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Infants' Neurodevelopmental Effects of $PM_{2.5}$ and Persistent Organohalogen Pollutants Exposure in Southern Taiwan

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ABSTRACT

Several studies have stated the harmful effects of $PM_{2.5}$ to population health, including disruption of neurological development. However, the mechanism behind the neurodevelopmental effects of ambient $PM_{2.5}$ and postnatal PBDEs and OCPs exposure is still unknown. Our goal was to determine influence of breastmilk residues, polybrominated diphenyl ethers (PBDEs) and organochlorine pesticides (OCPs), to the infants' neurodevelopment with respect to high and low $PM_{2.5}$ exposure areas. The participants were recruited from high $PM_{2.5}$ exposure areas (n = 32) and low $PM_{2.5}$ exposure areas (n = 23) of southern Taiwan. The extracted 14 PBDEs and 20 OCPs compounds were analyzed using gas chromatography coupled with mass spectrometer. The infants, aging from 8-12 months, were examined by Bayley Scales of Infants and Toddlers Development, Third Edition (Bayley-III) for neurodevelopment. Results showed that high $PM_{2.5}$ exposure caused reduced head circumference and had significant effects on the motor skill and social emotional development. For breastmilk PBDEs, a positive correlation between BDE-196 and social emotion, after multivariate analysis with adjustment of confounders, was observed while BDE-99, 196, 197, and 207 showed higher magnitudes in low $PM_{2.5}$ areas than in high $PM_{2.5}$ areas. For OCPs, only γ- hexachlorcyclohexanes (γ-HCH) presented the significant difference between high and low $PM_{2.5}$ exposure areas. Most breastmilk OCPs residues, including 4,4'-dichlorodiphenyltrichloroethane (4,4'-DDT), γ-HCH, endrin, and heptachlor epoxide showed negative impact on the Bayley-III scores after multivariate analysis. In conclusion, infants' neurodevelopment was significantly correlated with the location of $PM_{2.5}$ exposure and breastmilk intake of certain PBDEs and OCPs. Breastmilk OCPs might obviously affect infants' neurodevelopment more compared to breastmilk PBDEs based on our finding. Moreover, this study further employs awareness about viable effects of $PM_{2.5}$ in infants' neurodevelopment.

Keywords: $PM_{2.5}$; organochlorine pesticide; PBDEs; infant neurodevelopment; Bayley-III.

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INTRODUCTION

Particulate matters (PMs) are a complex mixture of organic and inorganic substances that are suspended in air, which consists of sulfates, nitrates, ammonia, sodium chloride, black carbon, mineral dust, and water (WHO, 2016). PMs are classified according to their morphology and elemental composition as geogenic, anthropogenic, and biogenic aerosols usually obtained from vehicular emissions, biomass burning, re-suspended road/soil dust (Zeb *et al.*, 2018), firecracker burning, and kitchen fumes (Shen *et al.*, 2019). Several other factors such as relative humidity, seasonal change, and transboundary pollution can also contribute to the levels of PMs in the environment (Chen *et al*., 2019). Fine PM, commonly known as $PM_{2.5}$ is characterized by its large surface area and small particle diameter enabling it to bear variety of toxic elements (Xing *et al.*, 2017). Due to this, it has been associated with greater mortality rate than larger particles such as PM_{10} (Cifuentes *et al.*, 2000). Owing to its size, $PM_{2.5}$ can carry various potentially harmful molecules and penetrate the lung tissue thereby affecting the respiratory, cardiovascular, and even the circulatory system of a person (Pun *et al.*, 2017). In 2015, $PM_{2.5}$ ranked as the fifth mortality risk factor due to its association with several causes of death such as lung cancer and cardiovascular diseases (Crouse *et al.*, 2015; Cohen *et al.*, 2017; Pun *et al.*, 2017) and further studies have shown the relationship between long-term exposure to $PM_{2.5}$ and its correlation with greater risks of chronic obstructive pulmonary disease, pneumonia, and respiratory disease (Pope III *et al.*, 2002; Chowdhury *et al.*, 2019). According to Chao *et al*. (2018), exposure to vehicle emitted-$PM_{2.5}$ increased the levels of the blood proinflammatory biomarker, tumor necrosis factor-α (TNF-α), which is an indication of increased systemic inflammation in humans. Moreover, an *in vivo* study by Chung *et al*. (2019) showed that acute exposure to ambient $PM_{2.5}$ affected the lifespan and the reproduction of *Caenorhabditis elegans* even at low concentrations. In addition to that, $PM_{2.5}$ can also alter the epigenetics of a pregnant woman chronically exposed to it via placental transmission which can endanger the fetus' health (Mazdai *et al.*, 2003; Maghbooli *et al.*, 2018). The developmental vulnerability of human brain to neurotoxicants such as $PM_{2.5}$ usually occur *in ute*ro, during infancy, and can persist up to early childhood (Sassá *et al.*, 2011). Loftus *et al.* (2019) found out that exposure to PMs can lower the IQ of a child which is indicative of its capacity to cause fetal neurodevelopmental delay. According to epidemiological studies, prenatal exposure to $PM_{2.5}$ has an adverse effect on the motor and cognitive development of an infant and it can also increase the child's risk of having autism spectrum disorder (ASD), which is a complex neurodevelopmental disorder, of up to 50% (Lertxundi *et al.*, 2015; Talbott *et al.*, 2015). Thus, the infant's health is extremely susceptible to the air pollutant, $PM_{2.5}$, and it can be considered as a toxic precursor to the impairment of a child's neurodevelopment.

