Recent studies show that young children can be exposed to pesticides during normal oral exploration of their environment and their level of dermal contact with floors and other surfaces. Children living in agricultural areas may be exposed to higher pesticide levels than other children because of pesticides tracked into their homes by household members, by pesticide drift, by breast milk from their farmworker mother, or by playing in nearby fields. Nevertheless, few studies have assessed the extent of children’s pesticide exposure, and no studies have examined whether there are adverse health effects of chronic exposure. There is substantial toxicologic evidence that repeated low-level exposure to organophosphate (OP) pesticides may affect neurodevelopment and growth in developing animals. For example, animal studies have reported neurobehavioral effects such as impairment on maze performance, locomotion, and balance in neonates exposed in utero and during early postnatal life. Possible mechanisms for these effects include inhibition of brain acetylcholinesterase, downregulation of muscarinic receptors, decreased brain DNA synthesis, and reduced brain weight in offspring. Research findings also suggest that it is biologically plausible that OP exposure may be related to respiratory disease in children through dysregulation of the autonomic nervous system. The University of California Berkeley Center for Children’s Environmental Health Research is working to build a community–university partnership to study the environmental health of rural children. This center for the Health Assessment of Mothers and Children of Salinas, or CHAMACOS in Monterey County, California, will assess in utero and postnatal OP pesticide exposure and the relationship of exposure to neurodevelopment, growth, and symptoms of respiratory illness in children. The ultimate goal of the center is to translate research findings into a reduction of children’s exposure to pesticides and other environmental agents, and thereby reduce the incidence of environmentally related disease. Key words: asthma, children, environment, exposure, growth, neurodevelopment, organophosphate, pesticide.


Nationally, approximately 750–800 million pounds of conventional pesticides are used annually in agriculture, excluding sulfur, oils and repellants (14). Total conventional pesticide use, including home, structural, and other applications, averages about 1 billion pounds in the United States. During the mid-1990s, national pesticide use levels have been stable (15), although trends vary by region. In California, which has the largest agricultural output of all 50 states, approximately 200 million pounds of pesticidal active ingredient are used annually in agriculture (16). Pesticide use data for California suggest a trend of increasing use between 1991 and 1995 for production agriculture, postharvest treatment, structural fumigation, and landscape maintenance (16). These changes may be due, in part, to unique meteorologic and economic factors, including heavy rains, shifts to lower toxicity compounds that require higher volume, and changes in planted acreage (16–18). Agricultural use of neurotoxic pesticides, including the OPs chlorpyrifos and diazinon, was also higher in 1995 than in 1991, most likely due to increased use on cotton, and to a lesser extent on oranges, alfalfa, apples, and broccoli (16,17). Overall, pesticide use in California appears to be stable or increasing, with annual fluctuations making it difficult to identify long-term trends.

Pesticide residue in food may also contribute to children’s exposures. In response to concern about low-level exposure, the Food Quality Protection Act of 1996 (P.L. 104–170) (19) was unanimously passed by the U.S. Congress to address pesticide food safety issues raised by the seminal 1993 National Academy of Sciences report Pesticides in the Diets of Infants and Children (13). This report drew the public’s attention to the specific vulnerability of children to many pesticides. The National Academy of Sciences committee found that current tolerances for pesticide levels in food are not health based and may not adequately protect children. Congress specifically directed the U.S. Environmental Protection Agency (U.S. EPA) to reevaluate food tolerances and establish health-based standards that account for children’s unique sensitivity to environmental toxicants. The law requires the U.S. EPA to consider all nonoccupational sources of pesticide exposure, especially exposure to compounds with similar mechanisms of toxicity. The National Academy of Sciences recommended in 1993 that the U.S. EPA modify its...
decision-making process for setting pesticide tolerances to reflect the unique characteristics of the diets of infants and children and account also for all nondietary intake of pesticides (13). Findings from several small, cross-sectional studies (3-6, 8, 12) indicate that nondietary exposures to young children from residential contamination may be an important component of total pesticide exposure. Unfortunately, our knowledge about the actual levels of pesticide exposures of children from food and environmental exposures and their potential health effects is extremely limited.

