Conference Paper

Effects of Dioxins (PCDDs, PCDFs) and Dioxin-like (PCBs) Exposure on Neuro-development in Children: A Review

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Abstract

Dioxins and dioxin-like compounds are widely spread in the environment and listed as POPs contaminants which in a certain level of exposure, it associated with neuro-developmental defects in childhood. Studies in animals resulted in the association between dioxins and dioxin-like exposure and neuro-developmental abnormalities. However, studies in human result varied association between exposure and neurodevelopment outcomes. This review was to observe variables in several publications about dioxins and dioxin-like exposure and its effects to neurodevelopment in children. Reviewed variables are dioxins and dioxin-like concentration in mother, breastfeeding duration, and neuro-developmental test scores. Six reviewed studies evaluated dioxins and dioxins like exposure and its effects in neuro-development in children. Reviewed studies were conducted in the highly contaminated area and area with no particular high exposure to dioxins or dioxin-like. This review resulted in the exposure through prenatal and perinatal, or breastfeeding was not clearly explaining the effects on neurodevelopment in children. A subtle difference of neuro-developmental defects may not be able to be assessed only by neuro-developmental assessment tools. This review suggested evaluating background level of dioxins and dioxin-like in the environment, dietary intake in mother, examining specific congeners and its effects to cognitive and motor development aspects, and consider other methods to examine mild changes in children neurodevelopment such as neuropsychological measurement.

Keywords: Dioxin; Dioxin-like; neurodevelopment; children

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1. Introduction

Poly-chlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are highly toxic compounds which listed as Persistent Organics Pollutants (POPs) (UNEP 2001) and have similar structures, characteristic of toxic responses, and mechanism (Poland and Knutson 1982). These are widely spread in the environment in recent decades as contaminants, persistent, accumulate in food chain mainly in adipose tissue of animals and human, and has an adverse health effect

in human (Ahlborget al. 1992;Skene 1989). Absorbed dioxins and dioxin-like can be transferred to human fetus and human infants via placenta and human milk respectively, due to the accumulation of dioxins in adipose tissue (Suzukiet al. 2005). Human fetuses and infants are more sensitive to toxicants from environmental exposure compared to adults (Needham and Sexton 2000; Patandinet al. 1999), and adverse effects were more severe in this population. Dioxins and dioxin-like exposure are associated with a poorer intellectual function in school-aged children and indicated deficits in general mental ability, short and long term memory, and focused and sustained attention (Jacobson and Jacobson 1996), and exposure through breastfeeding is associated with poorer cognitive ability (Patandinet al.1999).

Previous studies have resulted in different association from exposure and neurodevelopmental defects in children. Studies in human suggest dioxins and dioxin-like exposure were associated with lower motor skills (Gladen et al. 1988;Rogan and Gladen 1991;Lynch et al. 2012), lower cognitive skills (Laiet al. 1994), both motor and cognitive skills (Vreugdenhilet al. 2002;Nishijoet al. 2012), socio-emotional and behavioral skill (Pham et al. 2015), and attention performance (Neugebaueret al. 2015). Other studies suggested a negative association between dioxins and dioxin-like exposure with socioemotional and behavior (Konoet al. 2015), and motor and cognitive skills (Nakajima et al. 2006; Wilhelm et al. 2008; Hui et al. 2016). To elucidate varied results, a review study shall be conducted. This review is aimed to explain aspects which led to various results among reviewed studies by observing maternal characteristics which affect dioxins and dioxin-like concentration in blood and human milk, and dioxins and dioxin-like congeners which affect the neurodevelopment in children.

2. Materials and Methods

The review was conducted in adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 (Moher et al. 2009).

2.1. Search

The search was designed to identify peer-reviewed publications describing studies in human regarding dioxins and dioxin-like exposure effects in neurodevelopment in children. The studies which reviewed were quantitative studies, measuring dioxins and dioxin-like concentration in blood and human milk, and assessing neurodevelopment in children. The search terms used were ‘dioxins,’ ‘dioxin-like,’ ‘neurodevelopment,’ and ‘children.’ Publication restrictions are studies which published between the year 2006 to

present. Databases were searched for publications: ProQuest (2006 to offer), ScienceDirect (2006 to present), and Scopus (2006 to show), using Universitas Indonesia Remote Library facility. The last search date was 3 April 2016.

