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Systematic analysis of the relationship between standardized prenatal exposure to polychlorinated biphenyls and mental and motor development during follow-up of nine children cohorts

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ABSTRACT

Impact of prenatal exposure to polychlorinated biphenyls (PCBs) on mental and motor development has been investigated in various children cohorts, but findings show temporal inconsistencies. Because a direct comparison of results obtained from different cohorts remains difficult, temporal relationship between biological PCB concentrations and long-term developmental effects is still not clearly established. The objective of this research was to use a procedure previously developed to standardize PCB biological concentration data across cohorts in order to perform a systematic analysis of temporal associations between prenatal PCB exposure and mental and motor development from neonatal period (or a young age) until school age. Prenatal exposure data from nine cohorts were standardized in terms of total PCBs per kg of lipids in maternal plasma. Systematic analysis of the "standardized biological concentration–development" relationship during follow-up of each cohort was then conducted through the application of Hill criteria. This led to retain six of the studied cohorts in the final analysis. A biological level of prenatal PCB exposure below which risk of mental or motor development should be negligible was established in the order of 1000 μg/kg of lipids in maternal plasma.

1. Introduction

Polychlorinated biphenyls (PCBs) are well known persistent halogenated aromatic hydrocarbons extensively produced in the early 1930s as dielectric and coolant fluids for many industrial applications due to their low inflammability, chemical stability and miscibility (ATSDR, 2000; Erickson, 2001). They are ubiquitously present in ecosystems and bioaccumulate in the food chain (ATSDR, 2000; Carrier et al., 2006). Owing their slow biotransformation and high lipophilicity, they concentrate in lipidic components of the body (adipose tissues, blood lipids and maternal milk) (Carrier et al., 2006; Grandjean et al., 2008; James, 2001).

Following two accidental poisonings related to food contamination by PCBs, in Japan in 1968 (Yusho) and Taiwan in 1979 (Yucheng), their production and use were progressively banished in most industrialized countries in the late 1970s and subsequent decade. Children born to mothers who ingested contaminated rice oil (prior to or during pregnancy) presented growth retardation, cognitive and behavioral impairments (Guo et al., 2004). Despite the probable contribution of the much more potent toxicants polychlorinated dibenzofurans (PCDFs) to both Yusho and Yucheng poisonings (Buser and Rappe, 1979), various cohorts were formed around the world to study effects of pre- and postnatal exposure to PCBs on mental and motor development of children. Nonetheless, direct comparisons of reported results across cohorts have yet allowed establishing a clear causal relationship between prenatal PCB exposure and impairment of child development (Boucher et al., 2009; Faroon et al., 2001; Korrick and Sagiv, 2008; Schantz et al., 2003). This may be explained in part by the fact that PCB exposure was not uniformly expressed between studies (e.g., different biological matrices sampled or different units to express biological results). In some cohorts, a negative association between biological PCB concentrations and developmental aptitudes during neonatal period or childhood was reported (Gladen et al., 1988; Jacobson and Jacobson, 1996, 2003; Koopman-Esseboom et al., 1996; Sagiv et al., 2008, 2010; Stewart et al., 2000, 2005; Vreugdenhil et al., 2004a; Walkowiak et al., 2001). In other cohorts, follow-up of children failed to demonstrate any significant association (Coccini et al., 2009; Daniels et al., 2003; Gladen and Rogan, 1991; Grandjean et al., 2001a; Gray et al., 2005; Longnecker et al., 2005; Steuerwald et al., 2000).

Following a request made by Health Canada, we conducted a systematic analysis of the epidemiological literature to establish health risks related to PCB exposure in the Canadian population, including effects on mental and motor development (Carrier et al.,

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2006). Using toxicokinetic considerations and a standardization procedure of biological concentration data across studies, a direct comparison between published studies was performed for a given neuropsychological test or cognitive function. Boucher et al. (2009) employed a somewhat similar review to determine whether a distinctive cognitive profile associated with prenatal PCB exposure, based on data of Longnecker et al. (2003) for comparison of exposure levels between reviewed studies. The latter approach was however not applicable to all published epidemiological data. Recently, El Majidi et al. (2012) performed a systematic analysis of 20 published epidemiological studies on the concentration–response relationship between PCB exposure and birth weight, based on a more generally applicable standardization of PCB biological data across studies and application of causality criteria. The overall objective of the current work was to use such standardization procedure to perform a systematic analysis of associations between prenatal PCB exposure and mental and motor development during follow-up of children cohorts from neonatal period or a young age until school age.

2. Methodology

The steps followed for this systematic analysis were: (i) the identification of relevant epidemiological studies investigating effects of prenatal PCB exposure in cohorts on mental or motor development between neonatal period and school age; (ii) standardization of the various biological indicators of prenatal PCB exposure measured in the various cohorts; (iii) verification of a possible causal relationship between prenatal PCB exposure and development based on criteria recognized for this purpose; (iv) establishment of the "standardized biological concentration–response" relationship for an impaired development observed consistently throughout the follow-up of cohorts; (v) determination of a standardized biological concentration of PCBs below which the risk of adverse effect on development between neonatal period and school age would be negligible.

