Comparison of Personal BTEX Exposure and Pregnancy Outcomes among Pregnant Women Residing in and Near Petrochemical Industrial Area

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Abstract

Petrochemical industrial air pollution is a major problem in many cities in Asia, including Rayong, Thailand. Some of this pollution, e.g. benzene are human carcinogen. To determine the levels of exposure to BTEX compounds and examine the pregnancy outcomes among pregnant women living in and near petrochemical industrial area. 110 pregnancy women were monitored, using a combination of environmental and biological sampling for BTEX exposure. Results showed that personal exposures to BTEX were significantly higher in pregnant women living in the petrochemical industrial area than those living near the petrochemical industrial area ($P<0.001$). These were in agree with urinary metabolites of BTEX on Thursday afternoon, i.e. *t,t*-muconic acid, hippuric acid, mandelic acid and *methyl*-hippuric acid. The urinary metabolites of BTEX were also correlated well with personal exposure ($P<0.05$). For pregnancy outcomes, there were no difference between the groups in the prevalence of low birth weight for gestational age (<2,500 grams), and APGAR score below 7 at 1 and 5 minutes. Upon data analysis of relations between BTEX exposure level and maternal gain weight, gestation age, birth weight, and APGAR score at 1-minute and 5-minutes, no significant relationship was found. Our data indicates that pregnant women residing in a heavy industrial city such as MapTaPhut have exposed to toxic substances, i.e. BTEX in a higher level than those in more outer industrial city who are exposed to less industrial pollutions.

Keywords: benzene; toluene; ethylbenzene; xylene; pregnancy outcomes; pregnant women

1. Introduction

MapTaPhut Industrial Estate is a part of Thailand's Eastern Seaboard economic region which serves as the largest petrochemical industries hub for Thailand. At present, population in MapTaPhut is increasing at an accelerated rate. Therefore, environmental risk from exposure in the petrochemical industrial area are receiving increasing intention. Common volatile organic compounds, including aromatic hydrocarbons such as benzene, toluene, ethylbenzene, and xylene (BTEX), are widely used and emitted from the petrochemical industry, and mainly used as additives in gasoline to enhance octane rating, thus exerting adverse effects on environmental air quality and health. Neurotoxicity is the critical non-cancer effect of concern for BTEX mixtures. Haematotoxicity and carcinogenicity are additional concerns for exposure to BTEX based on strong evidence that benzene induces these health effects in humans. Regarding damage in fetal health, most studies show associations with exposure to air pollution during pregnancy (Sram *et al*., 2005; Lacasana *et al*., 2005). Women living in the vicinity of industrial districts where emission levels of air contaminants from multiple sources including petrochemical and petroleum industries are highly correlated with increased incidence of preterm births (Tsai *et al*., 2003; Yang *et al*., 2002; Lin *et al*., 2001).

Personal exposure data enable a more accurate estimate of exposure risk to these compounds and have shown to be significantly higher than stationary measures (Phillips *et al*., 2005). Although blood chemical analysis is highly specific biomarkers and directly correlated to toxic, it suffers from ethical and practical constraints and thus can have an adverse effect on susceptible pregnant women (Rockett *et al*., 2004). Therefore, it is important to identify non-invasive biomarkers for biomonitoring (Smolders *et al*., 2009).

Fetal growth is a key indicator of the health of newborns and childhood that may affect the health status in the adulthood. It may be altered by exposure to toxic substances (i.e., tobacco, alcohol), and by ambient pollutants (Maisonet *et al*., 2001; Dejmek *et al*., 2000). An assessment of aromatic hydrocarbon exposure is particularly important in studies on reproductive outcomes, where there is concern about the existence of potential windows of susceptibility. Here we aim to

assessBTEX exposure and the relationship between environmental exposure and pregnancy outcomes in the maternal residing in and near petrochemical industrial area.

