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TOXICITY OF ANTICHOLINESTERASE PESTICIDES IN NEONATES AND CHILDREN

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17.1   INTRODUCTION

There is increasing concern regarding the widespread use of pesticides in agricultural communities and potential impacts on public health. Organophosphorous pesticides (OPs) are currently the most commonly utilized pesticides in the world, consisting of nearly 40 different chemical members registered by the United States Environmental Protection Agency (U.S. EPA; www.epa.gov). In the 1990s some 2.5 million to 5.0 million agricultural workers were exposed to OP insecticides in the United States (Das et al., 2001). About 73 million pounds of OP pesticides were used in the United States in 2001 (70% of all insecticides; Kiely, 2004). Scientific field investigations have focused on delineating the extent of exposure and potential health effects in agricultural and nonagricultural communities. Children have been the focus of many of these field investigations. In this chapter we will review the factors that make exposures

to anticholinesterase pesticides of major public health concern, including the physiological uniqueness of infants and children, and the behavioral and developmental aspects that increase the likelihood of exposure. Animal models that have shown the particular vulnerability of infants and children will be reviewed, and the major epidemiological studies that are providing scientific information on the population impact will be discussed. Emphasis in this chapter will be on the emerging knowledge of the impact of anticholinesterase pesticides on the neurodevelopment of infants and children.

17.2   VULNERABILITY OF CHILDREN

Children are exposed to environmental chemicals through the air they breathe, the food they eat, and the water they drink (Amler and Gibertini, 1996). In light of the increasing prevalence of developmental disabilities, there is concern about the

impact of chemicals on neurodevelopment (Koger et al., 2005; Landrigan et al., 2004; NRC, 2000). Children from all cultures and backgrounds are at risk. However, minority groups and children from low-income families are often at greater risk because of poor nutrition, an impoverished environment, and limited access to medical care (Frumkin et al., 1999; Koger et al., 2005; Mott, 1995; Rhodes et al., 2000). Children have greater exposure to toxicants than adults due to both behavior (e.g., increased time spent crawling on the floor and increased hand-to-mouth behavior) and their increased food to body mass ratio (they consume a greater amount of food and drink compared to their body ratio than adults; CDC, 2002; Cohen Hubal et al., 2000; Reed et al., 1999). Children are considered to be more vulnerable because of the significant anatomical and maturational changes occurring in the brain during developmental periods including adolescence (Andersen, 2003), and also the increasing findings of animal studies indicating neurodevelopment effects of pesticides (Campbell et al., 1997; Dam et al., 2000; Gupta et al., 1998; Johnson et al., 1998; Moser and Padilla, 1998). Finally, because children have more years to live than adults, they have more time to develop diseases from those early exposures, and some effects may not become apparent until the child is older (Costa et al., 2004; Godfrey and Barker, 2001; Landrigan et al., 2004; National Academy of Sciences, 1993; Reuhl, 1991).

Neurotoxic effects of environmental chemicals can vary along a continuum from minor subclinical deficits in sensory memory, motor or cognitive functioning to mental retardation and clinical disease (Landrigan, 2001; Mendola et al., 2002). The type of exposure, the developmental stage, and the pattern and duration of exposure can all influence the outcome of exposure (Costa et al., 2004; Rice and Barone, 2000). Although severe effects of neurotoxic exposure are readily apparent, subtle effects are not easily detected—especially in a standardized clinical exam. Neurobehavioral tests have been used to identify adverse health effects of toxicants in both adults (Anger, 2003) and children (Dietrich and Bellinger, 1994).

17.3 EXPOSURE TO PESTICIDES

Although children can be exposed to pesticides through residential use of pesticides and diet, children of agricultural workers are considered to have a higher risk of exposure to pesticides compared to the general population because of the close proximity of their homes to the fields where pesticides are applied and from take-home exposure (Azaroff, 1999; Coronado et al., 2004; Fenske et al., 2000; Lu et al., 2000; McCauley et al., 2001; Quandt et al., 2004a; Thompson et al., 2003). Detectable levels of pesticides have been reported in home dust, primarily in families residing in agricultural areas (Arcury et al., 2005; Bradman et al.,

1997; McCauley et al., 2001; Quandt et al., 2004a; Simcox et al., 1995). Bradman et al. (1997) found that diazinon and chlorpyrifos house dust concentrations were higher among farm workers than non-farm workers. Others have reported higher levels of pesticides in house dust in homes that are located closer to fields (Quandt et al., 2004b) and in housing with larger numbers of farm workers (Azaroff, 1999; Lu et al., 2000; McCall, 1981; McCauley et al., 2001). After-work hygiene practices, such as leaving work boots outside, and promptly changing work clothes, are associated with reduced pesticide levels in the homes of farm workers (McCauley et al., 2003). While information is available on the impact of acute exposure in adults and occupational exposure, little information is available examining the impact of exposures in children.

