Science of the Total Environment 624 (2018) 377–384

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Association between maternal exposure to major phthalates, heavy metals, and persistent organic pollutants, and the neurodevelopmental performances of their children at 1 to 2 years of age- CHECK cohort study☆

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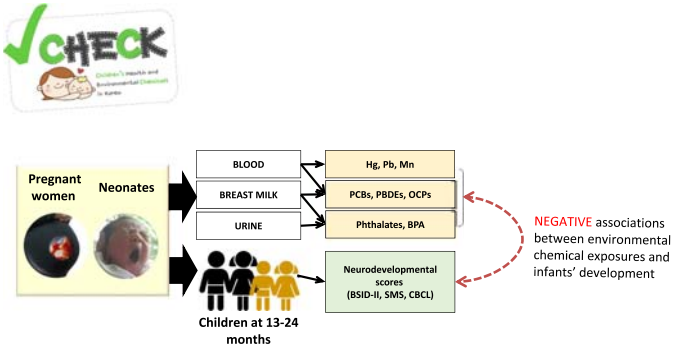
HIGHLIGHTS

- Prenatal Hg, Pb, BPA, or DEP exposures were associated with neuro-developmental delay.
- DEHP exposure through lactation showed negative association with mental index.
- Prenatal Hg, DEP, or PCB exposures showed positive associations on CBCL scores.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 14 May 2017
Received in revised form 5 December 2017
Accepted 5 December 2017
Available online xxxx

ABSTRACT

Exposure of the developing fetus and infants to toxic substances can cause serious lifelong health consequences. Several chemicals have been associated with adverse neurodevelopmental disorders in the early life stages of humans. However, most epidemiological studies have focused on a limited number of chemicals, and hence may exclude important chemicals from consideration or result in conclusions built on associations by chance. In the present study, we investigated the chemical exposure profile of the women, and associated these with

☆ For submission to: Science of the Total Environment (VSI) Asian Birth Cohorts.

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https://doi.org/10.1016/j.scitotenv.2017.12.058
0048-9697/

Editor: Adrian Covaci

Keywords:
Bayley scales of infant development (BSID)
Child behavior checklist (CBCL)
Prenatal exposure
Breast milk
Korea
Neurodevelopment

the early neurodevelopmental performance of their offspring at 13–24 months of age. The chemicals assessed include four phthalates, bisphenol A, three heavy metals, 19 polychlorinated biphenyls (PCBs), 19 organochlorine pesticides, and 19 polybrominated diphenyl ethers, which were measured from urine, whole blood, serum, and/or breastmilk of the pregnant or lactating women. For neurodevelopmental performance, the Bayley Scales of Infant Development-II (BSID-II), Social Maturity Scale (SMS), and Child Behavior Checklist (CBCL) were measured from a total of 140 toddlers. Among the measured chemicals, monoethyl phthalate (MEP) in maternal urine was significantly associated with early mental, psychomotor, and social development. In addition, breast milk di-ethylhexyl phthalate (DEHP) metabolite and blood lead concentrations were inversely associated with mental and psychomotor development indices, respectively. Maternal blood PCB153, heavy metals, and urinary MEP levels were also higher among the children with behavioral problems, as indicated by the CBCL range. Taken together, maternal exposure to several EDCs such as PCBs and DEHP was associated with adverse neurodevelopmental performances among the children aged 1–2 years. Confirmation of these association in larger populations, as well as longer-term consequences of such exposure warrant further investigation.

1. Introduction

The stages early of life are vulnerable to exogenous chemical exposures because of their rapid development and incomplete metabolic activities (Dencker and Dencker, 1998; Makri et al., 2004). People are exposed to a number of chemicals through the contact with consumer goods, personal care products, food, drinking water, and other sources. Such exposure may adversely affect the development of infants and children through various toxicological pathways including endocrine disruption (WHO, 2012). Especially, prenatal exposure to endocrine disrupting chemicals (EDCs) may influence the growth and development of the fetus (Eriksson and Talts, 2000; Gascon et al., 2011), and these adverse effects could persist throughout the life (Kraft et al., 2016).