$PM_{2.5}$-bound persistent organic pollutants (POPs) such as organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), and polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) were reported in previous studies (Chao *et al*., 2016; Chen *et al*., 2018b; Zhao *et al*., 2018). The high organic matter content of $PM_{2.5}$ as compared to coarse PMs can be attributed to a higher POPs sorption (Odabasi *et al.*, 2015). A significant correlation between POPs and $PM_{2.5}$ shown by Xu *et al.* (2005); Jiao *et al.* (2018) states that high temperature results to high POPs concentration in $PM_{2.5}$ and it is consistent with Wania and Mackay (1995) wherein they demonstrated that POPs are more likely to volatize in warm areas and they tend to condensate in cold areas. The slow deposition velocity of $PM_{2.5}$ allows the particle bound-POPs to be transported in a longer distance away from its original source, making it detectable in remote areas (Odabasi *et al.*, 2015). Cetin and Odabasi (2007) and Odabasi *et al.* (2015) found out that the most abundant PBDE found in Turkish $PM_{2.5}$ environments is the conger BDE-209 followed by BDE-99 and 47 while the abundant OCPs are p,p'-DDT, and p,p'-DDE. A similar study by Zhou *et al.* (2019) also indicated that OCPs such as p,p'-DDT and p,p'-DDE are predominant in Taiwan. PBDEs coming from diesel vehicles, which is the largest source of $PM_{2.5}$ in Tainan City (Lu *et al.*, 2019), has the highest emission concentration among other pollutants like PCDD/Fs, polychlorinated biphenyls (PCBs), polybrominated dibenzo-*p*-dioxins and dibenzofurans (PBDD/Fs) (Tsai *et al.*, 2017). Therefore, these dangerous POPs can be found in vicinities with $PM_{2.5}$ and can possibly risk human health living near the areas.

POPs are chemical compounds that can remain in the environment for years without showing any significant degradation, may it be from chemical or biological means (Porta and Zumeta, 2002). They are also found to be highly persistent, toxic, hydrophobic, and has bioaccumulation tendencies (Sander *et al.*, 2017). OCPs are volatile and stable chemical pesticides. PBDEs are a type of brominated flame retardants (BFRs) added as additives in the polymer matrix of consumer items such as electronic equipment, plastics, textiles, wood, and other materials, in order to reduce their flammability (Qian *et al.*, 2019). Humans and animals are mainly exposed to these compounds through dietary intake, insecticide spraying (dietary source) and inhalation of contaminated airborne particles, improper waste disposal, and indoor dust (non-dietary source) (Gou *et al.*, 2016; Aerts *et al.*, 2019). Due to the aforementioned characteristics of POPs, the scientific community is alarmed about the detrimental effects that PBDEs and OCPs pose to the well-being of humans. Epidemiological studies suggest that long exposure period to OCPs congeners can cause carcinogenic activities (Cohn *et al*., 2007; Kim *et al*., 2019), immunological and reproductive disorders (Weiss *et al*., 2006), and it can even cause ecotoxicity through aquatic environment contamination (Doong *et al.*, 2002) while other studies have shown that increased PBDE contamination in maternal blood and breastmilk can reduce the probability of a woman to get pregnant (Harley *et al*., 2010) and can be correlated with decreased birth outcomes (Chao *et al.*, 2006).

Breast milk, blood, and fatty tissue are important matrices in evaluating body burden of PBDEs and OCPs through bioaccumulation of these substances. Particularly, breast milk is considered as the matrix of choice in this study because it can be easily collected through non-invasive techniques.

Moreover, it provides information on the biomonitoring of PBDEs and OCPs levels in mother and their children. Breastfeeding is also a key exposure pathway from mother to child and it can show the negative impacts that it presents to infants during their important neurodevelopmental periods. Therefore, the aim of this study was to determine different associations between breastmilk PBDEs, OCPs, and $PM_{2.5}$, in correlation with the high and low $PM_{2.5}$ exposure areas, with the infant's neurodevelopment.

METHODS

Studying Population and Selective Areas

This study was a part of breast milk surveillance research. Our subjects, healthy mother-infant pairs, were randomly recruited from the hospitals in southern Taiwan from April 2007–April 2010. Our goal was to examine mother-infant pairs living in high and low $PM_{2.5}$ exposure areas whether airborne $PM_{2.5}$, breastmilk PBDEs, or breastmilk OCP affected the neurological behavior of infants. The study design or protocol was approved and reviewed by the institutional review boards of the Human Ethical Committees of Pingtung Christian Hospital (PCH) in 2007 (NO: IRB021). The ethical standards formulated in the Helsinki Declaration of 1964 and revised in 2004 were followed. Studying subjects gave informed consent after receiving detailed explanations of the study and potential consequences prior to enrollment. Our subjects, the pregnant women, were invited during the routine health check-up in the obstetric clinics of the hospitals in Kaohsiung and Pingtung as described in our previous reports (Chao *et al.*, 2011; Kao *et al.*, 2019). In brief, more than 350 pregnant women were invited and most of them joined our study. Of these participants, 265 agreed and answered the detailed questionnaire including maternal age, pre-pregnancy BMI, parity, smoking and drinking habits, socioeconomic status, dietary habits and consumption, medical history, and possible exposure to PBDEs and OCPs from different sources. Cord blood and breast milk were collected within the first month of delivery. The pediatrics recorded gestational age, birth weight, birth length, and head circumference of the infants at childbirth. The initial enrollment of 138 mothers were considered as our cohort due to collection of their cord blood, at birth, and breast milk, at home.