To assess risk to children it is necessary to associate measures of exposure with adverse outcomes, establishing a dose-response relationship. Studies examining pesticide exposure in children have used a variety of methods to classify exposure, including environmental monitoring (indoor air, dust samples, surface wipes), maternal and child exposure measures (urinary metabolites, acetyl cholinesterase level), and pesticide source information (pesticide use, home inventory, proximity to agricultural field, parent's occupations). Pesticide source information often relies on self-report and the link between these classifications and actual exposure is often unknown, and the amount of exposure in any given population may vary considerably (McCauley et al., 2006).

17.4 ANTICHOLINESTERASE EFFECTS IN ANIMAL MODELS

The neurotoxic effects of OP pesticides are thought to be mediated through the inhibition of acetylcholinesterase (AChE), the enzyme involved in the metabolism of acetylcholine (Karalliedde et al., 2001). The cholinergic system is involved in both learning and memory in animals and humans (Cohn and MacPhail, 1997). Disruption of this system in the developing animal has led to deficits in behavior (Carr et al., 2001). Data to date indicate that the acute toxicity of OPs is influenced by age, with young animals being more sensitive (Costa, 2006; Pope and Liu, 1997; Vidair, 2004). The data suggest that this developmental susceptibility is not due to intrinsic AChE activity, but rather to lower metabolic abilities of the young (Benke and Murphy, 1975). With some OPs, the lower detoxication activity in the young is due to the lower activity levels of PON1 (paraoxonase), and perhaps carboxylesterase (Costa, 2006; W. F. Li et al., 1997; Mortensen et al., 1996). The PON1 gene presents several polymorphisms in the coding and promoter regions that affect the ability of paraoxonase to catalyze different substances. PON1 detoxifies OPs by cleavage of active

oxons before they have a chance to inhibit cholinesterases (Chen et al., 2003). Transgenic animal model research has shown that the PON1 status plays a relevant role in modulating the acute toxicity of some but not all OPs (D. Li et al., 2000) and that the enzymatic systems responsible for metabolism of OPs show a developmental curve (Cole et al., 2003).

Studies of laboratory animals have demonstrated that low concentrations of OPs (primarily chlorpyrifos), below the threshold for systemic toxicity, are associated with several behavioral outcomes (Garcia et al., 2003; Icenogle et al., 2004; Levin et al., 2001; Meyer et al., 2004; Slotkin et al., 2002). Prenatal and early life exposure has led to impairments in cognitive functioning, including reference and working memory and locomotor activity (Icenogle et al., 2004; Levin et al., 2001; Levin et al., 2002). A selective learning deficit on a repeated acquisition task was found in rats exposed to OP pesticides (Cohn and MacPhail, 1997). Many of the effects associated with chlorpyrifos exposure demonstrated sex specific findings (Slotkin, 2004). When exposure occurred prenatally, females showed greater effects and males showed greater effects when exposure occurred postnatally (Dam et al., 2000; Garcia et al., 2003; Levin et al., 2001, 2002; Slotkin et al., 2001, 2002). Some of the behavioral effects are delayed from the time of exposure until adolescence or adulthood, which suggests that the behavioral manifestations are ongoing and possibly progressive with age (Colborn, 2006; Levin et al., 2001; Slotkin et al., 2001).

