Pesticides and child neurodevelopment

Lisa G. Rosas and Brenda Eskenazi

University of California at Berkeley, School of Public Health, Center for Children's Environmental Health Research, Berkeley, California, USA

Correspondence to Brenda Eskenazi, 2150 Shattuck Avenue, Suite 600, Berkeley, CA 94704, USA
Tel: +1 (510) 642 3496; fax: +1 (510) 642 9083; e-mail: eskenazi@berkeley.edu

Current Opinion in Pediatrics 2008, 20:191–197

Purpose of review

This review summarizes the recent research on pesticide exposure and child neurobehavioral development with a focus on in-utero exposure to organochlorine and organophosphate pesticides.

Recent findings

Recent studies on in-utero exposure to the organochlorine pesticide dichlorodiphenyltrichloroethane and its breakdown product, dichlorodiphenyldichloroethene, indicate that exposure is associated with poorer infant (6 months and older) and child neurodevelopment. Yet, the studies differ on the domain of development that is affected. Research on organophosphate pesticide exposure and neurodevelopment is limited but suggests some negative association of exposure and neurodevelopment at certain ages. Two reports agree that increased levels of organophosphate exposure *in utero* result in greater numbers of abnormal reflexes in neonates and studies in older infants and young children also point to a negative association with development. In young children (2–3 years) two separate studies observed an increase in maternally reported pervasive developmental disorder with increased levels of organophosphate exposure.

Summary

Given that the literature suggests a link between organochlorine and in-utero pesticide exposure and impaired child neurodevelopment, clinicians should educate parents about prevention of exposure, especially in populations living in agricultural areas or where household use is common.

Keywords

child, neurodevelopment, organochlorine, organophosphate

Curr Opin Pediatr 20:191–197
© 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins
1040-8703

Introduction

Pesticides are substances used to kill, repel or mitigate any pest. Worldwide, over 2.27 billion kg of pesticides are applied each year [1]. Herbicides, insecticides and fungicides are the most common types of conventional pesticide [1]. In the USA, just over three-quarters of conventional pesticide use is dedicated to agriculture, while the remainder is used in residential, commercial, governmental or industrial settings.

Paul Müller's 1939 discovery of dichlorodiphenyltrichloroethane (DDT), an inexpensive and effective insecticide, contributed to a marked increase in pesticide use in the 20th century. DDT, an organochlorine pesticide, is highly lipophilic, persists in the environment and bioaccumulates in animals and humans. In 1962, Rachel Carson in her book, *Silent Spring*, targeted DDT along with other pesticides for their environmental impacts and potential effect on human health. In 2001, over 90 countries signed the Stockholm Convention on Persistent Organic Pollutants (POPs) pledging to eliminate the use of 12 such persistent organic pollutants, including DDT, due to concerns for the environment and human health. The Convention made an exception for use of DDT in disease vector control (primarily for malaria-carrying mosquitoes), allowing it, while requiring signatory countries to strictly regulate public health usage and to implement alternative methods for reducing disease incidence.

Insecticides such as organophosphates, pyrethroids, and carbamates have become attractive alternatives to organochlorine pesticides because they do not persist in the environment. Organophosphate pesticides are currently the most heavily used insecticide in US agriculture whereas pyrethroids are the most common class of pesticide used in homes.

In this paper, we summarize the current literature regarding neurodevelopmental effects from exposure of children to pesticides. We focus on organochlorine and organophosphate pesticides as little is known about the neurodevelopmental effects of other classes of pesticides.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

For organochlorines, we concentrate on DDT and its breakdown product, dichlorodiphenyldichloroethene (DDE), although there is limited research on other organochlorines such as hexachlorobenzene. Some of the recent research is based on findings from our study known as CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas), which is the keystone project of the University of California at Berkeley Center for Children's Environmental Health Research.

Mechanisms for the effect of pesticides on the nervous system

The organochlorine pesticide DDT is known to cause excitation of the central nervous system and can lead to tremors, hyperexcitability and convulsions. DDT's effect on the central nervous system is likely through interrupting the movement of ions through the neuronal membranes, which leads to the inappropriate release of neurotransmitters [2].