The infant participants were recruited from the cohort for the follow-up health check. Firstly, the postcards were sent to our cohort after 4 months of giving birth to invite them to join the program. Secondly, if the mothers agreed to join this study, we informed them to bring their infants to the Department of Pediatrics in the Pingtung Christian Hospital for the evaluation of infants' development. Thirdly, infant participants at the age of 8–12 months would be examined by neurological development such as the Bayley Scales of Infants and Toddlers Development, Third Edition (Bayley-III) which were tested by psychologists or well-trained infant psychometrician. Fourthly, residues of PBDEs and OCPs in breast milk should be determined. Finally, 55 participants who had levels of PBDEs and OCPs in breast milk and Bayley-III scores were selected. Of these 55 subjects, 23 participants were from the high $PM_{2.5}$ exposure areas and 32 subjects were from the low $PM_{2.5}$ exposure areas. High and low $PM_{2.5}$ exposure areas are defined based on the longitudinal $PM_{2.5}$ data from Taiwan Environmental Protection Agency (TEPA) air quality monitoring sites in Kaohsiung and Pingtung areas since 2005. Two monitoring sites, Pingtung City and Chaozhou township, in Pingtung County are located at the $PM_{2.5}$ heavily contaminated areas which are more severely polluted compared to the rural areas in Pingtung. The final choice of high $PM_{2.5}$ exposure areas were Pingtung City, Chaozhou Township, and Kaohsiung City except for Meinong District based on the historical data from the TEPA monitoring sites. The rural areas in Kaohsiung City and Pingtung County are defined as the low $PM_{2.5}$ exposure areas. All of the participants (n = 55) were exclusively breastfed infants or partially breastfed for at least 6 months.

Analysis of PBDEs and OCPs

The chemicals and reagents utilized in the study are the following: OCPs standards (EPA method 8081 organochlorine pesticide mixture) were acquired from AccuStandard Inc. (New Haven, CT, USA); while the PBDEs standards were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). The $^{13}C_{12}$ internal standards of PBDEs were purchased from Wellington Laboratories (Guelph, Canada) and OCPs $^{13}C_{12}$ internal standards, 4,4'-DDT, and pentachloronitrobenzene were sourced from Cambridge Isotope Laboratories (Tewskbury, MA, USA). Every solvent used were of the highest quality from Tedia (Fairfield, OH, USA), Sigma-Aldrich (St. Louis, MO, USA), and Merck (Darmstadt, Germany).

For the collection of breastmilk samples, at least 60 mL were collected from the mother participants within 1 month of birth and it was placed in a chemical-free glass bottles. After collection, the samples were frozen (–4°C) at home and then transferred to the laboratory in National Pingtung University of Science and Technology and kept at –20°C. Extraction and clean-up procedure was done as described in previous studies (Chao *et al.*, 2011; Kao *et al.*, 2019). Fourteen PBDE congeners including BDE-28, 47, 99, 100, 153, 154, 183, 196, 197, 203, 206, 207, 208, and 209 were analysed by high-resolution gas chromatography (Hewlett-Packard GC 6970; Hewlett-Packard, Palo Alto, CA) coupled with a high-resolution mass spectrometer (Micromass Autospec Ultima, Waters, Milford, MA) using a DB-5HT column (J&W Scientific, Folsom, CA) and splitless injector. Twenty OCPs residues such as aldrin, α-HCH, β-HCH, γ-HCH, δ-HCH, cis-chlordane (cis-CHL) and trans-CHL, 4,4'-dichlorodiphenyldichloroethane (4,4'-DDD), 4,4'-dichlorodiphenyldichloroethylene (4,4'-DDE), 4,4'-DDT, dieldrin, endosulfan I & II, endosulfan sulfate, endrin, endrin aldehyde, heptachlor, endrin ketone, heptachlor, heptachlor epoxide, and methoxychlor were analysed using high-resolution gas chromatography coupled with a low-resolution mass spectrometer (Agilent 7890/5975C-GC/MSD, Hewlett-Packard, Palo Alto, CA) in the splitless mode with a capillary column of DB-5MS (J&W Scientific, Folsom, CA) and electron impact (EI) mode.

Quality assurance and quality control (QA/QC) of the samples strictly followed the standard method of the Taiwan

Environmental Protection Agency. The internal standards of 8 $^{13}C_{12}$-labeled PBDEs and 2 $^{13}C_{12}$-labeled OCPs were spiked to the breastmilk before extraction to ensure recovery in the chemical analysis process. The sets of blanks, standards, and pooled milk samples were added into each batch of 10 samples for QC control. The limits of detection (LODs) were thrice the signal-to-noise ratio and the value obtained for the twenty OCPs were ranging from 0.0151 to 0.0540 ng g^{-1} lipid and for 13 PBDE from BDE-28 to BDE-208 were between 0.001 and 0.017 ng g^{-1} lipid and BDE-209 was 0.11 ng g^{-1} lipid, respectively.