17.5 PHYSIOLOGICAL VULBERABILITY IN CHILDREN

The two major issues regarding exposure of fetuses and infants to OPs have centered on whether the young are more susceptible to the acute toxicity of OPs, and whether OPs cause developmental neurotoxicity (Costa, 2006). Developing human fetuses have much lower protective PON1 activities than do adults, with cord blood levels being several times lower in neonates compared to adults (Chen et al., 2003; Mueller et al., 1983). In recent years there have been several epidemiological investigations aimed at examining the effects of pesticide exposure during the prenatal period and during early childhood. Several studies have examined pesticide exposure in children in populations ranging from infants to adolescents, with varying exposures to pesticides, including prenatal exposure, acute poisoning incidents, or chronic exposure across the lifespan (see Table 17.1; —Dabrowski et al., 2003; Eckerman et al., 2006; Eskenazi et al., 2004, 2007; Grandjean et al., 2006; Handal et al., 2007; Kofman et al., 2006; Perera et al., 2004; Rauh et al., 2006; Rohlman et al., 2001, 2005, 2007a; Ruckart et al., 2004; Whyatt et al., 2004; Young

et al., 2004). The majority of studies have focused on chronic effects of pesticide exposure either from parental occupation or living in an agricultural community. These studies are providing compelling evidence of the developmental susceptibility of humans to these agents and add to the substantial animal and mechanistic data on the effects of pesticides on the young.

17.6 LONGITUDINAL STUDIES

Prospective studies are used to assess neurological and developmental effects over time. Because of the rapid growth and development of the child, there is a need for long-term studies to assess changes over time. Furthermore, functional effects of early exposure may not become apparent until later in life (Jacobson and Jacobson, 2005). Three longitudinal birth cohort studies are currently underway (Table 17.2): the Mt. Sinai Children's Environmental Health Study (CEHS), the Mother's and Newborns Cohort Study at the Columbia Center for Children's Environmental Health (CCCEH; Perera et al., 2002), and the University of California Berkeley Center for the Health and Assessment of Mothers and Children of Salinas (CHAMACOS; Eskenazi et al., 2004). The Mt. Sinai CEHS and the Columbia Center for Children's Health are focused on urban cohorts in New York City. The Columbia project is composed of minority (African American and Dominican) mothers and children and the Mt. Sinai project is an ethnically diverse cohort. These centers are concerned with pesticide exposure that occurs primarily through residential use of pesticides. The CHAMACOS study began in 1998 and is following primarily Latino mothers and children living in agricultural communities in California. In 75% of the homes at least one member of the household works in agriculture.

Mt. Sinai Cohort mother–infant pairs were recruited for the Mt. Sinai CEHS between 1998 and 2002 from clinics and private practices at Mt. Sinai Hospital in New York City (Berkowitz et al., 2004). A total of 404 children were enrolled in the birth cohort. During the third trimester, mothers completed a questionnaire about pesticide and other exposures, lifestyle habits, and demographics. At this time a maternal urine sample was collected along with a blood sample. Cord blood was collected at birth. The cohort includes women from ethnically diverse backgrounds, including Hispanic women (predominantly Puerto Rican), followed by African Americans and Caucasians. Approximately 72% of the sample report potential exposure to pesticides from residential use by a member of the household, fumigation, or exterminator application.

Columbia Cohort pregnant women were recruited from hospitals and enrolled in the Columbia study beginning in 1998. Women completed a questionnaire during their third trimester and personal air monitoring samples were also

TABLE 17.1 Description of Studies Examining Pesticide Exposure and Performance in Children

	Exposure Type	Population	Exposure Measures	Outcome Measures	Significant Findings
Willis et al., 1993	Prenatal	Infants and mothers (primarily Hispanic) in the U.S.	Maternal ChE questionnaire	Fetal growth[a] Gestational duration	No association
Dabrowski et al., 2003	Prenatal	Infants and mothers in central Poland	Questionnaire of maternal exposure during pregnancy	Fetal growth Gestational duration	Lower birth weight Shorter gestational duration
Handal et al., 2007	Chronic	Children (3–61 months) in Ecuador	Community of residence[b]	Growth measurement Ages and Stages Questionnaire (ASQ) Visual motor integration	Deficits on gross and fine motor and socioindividual skills
Guillette et al., 1998	Chronic	Preschool children (4–5 years) in Mexico	Community of residence[c]	Growth and development battery	Deficits in coordination, stamina, memory, figure drawing
Rohlman et al., 2005	Chronic	Preschool children (5–6 years) in the U.S.	Parental ocupation[d]	Neurobehavioral battery: BARS[e] + selected tests from PENTB	Deficits on response speed and coordination and longer test completion times
Lizardi et al., 2008	Chronic	School-age children (K–3rd grade) in Arizona	DAP metabolites	Cognitive battery Child Behavior Checklist (CBCL)	Deficits on Trail Making B and Wisconsin Card Sorting Test
Ruckart et al., 2004	Acute	School-age children in Mississippi and Ohio	Methyl parathion exposure (wipe samples and metabolite levels)	PENTB[f] Parent questionnaires	Difficulty in tasks involving STM and attention
Grandjean et al., 2006	Prenatal	School-age children (≤ 9 years) in Ecuador	Maternal occupation during pregnancy ChE and urinary metabolites	Neurobehavioral battery[g] Medical exam	Deficits on visuospatial and response speed Increased metabolites associated with reaction time deficits