Organophosphate pesticides act through inhibition of acetylcholinesterase in synaptic clefts, thereby deregulating the metabolism of acetylcholine. Acetylcholine is a neurotransmitter critical to skeletal-muscle motor neurons, peripheral parasympathetic and sympathetic neurons, and multiple fibers in the central nervous system including those which help regulate memory acquisition. Inhibition of acetylcholinesterase by organophosphate pesticides causes accumulation of acetylcholine at the neuronal junctions and results in continued stimulation and then suppression of neurotransmission [3,4]. Some organophosphate pesticides also affect the nervous system by inhibiting neuropathy target esterase, which can result in a rare condition known as organophosphate-induced delayed neuropathy [5].

Exposure of pregnant women and children to pesticides

Biological monitoring in the USA indicates widespread exposure to organochlorine and organophosphate pesticides in the general population with higher levels of some pesticides in certain subpopulations [6].

Organochlorines

DDT, although not used in the USA for over 30 years, was still detected in 15% of serum collected from women aged 18–40 in the Third National Health and Nutrition Survey (NHANES-III) in its *p*,*p*'-DDT form [6]. Serum half-life estimates range from 2 to 15 years. Levels of DDT are higher among Mexican-American women in the USA, with 46% having detectable levels [6] due to Mexico's use of DDT until 2000. DDE was detected in blood samples from almost 100% of women in NHANES-III [6]. Serum DDE levels were significantly higher in the CHAMACOS cohort of Latina pregnant women from the agricultural Salinas Valley, California (median = 1052 ng/g of lipid), compared with US women in general and Mexican-American women (133 ng/g of lipid in NHANES women aged 18–40 and 541 ng/g of lipid in NHANES Mexican-American women) [7]. About half of the CHAMACOS women from the Salinas Valley had been in the USA for 5 years or less and the majority of these women had previously lived in Mexico [7]. Breast milk is a likely source of organochlorine pesticide exposure for young infants. In a study of mother–infant pairs in Spain, children who were breastfed had higher serum concentrations of DDE and hexachlorobenzene at 12 months than children who had been breastfed for a shorter amount of time or formula-fed [8,9].

Organophosphates

Although erythrocyte cholinesterase measurement is useful in the diagnosis of high levels of organophosphate pesticide exposure and acute toxicity, it is not a useful biomarker for chronic low-level exposures. Exposure to organophosphate pesticides is therefore assessed by measuring the parent compound in blood or specific (e.g. 3,5,6-trichloropyridinol for chlorpyrifos, a common organophosphate pesticide) and nonspecific metabolites in urine known as dialkyl phosphate (DAP) metabolites [10].

Organophosphate pesticides have been measured in pregnant women. Whyatt *et al.* [11] measured parent organophosphate compounds in blood samples from low-income pregnant women in New York City and found detectable levels of the organophosphate pesticide chlorpyrifos in 70% of the women. We found higher DAP levels in pregnant women from the CHAMACOS cohort compared with pregnant women from NHANES [12]. Efforts to model sources of exposure to pregnant women in the CHAMACOS cohort suggest that diet was a major source of exposure, but that local agricultural pesticide use also contributed significantly to their total exposure [13].

Children are likely exposed to organophosphate pesticides *in utero* and postnatally, in breast milk, residues in food, and by ingesting (such as through hand-to-mouth behavior), inhaling and absorbing pesticides in their environment [14]. Evidence for in-utero exposure comes from studies that have detected pesticides in amniotic fluid, umbilical cord blood, and meconium [11,15–17]. For example, 64% of the newborns in New York City had detectable levels of chlorpyrifos in cord-blood samples and a mean exposure level similar to their mothers [11]. Young children have increasingly higher DAP levels as they get older and interact more with their environment. DAP levels increased with age from 6 to 24 months in the CHAMACOS cohort and were lower than levels from

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

an older group of children aged 2–6 years from an agricultural area of Washington [18]. In addition, NHANES DAP levels in grade-school-age children tend to be higher than both teenager and adult levels [6].