Children’s Exposure to Pesticides

National population-based surveys of pesticide urinary metabolites in adults indicate widespread exposure to pesticides, including organophosphates, carbamates, wood preservatives, and fungicides (20, 21). For example, Hill et al. (20) detected chlorpyrifos, an OP pesticide, in 82% of 993 adults tested through the National Health and Nutrition Examination Survey, and found a 5-fold increase in the proportion of adults with levels over 5 μg/L compared to earlier surveys, suggesting increasing exposure in the general population. OPs are eliminated from the body after 3–6 days (22), so the widespread detection of these compounds indicates continuing exposure.

Biologic information on children’s pesticide exposure is very limited. Hill et al. (23) reported detections of dichlorobenzene and wood preservatives in 96% and 100%, respectively, of 197 Arkansas children, whereas phenoxy herbicide metabolites were found in 20% of all samples. Preliminary results from the federal Agricultural Health Study indicate detectable pesticide residues in children’s urine (8). Loewenherz et al. (24), working in Washington state, found that 44% of children of pesticide applicators and 27% of nonfarm, rural children had detectable OP residues. In preliminary data from Arizona, chlorpyrifos was detected in 100% of about 40 children >6 years of age sampled in a population-based survey, and approximately 25% of 150 children ≤6 years of age sampled in an agricultural area. Detection limits in the second survey were higher (25). Comparison of these studies to each other and to data reported by Hill et al. (20) is difficult because of differences in detection limits, sample type (spot samples vs. first morning void), and ages of participants. Overall, these studies suggest the potential for widespread low-level pesticide exposure in children and the need for population-based studies to establish norms.

Pesticides enter children’s bodies via dermal absorption, ingestion, and inhalation. Exposure in the home depends on the frequency, duration, and nature (i.e., dermal contact, hand-to-mouth behavior) of the child’s interaction with contaminated media such as house dust. Children may have higher exposure to pesticides than other residents living in the same contaminated environment, in part because young children spend more of their time indoors at home (26, 27). Thus, they are likely to spend more time in proximity to any pesticides present in their immediate environment. The importance of specific exposure-related behaviors, such as hand-to-mouth activity, will be age dependent, suggesting that consequent exposure levels and pathways will vary with age, as has been observed for lead exposure (28). For example, children younger than 6 months of age may receive their greatest exposures through breast milk or inhalation, but dermal absorption and ingestion may be the major pathway of exposure when children begin crawling and placing their hands on dusty surfaces and increasing their hand-to-mouth behavior. The level of exposure may continue to increase, given that the normal tendency of young children to explore their environment orally increases through 2 years of age. The actual dose to the child will depend on environmental concentrations and the efficiency of pesticide uptake for the different types of exposure routes, i.e., dermal contact versus ingestion. To date, direct observation and quantification of children’s exposure-related activity patterns and their interaction with their environment is very limited. Time-activity analysis thus could provide information about age-specific exposure pathways.

To assess time-activity patterns, most researchers have preferred self-administered time diaries and interviews (29, 30). However, these diaries are subject to inaccurate recall and thus have limited validity (31–33). Moreover, they fail to document microactivities such as dermal and hand-to-mouth contacts, which are important pathways of exposure in young children. Observational techniques are more detailed and accurate than conventional methods of questionnaires and diaries for recording such microscopic data (34–37). Leckie and Zartarian and co-workers (36–39) have successfully developed videotaping methodologies and video translation software to quantify children’s activity patterns for dermal and nondietary contacts, and have piloted these techniques on 2–to-4-year-old children of Mexican American farmworkers in California (36). More extensive data collection is needed on children of various ages to assess the changing pathways and routes of exposure as children develop.

