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# Maternal dietary exposure to dioxins and polychlorinated biphenyls (PCBs) is associated with language delay in 3 year old Norwegian children

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ABSTRACT

*Background:* Prenatal exposure to dioxins and PCBs is potentially harmful to the developing fetus and may increase the risk of delayed or impaired neurodevelopment. Several studies have reported negative associations between prenatal exposure to these compounds and aspects of cognition related to language in early childhood.
*Objectives:* The aim was to examine the association between maternal low level dietary exposure to dioxins and PCB during pregnancy and language development in 3 year old children in a large group of mother-child pairs participating in the Norwegian Mother and Child Cohort Study (MoBa).
*Methods:* This study includes 44,092 children of women who were recruited to the Norwegian Mother and Child Cohort Study (MoBa) during the years 2002–2009. Maternal dietary exposure to dioxins and PCBs was estimated based on a validated food frequency questionnaire (FFQ) answered mid-pregnancy and a database of dioxin and PCB concentrations in Norwegian foods. Exposure to dioxins and dioxin-like PCBs (dl-compounds) was expressed in total toxic equivalents (TEQ), and PCB-153 was used as marker for non-dioxin-like PCBs (ndl—PCBs). Children's language skills at age 3 were assessed by parental report including a Dale and Bishop grammar rating and questions about communication skills from the Ages and Stages Questionnaire (ASQ). Logistic regression models adjusted for confounders were used to examine the association between maternal dietary exposure to dl-compounds or PCB-153 and language development in children.
*Results:* The maternal dietary exposure to dl-compounds and PCB-153 was generally low, and 98% of women had intakes of dl-compounds ≤14 pg TEQ/kg bw/week, which is the tolerable weekly intake set by EU's Scientific Committee for Food (SCF). High maternal exposure (>14 pg TEQ/kg bw/week of dl-compounds (median 2.6 pg/kg bw/day, range 2–16) or >97.5-percentile intake of PCB-153 (median 11 ng/kg bw/day, range 5–28) was associated with higher odds of incomplete grammar (in boys and girls, adjusted ORs 1.1 to 1.3) and severe language delay in girls, adjusted ORs 2.8 [95% CI 1.1, 7.1] for PCB-153 and 2.9 [95% CI 1.4, 5.9] for dl-compounds. Furthermore, high exposure to dl-compounds was associated with moderate language delay 1.4 [95% CI 1.0, 2.0] and lower communication score (ASQ), adjusted OR 1.4 [95% CI 1.1, 1.9] in girls.
*Conclusions:* The main findings of this study were: 1) Girls born to mothers who exceeded the tolerable weekly intake for dl-compounds or had a PCB-153 intake above the 97.5 percentile in early pregnancy may have increased risk of language delay at age 3 years. 2) Negative associations with maternal exposure to dl-compounds or PCB-153 were observed for both boys and girls having incomplete grammar, which is a subtle reduction in language skills. This interesting finding should not be considered as deviant at this age.



## 1. Introduction

Early-life exposure to polychlorinated dibenzo-p-dioxins/dibenzofurans (PCDDs/PCDFs, dioxins) and polychlorinated biphenyls (PCBs) may affect brain development, potentially resulting in impaired cognitive functions during childhood and adult life (Boucher et al., 2014; Dzwilewski and Schantz, 2015; Jacobson and Jacobson, 1996). Dioxins and PCBs are persistent lipophilic substances which accumulate in fat tissue and readily cross the placenta. The fetal exposure to these compounds is determined by the accumulated maternal body burden, which because of the long half-lives of these compounds depends on her long-term exposure from the diet. Food of aquatic origin is considered to be an especially important source of exposure to dioxins and PCBs (EFSA, 2012; Liem et al., 2000).

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Although the environmental levels of PCBs have been declining after restriction and ban in the US and Europe during the 1970's and 1980's, the dietary exposure may still exceed the tolerable weekly intake for dioxins and dl-PCBs in subgroups of the European population (EFSA, 2012). In the majority of Norwegian pregnant women participating in The Norwegian Mother and Child Cohort Study (MoBa), the exposure to these compounds from oily fish is low (Caspersen et al., 2013). However, consumers of special food items such as seagull eggs and fish liver often had intakes exceeding the tolerable weekly intake (TWI) for dioxins and dioxin-like PCBs (dl-compounds) of 14 pg toxic equivalents (TEQ)/kg bw (Scientific Committee on Food, 2001). For ndl—PCBs, no tolerable weekly intake has been established (EFSA, 2005). Seagull egg consumers in MoBa have a 9-fold higher estimated median intake of PCB-153 (indicator of ndl—PCBs) than non-consumers.

Language is considered an indicator of the child's cognitive development, and delayed language development may, for some children, be the first early sign of one or more neurodevelopmental disorders (Clegg et al., 2005; Miniscalco et al., 2006). It is well recognized that the perinatal period is a critical time window when chemical exposures could impact cognitive development, however, it is still unclear which impact such exposures during this vulnerable time period have on language development and long-lasting effects on cognitive functions (Dzwilewski and Schantz, 2015).