Evaluation of Bayley-III

Bayley-III composite scores, including 5 domains such as cognitive, language (receptive and expressive communication), motor (fine and gross), social-emotional, and adaptive behaviour was evaluated for the neurodevelopment of infants between 8–12 months old. The three domains namely cognitive, language, and motor were assessed by well-trained experts. The two domains, social-emotional and adaptive behaviour, were incorporated to assess their neurodevelopment via parent-report questionnaires. The 5 domains of assessment provided the neurodevelopmental quotient of standardizing raw scores and adjusting chronological age to generate continuous scores. A standard score for the Bayley-III, with a mean of 100 and a standard deviation (SD) of 15, was derived for each scale.

Statistical Analysis

Measurements of PBDE and OCP concentrations in breast milk below LODs were detected as half of the LODs. The 5 domains of Bayley-III composite scores were fulfilled with normal distribution, but breastmilk levels of OCPs and PBDEs were not normally distributed for testing normality by the Kolmogorov-Smirnov method. The initial examination was made to determine whether Bayley-III scores, PBDE levels, and OCP concentrations had significant differences between high and low $PM_{2.5}$ exposure areas by using Spearman's rank correlation coefficients tests. Furthermore, Bayley-III scores were predicted by the dependent variables of 14 PBDE congeners, 20 OCP residue compounds, and two $PM_{2.5}$ exposure-type areas after examining through the use of multivariate stepwise linear regression models with adjustment of maternal age, pre-pregnant BMI, and parity. Analyses were carried out using the Statistical Package for Social Science (SPSS) version 12.0 (SPSS Inc., Chicago, USA).

RESULTS AND DISCUSSION

Table 1 shows the descriptive statistics of the demographic variables used in the study and it is grouped according to the locations of the high and low $PM_{2.5}$ exposure areas. The age, height, weight, pre-pregnant BMI, and the parity of the mothers did not show any significant results, however, the infant's head circumference was significantly affected by the $PM_{2.5}$ exposure areas (p = 0.030). Its range and mean ± standard deviation (SD) at the high and low $PM_{2.5}$ exposure areas were 32.0–36.0 and 34.0 ± 1.15, and 30.5–35.5 and 33.1 ± 1.11, respectively. In a study conducted by Schembari *et al.* (2015), they found out that there was a positively significant correlation between $PM_{2.5}$ exposure and decrease in the head circumference in British Caucasian birth population and it was in agreement with our result. Table 1 also shows that not only is the head-circumference growth of the infant affected, but also its neurodevelopment. In Fig. 1, among the five neurodevelopmental domains such as cognitive, language, motor, social emotional, and adaptive behavior, there is a significant impact on the motor (p = 0.043) and social emotional (p = 0.040) skills of the infants.

Table 1. Descriptive statistics of studying participants between high and low $PM_{2.5}$ exposure areas.

Demography	High $PM_{2.5}$ areas (n = 23)		Low $PM_{2.5}$ areas (n = 32)		p value
	Range	Mean ± SD [a]	Range	Mean ± SD	
Mothers					
Age (year)	23.0–35.0	29.9 ± 3.11	17.0–40.0	29.2 ± 5.52	0.560
Height (cm)	148–170	159 ± 6.05	150–166	158 ± 4.79	0.614
Weight (kg)	44.0–76.0	55.2 ± 8.94	39.0–86.0	53.0 ± 11.8	0.589
Pre-pregnant BMI (kg m^{-2})	17.2–29.1	21.9 ± 3.29	15.4–34.9	23.0 ± 4.62	0.517
Parity (number)	1.00–3.00	1.86 ± 0.756	1.00–3.00	1.81 ± 0.750	0.828
Infants					
Gestational age (week)	32.0–40.0	38.4 ± 1.86	36.0–40.0	38.1 ± 1.16	0.180
Birth length (cm)	46.0–52.0	49.1 ± 1.63	46.0–52.0	49.1 ± 1.67	0.729
Birth weight (gram)	2480–4000	3120 ± 429	2300–3840	3060 ± 347	0.946
Head circumference (cm)	32.0–36.0	34.0 ± 1.15	30.5–35.5	33.1 ± 1.11	0.030*
Infant Neurodevelopment					
Cognitive (score)	85.0–125	102 ± 11.6	85.0–120	101 ± 9.48	0.965
Language (score)	79.0–125	100 ± 10.2	77.0–121	100 ± 10.5	0.952
Motor (score)	82.0–112	100 ± 7.34	79.0–121	96.3 ± 9.25	0.043*
Social Emotional (score)	65.0–130	104 ± 15.5	55.0–140	94.7 ± 19.2	0.040*
Adaptive behavior (score)	77.0–121	102 ± 12.1	62.0–131	96.4 ± 15.6	0.129

* $p < 0.05$.

[a] SD: standard deviation.