A study of 3–11-year-olds from Seattle, Washington, showed that children's exposure to organophosphate pesticides in a suburban community resulted primarily from ingestion of pesticide residues on food [19]. The median level of malathion dicarboxylic acid (MDA), a metabolite of the organophosphate pesticide malathion decreased from 1.5 μg/l when children were eating conventionally grown food to a median level of zero when the children consumed exclusively organic food [19]. Results for the metabolite of chlorpyrifos, another common organophosphate, were similar [19]. Although this study suggests that diet is children's main source of exposure, children who live in agricultural areas or in households where pesticides are used regularly have additional sources of exposure. Studies of pesticide residues in household dust have found higher levels in farmworker homes compared to nonfarmworker homes [20–23]. Studies have also shown that urinary DAP metabolite levels are higher in farmworker children compared with nonfarmworker children [20,24,25] with the exception of one study comparing farmworker children in Central Washington with children in Seattle that found no difference [18]. However, most of the farmworker children's samples in this study were collected after the peak spraying season. Because DAP metabolite measurements probably only reflect exposures from the previous 3–5 days, they did not capture peak exposure levels. Additionally, researchers from this study noted that farmworker children probably did not have a diet rich in fresh fruits and vegetables, yet their levels were much higher than Seattle children's levels who were consuming organic produce [18].

Pesticide exposure and neurodevelopment

Numerous case reports and studies have shown that high-dose exposure to organochlorine and organophosphate pesticides may have neurological effects. Recently, evidence is also emerging to support the adverse association of lower-dose exposure to organochlorine and organophosphate pesticides and neurobehavior.

Effects of high-dose acute exposure

The incidence of pesticide poisoning is commonly underreported partially due to the fact that some symptoms can resemble those of other common ailments. Symptoms of acute exposure to high doses of the organochlorine pesticide DDT can cause neurological symptoms such as paresthesias of the tongue, lips, and face, hypersensitivity to external stimuli, irritability, dizziness, vertigo, tremor, and tonic and clonic convulsions [2]. Symptoms of organophosphate pesticide poisoning in children include miosis, excessive salivation, nausea and vomiting, lethargy, muscle weakness, tachycardia, hyporeflexia and hypertonia, and respiratory distress [26]. A recent study of the long-term sequelae of acute exposure to organophosphate pesticides revealed that 6–12-year-old children who had been hospitalized for acute organophosphate pesticide poisoning before the age of 3 ($n = 26$) exhibited significantly more impairments in verbal learning and motor inhibition tasks than control children ($n = 26$) [27].

Effects of low-level chronic exposure

A substantial body of animal research supports the notion that low-levels of prenatal and postnatal pesticide exposure can affect neurodevelopment in children [14,28,29]. Additionally, ecologic studies have implicated a link between pesticide exposure and impaired neurodevelopment as well as autism in children [30,31]. However, until recently, few studies have examined the neurobehavioral consequences in children resulting from chronic, low-level exposure to common pesticides using biologic markers of exposure. Evidence of the potential neurodevelopmental effect arising from children's exposure to pesticides comes mainly from studies of in-utero exposure to DDT/DDE and organophosphate pesticides. A summary of these findings can be found in Tables 1–3 [30–33,34•,35•,36–39,40•,41–44,45••,46,47].

Organochlorines: dichlorodiphenyldichloroethene and neurodevelopment

Most studies of neonates exposed to DDT and DDE *in utero* have observed no effect on neurodevelopmental functioning as measured by the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), except for one study in North Carolina (see Table 1). This study of neonates born between 1978 and 1982 found that higher levels of DDE in cord serum and breast milk were associated with hyporoflexia on the BNBAS [32]. Several subsequent studies have failed to replicate this finding in cohorts in Oswego, New York, of children born between 1991 and 1994; the CHAMACOS cohort who were born between 1999 and 2000 in the Salinas Valley, California; and a cohort of children born from 1998 to 2002 recruited at Mt Sinai Medical Center in New York City. In studies from all three cohorts, maternal serum DDT and DDE levels were not significantly associated with neonate performance on the BNBAS [33,34•,35•]. The discrepancy between the earlier North Carolina study and the later studies from Oswego, Salinas Valley and New York City might be explained by higher average DDT and DDE exposure levels in North Carolina during the time the data were collected and potentially by concurrent exposure to other toxicants (e.g. polychlorinated biphenyls).