2.2. Data collection process and study selection

Data were independently collected and tabulated. Eligibility was decided separately by the author. Inclusion criteria were: published in the peer-reviewed journal; describing the study of dioxins and dioxin-like exposure to neurodevelopment in children; measuring dioxins and dioxin-like compounds in blood and human milk; involving pairs of mother and children in the study; published in English.

3. Results

A search of databases yielded 132 peers reviewed articles. Articles sorted by duplication of the title, title of the articles and appropriateness with the review topic, and review of abstracts and full texts. 2, 116, and eight items further discarded respectively. Six articles fulfilled the inclusion criteria and included in this review.

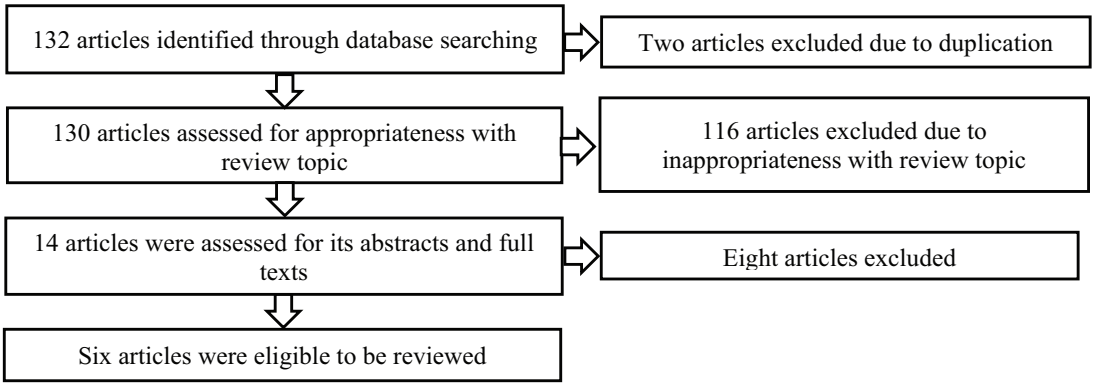

Figure 1: Data Collection Process.

3.1. General study characteristics

Studies in Vietnam (n=2) were conducted in the highly contaminated area with dioxins and dioxin-like compounds from Agent Orange from 1961 to 1971 (Nishijoet al.2012; Phamet al. 2015). A study in Germany (n=2) was conducted in areas which high exposure to heavy metals and dioxins (Neugebauer et al. 2015; Wilhelm et al. 2008). A study in Japan (n=2) were conducted in cities with no particular dioxins exposed area (Nakajimaet al. 2006;Kono et al. 2015). All studies used questionnaire related to exposure regarding

maternal age, parity, maternal dietary intake, working, and smoking during pregnancy. All studies used multiple regression analysis to explain the association between dioxin and dioxin-like exposure and neurodevelopment in children.

Table 1: Study Characteristics.

No.	Author	Country	Year Published	Sample size	Measured exposure	Reference
1	Nakajima, S. et al.	Japan	2006	Mother = 134 Children = 134	Biological samples of dioxins in blood during pregnancy, questionnaire	35
2	Wilhelm, M. et al.	Germany	2008	Mother = 232 Children = 232	Biological samples of dioxins in blood and human milk, a biological sample of PCBs in thyroid hormone in a child, questionnaire	45
3	Nishijo, M. et al.	Vietnam	2012	Mother = 219 Child = 219	Biological samples of dioxins in human milk, questionnaire	38
4	Pham, TT. et al.	Vietnam	2015	Mother = 214 Children = 214	Biological samples of dioxins in human milk, questionnaire	31
5	Kono, Y. et al.	Japan	2015	Mother = 175 Children = 175	Biological samples of dioxins in human milk, questionnaire	32
6	Neugebauer et al.	Germany	2015	Mother = 234 Children = 234	Categorized level of concentration from the previous study, questionnaire	55

3.2. The concentration of dioxins and dioxin-like compounds in mother

Exposure measure used the quantification of PCDDs, PCDFs, and PCBs in biological samples, from blood (n=1), human milk (n=3), blood and human milk (n=2). From table 2, a study in Germany (2008 and 2015) indicated that respondents had the highest dioxins concentration in human milk and blood respectively. Studies in Japan (2006 and 2015) showed the lowest concentration among reviewed studies.

3.3. Breast feeding duration

Most mothers in studies gave breastfeed up to 3 months. The most extended range was shown in research in Germany (2008), which ranged 1.45-12.65 months. Exclusive

Table 2: The concentration of Dioxins and Dioxin-like Compounds in Mother.