Kofman et al., 2006	Acute	School-age children (6–12 years) in Israel	OP poisoned during infancy vs. kerosene poisoned vs. matched controls	Neuropsychological battery[h]	Deficits on long-term memory, learning, inhibitory motor control
Abdel Rasoul et al., 2008	Chronic	Adolescent (9??–18 years) in Egypt	Occupational exposure (pesticide applicators vs. controls) ChE	Neuropsychological battery Symptom checklist	Deficits on all neuropsychological measures Lower ChE levels associated with deficits on Trail Making Increased symptom reporting
Eckerman et al., 2007	Chronic	Adolescents (10–18 years) in Brazil $N = 38$ rural and $N = 28$ urban	Occupational exposure (living and working on a farm vs. controls) Exposure Index	Neurobehavioral battery: BARS	Deficits on response speed, coordination, attention, complex functioning
Rohlman et al., 2001	Chronic	Adolescents (13–18 years) in the U.S.	Occupational exposure	Neurobehavioral battery: BARS	Deficits on response speed, attention, complex functioning
Rohlman et al., 2007a	Chronic	Adolescents (13–18 years) and adults in the U.S.	Occupational exposure	Neurobehavioral battery: BARS	Deficits on attention, response speed, complex function, visual memory

[a]Fetal growth includes birth weight and length and head circumference.

[b]Exposed children were from communities with a high potential for exposure to OP pesticides and carbamates and control children were from communities with a low potential for exposure.

[c]Exposed children were from an agricultural community in the Yaqui Valley, where pesticides are applied. The control children are from the foothills, where pesticides are not applied.

[d]Children whose parents worked in agriculture were compared to children whose parents did not work in agriculture.

[e]Behavioral Assessment and Research System (BARS).

[f]Pediatric Environmental Neurobehavioral Test Battery (PENTB) includes Visual Motor Integration, Kaufman Brief Intelligence Test Purdie Pegboard, Story Memory, Trail Making, and Verbal Cancellation.

[g]Includes tests of simple reaction time, Santa Ana Pegboard, Stanford Binet Copying, and Digit Span Forward.

[h]Includes tests of long-term verbal memory, Digit Span, inhibitory control/motor inhibition (Statue and Knock Tests from the NEPSY), and the Corsi Block Test.