2. Materials and Methods

2.1. Sampling sites

Rayong consists of 6 districts and 2 subdistricts with a total area of 3,552 km^2 and the average population density of 362.66 people km^{-2} (MapTaPhut Municipality, 2010). MapTaPhut Industrial Estate consists of 32 petrochemical companies and 2 oil refineries. Selection criteria of sampling location was based on the location of petrochemical industries which most of them situated in MapTaPhutdistrict. The low exposure sites were NhongRai district which was selected by following the environmental database of Pollution Control Department as to be the control area. The residence locations of exposed group were shown in the Fig.1

2.2. Study population

The study subjects included pregnant women from two governmental sub-provincial hospitals in the area of MapTaPhut and NongRai, Rayongas exposed and control group, respectively. The subjects recruited in this study were randomly sampled from hospital number (HN) of pregnant women in the obstetric&gynaecologicaldepartment. The following equation as shown below was used to calculate the sample size in the exposed group.

$$n = \frac{(Z_{\alpha/2} + Z_{\beta}) \, \sigma^2}{\Delta^2}$$

Because of no data of BTEX exposure in pregnancy women during the study time, our preliminary data of level of benzene exposure (*n = 10*), as the human carcinogen, was used be the representative for calculating the sample size. Where average benzene level was $19.16 \pm 2.74 \, \mu g/m^3$, $\alpha = 0.05$, $\beta = 0.10$. There was no preliminary data in control group, therefore we used the acceptable minimum different at 5% of exposed group. For control group, we used the sample size of 30 (Cohen J, 1990; Hogg RV, 2005). All study subjectsdid not to be occupationally exposed to BTEX, lived in MapTaPhut area at least 1 year, age >18 yrs, and also not involved with the special activities using BTEX such as painting. All subjects are healthy and nonsmoking volunteers at the time of entry into the study. A consent form was signed before completing a questionnaire about personal history, health history and their routine lifestyle activities and food habits. To avoid the interference, we recommend the pregnant women keeping to a milk–fruit diet and advised not to consume canned and preservative foods, coffee and tea 12 hrs before collecting urine specimen on each time frame. After giving birth, information on maternal and infant completed by the physician attending the delivery was collected again. This study was approved by the Ethic Review Committees for Research on human subjects, Burapha University.
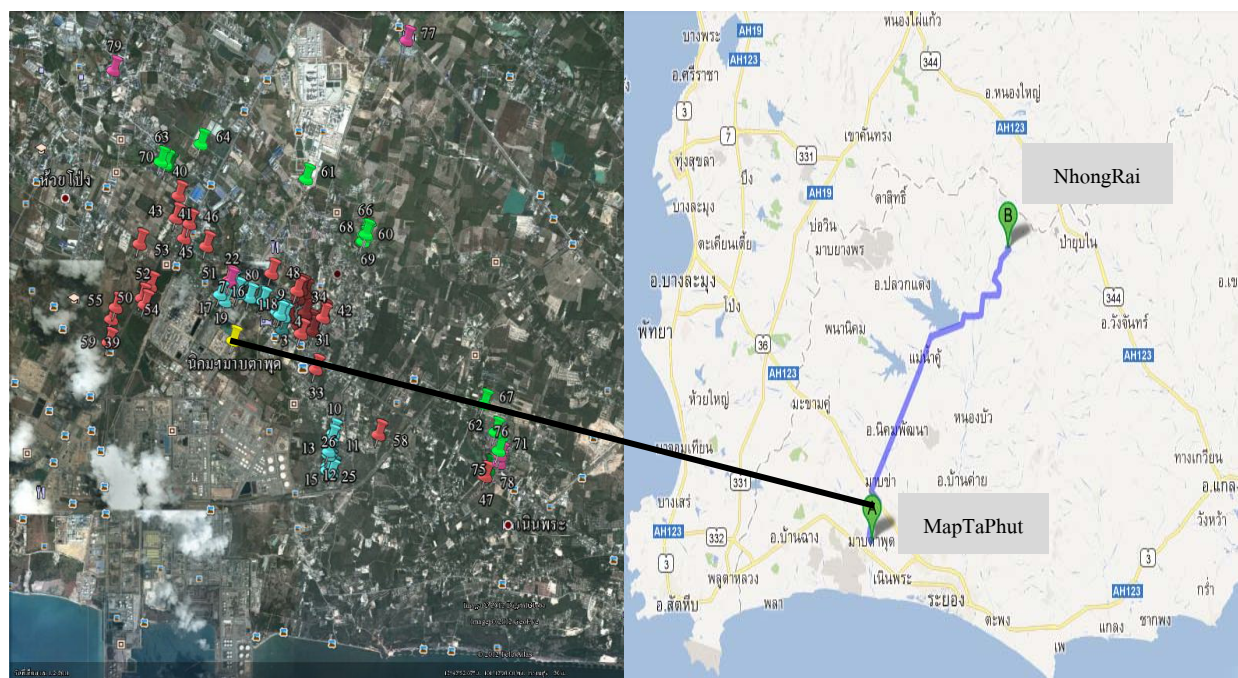