Author	Toxic Equivalent (TEQ) in pg/g							
	In blood				In human milk			
	PCDD	PCDF	PCB	Total	PCDD	PCDF	PCB	Total
Nakajima, S. et al.	7.7	4.2	6.9 *)	18.8	-	-	-	-
Wilhelm, M. et al.	13.06 **)		5.71**)	19.33 **)	11.03 **)		8.52 **)	19.69 **)
Nishijo, M. et al.	-	-	-	-	7.28	6.82	-	14.22
Pham, TT. et al.	-	-	-	-	5.5-12.9 ***)	1.7-4.8 ***)	4-10 *) ***)	12.1-26.9 ***)
Kono, Y. et al.					1.9-39.8	1.4-25.7	-	3.3-64.4
Neugebauer, etal.	-	13.55 ****)	6.32 ****)	-	43.80 ****)		33.12 ****)	-

*)coplanar **)median ***)range ****)geometric mean

breastfeeding cannot infer from all reviewed studies. However, a study in Vietnam (2015) showed all mothers in the study breastfeeded their infant up to 4 months.

Table 3: Maternal Characteristics.

Author	Age of Mother (years) (Mean±SD)	Breastfeeding Duration
Nakajima, S. et al.	31.1±4.7	≥3 months = 58.2%
Wilhelm, M. et al.	31.2±4.6	28.2 ±22.4 weeks (1.45 – 12.65 months) (Mean±SD)
Nishijo, M. et al.	20.9-36.8 **)	
Pham, TT. et al.	27.8±6	≥4 months = 100%
Kono, Y. et al.	Boys = 29.8±2.5	0–2 months = 0.73 ± 0.27 *) 3–5 months = 0.61 ± 0.41 *) 6–8 months = 0.52 ± 0.46 *) 9–11 months = 0.43 ± 0.46 *)
	Girls = 29.5±2.7	0–2 months = 0.81 ± 0.24 *) 3–5 months = 0.69 ± 0.39 *) 6–8 months = 0.59 ± 0.44 *) 9–11 months = 0.43 ± 0.45 *) (Mean±SD]
Neugebauer, et al.	NA	18.1 ± 11.2 weeks (Mean±SD)

*) Breastfeeding ratio: 1 when feeding only on breast milk, 0.75 when breastfeeding exceeded formula feeding, 0.5 when breastfeeding and formula feeding was equal, 0.25 when formula feeding exceeded breastfeeding and 0 when feeding only on feeding formula (Kono et al.2015)

**) Range

3.4. Neuro-developmental test results

Assessment tools used to assess neurodevelopment in children were Bayley Scale of Infant and Toddler Development (BSID), Neurological Optimality Score (NOS),Total Difficulties Score (TDS) of Strength and Difficulties Questionnaire (SDQ), computerized test battery for attentional performance for children (KITAP), Attention Deficit Hyperactivity Disorder (ADHD), and attention deficit hyperactivity disorder instrument (FBB ADHS). Three domains examined in reviewed studies were: motor, cognitive, and behavior. Reviewed studies resulted in a tendency in lower test results than usual standard from each neuro-developmental test (data not shown).

In the motor domain, a study in Japan (2006) resulted in PCDDs, and PCDFs concentration in blood and TEQ values were not significantly associated with PDI. However, specific congeners of dioxins and furans were significantly associated with lower PDI score in children, with p-value<0.05. A study in Germany (2008) resulted in motor scores were on the average level, although dioxins and dioxin-like concentration in mother were the highest among the reviewed studies. A study in Vietnam (2012) resulted in boys whose in the highly exposed group has significantly lower motor scores. High exposed groups PCDDs/Fs TEQ in mother was significantly associated with an excellent motor in boys with p-value < 0.05. A study in 1-year-old toddler in Vietnam (2015) showed no significant association between dioxins concentration and motor skills in the toddler. However, PCDDs/Fs-TEQ in mildly exposed children showed a significant association in the composite motor subtest.