TABLE 17.2   Longitudinal Studies

	Exposure Type	Population	Exposure Measures	Outcome Measures	Significant Findings
			Mt. Sinai		
Berkowitz et al., 2004	Prenatal	Infants from multiethnic cohort of women in New York City (CECS)	Questionnaire Urinary metabolites Cord blood PON1 activity	Fetal growth[a] Gestational duration	Decrease in head circumference associated with TCPy metabolite levels and maternal PON1 activity
Wolff et al., 2007	Prenatal	Infants from multiethnic cohort of women in New York City (CECS)	Questionnaire Urinary metabolites Cord blood PON1 activity	Fetal growth Gestational duration	Lower birth weight and length associated with DEP and DMP metabolites associated with maternal PON1 activity
Engel et al., 2007	Prenatal	Infants from multiethnic cohort of women in New York City (CECS)	Questionnaire Urinary metabolites Cord blood PON1 activity	BNBAS[b]	Increased abnormal infant reflexes
			Columbia		
Perera et al., 2003	Prenatal	Infants from a cohort of minority (African American and Dominican) mothers in New York City (CCCEH)[c]	Maternal blood and cord blood Maternal personal air samples	Fetal growth	Decreased birth weight and length
Whyatt et al., 2004	Prenatal	Infants from a cohort of minority (African American and Dominican) mothers in New York City (CCCEH)	Maternal blood and cord blood Maternal personal air samples	·Fetal growth Gestational duration	Decreased birth weight and length
Rauh et al., 2006	Prenatal	Children (12, 24, and 36 months) from a cohort of minority (African American and Dominican) mothers in New York City (CCCEH)	Chlorpyrifos levels in cord blood	Bayley[d] Child Behavior Checklist (CBCL)	At 36 months: – Decreased Bayley scores (PDI and MDI) –Increased attention, ADHD, and pervasive developmental disorder problems
			CHAMACOS		
Eskenazi et al., 2004	Prenatal	Infants from Latina women in agricultural communities in California (CHAMACOS)[e]	OP metabolites in maternal urine ChE maternal and cord blood	Fetal growth Gestational duration	Shortened gestational duration No adverse association with fetal growth measures[f]
Young et al., 2004	Prenatal	Infants (<2 months) from Latina women in agricultural communities (CHAMACOS)	Maternal DAP metabolites	BNBAS[g]	Increased abnormal infant reflexes
Eskenazi et al., 2007	Prenatal/ current	Infants (at 6, 12, and 24 months) from Latina women in agricultural communities (CHAMACOS)	Maternal and child DAP metabolites and OP metabolites in urine	Bayley[d] Child Behavior Checklist (CBCL)	At 24 months: Bayley MDI[h] Risk of pervasive developmental disorder

[a]Fetal growth includes birth weight and length and head circumference.
[b]Brazelton Neonatal Behavior Assessment Scale (BNBAS).
[c]Columbia Center for Children's Environmental Health (CCCEH).
[d]Bayley Scales of Infant Development (Bayley) include Mental Development (MDI) and Psychomotor Development (PDI) indices.
[e]Center for the Health and Assessment of Mothers and Children of salinas (CHAMACOS).
[f]Increases in body length and head circumference were associated with some exposure measures.
[g]Brazelton Neonatal Behavior Assessment Scale (BNBAS).
[h]Prenatal DAP metabolites were negatively associated with Bayley MDI; however, child DAP metabolites were positively associated with Bayley MDI.

collected (Whyatt et al., 2002). The study is focused on the impact of urban pollution, environmental tobacco smoke, and pesticides on neurodevelopmental outcomes.

The CHAMACOS cohort, unlike the other two studies, focused on a population primarily exposed to pesticides from living near and working in agricultural fields. Mothers were recruited, during prenatal clinic visits. Questionnaires were collected from the mother at different time points during the pregnancy. Urine and blood samples were collected from the mothers and cord blood and urine samples are collected from the children at each visit. The children were followed and assessed at 6, 12, and 24 months and are continuing to be followed as they begin to enter school.

17.7 ACUTE EXPOSURES IN CHILDREN

Two studies examined the impact of acute exposure to OP pesticides. Kofman et al. (2006) examined children poisoned during infancy and Ruckert et al. (2004) examined children recently exposed to methyl parathion. The methods used to assess development and performance and to measure exposure also varied across studies. Although there are inconsistencies across the studies, the evidence suggests that there are performance deficits associated with exposure and an increase in the reporting of developmental and behavioral problems associated with exposure.

17.8 METHODOLOGICAL ISSUES IN STUDIES OF DEVELOPMENT AND NEUROBEHAVIORAL PERFORMANCE

Because a variety of factors can influence the association between exposure to a neurotoxicant and effects on behavior and learning, it is important to include measurement of these factors as part of the study (Jacobson and Jacobson, 2005). Demographic variables are known to impact performance on neurobehavioral tests in adults and children (Anger et al., 1997; Rohlman et al., 2007b) but other influences also need to be considered. These include, but are not limited to, exposure to other toxicants, prenatal influences, nutrition, genetic predisposition, and socioenvironmental influences throughout the child's lifetime (Dietrich and Bellinger, 1994; Jacobson and Jacobson, 2005; Weiss and Bellinger, 2006). These variables impact performance on neurobehavioral tests and, if they are included, are typically treated as covariates or confounders in the studies. However, while this approach is commonly used, it fails to examine the impact of the joint contributions of the factors that impact development and influence exposure (Weiss and Bellinger, 2006). Simply controlling for covariates and confounders in order to examine the impact of a neurotoxicant on performance does not recognize that most adverse effects involve

a combination of factors. Although there has been an increase in the inclusion of these factors in research, more work is needed to ensure we are accurately measuring the early social environment of the child and its impact and interaction with the environment and genetic predisposition of the child.

