, especially those occurring through *in utero* exposure, and the growing hydraulic fracturing industry in this region, this first biomonitoring initiative certainly highlights the need of further research to better delineate associated health risks.

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