Perinatal exposure to PCBs and cognition and language development has been studied in several prospective birth cohort studies where the exposure has been assessed by blood and/or breastmilk sampling and not by dietary intake. This includes studies from the Netherlands (Patandin et al., 1999), Dusseldorf, Germany (Walkowiak et al., 2001), Duisburg, Germany (Wilhelm et al., 2008), Faroe Islands (Grandjean et al., 2001), Michigan, US (Jacobson et al., 1990), North Carolina, US (Gladen and Rogan, 1991), Oswego, US (Stewart et al., 2003) and Quebec, Canada (Boucher et al., 2014), see e.g. Dzwilewski and Schantz, 2015 for overview. In studies where PCB exposure were studied in relation with language abilities directly, negative associations were found at 3.5 years (Patandin et al., 1999) and at 11 years (Jacobson and Jacobson, 1996), while no effects were found on expressive language assessed at 7 years in the Faroe Islands cohort (Grandjean et al., 2001). In terms of cognitive function assessments, the evidence for a negative effect of PCB exposure is more consistent in early and late childhood than in infancy, but the picture is not entirely clear (Dzwilewski and Schantz, 2015).

Maternal serum concentrations of PCB-153 (either measured in serum or estimated from breast milk) in these cohorts (Netherlands, Dusseldorf, Duisburg, Faroe Islands, Michigan, North Carolina, Oswego, Quebec) ranged from (median) 40 ng/g lipid (Oswego) to 450 ng/g lipid (Faroe Islands) (Dzwilewski and Schantz, 2015; Longnecker et al., 2003). In a subsample ($n = 96$) of women participating in MoBa, the median plasma concentration of PCB-153 was 38 ng/g lipid (range 13–133) (Caspersen et al., 2016). Thus, the level of exposure in MoBa is in the lower range of what has been studied previously in relation to language and cognition in children. Language development in children has to our knowledge not yet been studied in relation to maternal dietary exposure to dioxins and PCBs in a large pregnancy cohort such as the Norwegian Mother and Child Cohort Study.

The aim of this study was to examine the association between low-level maternal dietary exposure to dl-compounds (TEQ) and PCB-153 and language development measured as sentence and grammar complexity and communication skills in 3 year old children in a large pregnancy cohort in Norway.

## 2. Methods

### 2.1. Study participants

This study is part of the Norwegian Mother and Child Cohort Study (MoBa), a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus et al., 2006). Participants were recruited from hospitals and maternity units all over Norway from 1999 to 2008, and 40.6% of invited women consented to participate. Women giving their consent received three questionnaires during pregnancy: in gestational week 17, week 22, and week 30. They later received questionnaires after delivery, when child's age was 6 months, 18 months, and 3 years (questionnaires are available at http://www.fhi.no/moba), and the study is still ongoing. The cohort now embraces 114,500 children, 95,200 mothers and 75,200 fathers. The study also includes information from the Medical Birth Registry of Norway (MBRN), which comprises data on all births in Norway (Irgens, 2000). The study is approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway.

A total of 51,847 mother-child pairs (with singleton births) had been registered in MBRN, had completed questionnaires at gestational weeks 17 and 22 and when the child was aged 3, and were thus eligible for the study. We excluded participants if the pregnancy had a length < 37 and >42 gestational weeks (n = 2743), missing birth weight (n = 21), with no recorded maternal height and weight prior to pregnancy for BMI calculation (n = 1073), or estimated maternal daily energy intake <4.5 or >20 MJ (n = 586). We also excluded participants with missing data on the grammar rating at 3 years (n = 674). Moreover, children who were younger than 36 months and older than 40 months at the time when language skills were reported (n = 874) or with missing information on the age (n = 1784) were not included in the analysis. In total, n = 44.092 mother-child pairs were included in the study (85% of those eligible).

### 2.2. Estimating maternal dietary exposure to dioxins and PCBs

The maternal dietary exposure to dioxins and PCBs in MoBa and has been described previously (Caspersen et al., 2013) and evaluated against plasma concentrations in pregnant women and children (unpublished). In brief, the dietary exposure was estimated by combining information on food consumption with a database of concentrations of dioxins and PCBs in Norwegian foods (Kvalem et al., 2009). Food consumption in MoBa was assessed by a validated semi-quantitative food frequency questionnaire (FFQ) answered in gestational week 22 (Brantsaeter et al., 2008). Women reported their habitual food consumption since they became pregnant or, for seasonal foods, during the last year. For each participant, the dietary intakes of 17 2,3,7,8-substituted PCDD/PCDFs, 12 dl-PCBs (of which the non-ortho substituted PCBs (no-PCBs) PCB-77, 81, 126, 169, and the mono-ortho substituted PCBs PCB-105, 114, 118, 123, 156, 157, 167, 189) as well as 6 ndl—PCBs were calculated in lower bound (non-detected congeners set to be zero). The dietary exposure was evaluated relative to pre-pregnancy body weight as reported by participants in gestational week 17. The intake of dl-compounds (dioxins and dl-PCBs) was calculated in toxic equivalents (TEQ) using toxic equivalence factors established by the World Health Organization in 2005 (TEF2005) (Van den Berg et al., 2006). PCB-153 was considered an indicator of ndl—PCBs.

### 2.3. Measures of language and communication skills

The child's grammar complexity at 3 years was measured with a grammar rating (Dale et al., 2003) where the parent was asked to choose one of the following categories that best described their child's sentences: Not yet talking (severe language delay, SLD); one-word utterances (also grouped as severe language delay, SLD); talking, but unintelligible (speech problems, SP); short sentences of 2–3 words (moderate language delay, MLD); fairly long sentences (incomplete grammar, IG) and; long and complicated sentences (complete grammar). The groups 'severe language delay', 'moderate language delay, 'incomplete-" and "complete grammar' describe length of sentence/grammar complexity, while the 'speech problems' group is more related to speech development, where the child is talking, but with poor pronunciation. Further, six questions (Table 1) from the