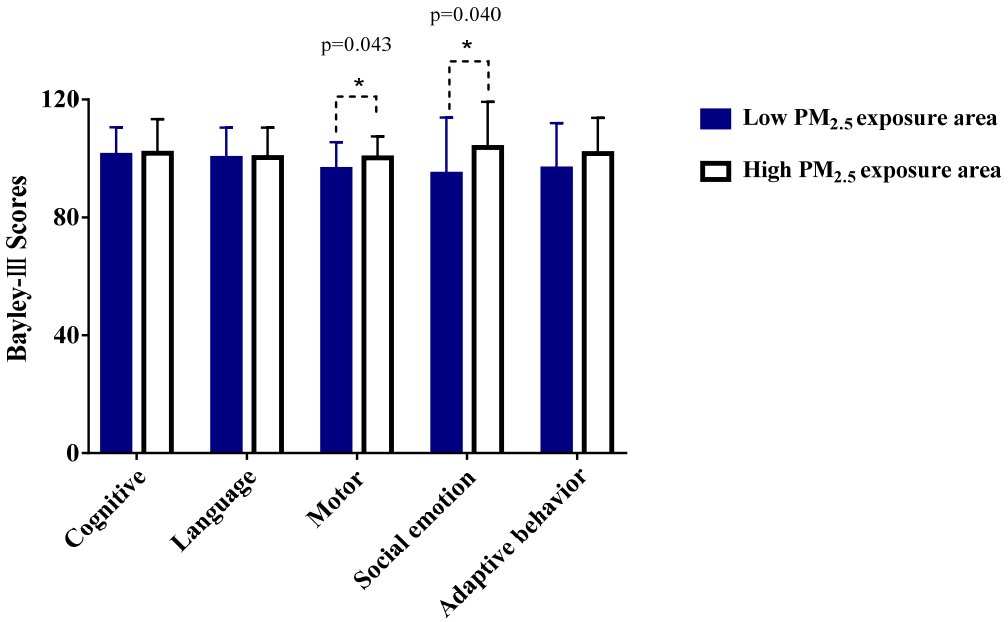

Fig. 1. Five domains of Bayley III Scales used to determine the scores of the infant's neurodevelopment based from the high and low $PM_{2.5}$ areas.

The high $PM_{2.5}$ areas exhibited higher mean, 100 (SD = 7.34) for the motor skill and 104 (SD = 15.6) for the social emotion, compared to the low $PM_{2.5}$ areas with the means of 96.3 (SD = 9.25) and 94.7 (SD = 19.2) for motor and social emotional scales, respectively. Also, the reduced growth of the head circumference or microcephaly may have contributed to the neurodevelopmental impairment of the infant. Using the Bayley Scales of Infant Development (BSID), Neubauer *et al.* (2013) was able to show that suboptimal size of the head has a negative impact on the infants neurodevelopment. However, further studies are recommended in order to prove whether the reduced head size of infants with *in-utero* exposure to $PM_{2.5}$ affects their neurodevelopment.

Although our study did not find an association between cognitive development and $PM_{2.5}$, other studies have shown that $PM_{2.5}$ has an adverse effect on the cognition of an infant (Basagaña *et al.*, 2016; Chiu *et al.*, 2016). According to Chiu *et al.* (2016), prenatal exposure to $PM_{2.5}$ have induced lower IQ among boys and poorer memory function in girls, which is an indication of the impaired development of the child. A similar result obtained by Basagaña *et al.* (2016), after 1-year of longitudinal observational study in urban $PM_{2.5}$ exposure area, showed that children attending primary school have reduced cognitive function. However, they did not consider factors such as socioeconomic factors and level of social interactions which may also affect the cognitive development of the children. Likewise, additional *in vivo* studies of rat models subjected to $PM_{2.5}$ presents compromised learning and memory dysfunction in the offspring (Zhang *et al.*, 2018; Zheng *et al.*, 2019).

As illustrated in Fig. 2, different congeners of PBDEs were found in the breastmilk sample of the mothers from high and low $PM_{2.5}$ exposure areas. Out of the 14 PBDE congeners that the sample contains, only 4 congeners are found to have an effect on the neurodevelopment of the child and these are the following: BDE-99 (low $PM_{2.5}$ exposure areas = 810 pg g^{-1} $lipid^{-1}$) (high $PM_{2.5}$ exposure area = 163 pg g^{-1} $lipid^{-1}$, $p = 0.041$), BDE-196 (low $PM_{2.5}$ exposure area = 47.8 pg g^{-1} $lipid^{-1}$) (high $PM_{2.5}$ exposure area = 27.0 pg g^{-1} $lipid^{-1}$, $p = 0.018$), BDE-197 (low $PM_{2.5}$ exposure area = 349 pg g^{-1} $lipid^{-1}$) (high $PM_{2.5}$ exposure area = 195 pg g^{-1} $lipid^{-1}$, $p = 0.044$), and BDE-207 (low $PM_{2.5}$ exposure area = 249 pg g^{-1} $lipid^{-1}$) (high $PM_{2.5}$ exposure area = 138 pg g^{-1} $lipid^{-1}$, $p = 0.008$). Low $PM_{2.5}$ exposure areas exhibited higher PBDEs concentrations in breast milk for all the congeners compared to those of the high $PM_{2.5}$ exposure areas and this may possibly be associated with the dietary intake. Dietary intake is a key exposure pathway and it may be the major source of the increased bioaccumulation levels of PBDEs in people living in rural areas (low $PM_{2.5}$ exposure area) compared to those living in urban areas (high $PM_{2.5}$ exposure area). Also, inhalation and ingestion of released PBDEs from non-point sources such as furniture, digital equipment, couch, and etc., in the microenvironment is an important exposure route that can contribute to human's body burden (Sjodin *et al.*, 2004; Shy *et al.*, 2015). According to our previous study (Chao *et al.*, 2016), the migration of $PM_{2.5}$-bound PBDE from outdoor to indoor air and vice versa might have an effect on the levels of $PM_{2.5}$-bound PBDE in different environments (indoor and outdoor). Our finding suggests that BDE-207 is the most statistically negative congener among BDE-99,196, and 197, and the same result was demonstrated by Lin *et al.* (2010), in which they found out that the postnatal exposure of infants to PBDEs via ingestion of breastmilk have shown that high levels of BDE-207, 208, and 209 can influence the reduction of the adaptive behavior of an infant. Previous study regarding prenatal exposure to PBDEs through cord blood sample that was evaluated using the second edition of Bayley Scales for Infant Development (BSID II) determined that BDE-99 is