In the cognitive domain, a study in Japan (2006) about PCDDs, and PCDFs concentration in blood showed that there was a negative association with MDI scores, and values were not significantly associated with MDI. However, total PCDDs, total PCDD/Fs, and 1,2,3,4,6,7,8-HpCDD were significantly associated with lower MDI score in children, with p-value 0.009, 0.014, and 0.017, respectively. A study in Germany (2008) resulted in mental scores were on the average level as well as neurological examination scores. An investigation in Vietnam (2012) led in highly exposed groups PCDDs/Fs TEQ in mother was significantly associated with language and cognitive in boys and cognitive in girls, with p-value < 0.05. The study also resulted boys were more susceptible than girls. A survey in 1-year-old toddler in Vietnam (2015) showed a significant association between daily dioxin intake (DDI) and cognitive skills in toddler in mild, moderate, and high exposed children. Result test scores showed a similar cognitive level among groups (score range between 101-104.6), hence no association of PCDDs/Fs-TEQ and TCDD exposure with cognitive test results.

In the behavior domain, a study in 1-year-old toddler in Vietnam (2015) showed a significant association between exposure and social-emotional skills in highly exposed children. However, a study in Japan (2015) showed no significant association of dioxin level in human milk with SDQ scores in children, and research in Germany (2015) showed that the ADHD traits test negatively associated with dioxin levels in biological samples from mothers.

4. Discussion

Elements which determine exposure were the frequency of exposure, dose, and duration of exposure (ATSDR 2005). In this context, maternal age determines the concentration of PCDDs/Fs and dioxin-like PCBs in blood and human milk (Nakamuraet al. 2008; Todakaet al. 2007), as explained in the previous study which resulted a significant correlation between age and dioxin and dioxin-like concentration in human milk (Ulaszewskaet al. 2011). This finding is similar with a survey in Germany (2008) which has the oldest age range and higher concentration in blood and human milk compared to other studies, and study in Vietnam (2012) which resulted in a significant association between age and frequency of PCDDs and PCDFs in mother. Also, parity is one of a significantly associated factor which determines dioxins and dioxin-like concentration in blood and human milk (Todakaet al. 2007;Nghiet al. 2015).

Dioxins and dioxin-like in human milk describe body burden in mother and indicated a prenatal exposure which may occur in infants (Taiet al.2016). The half-lives may contribute to dioxins and dioxin-like level in the human body, determined by age, a measure of body fat, smoking habits, breastfeeding status (Milbrathet al. 2009), and lipid excretion (Mitoma et al.2015), as an example is breastfeeding. Reviewed studies showed that there was no no association between breastfeeding duration and neurodevelopment, similar to study in Hongkong, stating that there was no association between breastfeeding and neurocognitive development in 11-year-old children (Hui et al.2016). In addition, background level and residency period in exposed areas also contributed exposure in mothers, as well as dietary intake in mother, due to the exposure pathway of dioxins and dioxin-like was through the food chain, particularly food source from plants/animals from high exposed areas (Malisch and Kotz2014;Pemberthyet al.2016)..

A study in Germany (2008 and 2015) was similar to a Dutch study in 1996 which resulted from no significant association between lower PDI scores and PCB/dioxin exposure in children (Koopman-Esseboom 1996; Taiet al. 2013). However, a significant association between exposure from dioxins and dioxin-like congeners and neurodevelopment in children found in the reviewed study in Japan (2006) and Vietnam (2012), similar to

study in Vietnam (Nishijo et al. 2014, Tranet al. 2016). Dioxin-like PCBs was also observed and has no association in lower motor skills scores, but even the slightest exposure of dioxins and furans might indicate a mild changes motor skills. Although the findings not significantly associated with exposure, in highly exposed children, the results tend to be lower than standard and in other locations. This finding indicates that dioxins and dioxin-like exposure are contributed to lower performance in socioemotional and behavioral aspects in children. Reviewed studies resulted in specific congeners also have a different impact than the TEQ and total dioxins and dioxin-like compounds. Difficulties to find out the mechanism of exposure of dioxins and dioxin-like congeners and its implications to neurodevelopment is due to the potential interaction between dioxins and dioxin-like congeners which resulted in variation in neuro-developmental changes and due to the most applicable and valid method which is only by analyzing it statistically. It indicates subtle differences in neurodevelopment which are unable to be detected only by neuro-developmental assessment tools.

5. Conclusions

Reviewed studies resulted in a different association between dioxin and dioxin-like exposure from mother to children with neurodevelopment in children. Low exposure from mother to children which cause mild differences in neurodevelopment in children may be unable to be assessed only by neurodevelopment assessment tools. The evaluating background level in the environment, dietary intake in mother, examining specific congeners and its effects on cognitive and motor development aspects, and neuropsychological measurement shall be considered for future study.

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