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Table 1 Summary of literature on prenatal dichlorodiphenyldichloroethene (DDE) exposure and neurodevelopment in children

Age	Development effect	Test	Reference
Neonatal	↓ Reflex response	Brazelton	[32]
	= All domains	Brazelton	[33]
	= All domains	Brazelton	[34•]
	= All domains	Brazelton	[35•]
3 months	↓ Psychomotor; = mental	Bayley	[40•]
6 months	= Psychomotor; ↑ mental	Bayley	[36]
	=	Fagan	[38]
	↓ Psychomotor; = mental	Bayley	[43]
	↓ Psychomotor; = mental	Bayley	[40•]
12 months	= Psychomotor; = mental	Bayley	[36]
	=	Fagan	[38]
	↓ Psychomotor*; = mental	Bayley	[43]
	↓ Psychomotor; = mental	Bayley	[40•]
13 months	↓ Cognitive, psychomotor and social	Bayley, Griffiths	[39]
18 months	= Psychomotor; = mental	Bayley	[37]
24 months	= Psychomotor; = mental	Bayley	[37]
	= Psychomotor ↓ mental*	Bayley	[43]
3–5 years	= All domains†	McCarthy	[41]
4 years	↓ Memory; = all other domains	McCarthy	[42]

The meaning of the symbols is as follows: ↓, negative (inverse) association with exposure; ↑, positive association with exposure; =, no association with exposure.
* Negative association with exposure was observed when comparing children in the upper and lower quartiles of DDE exposure but not when analyzing DDE exposure continuously.
† The quantitative scores varied by exposure category but not in a dose-responsive manner. The children in the low- and high-exposure categories had the highest scores with the lowest scores found among those in the middle-exposure category.

Significantly more research has been dedicated to examining the relationship between DDE exposure and neurodevelopment in older infants and children (see Table 1); however, this research is also not conclusive. In the same North Carolina birth cohort, researchers observed a *positive* association between in-utero exposure to DDE and mental development of the infants at 6 months as measured by the Mental Development Index (MDI) of the Bayley Scales of Infant Development (BSID) [36] and no association with either in-utero or postnatal DDE exposure and children's scores on the MDI during subsequent assessments of the children at 12, 18 and 24 months [36,37]. Similarly, neither prenatal nor postnatal DDE exposure appeared to be associated with psychomotor development as measured by the Psychomotor Development Index (PDI) of the BSID [36,37]. In the Oswego cohort, researchers observed a significant negative correlation between DDE and scores on the Fagan Test of Infant Intelligence (FTII) at 12 months; however, they concluded that exposure was not associated with FTII scores at either 6 or 12 months [38]. We examined children's neurodevelopment at 6, 12 and 24 months in the CHAMACOS cohort in relation to in-utero DDE exposure as a continuous measure and by comparing children from the upper and lower quartiles of exposure. Using the continuous measure, we found that in-utero DDE exposure was significantly associated with decreases in PDI scores at 6 months but not at 12 or 24 months. We found no associations with MDI scores at any age using the continuous measure. Comparing the extreme exposure levels, children from the highest quartile of in-utero DDE exposure scored 3.3 points lower at 6 months and 4.4 points lower at 12 months on the PDI than children in the lowest quartile of exposure. Also, compared to children in the lower quartile of exposure, children from the upper quartile of exposure scored 4.9 points lower on the MDI at 24 months. Similarly, researchers in Spain found that umbilical cord-serum DDE levels were inversely associated with social, mental and psychomotor development at 1 year as measured by the Griffiths Scales of Infant Development and the BSID [39]. In a cohort of infants from Mexico, higher maternal serum DDE levels were associated with lower PDI scores on the BSID at 3, 6, and 12 months [40•]. However, these researchers did not observe an association of DDE serum concentrations and infants' MDI scores at any age [40•]. Thus, the Mexico and the CHAMACOS studies demonstrate similar patterns in the results of associations between psychomotor development and DDE levels at 6 and 12 months.

Two studies have reported on the relation of in-utero DDE levels and neurodevelopment in children 3 years and older (see Table 1). Assessments of the North Carolina birth cohort when the children were 3, 4 and 5 years old using the McCarthy Scales of Children's Abilities (MSCA) did not reveal any dose–response relationship between either prenatal or postnatal exposure to DDE [41]. However, Spanish researchers examined 4-year-old children from Ribera d'Ebre, Spain, and 4-year-old children from Menorca, Spain, and found that in-utero DDE exposure

Table 2 Summary of literature on prenatal dichlorodiphenyltrichloroethane (DDT) exposure and neurodevelopment in children

Age	Development effect	Test	Reference
Neonatal	= All domains	Brazelton	[34•]
6 months	↓ Psychomotor; = mental	Bayley	[43]
12 months	↓ Psychomotor ↓ Mental	Bayley	[43]
24 months	↓ Psychomotor*; ↓ mental	Bayley	[43]
4 years	↓ General cognitive, memory, quantitative, verbal, and executive function	McCarthy	[42]