17.9 NEUROBEHAVIORAL EFFECTS IN INFANTS AND TODDLERS

In the Mt. Sinai cohort study, urinary metabolite levels from the chlorpyrifos metabolite (TCPy) and the ethyl and methyl dialkyl phosphates and low PON1 activity were correlated with a decrease in head circumference, and lower birth weight and length, respectively (Berkowitz et al., 2004; Wolff et al., 2007). A subset of infants were also administered the Brazelton Neonatal Behavioral Assessment Scale (BNBAS). Prenatal levels of OP pesticide metabolites were associated with an increase in abnormal reflexes (Engel et al., 2007).

In the Columbia Cohort Study associations between pesticide levels in maternal blood and decreased birth weight and length were found in infants born prior to 2001 (Perera et al., 2003; Whyatt et al., 2002). As regulatory actions required the phasing out of chlorpyrifos and diazinon in residential applications, a decline in levels of pesticides were seen in personal air samples and blood samples collected from mothers and infants born after 2001 (Whyatt et al., 2005). Children were followed through the first 3 years of life and developmental deficits were associated with higher levels of exposure (Rauh et al., 2006).

The CHAMACOS longitudinal birth cohort study has reported an association between *in utero* OP exposure and decreases in gestational duration (Eskenazi et al., 2004) and an increased number of abnormal reflexes were seen on the BNBAS (Young et al., 2004). The Bayley Scales of Infant Development were administered in both the CHAMACOS study at 6, 12, and 24 months and the Columbia Study at 12, 24, and 36 months. The results from these studies are inconsistent (Rosas and Eskenazi, 2008). Although neither study found an association between measures of prenatal exposure and performance at 6 or 12 months, the CHAMACOS study did see increased DAP levels associated with decrease on mental developmental scores but with improved psychomotor scores (Eskenazi et al., 2007). Deficits associated with chlorpyifos in cord blood were only seen at 36 months in the Columbia study. However, both studies report an association between prenatal exposure and pervasive developmental disorder assessed by the Child Behavior Checklist (Eskenazi et al., 2007; Rauh et al., 2006). The similar findings across studies, in spite of differences in exposure and methods of assessing exposure, indicate that exposure to organophosphate pesticides may impact the neurodevelopment of children.

Two other studies have examined prenatal effects of pesticide exposure on infants and toddlers (Dabrowski et al., 2003; Willis et al., 1993). These studies evaluated prenatal exposure by maternal questionnaires, and Willis included maternal cholinesterase levels (Willis et al., 1993). Although no significant association between exposure and birth outcomes was reported in a study of U.S. infants (Willis), lower birth weight and shorter gestational period were associated with infants from Central Poland (Dabrowski).

17.10 NEUROBEHAVIORAL EFFECTS IN PRESCHOOL CHILDREN

Studies examining preschool children found deficits associated with living in an agricultural community and parents working in agriculture (Guillette et al., 1998; Handal et al., 2007; Rohlman et al., 2005). These studies were conducted in different countries and used different methods, but all showed performance deficits. An anthropological study of children in Mexico found that children living in an agricultural area showed impaired stamina, coordination, memory, and capacity to represent a familiar subject in drawings (Guillette et al., 1998). Performance differences were also seen between children in the United States whose parents work in agriculture compared to those not working in agriculture on response speed and coordination (Rohlman et al., 2005). A study of children living in Ecuador found that children living in communities with a high potential exposure to pesticides because of a cut-flower industry, demonstrated developmental delay compared to children living in communities with low potential exposure to pesticides, and they scored lower on gross and fine motor skills, socio-individual skills, and a figure copying test (Handal et al., 2007). Furthermore there was a link between malnutrition (as measured by stunting) and worse performance.