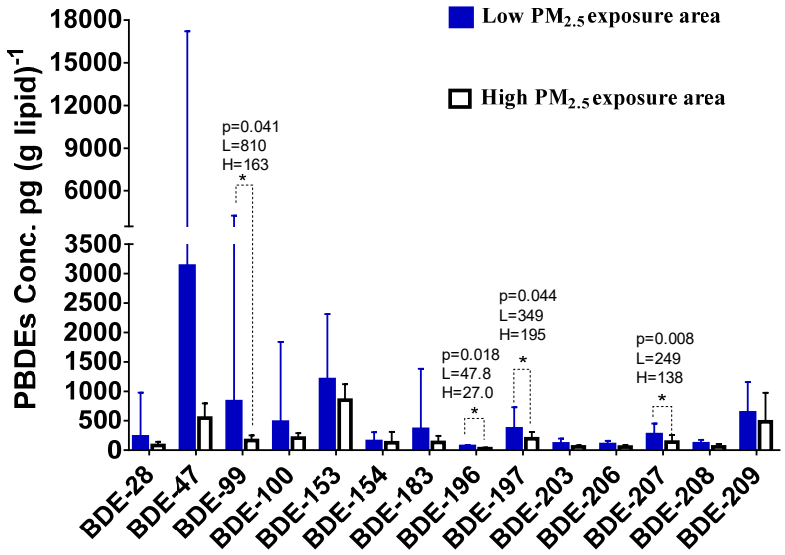

Fig. 2. PBDE congeners found in the breastmilk sample of the mothers from high and low $PM_{2.5}$ areas that has negative impact on the neurodevelopment of infants.

negatively correlated with the 12-month Mental Development Index (MDI) and 48-month full-scale and verbal IQ, while BDE-100 is significantly associated with 36-month MDI and 48 and 72-month full-scale performance IQ (Herbstman *et al.*, 2010). Similar results have been obtained by Gascon *et al.* (2011) and Eskenazi *et al.* (2013) where they demonstrated that prenatal exposure to PBDEs have led to a diminished and poorer attention, cognitive, and fine motor skills of children 4, 5, and 7 years of age. Gascon *et al.* (2011) have also statistically linked BDE-47 to an increased possibility of acquiring the symptom of attention deficit subscale of Attention Deficit Hyperactivity Disorder (ADHD) but no correlation was found for the hyperactivity scale. Additionally, Gascon *et al.* (2012) reported that not only BDE-47 impairs the neurodevelopment but conger BDE-209 is also a contributing factor and it is found to be the main conger associated with the decrease in the mental development of children and this result agrees with the previous study of Chao *et al.* (2011) which indicates that BDE-209 is negatively correlated with the cognitive development of a toddler at 1 year of age. However due to the differences in evaluation tools used (Bayley-III in our case) and different set of constraints (e.g., population number, age, and exposure levels), congener patterns exhibited (BDE-99, 196, 197, and 207) in our study differs from previous researchers', wherein Gascon *et al.* (2011) utilized McCarthy Scales of Children's Abilities, Eskenazi *et al.* (2013) used Peabody Picture Vocabulary Test (PPVT), Child Behavior Checklist, Conners' Kiddie Continuous Performance Test (K-CPT), Conners' ADHD/DSM-IV Scales (CADS), and Behavior Assessment System for Children, 2nd edition (BASC), and Herbstman *et al.* (2010) followed the BSID-II assessment tool.