2.1. Identification of epidemiological studies published on the topic

A complete bibliographical review was conducted on studies published until 2012 on effects of prenatal PCB exposure on child development. Databases such as Medline, PubMed, Toxline, Poltox and Current Contents were consulted. Our search strategy was limited to English and French articles. Published studies were included in this research if: (i) they have been published in peer review journals; (ii) they have been conducted in prospective cohorts; (iii) they have analyzed the relationship between prenatal PCB concentrations (e.g., total PCBs, specific congeners or groups of congeners) in any biological matrix and mental or motor development from neonatal period until school age. As in El Majidi et al. (2012), published studies were excluded if: (i) they have focused on Yucho (Japan) or Yucheng (Taiwan) cohorts, as the toxic effects seen in these populations have been mainly attributed to PCDFs (Buser and Rappe, 1979); (ii) exposure conditions differed from those of the general population or populations whose source of PCB exposure is consumption of contaminated fish. In addition, since this work focussed on follow-up of cohorts, cohorts were excluded if developmental effects were assessed only at a certain age period (*i.e.*, at birth or at school age only).

2.2. Standardization of bioindicators of PCB body burden across studies

Biological PCB concentrations reported in the various studies were converted to total PCB equivalent in maternal plasma per kilogram of lipids, and the term "PCB_{MPEQ}" was used to refer to standardized concentrations (μg PCB_{MPEQ}/kg lipids). The full description of the method employed is described in El Majidi et al. (2012). Briefly, for conversion of given PCB congener concentrations to total PCB values in a reviewed study, mean concentration ratios of given PCB congeners to total of the 40 PCB congeners measured in breast milk of Canadian women by Newsome et al. (1995) were used as a reference. For example, when concentration of congeners 118, 138, 153 and 180 was reported, a multiplier of 2.3 was applied as proportion of these four congeners accounted for 43.5% of total PCB concentration in the study of Newsome et al. (1995). Wet-weight concentrations in plasma were converted to lipid-adjusted concentrations using conversion factors presented in Table 1. Lipid-adjusted concentrations in breast milk or umbilical cord plasma were converted to maternal plasma equivalents using a mean conversion factor of 0.75 and 1.63, respectively, on the basis of published epidemiological data (Butler Walker et al., 2003; Dallaire et al., 2002, 2003; Hamel et al., 2003; Longnecker et al., 2003; Muckle et al., 2001). When distribution of PCB exposure was not provided, arithmetic mean ± (2 × standard error) was used to estimate 95% confidence interval.

2.3. Systematic analysis of indexed epidemiological studies

A systematic analysis of the indexed epidemiological studies was then performed to investigate whether an effect on mental or motor development observed in a cohort at birth or at young age persisted at later age. Firstly, a descriptive analysis of each study was achieved by compiling study objective, study population, exposure metrics, developmental outcome measured, statistical analyses and findings. Based on neuropsychological tests commonly used to assess mental and motor abilities of children in the epidemiological literature, and according to the classification of these tests by Strauss et al. (2006), five mental aptitudes were studied in this work: attention, memory, IQ, language and executive function. The processes: (i) that reach beyond encoding information (attention), (ii) by which the individual encodes, stores and retrieves information (memory), or (iii) that are guiding and managing cognitive and behavioral functions, in particular when confronted with a novel problem solving (executive function) were evaluated. The interest of IQ tests is that they are useful in evaluating some achievements especially school achievement. Verbal performance was also included in this work because it is central

Table 1
Conversion of volume-weighted PCB concentrations in plasma or blood into plasma lipid-adjusted concentrations.

Target groups	Reported concentration expressed in	Mean conversion factor to express PCB concentration in μg/kg of plasma lipids
Men and non-pregnant women[a]	μg/L plasma	136.05
	μg/L whole blood[d]	222.63
Pregnant women[b]	μg/L plasma	107.53
	μg/L whole blood[d]	175.95
Newborns (umbilical cord)[c]	μg/L plasma	357.14
	μg/L whole blood[d]	584.42

Note: To express the concentration in μg/kg plasma lipids, the reported concentration expressed in μg/L simply needs to be multiplied by the conversion factor.

[a] Assuming that concentration of total lipids in plasma is of 7.35 g/L (ICRP, 1994).

[b] Assuming that concentration of total lipids in pregnant women plasma is of 9.3 g/L (Butler Walker et al., 2003).

[c] Assuming that concentration of total lipids in umbilical cord plasma is 2.8 g/L (Butler Walker et al., 2003).

[d] Assuming that 90% of PCB molecules in blood are found in plasma lipids (Wolff, 1985) and that hematocrit is of 45% (McGeown, 2003).