For meaning of the symbols, see Table 1.
* Negative association with exposure was observed when comparing children in the upper and lower quartile of DDT exposure but not when analyzing DDT exposure continuously.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Table 3 Summary of literature on prenatal organophosphate pesticide exposure and neurodevelopment in children

Age	Development effect	Test	Reference
Neonatal	↓ Reflex response	Brazelton	[35•]
2 months	↓ Reflex response	Brazelton	[44]
6 months	= Psychomotor; = mental	Bayley	[45••]
12 months	= Psychomotor; = mental*	Bayley	[46]
	= Psychomotor; = mental	Bayley	[45••]
24 months	= Psychomotor; = mental*	Bayley	[46]
	= Psychomotor; ↓ mental	Bayley, Child Behavior Checklist	[45••]
	↑ Pervasive developmental disorder		
	= Attentional problems		
	= Attention-deficit/hyperactivity disorder		
3 years	↓ Psychomotor; ↓ mental	Bayley, CBCL	[46]
	↑ Pervasive developmental disorder		
	↑ Attention problems		
	↑ Attention-deficit/hyperactivity disorder*		
7 years	↓ Stanford–Binet copying†; = all other tests	Catsys, WISC-R, Santa-Ana Pegboard, Stanford-Binet	[47]

For meaning of the symbols, see Table 1.
* This study compared children in high and low-exposure levels. They reported no differences in children when exposure was analyzed continuously.
† Exposure was assessed by maternal questionnaire and not by biomarker.

was associated with decrements in the memory domain from the MSCA [42].

Dichlorodiphenyltrichloroethane and neurodevelopment

Although a number of studies have examined associations of neurodevelopment and DDE serum levels, only two studies have also measured DDT levels (see Table 2). In the CHAMACOS cohort, we found that levels of maternal serum DDT were negatively associated with mental development on the BSID assessed at 12 and 24 months [43]. This finding was the same when children from the highest quartile of in-utero DDT exposure were compared with children from the lowest quartile of exposure. Conversely, using a continuous measure of exposure, we found that psychomotor development was negatively associated with in-utero DDT levels at 6 and 12 months, but not at 24 months [43]. When we compared the upper and lower quartiles of exposure, we confirmed the significantly lower psychomotor development scores in the upper quartile at 6 (3.6 points lower) and 12 (5.8 points lower) months, but we also now observed decreased psychomotor scores at 24 months (2.8 points lower). Finally among 4-year-old children from Ribera d'Ebre and Menorca, Spain, cord-serum DDT levels were significantly associated with poorer scores in the general cognitive, memory, quantitative, verbal and the executive function domains on the MSCA [42].

Overall, the research on both DDE and DDT suggests that in-utero exposure may be associated with decrements in neurodevelopment in older infants and children, although the results are inconsistent. The negative associations between serum DDT levels and neurodevelopment seem stronger than with DDE, although there are few studies.

Organophosphates

The association between organophosphate pesticide exposure and neurodevelopment has been studied only recently, but a few similarities across studies have emerged (see Table 3). Evidence from both the CHAMACOS and Mt Sinai birth cohorts suggests that higher in-utero exposure to organophosphate pesticides as measured by maternal DAP metabolite levels is associated with increased numbers of abnormal reflexes as measured in the BNBAS [35•,44]. Neither group observed any relation of exposure with any other clusters of the BNBAS [35•,44].

In older infants and children, the results are less consistent as shown in Table 3. In the CHAMACOS cohort, we did not observe any associations between maternal DAP levels and MDI scores on the BSID at 6 or 12 months or with PDI scores at any age [45••]. However, we found that higher maternal DAP levels during pregnancy were related to lower MDI scores in 24-month-old infants. Paradoxically, DAP levels of the children were unexpectedly *positively* associated with mental development [45••]. We hypothesized that children with higher mental development scores may be more interactive with their environment, thereby coming into contact with more pesticide residues. Researchers from Columbia University reported lower mental and psychomotor development scores in 36-month-old children exposed to higher cord-blood levels of chlorpyrifos, a common organophosphate pesticide. They did not observe any association of exposure levels and neurodevelopment at 12 or 24 months [46]. Although researchers from both the CHAMACOS and Columbia cohorts observed an association between a biomarker of organophosphate pesticide exposure and neurodevelopment, the association was observed with different organophosphate pesticides. In the CHAMACOS cohort, the

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

strongest association with neurodevelopment was seen with dimethyl DAPs with little association with diethyl DAPs; in contrast, blood levels of chlorpyrifos, which metabolize to diethyl DAPs, were responsible for the observed associations with neurodevelopment in the Columbia New York City cohort.