Figure 1. Residence locations in the petrochemical industrial area

2.3. Determination of individual exposure to BTEX

Air sampling was carried out during the dry season (December–February, 2012). Due to a small variation fromday to day and a slight increase from Monday to Saturday, the exposure was measured on Thursday asrepresentative of 6-day monitoring data. Personal air sampling of BTEX was conducted by using Carbopack B[TM]packed into the stainless steel tube which was set in the respiratory zone. The tubes were precleaned before each sampling period by heating under a stream of ultra high purity helium for removing any contaminating species trapped on the adsorbent bed. Individual personal exposure to BTEX was monitored for a 8-hr period of a working day (from 8:00 to17:00),while subjects were performing their usual activities. At the end ofsampling, the cartridgewas sealed, transported to the laboratory and kept in refrigerated (-20°C) until analysis.Sample tubes were loaded into Gas Chromatography System and were heated to 300°C to desorb the BTEX. The desorbed BTEX gases were transferred via a heated line to the gas chromatography where they were separated in a capillary column and detected with a flame ionization detector.

2.4. Determination of urinary exposure to BTEX

Urine spot samples were collected three times during the same week; before the beginning of air sampling on Monday morning (baseline) and Thursday morning, and the end of the air sampling (Thursday afternoon). Urine was initially collected inbottles and stored in a cooling box until they were returned to the laboratory. Urinary creatinine was analyzed using a Sigma Diagnostic creatinine kit.

2.4.1. Determination of urinary benzene metabolite, t,t-MA

Urine samples were purified by extracting through strong anion exchange (SAX) column. Then urinary t,t-MA was determined by HPLC with C18 reversed phase column and equipped with UV detector, adopted from Boogard *et al.* (1996). Urine samples were thawed at room temperature for 15 min, and then centrifuged at 10,000g for 10 min. The supernatant (1 ml) was applied to SAX column (VertiPak[TM]SAX Tube) and washed with 2 ml H$_2$O and 1% (v/v) acetic acid. The *t,t*-MA was eluted with 1 ml 10% (v/v) acetic acid and then analyzed by HPLC-UV (Hewlett Packard series 1100,USA) with a Hypersil ODS C18 column 250 mm x 4.6 mm, 5 µm (Agilent Technologies, USA) equipped with a UV detector (264 nm.). The mobile phase was 1% acetic acid in H$_2$O/MeOH (90:10, v/v) with a flow rate 1.0 ml/min under isocratic condition. The column temperature was 35°C and the injection volume was 20 µl. The calibration curve was prepared by diluting standard *t,t*-MA with mobile phase over the concentration range of 0-5 µg/ml. Standard curves were consistently linear with $R^2 > 0.999$. The levels of urinary *t,t*-MA was expressed as µg/g creatinine.

