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A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure

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HIGHLIGHTS

- This review studied the effects of OP pesticide exposure on child neurodevelopment.
- Prenatal exposure was associated with negative effects on child mental development.
- Evidence on postnatal exposure effects on child neurodevelopment is less consistent.
- The high variability of methodologies across studies made comparisons difficult.
- Standardised methodologies are needed to perform quantitative meta-analysis.

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ABSTRACT

Agricultural and residential use of organophosphate (OP) pesticides has increased in recent decades after banning some persistent pesticides. Although there is evidence of the effects of OPs on neurodevelopment and behaviour in adults, limited information is available about their effects in children, who might be more vulnerable to neurotoxic compounds. This paper was aimed at analysing the scientific evidence published to date on potential neurodevelopmental and behavioural effects of prenatal and postnatal exposure to OPs. A systematic review was undertaken to identify original articles published up to December 2012 evaluating prenatal or postnatal exposure to OPs in children and effects on neurodevelopment and/or behaviour. Articles were critically compared, focusing on the methodology used to assess exposure and adverse effects, as well as potential contributing factors that may modify both exposure and outcomes, such as genetic susceptibility to certain enzymes involved in OPs metabolisation (e.g. paraoxonase-1) and gender differences. Twenty articles met the inclusion criteria, 7 of which evaluated prenatal exposure to OPs, 8 postnatal exposure and 5 both pre- and postnatal exposure. Most of the studies evaluating prenatal exposure observed a negative effect on mental development and an increase in attention problems in preschool and school children. The evidence on postnatal exposure is less consistent, although 2 studies found an increase in reaction time in schoolchildren. Some paraoxonase-1 polymorphisms could enhance the association between OPs exposure and mental and psychomotor development. A large variability in epidemiological designs and methodologies used for assessing exposure and outcome was observed across the different studies, which made comparisons difficult. Prenatal and to a lesser extent postnatal exposure to OPs may contribute to neurodevelopmental and behavioural deficits in preschool and school children. Standardised methodologies are needed to allow results to be better compared and to perform a quantitative meta-analysis before drawing any final conclusions.

1. Introduction

Earlier restrictions on the use of some persistent pesticides have led to the use of non-persistent alternatives such as organophosphates (OPs), carbamates and pyrethroids, which are very useful for controlling pests in both agricultural and residential settings.

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Intensive use of these compounds is posing a significant risk to public health because of their potential adverse effects. Exposure to pesticides does not only affect those who use them occupationally, as the general population is also exposed to low concentrations through foodstuffs and the environment throughout their lifetime. There is scientific evidence of the carcinogenic, neurological, reproductive, immunological and genotoxic effects associated with exposure to non-persistent pesticides in adults (Koureas et al., 2012). However, little information is available about the effects in children, although researchers have observed a higher risk of adverse reproductive effects (Eskenazi et al., 2004; Lacasaña et al., 2006; Rauch et al., 2012) and changes in the nervous system and in neurobehavioural development (Bouchard et al., 2010; Engel et al., 2011; Eskenazi et al., 2007; Marks et al., 2010; Rauh et al., 2012). This means that the neurotoxic effects of these compounds on children's central nervous systems could be causing a series of subclinical neurodevelopmental disorders. This has been termed a 'silent pandemic' and could have major health, economic and social impact (Grandjean and Landrigan, 2006).

Toxicological studies in animals have provided information about the neurotoxicity mechanisms and adverse effects of non-persistent pesticides. For example, Maurissen (2000) and Rice and Barone (2000) observed changes in the nervous system development and sensory, motor and cognitive cerebral function of rodents associated with prenatal and early postnatal exposure to chlorpyrifos. Prenatal exposure even to low concentrations of chlorpyrifos also affects rodents' organogenesis (Tian et al., 2005) and leads to behavioural changes such as hyperactivity and working and reference memory deficit.