Among the 20 individual OCPs (pg g^{-1} $lipid^{-1}$) shown in Fig. 3, high concentration (mean ± SD) of 4,4'-DDE in breast milk were found in both low $PM_{2.5}$ exposure areas (10.49 ± 7.83) and high $PM_{2.5}$ exposure areas (10.14 ± 7.83). Studies by Chao *et al*. (2006); Chen *et al*. (2018a); Kao *et al*. (2019) also showed similar results proving that 4,4'-DDE is the principal OCP residue that can be found in the breast milk. Elimination of 4,4'-DDE in the body is slower with an estimated half-life of six years as compared to 4,4'-DDT (Noren and Meironyte, 2000). 4,4'-DDD, 4,4'-DDT and heptachlor also showed adequate concentrations in the breast milk with mean ± SD of 0.85 ± 1.39, 0.78 ± 0.81 and 0.64 ± 0.72 in low $PM_{2.5}$ areas and 1.21 ± 1.49, 0.63 ± 0.65 and 0.69 ± 0.64 in high $PM_{2.5}$ areas, respectively. However, the results based from Fig. 3 showed γ-HCH (low $PM_{2.5}$ exposure area: 0.095 ± 0.081; high $PM_{2.5}$ exposure area: 0.17 ± 0.14) is the OCP residue that has significant effect in the neurodevelopment of infants and as shown in Table 2, γ-HCH is negatively associated with the language skill of the infant. A potential mechanism regarding the effects of breastmilk contaminants, OCPs and PBDEs, on the neurological behavior of the infant have been proposed by researchers and according to previous reports (Hallgren *et al*., 2001; Viberg *et al*., 2003; Kao *et al*., 2019), the endocrine disruption capability of PBDEs and OCPs may be a crucial pathway for the delayed brain development of the fetus. Hallgren *et al*. (2001) have demonstrated that pregnant NMRI mice exposed to PBDEs have induced alteration on the cholinergic system of their offspring thus affecting their learning and memory skills while Kao *et al.* (2019) have shown that OCPs residues on breastmilk are associated with changes in the thyroid hormones (THs) and insulin-like growth factor-1 (IGF-1) of the infant which affected their neurodevelopment.

Table 2 shows the different associations of PBDEs, OCPs, and $PM_{2.5}$ with regards to the high and low $PM_{2.5}$ areas to the Bayley-III scores of the infant by using stepwise linear regression after the confounders such as maternal age, pre-pregnant BMI, and parity were adjusted. The organochlorine compounds (4,4'-DDT, γ-HCH, endosulfan I, endrin, and heptachlor epoxide), PBDE-196 congener, and $PM_{2.5}$'s location have been found to have an influence on the infant's neurodevelopment. 4,4'-DDT significantly lowered the infant's

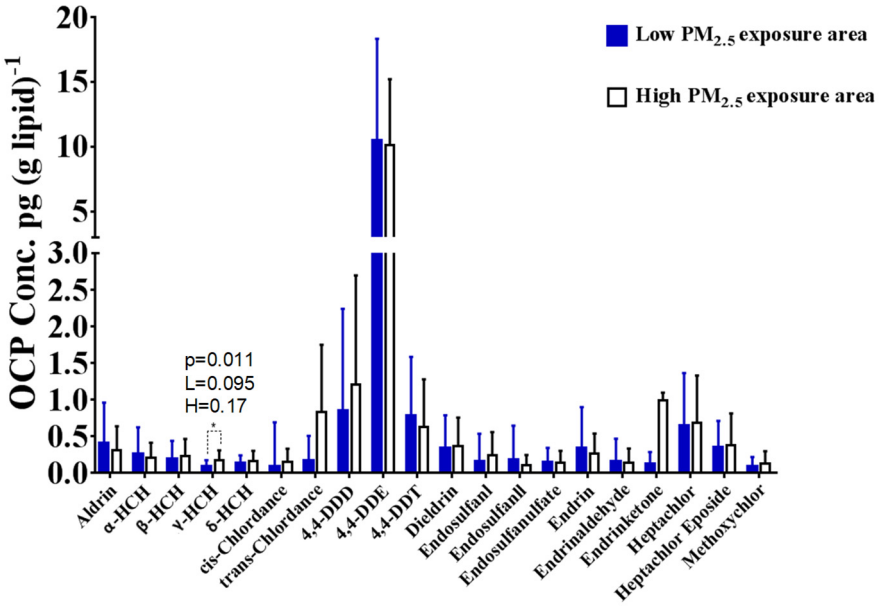

Fig. 3. OCP residues found in the breastmilk sample of the mothers from high and low $PM_{2.5}$ areas that has negative impact on the neurodevelopment of infants.

Table 2. Association of breastmilk PBDEs, OCPs, and $PM_{2.5}$ (high and low $PM_{2.5}$ exposure areas) in the neurodevelopment of an infant through the use of multivariate stepwise linear regression models[a].

Bayley-III scores	Independent variable	β estimate	*p*-value
Cognitive			
(Adjusted R^2 = 0.105)	DDT	–0.341	0.32*
	Maternal age	0.066	0.680
	Pre-pregnant BMI	–0.077	0.610
	Parity	–0.148	0.368
Language			
(Adjusted R^2 = 0.441)	DDT	–0.439	0.010*
	γ-HCH	–0.409	0.020*
	Endosulfan I	0.368	0.030*
	Maternal age	0.048	0.714
	Pre-pregnant BMI	0.192	0.121
	Parity	0.079	0.556
Motor			
(Adjusted R^2 = 0.161)	DDT	–0.378	0.015*
	Maternal age	0.169	0.282
	Pre-pregnant BMI	–0.152	0.300
	Parity	0.019	0.906
Social emotion			
(Adjusted R^2 = 0.437)	Endrin	–0.515	< 0.001***
	Location	0.442	0.001**
	BDE-196	0.407	0.006**
	Maternal age	–0.193	0.145
	Pre-pregnant BMI	0.043	0.736
	Parity	0.072	0.587
Adaptive behavior			
(Adjusted R^2 = 0.501)	Heptachlor epoxide	–0.415	0.003**
	Location	0.280	0.042*
	Maternal age	–0.062	0.676
	Pre-pregnant BMI	0.087	0.516
	Parity	0.040	0.787