2.4.2. Determination of urinary hippuric acid (HA), mandelic acid (MA)and methyl hippuric acid (MHA)

The urinary concentrations of HA,MA, and MHA as metabolite of toluene, ethylbenzene and xylene, respectively was directly determined by automated high performance liquid chromatography (HPLC). Urine was centrifuged and the supernatant was injected into HPLC with C18 column and equipped with UV detector, adopted from Ogata and Tagachi (1988). Urine sample were thawed at room temperature for 15 min, and then centrifuged at 10,000g for 10 min. The supernatant (10 µl) was injected into the HPLC (Hewlett Packard series 1100, USA) with a Ultra Aqueous C18 column (250 mm x 4.6 mm, 5 µm by Restek Corpolation,USA) equipped with a UV detector (210 nm.). The mobile phase was 10 mM KH$_2$PO$_4$ (adjust to a pH 3 with phosphoric acid)/tetrahydrofuran (95:5, v/v) with a flow rate 1.5 ml/min under isocratic condition. The column temperature was 35°C. The calibration curves were prepared by diluting standard HA, MA, MHA with mobile phase over the concentration range of 0-500 µg/ml. Standard curves were consistently linear with $R^2 > 0.999$.

2.5. Maternal and perinatal outcomes

We used the self-reported pre-gestational weight in kilograms (kg) and the height measured during the interview in metres squared (m^2) to calculate maternal body mass index (BMI; kg/m^2). BMI is classified as underweight if < 18.5; normal if 18.5–22.9 and overweight if ≥ 23.0 (Erratum, 2004). Maternal weight gain was classified into 3 groups; 10-12 kg; 12-15 kg, and >15 kg. A normal pregnancy can range from 37 to 42 weeks. Infants born before 37 weeks are considered premature. Infants born after 42 weeks are considered postmature. Low birth weight is defined as a birth weight of a liveborn infant of less than 2,500 g, regardless of gestational age (WHO-ICD, 2010). The Apgar score was used to assess the health of newborn children immediately after birth at 1 and 5 minutes. The resulting Apgar score ranges from 0 to 10. Scores 7 and above are generally normal, 4 to 6 fairly low, and 3 and below are generally regarded as critically low (Finster and Wood, 2005).

2.6. Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Version 17). Exposure levels for BTEX, and urinary biomarkerswere analyzed and compared betweenMapTaPhut and NhongRai pregnant women by Independent T-test. The correlation among BTEX concentrations was computed by Pearson's correlation. The pregnancy outcomes were analyzed and compared between MapTaPhut and NhongRai group by Chi-square. A *p*-value <0.05 was considered statistically significant.

3. Results and Discussions

3.1. General characteristics of pregnant women

The pregnant women residing in MapTaPhut had mean ages of 24.6 yrs, with mean body weight 61.21 kgs whereas NhongRai group had mean ages of 26.13 yrs, with mean body weight 62.20 kgs. Those with underweight, normal and overweightindicated by BMI accounted for 18.75%, 46.25% and 35% of the MapTa-Phut women and 20%, 50% and 30% of the NhongRai women, respectively.Most women (63.75%) has duration of living in the present address in the range of 1-5 yrs both MapTaPhut and NhongRai with mean years of 6.36 and 9.41, respectively. Time spent outdoor of pregnant women living in MapTaPhut was found to be significantly higher than those living in NhongRai with the average of 2.74 and 2.15 hrs per day, respectively. Both cities indoor pregnant women's activity patterns were similar. More than 75 percentages of women in MapTaPhutcooked by usage of petroleum-related fuels which were regarded as another major source of BTEX exposure. The general characteristics of pregnant women were summarized in Table 1.