Although the results from the CHAMACOS and New York City cohorts differed somewhat in their conclusions related to mental and psychomotor development, both studies discovered an association between in-utero exposure to organophosphate pesticides and maternal report of pervasive developmental disorder [45••,46]. Pervasive developmental disorder, which represents a constellation of behaviors consistent with Asperger's syndrome and autism-spectrum disorder, is one of many behavior problems that can be assessed using the Child Behavior Checklist. Higher in-utero organophosphate pesticide exposure was associated with increased odds of maternally reported pervasive developmental disorder at 24 months in the CHAMACOS cohort [45••] and at 36 months in the Columbia New York City cohort [46]. Additionally, researchers from Columbia University detected a negative association of exposure on attention problems with and without hyperactivity at 36 months [46].

Only one study has been conducted examining the relation of organophosphate exposure and the development of school-age children. Researchers assessed the development of 7-year-old children from Ecuador, of whom 35 were exposed prenatally to organophosphate pesticides. The children were evaluated on the Santa Ana Pegboard, Weschler Intelligence Scale for Children (WISC-R), two subscales of the Stanford–Binet and the Catsys force plate [47]. They found that prenatal exposure assessed with a maternal occupational questionnaire was associated with decreased scores on the Stanford–Binet copying test. The children's urinary DAP levels were associated with an increase in simple reaction time. No differences were reported on the other tests [47]. The negative associations of child DAP measurements and neurodevelopment in the study from Ecuador differ from the positive association observed with younger children in the CHAMACOS study.

Conclusion

Many of the pesticides currently in use came into being after World War II. In the last 2 years, a number of key papers have been published suggesting that exposure of fetuses and children commonly occurs and that exposure to certain pesticides, including organophosphates, may be higher in children living in agricultural areas. Also, with recent policy changes, organochlorines such as DDT are likely to be increasingly used in malaria-endemic areas. Although many of these pesticides are widely used and are clearly neurotoxicants at high doses, there is a paucity of data on the potential short- and long-term developmental effects of low-level exposure to children from in-utero and childhood exposure.

At least two studies with similar exposure levels have observed an association of psychomotor deficits and in-utero exposure to DDE exposure. Only two studies have examined the relation of DDT exposure and neurodevelopment and both also observed cognitive deficits. In relation to in-utero exposure to organophosphates, both studies which examined neonates found a relation of abnormal reflexes and maternal organophosphate exposure. Findings from two studies which have focused on the development of older infants and children have suggested that in-utero exposure is associated with deficits in mental development and with maternal report of pervasive developmental disorder in children aged 2–3 years old.

There are some inconsistencies across studies which may arise from differences in exposure and in the method of exposure assessment, but overall there is surprising consistency in the few studies that have been conducted. These studies suggest that there is reason to be cautious about exposure of pregnant women to DDT/DDE and organophosphates because of the potential effect on the neurodevelopment of their children. Policy-makers and pregnant women should be educated accordingly.

Acknowledgements

The University of California at Berkeley Center for Children's Environmental Health is supported by EPA (RD 83171001) and NIEHS (P01 ES009605)

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 226).

1 Kiely T, Donaldson D, Grube A. Pesticide industry sales and usage: 2000 and market estimates. Washington, DC: EPA; 2004.

2 Agency for Toxic Substances and Disease Registry. Toxicological profile for DDT, DDE and DDD. Atlanta, Georgia: US Department of Health and Human Services; 2002.

3 Dam K, Seidler FJ, Slotkin TA. Transcriptional biomarkers distinguish between vulnerable periods for developmental neurotoxicity of chlorpyrifos: implications for toxicogenomics. Brain Res Bull 2003; 59:261–265.

4 Slotkin TA, Tate CA, Ryde IT, *et al.* Organophosphate insecticides target the serotonergic system in developing rat brain regions: disparate effects of diazinon and parathion at doses spanning the threshold for cholinesterase inhibition. Environ Health Perspect 2006; 114:1542–1546.