*$p < 0.05$; **$p < 0.01$; *** $p < 0.001$

[a] The confounders are maternal age, pre-pregnant BMI, and parity.

cognitive score (p = 0.32), language score (p = 0.010), and motor score (p = 0.015) which is indicative of its negative impact on the child's neurodevelopmental delay. Previous study of Eskenazi *et al.* (2006) showed that high levels of *p,p'*-DDT and *o,p'*-DDT in maternal serum can lower the MDI score of a child by 1.71 points (1 year old) and 2.12 points (2 years old), and 2.56 points (1 year old) and 3.06 points (2 years old), respectively. And *p,p'*-DDT is also associated with a poorer Psychomotor Development Index (PDI) for infants at 6–12 months but it did not persist until 24 months, which is in accordance to our findings. Even though our study did not find a significant association between 4,4'-DDT and the social emotional developmental domain of the infant, Kao *et al.* (2019) have demonstrated that there is an inverse relationship between breastmilk 4,4'-DDT and the cognitive, language, and social emotional factors. Other organochlorine compounds especially γ-HCH (p = 0.020), endrin (p < 0.001), and heptachlor epoxide (p = 0.003) displayed negative correlations with language, social emotion, and adaptive behavior, respectively, which is similar to the investigation of Kao *et al.* (2019) wherein they indicated that apart from 4,4'-DDT, endrin and heptachlor epoxide decreased the social emotional, adaptive behavior, and motor skills of the infant. However, the language domain was positively correlated with endosulfan I with a β-estimate of 0.368 and p-value of 0.030 and it is comparable with the previous study of Kao *et al.* (2019) in which the endosulfan I (β = 21.5, p = 0.015) and heptachlor (β = 18.5, p = 0.010) presented statistically positive significant association with the language and motor scores. While our findings are similar to that of the previous research of Kao *et al.* (2019), further studies that consider a large sample size are still needed in order to ensure the validity of the possible benefits that endosulfan I might pose to the infant's neurodevelopment. The conger BDE-196 was found to be positively correlated to the social emotion of the infant, increasing their score by 0.407 points (p = 0.006). This result is comparable to our previous study (Chao *et al.*, 2011), which indicates that BDE-196 helps in the language development of an infant. The reason and mechanism behind the positive impacts of this BDE congener is still unclear since only a few *in vivo* studies have been made but a longitudinal study is recommended in order to attain more accurate results. Furthermore, past studies indicate that $PM_{2.5}$ is a neurotoxicant (Basagaña *et al.*, 2016; Chiu *et al.*, 2016; Zhang *et al.*, 2018; Zheng *et al.*, 2019) but from the obtained results using Bayley-III, we have found out that location of $PM_{2.5}$ has a positive correlation with the social emotion (β = 0.442, p = 0.006) and adaptive behavior (β = 0.280, p = 0.042) scores and this suggests that infants exposed to $PM_{2.5}$ might have a better neurobehavioral outcome in their childhood. Varying results may be due to the different sampling site or location of the exposed mothers and additional studies can help in understanding the underlying mechanism of the impacts that $PM_{2.5}$ presents to human health.

CONCLUSIONS

Breastfeeding mothers that have been exposed to high and low $PM_{2.5}$ exposure areas affected the development of the infant's head circumference and neurodevelopment. High $PM_{2.5}$ vicinities exhibited higher mean for the social emotional and motor skills of the infants which may suggest that the higher the exposure level, the greater is the adverse impact on the child's development. Also, based from the data gathered, neonates are more vulnerable to the harmful effects of $PM_{2.5}$ because they can still experience negative effects even at low levels while the mothers did not show any significant results. Moreover, BDE-196 demonstrated to be beneficial for the child's social emotion, increasing their Bayley-III scores by 0.407 points while the other congeners such as BDE-99,197, and 207 are statistically negatively correlated with the neurodevelopment. Despite having 4,4'-DDE as the principal OCP in breastmilk sample, it showed no significant association with neurodevelopment. After analyzing the effects of OCPs using multiple stepwise linear regression model, only the DDT, γ-HCH, endosulfan I, endrin, and heptachlor epoxide were found to affect the infant's neurodevelopment at 8–12 months of age. Even though this study has limitations such as small sampling size (n = 55), indirect $PM_{2.5}$ concentration measurement, and lack of absolute effect of breastmilk residues to the body burden of infant, our study imparts significant correlations between exposure of $PM_{2.5}$, PBDEs, and OCPs to breastfeeding mothers and infant neurodevelopment. Further studies with larger and wider sample size are still needed to completely identify whether breastmilk PBDEs, OCPs, and $PM_{2.5}$ is a toxic precursor to the child's neurodevelopment.

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DISCLAIMER

There is no conflict of interest to be reported from the authors of this paper.

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