3.2. Measurement of individual BTEX exposure and their urinary metabolite level

Results on individual exposure levels and biological markers were presented in Table 2. The average ambient benzene and toluene exposure level in pregnant women living in MapTaPhut was approximately 1.5-fold higher than that in NhongRai group. All individual exposure to BTEX were significantly higher in MapTaPhut pregnant women than in NhongRai pregnant women (*P<0.001*) and were highly correlated with each other (data not shown). In comparison with other urban cities, the BTEX exposurelevels in pregnant women (18.89, 29.4, 10.25, 17.98 $\mu g/m^3$) werehigher than general population in Tian, China (6.65, 13.07, 2.27 and 3.92 $\mu g/m^3$) (Zhou *et al*., 2011) and indoor traffic policeman (6.2, 3.2, 3.2, 12.1 $\mu g/m^3$) (Manini *et al*., 2008) but lower than outdoor workers in Mexico city (59, 256, 36, 130 $\mu g/m^3$) (Tovalin-Ahumada *et al*., 2007). No data on personal exposure to environmental BTEX in the pregnant women was found. In comparison to general population in Bangkok, pregnant women residing in MapTaPhut area were exposed to benzene in comparable levels of schoolchildren (17.75 $\mu g/m^3$) (Buthbumrung *et al*., 2008), but lower than in monks and nuns living in inner-city Bangkok (40.58 $\mu g/m^3$) (Ruchirawat *et al*., 2005).

In this study, we have been able to observe statistically significant differences in the urinary metabolite level of BTEX in samples collected in MapTaPhut and NhongRai pregnant women despite the relatively low levels of personal exposure. The mean level of urinary

Table 1. Basic characteristics of pregnant women

Personal Information	MapTaPhut (*n= 80*)	NhongRai (*n= 30*)	p-value*
Age (yrs)	24.60±5.79 (41-16)	26.13±5.72 (39-18)	NS
BMI (kg/m^2)	21.94 ± 4.91 (12.17-50.89)	22.35± 4.74 (16.84-40.47)	NS
Duration of living in the present address (yrs)	6.36 ± 7.29 (35-1)	9.41 ± 8.09 (35-2)	NS
Time spent outdoor (hrs/day)	2.74± 1.58 (6-0.5)	2.15± 1.27 (5-0.5)	0.045
Distance from residence to main road (kms)	1.23± 0.17 (0.5-0.1)	0.08± 0.12 (0.55-0.1)	NS
Maternal education†			
Primary education	20 (25)	9 (30)	NS
Secondary education	59 (73.75)	21 (70)	
University degree	1 (1.25)	-	
Alcohol drinking†	8 (10)	1 (3.3)	NS
Cooking by usage of petroleum-related fuels†	62 (77.5)	23 (76.7)	NS

Values were expresses as mean±S.D.(max-min)

†Values were expressed as number (%).

*Difference between Maptaphut and Nongrai, NS: Not significant

metabolites of BTEX in the morning Thursday was slightly higher than those in the morning Monday but lower than those in Thursday afternoon. During the day, the pregnant women may expose to outdoor pollutants (i.e., industrial emission, traffic) and also indoor pollutants (i.e., cooking by usage of petroleum-related fuel, household products for cleaning and personal care). Urinary *t,t*-MA, HA and *methyl*-HA that were significantly higher in samples of MapTaPhut pregnant women collected three times: Monday morning, Thursday morning and Thursday afternoon (*P<0.005*) confirmed higher exposure levels in these pregnant women at all times i.e., in the outdoor environment and in their home environment. Significant correlations were

Table 2. Individual exposure levels of BTEX and biomarkers of exposure in pregnant women