A number of epidemiological cross-sectional studies have reported the negative effects of chemical exposure on children's cognitive and/or behavioral performances (Cowell et al., 2015; Falck et al., 2015; Kraft et al., 2016; Takser et al., 2003). Phthalates are among those chemicals that have been identified as having adverse neurodevelopmental effects (Boas et al., 2006; Jurewicz and Hanke, 2011). Urinary mono-n-butyl phthalate (MnBP) and mono-isobutyl phthalate (MiBP) concentrations during pregnancy were associated with a decrease in psychomotor development and with increased odds of psychomotor delay (Whyatt et al., 2012). Other observational studies have also identified adverse developmental effects of phthalate exposure in children, but with different responsiveness by sex (Kim et al., 2011; Kobrosly et al., 2014; Tellez-Rojo et al., 2013). In addition, several other contaminants have also been associated with adverse neurodevelopmental effects among children. Bisphenol A (BPA) has been reported to be associated with adverse neurodevelopmental effects in cross-sectional observational studies (Casas et al., 2015; Lin et al., 2017), but there are other reports that suggest otherwise (Braun et al., 2011; Yolton et al., 2011). Heavy metals are well-known neurotoxins, and have been reported in a number of studies to be associated with developmental toxicity. Prenatal exposure to manganese (Chung et al., 2015), lead, and mercury (Kim Y. et al., 2013b; Marques et al., 2014; Weston et al., 2014) were inversely associated with developmental status in infants and children. Various persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), are also widely recognized to have neurodevelopmental effects. PCBs exposure is associated with impaired cognitive function and behavioral deficits among children of many geographical regions worldwide (Eubig et al., 2010; Schantz et al., 2003). Scores for cognitive and motor functions were also lower in children who were pre- and post-natally exposed to the brominated flame retardant, BDE47 (Gascon et al., 2011). Even at four years of age, negative associations between prenatal exposure to polybrominated diphenyl ethers (PBDEs) and child attention and behavioral problems were observed (Chen et al., 2014; Cowell et al., 2015).

Most of the association studies for neurodevelopmental effects, however, have looked at a rather limited number of chemicals. Since the general population can be simultaneously exposed to multiple EDCs, the potential effects of other substances that might occur together but were not measured, were often ignored, in the association studies. Typically, some of the chemicals may share common exposure sources, and the observed association of one chemical with negative health effects may be coincidental and simply reflects the real association of others that share the common sources of exposure. For example, humans may be simultaneously exposed to di-ethylhexyl phthalate (DEHP) and BPA through contacts to plastic products (CDC, 2009). A significant association of BPA with a certain adverse health effect may in reality reflect an association with DEHP, or other EDCs (Kim et al., 2017b). Whereas it is impossible to measure and to consider all chemicals in epidemiological studies, however, some studies that have reported one chemical-one effect correlations inevitably have limitations in these perspectives, and their conclusions should be considered with caution. Measuring multiple chemicals and looking at their respective associations with given health effects will allow an in-depth analysis of the association and result in more reliable conclusions.

Our group has reported the levels of POPs, phthalates, BPA and heavy metals in a matched pregnant woman and fetus population, i.e., the Children's Health and Environmental Chemicals in Korea (CHECK) cohort, and their associations with several adverse health outcomes including thyroid hormone balances, growth, and obesity related indicators of the infants (Kang et al., 2013; Kim et al., 2016b; Kim et al., 2017a; Kim et al., 2013a; Kim et al., 2015b; Kim et al., 2015c). From the same cohort, we reported that exposure to several POPs during pregnancy was significantly associated with thyroid hormone balances of newborn infants (Kim et al., 2015b). Association between phthalates and BPA, and thyroid functions has been widely documented in human populations (Boas et al., 2010; Johns et al., 2016; Rochester, 2013). Heavy metals like lead and mercury were also associated with thyroid hormone toxicity (Lidsky and Schneider, 2003; Soldin et al., 2008). As thyroid hormones play a critical role in neurodevelopment during early life stages of humans, those thyroid disrupting chemicals may also influence the normal neurodevelopment of infants.

The purpose of this study is to investigate the association between prenatal or lactational exposure to multiple chemicals and neurodevelopment of their infants. For this purpose, the CHECK cohort population whose exposure profile has been documented for major POPs, phthalates, BPA, and heavy metals was employed. For assessing neurodevelopmental performances of the participating children, several developmental test indexes, including the Bayley Scales Index for Development-II (BSID-II), Social Maturity Scale (SMS), and Child Behavior Checklist (CBCL), were measured from the offspring at 13–24 months of age. The results of this study will help better understand the association between chemical exposures during pregnancy or lactation, and neurodevelopmental effects in early life stages.