17.11 NEUROBEHAVIORAL EFFECTS IN SCHOOL-AGE CHILDREN

Deficits on neurobehavioral performance associated with pesticide exposure were also seen in school-age children. Two studies examined exposure early in the child's life, either prenatally (Grandjean et al., 2006) or in the infant (Kofman et al., 2006). Children whose mothers had occupational exposure to pesticides during pregnancy demonstrated visuospatial deficits (increased drawing score on the Stanford-Binet copying test) and higher systolic blood pressure (Grandjean et al., 2006). Stunting was also associated with a lower score on the test. Current exposure, measured by urinary metabolites, was also associated with longer reaction time latencies. Children who were hospitalized as infants because of exposure to OP pesticides had impaired long-term memory

compared to controls (Kofman et al., 2006). The exposed children demonstrated impairment during the acquisition phase of a verbal learning task and in inhibitory motor control. Children living in an agricultural community had decreased performance on the Trail Making and Wisconsin Card Sorting Test (Lizardi et al., 2008). Exposure of children 6 years or younger to methyl parathion spraying has been associated with difficulties performing tasks involving short-term memory and attention, and more behavioral and motor skill problems than the unexposed children (Ruckart et al., 2004).

17.12 NEUROBEHAVIORAL EFFECTS IN ADOLESCENTS

By adolescence, children are often working in agriculture and exposure occurs occupationally. During adolescence there are significant neuroanatomical and neuromaturation changes occurring that are reflected in maturation of abstract reasoning, affect, and cognition (Andersen, 2003; Brown et al., 2000). Although the effect of pesticides on the nervous system of adolescents is unknown, mostly due to limited studies (Adams et al., 2000; Brown et al., 2000), it is reasonable to assume that children up to the age of 18 who still experience rapid changes in their body systems are at high risk for chemical insult (Spear, 2002).

Studies have demonstrated performance deficits associated with children working in agriculture. Adolescent farm workers in Brazil showed impairment on several neurobehavioral measures, including attention, response speed, and coordination when compared to children living in an urban area and not working in agriculture (Eckerman et al., 2006). Although the sample size was small, younger children (10 to 11 years old) showed more impairment than older children. Adolescents working in agriculture in the United States showed impairment on cognitive tests and response speed (Rohlman et al., 2001). Years working in agriculture and handling pesticides were also associated with worse performance in another adolescent population (Rohlman et al., 2007a). The most extensive range of deficits was shown in a population of adolescents applying pesticide in Egypt (Abdel Rasoul et al., 2008). Children who apply pesticides show impaired neurobehavioral performance, report more symptoms, and have lower AChE levels than children from the same communities that do not apply pesticides. This study also shows a correlation between days worked during the current season and increased symptom reports and also with decreased neurobehavioral performance.

Although there is overlap in the methods used to assess cognitive functioning, particularly in infants and toddlers, the studies with older children tend to use a variety of methods. As the longitudinal studies demonstrate, having comparable methods allows broader conclusions to be

drawn. Studies examining infants and toddlers typically use the Bayley Scales of Infant Development which are standardized for ages 0 to 3 years (Black and Matula, 1999). As the children become older other neurobehavioral and neuropsychological tests are used to assess cognitive functioning. Although the Pediatric Environmental Neurobehavioral Test Battery (PENTB) was developed by the Agency for Toxic Substances and Disease Registry (ATSDR) as a screening tool for children, it has had very little use. One study used the PENTB to examine children exposed to methyl parathion (Ruckart et al., 2004). Other studies have used subtests from the PENTB as part of their battery, the Visual Motor Integration Test (VMI) in particular (Handal et al., 2007; Rohlman et al., 2005, 2007b). Studies with older children have also incorporated computerized test methods, particularly the Behavioral Assessment & Research System (BARS; Eckerman et al., 2006; Rohlman et al., 2001, 2007a).

17.13 CONCLUSIONS

While it is well established that OPs can be very toxic to young children if they are ingested or children are exposed to them in large quantities, research findings from the last decade has greatly increased our knowledge of the increased exposure among young children and their developmental vulnerability. The current longitudinal studies currently being conducted in the United States will continue to provide new knowledge regarding the extent of the risk of exposure to low levels of OPs and other pesticide groups. This increasing body of evidence will provide a sound platform upon which to base public health policy to provide the protection that is needed for our vulnerable populations.

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ANTICHOLINESTERASE PESTICIDES

Metabolism, Neurotoxicity, and Epidemiology

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