	Residing area	
	MapTaPhut (n= 80)	**NhongRai (n= 30)**
Benzene exposure ($\mu g/m^3$)	18.89± 1.39***	13.03± 1.21
	19.55 (8.01-42.78)	13.23 (9.01-18.18)
Urinary t,t-MA ($\mu g/g$ creatinine)		
Monday Morning	48.98± 1.75***	19.44± 1.49
	53.59 (11.50-153.74)	21.56 (6.31-35.42)
Thursday Morning	55.65± 1.66***	21.33± 1.57
	56.75 (13.88-149.93)	22.31 (5.88-46.87)
Thursday Afternoon	143.60± 1.68***,##,+++	45.61± 1.24###,+++
	142.59 (36.65-506.99)	46.54 (27.89-63.50)
Toluene exposure ($\mu g/m^3$)	29.40± 1.59***	17.50± 1.15
	28.10 (4.27-116.16)	18.03 (13.21-21.59)
Urinary HA(mg/g creatinine)		
Monday Morning	46.57± 3.08***	13.54± 1.21
	47.45 (0.43-385.43)	13.09 (9.68-22.32)
Thursday Morning	53.89± 2.87***	11.87± 3.79
	52.58 (1.06-622.11)	15.13 (0.01-26.22)
Thursday Afternoon	182.20± 2.42***,##,+++	24.70± 1.14###,+++
	199.14 (24.83-999.81)	24.55 (19.33-35.14)
Ethylbenzene ($\mu g/m^3$)	10.25± 2.12 ***	8.19± 1.08
	10.57 (7.43-19.77)	8.18 (7.35-10.00)
Urinary MA(mg/g creatinine)		
Monday Morning	1.56± 3.45***	1.41± 2.62
	1.44 (0.16-55.74)	1.61 (0.28-7.87)
Thursday Morning	1.65± 3.23	1.17± 2.92
	1.60 (0.12-36.59)	1.40 (0.12-8.30)
Thursday Afternoon	4.98±3.62***,##,+++	2.65± 3.09
	3.87(0.47-320.58)	2.17 (0.46-97.41)
Total Xylene ($\mu g/m^3$)	17.98± 1.28***	14.44± 1.12
(m+p) Xylene	17.61 (12.46-85.59)	14.20 (12.66-21.83)
(o) Xylene	9.79 ± 1.32***	7.58 ± 1.14
	9.69 (6.20-48.44)	7.41 (6.5-12.21)
	8.06 ± 1.26***	6.85 ± 1.10
	7.83 (4.65-37.15)	6.79 (6.16 – 9.62)
Urinary *methyl*-HA(mg/g creatinine)		
Monday Morning	13.79± 3.98***	6.30± 3.79
	15.51 (0.28-138.00)	7.27 (0.14-78.57)
Thursday Morning	45.21± 3.30***	7.36± 3.69
	58.84 (0.71-287.45)	8.38 (0.21-77.11)
Thursday Afternoon	46.96± 4.42**,##,+++	18.49± 3.06###,+++
	62.19 (0.61-957.04)	18.26 (0.56-102.02)

Values were expresses as mean±S.D., median (min-max)
, * Statistically significant difference from NhongRai at *p<0.005* and 0.001, respectively
##,###Statistically significant difference between Thursday morning and Thursday afternoon at *p<0.005* and 0.001, respectively
+++ Statistically significant difference between Monday morning and Thursday afternoon at *p<0.001*

found between levels of personal BTEX exposure and their corresponding urinary metabolite, with *r* ranging from 0.319 (xylene *vs. methyl*-HA) to 0.661 (benzene *vs. t,t*-MA).

Biomarkers reflect the whole absorbed dose of BTEX whereas ambient monitoring only mirrors the uptake from the air. The formation of urinary *t,t*-MA in the body is believed to be mainly through benzene metabolism with possible small contribution from metabolism of sorbic acid from foods; thus *t,t*-MA is fairly specific to benzene exposure (Johnson and Lucier, 1992). The low background levels of *t,t*-MA in NongRai pregnancy women demonstrated that the contribution to *t,t*-MA formation from other sources was minor. This finding was in accordance with some previous reports which indicated the average daily sorbic acid intake with diet did not show a correlation with urinary *t,t*-MA excretion (Cocco *et al.*, 2003). Nevertheless, uses of a more complex dietary questionnaire to assess sorbic and benzoic acid intake or the simultaneous determination of sorbic acid in urine to correct *t,t*-MA levels (Negri *et al.*, 2005) would be necessary, but it was out of the scope of this investigation. Due to inherent methodological limitations, future investigation of other reliable urinary biomarkers of benzene and toluene should

include more accurate means of exposure assessment.

3.3. Pregnancy outcomes

Table 3 shows the pregnancy outcomes of maternal and infant. Most of pregnant women (>80%) had gestation weight gain in the range of 10-15 kgs and had mean gestation age of ~37 wks. There were no differences between the groups in the prevalence of low birthweight for gestational age (<2,500 grams), and APGAR score below 7 at 1 and 5 minutes. Upon data analysis of relations between BTEX exposure level and maternal gain weight, gestation age, birth weight, and APGAR score at 1-minute and 5-minutes, no significant relationship was found.