Factors such as age, sex, nutritional status, lifestyle and genetic variability can modify the effects of non-persistent pesticides in children, who are particularly susceptible to these compounds. The health risks derived from exposure to toxic agents are strongly influenced by genetics as a result of the variability of the genes that code for metabolising enzymes (Costa et al., 2003; Eaton et al., 1998; Furlong, 2007). The different possible combinations of these polymorphisms can determine favourable or unfavourable metabolic configurations, either facilitating the breakdown of some neurotoxic compounds, or bioactivating initially inactive compounds or delaying the metabolic breakdown of active compounds (Costa et al., 2005a,b; Guo et al., 2012). Recent studies have analysed the effect of different paraoxonase-1 (PON1) polymorphisms on neurodevelopment in children. Certain genotypes ($PON1_{-108TT}$, $PON1_{192QR}$ and $PON1_{192RR}$) may be associated with reduced mental and motor development in children exposed to OP pesticides (Engel et al., 2011; Eskenazi et al., 2010).

The limited number of epidemiological studies available and the huge variability of the methodologies used to assess exposure to OP pesticides and its effects on neurodevelopment in children make it difficult to compare their results. The aim of this review is to carry out a detailed analysis of the evidence gathered in the studies performed to date, taking into account some of the factors that can modify the effects of these pesticides, such as sex and gender differences, genetic variability and epigenetic factors. This will provide a better overview of the relationship between exposure to OP pesticides and neurodevelopment and behaviour in children.

2. Material and methods

2.1. Search strategy

A systematic review of articles in the PubMed, Scopus, Embase and Lilacs databases was carried out using the following key words or text word combinations: "organophosphates" OR "organophosphorus", "child" OR "infant", "neurodevelopment", "neurobehavioral" OR "neurobehavioural" (for more details see Supplemental Material, annex I).

2.2. Inclusion and exclusion criteria

The articles selected for the review met the following inclusion criteria: (a) original articles; (b) published before or during December 2012; (c) written in Spanish, English, French or Portuguese; (d) carried out in children and adolescents up to 16 years of age; (e) evaluating prenatal and/or postnatal exposure to OP pesticides; (f) using general intelligence tests or specific tests to assess changes in mental and motor development or behaviour in children.

Case series studies were not included and literature reviews were only used to identify other original articles which had not been found using the search syntax used.

2.3. Data analysis

Studies that met the inclusion criteria were sorted into categories based on exposure type (prenatal or postnatal) and compared using the following criteria: (a) study design; (b) sample size; (c) age of participants; (d) exposure assessment; (e) levels of exposure to compounds; (f) neurodevelopment tests used; (g) effects observed; (h) adjustment variables. Table 1 provides a summary of the neuropsychological tests used in the studies included in this review, categorised based on age range and the areas (mental, motor and behavioural development) and/or specific functions evaluated.

The level of exposure to OP pesticides is usually measured by determining the total dialkylphosphate (DAPs) levels in the urine. DAPs usually include the following 6 metabolites: dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP) and diethyldithiophosphate (DEDTP). In these studies, the results are expressed in nanomoles per litre (nmol/L) once all the figures expressed in μg/L have been converted.

2.3.1. Assessment of methodological quality of the articles

The methodological quality of the studies included in the review was assessed using the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) - Statement' checklist (von Elm et al., 2008). This tool was designed to evaluate the clarity of the results of observational studies, but it has been used in other systematic reviews for the same purposes because no other tools are available (Olmos et al., 2008; Ricci-Cabello et al., 2010; Rodríguez-Barranco et al., 2013).

The checklist is made up of 22 items in 6 sections (title, introduction, methods, results, discussion and other information). Each item specifies the aspects that should be included in the study and can be used to assess its quality. For this review, the 9 items included in the methods section were used to give a score for the methodological quality of each study. The studies were categorized as low quality (0–3 of the 9 items), moderate quality (4–6 items) and high quality (7–9 items) (see Supplementary Material; annex II). The methodological quality scores are summarised in Tables 2 and 3.

3. Results

134 articles were identified using the search strategy described above. Twenty of those met the inclusion criteria, 7 of which analysed prenatal exposure to OP pesticides, 8 analysed postnatal exposure, and 5 analysed both pre- and postnatal exposure. Cohort studies were the most frequent design ($n = 10$), followed by cross-sectional ($n = 9$) and case-control ($n = 1$) studies. The methodological quality of studies on prenatal exposure was high ($n = 9$) or