5 Vose SC, Holland NT, Eskenazi B, *et al.* Lysophosphatidylcholine hydrolases of human erythrocytes, lymphocytes, and brain: sensitive targets of conserved specificity for organophosphorus delayed neurotoxicants. Toxicol Appl Pharmacol 2007; 224:98–104.

6 Centers for Disease Control and Prevention. Third national report on human exposure to environmental chemicals. Atlanta, Georgia: Centers for Disease Control and Prevention, National Center for Environmental Health; 2005.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

7 Bradman AS, Schwartz JM, Fenster L, *et al.* Factors predicting organochlorine pesticide levels in pregnant Latina women living in a United States agricultural area. J Expo Sci Environ Epidemiol 2006; 17:388–399.

8 Ribas-Fito N, Grimalt JO, Marco E, *et al.* Breastfeeding and concentrations of HCB and p,p'-DDE at the age of 1 year. Environ Res 2005; 98:8–13.

9 Ribas-Fito N, Julvez J, Torrent M, *et al.* Beneficial effects of breastfeeding on cognition regardless of DDT concentrations at birth. Am J Epidemiol 2007; 166:1198–1202.

10 Barr D, Bravo R, Weerasekera G, *et al.* Concentrations of dialkyl phosphate metabolites of organophosphorus pesticides in the U.S. population. Environ Health Perspect 2004; 112:186–200.

11 Whyatt RM, Camann D, Perera FP, *et al.* Biomarkers in assessing residential insecticide exposures during pregnancy and effects on fetal growth. Toxicol Appl Pharmacol 2005; 206:246–254.

12 Bradman A, Eskenazi B, Barr D, *et al.* Organophosphate urinary metabolite levels during pregnancy and after delivery in women living in an agricultural community. Environ Health Perspect 2005; 113:1802–1807.

13 McKone TE, Castorina R, Harnly ME, *et al.* Merging models and biomonitoring data to characterize sources and pathways of human exposure to organophosphorus pesticides in the Salinas Valley of California. Environ Sci Technol 2007; 41:3233–3240.

14 Eskenazi B, Bradman A, Castorina R. Exposures of children to organophosphate pesticides and their potential adverse health effects. Environ Health Perspect 1999; 107 (Suppl 3):409–419.

15 Bradman A, Claus B, Barr D, *et al.* Pesticides and other toxicants in amniotic fluid: A pilot study. J Expo Anal Environ Epidemiol 2002; 111:1779–1782.

16 Ostrea EM Jr, Bielawski DM, Posecion NC Jr, *et al.* A comparison of infant hair, cord blood and meconium analysis to detect fetal exposure to environmental pesticides. Environ Res 2007; 106:277–283.

17 Whyatt RM, Barr DB. Measurement of organophosphate metabolites in postpartum meconium as a potential biomarker of prenatal exposure: a validation study. Environ Health Perspect 2001; 109:417–420.

18 Fenske RA, Lu C, Curl CL, *et al.* Biologic monitoring to characterize organophosphorus pesticide exposure among children and workers: an analysis of recent studies in Washington State. Environ Health Perspect 2005; 113:1651–1657.

19 Lu C, Toepel K, Irish R, *et al.* Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. Environ Health Perspect 2006; 114:260–263.

20 Lu C, Fenske RA, Simcox NJ, *et al.* Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways. Environ Res 2000; 84:290–302.

21 Bradman MA, Harnly ME, Draper W, *et al.* Pesticide exposures to children from California's Central Valley: results of a pilot study. J Expo Anal Environ Epidemiol 1997; 7:217–234.

22 Fenske RA, Lu C, Barr D, *et al.* Children's exposure to chlorpyrifos and parathion in an agricultural community in central Washington State. Environ Health Perspect 2002; 110:549–553.

23 Simcox NJ, Fenske RA, Wolz SA, *et al.* Pesticides in household dust and soil: exposure pathways for children of agricultural families. Environ Health Perspect 1995; 103:1126–1134.

24 Loewenherz C, Fenske RA, Simcox NJ, *et al.* Biological monitoring of organophosphorus pesticide exposure among children of agricultural workers in central Washington State. Environ Health Perspect 1997; 105:1344–1353.

25 Curwin BD, Hein MJ, Sanderson WT, *et al.* Urinary pesticide concentrations among children, mothers and fathers living in farm and nonfarm households in Iowa. Ann Occup Hyg 2007; 51:53–65.