Exposures of Farmworkers and Their Families

Nationally, an estimated 5 million farmworkers work on America’s farms, including approximately 1 million California residents (40). A growing body of literature indicates that resident farm families, hired farmworkers, and their children are among those most highly exposed to pesticides (5, 6, 8, 10, 12, 24, 41–49). These studies suggest that farm children can be exposed by the same pathways as other children, namely through consumption of contaminated food, by household use of pesticides, as a result of drift from nearby agricultural applications, by contaminated breast milk from their farmworker mothers, by playing in the fields, and through pesticides tracked into their homes by their parents or other household members working in fields (5, 6, 8, 10, 12, 24, 41–43, 50, 51). For example, preliminary data from pilot studies conducted for the Agricultural Health Study in North Carolina and Iowa indicate elevated levels of recently applied pesticides in the food, homes, and bodies of farm families and their children (8, 10, 12, 43, 44). In a study of 88 children in the Yakima Valley, Washington, Loewenherz et al. (24) reported more frequent detection of OP metabolites in children of pesticide applicators compared to nonaplicators, particularly those living less than 200 ft from orchards. Trends of increasing exposure with decreasing age also suggested that child activity is an important exposure variable.

Simcox et al. (5) studied 59 families in the Yakima Valley, and compared levels of four organophosphate (OP) pesticides in the homes of hired farmworkers, families residing on farms, and nonagricultural families. Chlorpyrifos was detected in 95% of the homes. House dust concentrations were consistently higher for agricultural families than for nonagricultural families, and pesticide applicators tended to have higher house dust concentrations compared to nonaplicators. There was a 3-fold difference in median chlorpyrifos house dust concentration between farmworkers who did not directly handle pesticides and reference families of nonfarmworkers living in agricultural communities (median
where there and in an of pesticides, is limited by small sample size, utilization of a convenience sample, the lack of individual exposure data, and no statistical control of potential confounders. At present, the only prospective study investigating pesticides and adverse health effects is the National Cancer Institute/ U.S. EPA Agricultural Health Study, which is a large cohort study of cancer in midwestern and eastern farmers and their families (49). In spite of the paucity of information concerning the potential health effects in children of chronic low-level exposure to organophosphates, there is substantial evidence in developing rodents and limited evidence in adult humans who have been chronically exposed to OPs that low-level chronic exposure to organophosphates may affect neurologic functioning, neurodevelopment, and growth. Because OP exposure may cause dysregulation of the autonomic control of airways, it is biologically plausible that exposure may be related to the occurrence of asthma in children.

Effects of Acute Exposure to OP and Carbamate Pesticides in Children

The primary effects of OP and carbamate acute exposure are on the parasympathetic, sympathetic, and central nervous system. These pesticides interfere with the metabolism of acetylcholine (ACh) by inhibiting the enzyme that hydrolyzes it, acetylcholinesterase (AChE) (59). ACh accumulates at the neuronal junctions, resulting in the continued stimulation and then suppression of neurotransmission to organs. ACh is the chemical transmitter of somatic motor neurons to skeletal muscle, postganglionic parasympathetic nerve fibers, preganglionic fibers of both sympathetic and parasympathetic nerves, and some fibers in the central nervous system. The accumulation of ACh at the motor nerves results in weakness, fatigue, muscle cramps, fasciculations, and muscular weakness of respiratory muscles. Accumulation at the autonomic ganglia results in increased heartbeat and blood pressure, pallor, and hypoglycemia. Accumulation of ACh at muscarinic receptors results in visual disturbances, tightness in the chest and wheezing due to bronchoconstriction and increased bronchial secretions, and increased salivaion, lacrimation, sweating, peristalsis (resulting in nausea, vomiting, cramps, diarrhea), and urination. Central nervous system effects from ACh accumulation include anxiety, headache, confusion, convulsions, ataxia, depression of respiration and circulation, slurred speech, tremor, and generalized weakness (59,60). Carbamates, unlike OPs, do not irreversibly inhibit AChE. Thus, their activity is quickly reversed after exposure to the pesticide (61). Pregnancy may pose a time of increased risk because plasma AChE activity is already reduced, at least during the first two trimesters (62,63).

The most frequent acute symptoms of OP poisoning in children include miosis, excessive salivation, nausea and vomiting, lethargy, muscle weakness, tachycardia, hyporeflexia, and hypertension, and respiratory distress (60,64). Duration of symptoms depends on the dose, with the highest doses resulting in death. In one study, pneumonitis developed in about one-third of poisoned children (64). OP-induced delayed onset peripheral neuropathy (OPIDN), reported for adults, has not been reported in children.