Despite we have excluded subjects from occupational exposure and smoker's families, it is obvious that pregnant women residing in petrochemical industrial area that involve potential exposure to BTEX increase personal exposure. It can also be observed that MapTa-Phut pregnant women have significant higher levels of *t,t*-MA, HA, MA and MHA than NhongRai pregnant women. Moreover, levels of benzene was higher than the Thailand's dailyand annual average levels of volatile organic compounds limit of 7.6 and 1.7 $\mu g/m^3$,

Table 3. Data on maternal and infant residing in and near petrochemical industrial area

Maternal and infant characteristics	Number (Percent)	
	MabTa Phut (n=78)	NhongRai (n=29)
Maternal weight gain (kg)		
10-12	16 (20.51)	-
>12-15	52 (66.67)	24 (82.76)
> 15	10 (12.82)	5 (17.24)
Mean weight ± SD	12.79 ± 1.79	13.24 ± 1.09
Gestational age (wk)		
37-42 (Full term)	47 (60.25)	21 (72.41)
<37, >42 (Pre term or post term)	31 (39.74)	8 (27.58)
Mean gestation age ± SD	36.94 ± 2.42	37.44 ± 1.29
Birth weight of the newborn(g)		
< 2,500	7 (8.97)	2 (6.89)
2,500 - 2,999	50 (64.10)	20 (68.96)
3,000 - 4,000	21 (26.92)	7 (24.13)
Mean birth weight ± SD	2,842 ± 298.57	2,868 ± 255.05
APGAR score at 1-minute		
0-3 scores	-	-
4-6 scores	3 (3.84)	1 (3.44)
7-10 scores	75 (96.15)	28 (96.55)
Mean score ± SD	8.70 ± 1.57	8.77 ± 1.79
APGAR score at 5-minutes		
0-3 scores	-	-
4-6 scores	1 (1.28)	1 (3.44)
7-10 scores	77 (98.71)	28 (96.55)
Mean score ± S.D.	9.72 ± 1.58	9.67 ± 1.82

respectively (National Environmental Board, 2007). This would seem to indicate risk for health effects of pregnant women and fetus. The more exposure duration increase, the more health effects could be manifest. Although poor perinatal outcomes (i.e.,gestation age, birth weight) were found in more percentage among pregnant women living in the inner city of Rayong, BTEX exposure did not appear to significantly affect pregnancy outcomes in our study. This finding was in accordance with some previous reports which indicated not significantly associated with perinatal outcomes in maternal exposed to environmental BTEX (Aguilera *et al.*, 2009; 2010). Lupo (2011) also found that there were association between BTEX exposure and adverse effects in offspring; however, these associations were not statistically significant. Incontrast, a few studies conducted in Taiwan in the petrochemical (Yang *et al.*, 2002) and petroleum (Lin *et al.*, 2001) industrial areas, data showed an increased incidence of adverse pregnancy outcome (e.g., preterm delivery) in mothers residing in these locations. We are aware that this is a relatively small study, but the indication is that there seems to be no effects of biomarker levels at the exposure concentrations on the pregnancy outcomes observed in this study. Additional studies with larger number of study subjects may be needed to confirm this finding.

4. Conclusions

Pregnancy women living in MapTaPhutarea exposed to environmental BTEX in significantly higher level than those living in NhongRai. The study showed significant associations between ambient BTEX and their urinary metabolites in both groups. Although pregnancy outcomes were not significant difference between two groups, maternal as well as infant living in the petrochemical industrial areas may have an increased health risk of development of certain diseases. Exposure monitoring in pregnant women through measurement of individual exposurelevel, biomarkers of exposure and pregnancy outcomes will allow for the timely initiation of preventive or corrective measures such that the health risks from these exposures may be minimized.

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