26 Zwiener RJ, Ginsburg CM. Organophosphate and carbamate poisoning in infants and children. Pediatrics 1988; 81:121–126.

27 Kofman O, Berger A, Massarwa A, *et al.* Motor inhibition and learning impairments in school-aged children following exposure to organophosphate pesticides in infancy. Pediatr Res 2006; 60:88–92.

28 Slotkin TA, Levin ED, Seidler FJ. Comparative developmental neurotoxicity of organophosphate insecticides: effects on brain development are separable from systemic toxicity. Environ Health Perspect 2006; 114:746–751.

29 Colborn T. A case for revisiting the safety of pesticides: a closer look at neurodevelopment. Environ Health Perspect 2006; 114:10–17.

30 Guillette EA, Meza MM, Aquilar MG, *et al.* An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico. Environ Health Perspect 1998; 106:347–353.

31 Roberts EM, English PB, Grether JK, *et al.* Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. Environ Health Perspect 2007; 115:1482–1489.

32 Rogan WJ, Gladen BC, McKinney JD, *et al.* Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr 1986; 109:335–341.

33 Stewart P, Reihman J, Lonky E, *et al.* Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. Neurotoxicol Teratol 2000; 22:21–29.

34 • Fenster L, Eskenazi B, Anderson M, *et al.* In utero exposure to DDT and performance on the Brazelton neonatal behavioral assessment scale. Neurotoxicology 2007; 28:471–477.

This investigation finds no relationship between in-utero exposure to DDT/DDE and neurodevelopment on the Brazelton Neonatal Behavioral Assessment Scale in neonates in the CHAMACOS cohort.

35 • Engel SM, Berkowitz GS, Barr DB, *et al.* Prenatal organophosphate metabolite and organochlorine levels and performance on the Brazelton neonatal behavioral assessment scale in a multiethnic pregnancy cohort. Am J Epidemiol 2007; 165:1397–1404.

The results of this study of a New York City birth cohort suggested that higher prenatal organophosphate pesticide exposure is associated with higher number of abnormal reflexes among neonates measured using the Brazelton Neonatal Behavioral Assessment Scale.

36 Gladen BC, Rogan WJ, Hardy P, *et al.* Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. J Pediatr 1988; 113:991–995.

37 Rogan W, Gladen B. PCBs, DDE, and child development at 18 and 24 months. Ann Epidemiol 1991; 1:407–413.

38 Darvill T, Lonky E, Reihman J, *et al.* Prenatal exposure to PCBs and infant performance on the Fagan test of infant intelligence. Neurotoxicology 2000; 21:1029–1038.

39 Ribas-Fito N, Cardo E, Sala M, *et al.* Breastfeeding, exposure to organochlorine compounds, and neurodevelopment in infants. Pediatrics 2003; 111:e580–e585.

40 • Torres-Sanchez L, Rothenberg SJ, Schnaas L, *et al.* In utero p,p'-DDE exposure and infant neurodevelopment: a perinatal cohort in Mexico. Environ Health Perspect 2007; 115:435–439.

This Mexican study of prenatal DDE exposure and neurodevelopment shows a negative association between exposure and psychomotor development during the first year of life.

41 Gladen BC, Rogan WJ. Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development. J Pediatr 1991; 119:58–63.

42 Ribas-Fito N, Torrent M, Carrizo D, *et al.* In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. Am J Epidemiol 2006; 164:955–962.

43 Eskenazi B, Marks AR, Bradman A, *et al.* In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children. Pediatrics 2006; 118:233–241.

44 Young JG, Eskenazi B, Gladstone EA, *et al.* Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates. Neurotoxicology 2005; 26:199–209.

45 •• Eskenazi B, Marks AR, Bradman A, *et al.* Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect 2007; 115:792–798.

In the CHAMACOS cohort, prenatal DAPs were inversely associated with mental development during the first 2 years of life while child DAP levels were positively associated with mental development. Both prenatal and postnatal DAP levels were associated with an increased risk of pervasive developmental disorder at 2 years.

46 Rauh VA, Garfinkel R, Perera FP, *et al.* Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics 2006; 118:e1845–e1859.

47 Grandjean P, Harari R, Barr DB, *et al.* Pesticide exposure and stunting as independent predictors of neurobehavioral deficits in Ecuadorian school children. Pediatrics 2006; 117:e546–e556.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.