Long-Term Sequelae of Acute Exposure to OP and Carbamate Pesticides in Adults

Although no studies have examined the long-term sequelae of acute pesticide poisoning in children, some studies in adults suggest that there are residual effects. Neuropsychologic investigations of poisoned farmworkers, pest control workers, and industrial workers tested a number of months to years after acute exposure to various OP pesticides have revealed deficits in overall abstraction, verbal and visual attention, visual memory, visuomotor speed, sequencing, visuomotor problem solving, motor steadiness, motor dexterity, and fine motor speed (65–68). These workers report anxiety, depression, irritability, confusion, and impaired concentration and memory. On neurologic exam, lower vibrotactile sensitivity has been reported (68,69). High acute or subchronic exposures to OPs may also result in delayed neurotoxicity or OPIDN (59,70,71). OPIDN usually manifests 1 to 6 weeks after exposure and may result in moderate to severe peripheral neuropathies lasting months, years, or indefinitely (59).

Effects of Chronic Exposure to OP and Carbamate Pesticides in Adults

Although there are no studies in children on the neuropsychologic effects of chronic pesticide exposure, small studies of chronic low-level exposures of farmers or pest
control workers who had levels of AChE within normal limits found no differences in tests of their neurobehavioral functioning compared to those of unexposed controls (72) or in a pre/post exposure comparison (73). Results of other studies in adults indicate that there may be mild peripheral effects of chronic lower level exposure as indicated by slower reaction times (74), impaired proprioception (postural sway) (75), decreased conduction velocities in motor (median and peroneal) and sensory (median and sural) nerves (76), wider two-point discrimination (77), as well as some neurobehavioral effects such as increased anxiety (78), decreased visual-motor speed (65,79,80), and short-term verbal memory (79). Daily exposure to OPs that are insufficient to cause signs and symptoms of acute poisoning may also produce an influenza-type illness characterized by weakness, anorexia, and malaise (81). In chronic lower level exposures, depression of cholinesterase activity may be cumulative, and there is no predictable correlation between the severity of symptoms and the degree of cholinesterase inhibition.

**Animal Evidence for Neurodevelopmental Effects of Exposure to OP Pesticides**

There is a strong and growing body of evidence linking exposure to OP pesticides during gestation or the early postnatal period and neurodevelopmental effects in animals. These effects may be due to the direct impact of OPs on the cholinergic system of the fetus, although effects on cellular intermediates such as adenylyl cyclase (82) and altered DNA synthesis in the brain through noncholinergic mechanisms (83–85) have been hypothesized. Table 1 summarizes animal studies investigating different organophosphate pesticides, dosing regimes, and exposure routes and their impacts on the developing nervous system.

**Chlorpyrifos**

Neurobehavioral tests given postnatally found that animals exposed in utero demonstrated decreased balance (86), increased righting reflex time, and poorer cliff avoidance (87,88). When exposure occurred in the early postnatal period, there was a lowered threshold for convulsions (89) as well as increased gait abnormalities and tremors (90) and deficits in delayed alternation on mazes (91).

Some studies suggest that early gestation may be a critical period for the neurodevelopmental effects of certain pesticides. Muto et al. (86) studied the effects of exposure to chlorpyrifos in rats occurring both during gestation (gestation days 0–7 and 7–21) and the postnatal period. They reported that early prenatal exposures were more likely to result in poorer performance on the rotord test than exposures during later gestation, which was in turn, more likely to result in deficits than those occurring postnatally.

A number of mechanisms have been proposed to explain the observed neurobehavioral effects in animals. Chanda and Pope (88) found that repeated exposure of rodents to low levels of chlorpyrifos during gestation was related to inhibited levels of AChE and downregulated muscarinic receptors in the fetal brain. Transient brain AChE inhibition also has been consistently reported in neonates postnatally exposed to chlorpyrifos (90–94). Other effects of chlorpyrifos that, in part, could explain the neurobehavioral impairment include decreased muscarinic receptor binding (90,94,95), altered brain RNA concentrations (96), and inhibition of brain DNA synthesis (84,85,97). For example, after treating rats on postnatal days 1–4 with a dosage that produced minimal AChE inhibition (1 mg/kg), Dam et al. (85) reported large deficits in DNA synthesis in the brain stem and forebrain, with lesser effects on the cerebellum. Similar deficits in DNA synthesis were observed after a single early postnatal exposure but at a slightly higher dose (97). Early postnatal exposure to chlorpyrifos (postnatal days 1–4 or 11–45) also altered RNA concentrations in the brain stem and forebrain of rats (96). By targeting RNA, the macromolecule that controls postmitotic processes of cell differentiation and growth, the chemical may evoke alterations in cell function and number in developing organisms (96).

The results of these studies indicate that OP pesticides could contribute to behavioral abnormalities in young animals by producing cellular deficits in the developing brain. Recently, Campbell et al. (84) concluded that regions rich in cholinergic projections, such as the brain stem and forebrain may be more affected than the less cholinergic regions such as the cerebellum. However, the maturational timetable of each region (brain stem then forebrain then cerebellum) may be an important factor in determining relative vulnerability. Nevertheless, there is reasonable evidence that even subtoxic exposure to chlorpyrifos during the critical period of brain development could produce cellular, synaptic, and neurobehavioral aberrations in animals (97).

**Other OP Pesticides**

OPs other than chlorpyrifos have been associated with lowered AChE in the brain of rodents exposed prenatally [bromophos (98), dichlorvos (99), dimethoate (100), methyl parathion (101), quinalphos (102)]. Studies in which animals were exposed early in the postnatal period to these other organophosphate pesticides have also reported inhibition of brain AChE [dichlorvos (103), diisopropylfluorophosphate (104), quinalphos (105), parathion (92,93,95,106)] and downregulation of muscarinic receptors [diisopropylfluorophosphate (104,107), parathion (95,106)]. In addition, evidence from a single in vitro study suggests that prenatal exposure to organophosphates could alter human fetal brain AChE levels. For example, Banerjee et al. (108) reported a dose-dependent inhibition of cerebellar AChE activity in human fetal brain cells (8–10 weeks gestation) treated with 5 × 10⁻¹¹ – 5 × 10⁻⁸ M diisopropylfluorophosphate. Further research in rodents has found reductions in brain weight, most pronounced in the cerebellum and brainstem, following OP exposure during gestation [dichlorvos (109), trichlorfon (109–111)].

Neurobehavioral deficits such as impaired maze performance [dichlorvos (99), diazinon (112)], decreased open-field activity [sumithion (113)], impaired locomotion or swimming [trichlorfon (110), diazinon (112)], and reduced time on the rotord test [diazinon (112), sumithion (113)] have also been associated with prenatal organophosphate exposure. In addition, permanent alterations in spontaneous motor behavior (i.e., locomotion, rearing, and total activity) have been observed in mice exposed to a single subtoxic dose of diisopropylfluorophosphate early in the postnatal period (107).

**Other Potential Developmental Effects of OP Pesticides**

**Decreased Birth Weight and Altered Growth**

A number of the animal studies reported above have demonstrated a decrease in birth weight or body weight in developing animals exposed to OPs. Anticholinesterase agents such as OPs may have a nonspecific regulatory effect on growth, perhaps by an influence on placental transport of nutrients (112,114) or by altering the activity and reactivity of the adenylyl cyclase...
Table 1. Review of the literature of the effects of organophosphate pesticides on neurobehavioral functioning in developing animals.*

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Species</th>
<th>Agent (dose mg/kg) Route</th>
<th>Exposure period</th>
<th>Neurodevelopmental effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spyker and Avery, 1977 (112)</td>
<td>Mouse</td>
<td>Diazinon (0.18, 9) Oral</td>
<td>Throughout gestation</td>
<td>Lower birth weight. Decreased rate of postnatal weight gain. Balance (rotorod), swimming, and maze (speed) effects. No differences in auditory startle, visual cliff response, or open-field motor activity.</td>
</tr>
<tr>
<td>Crowder et al., 1980 (132)</td>
<td>Rat</td>
<td>Methyl parathion (1.0) Gavage</td>
<td>GD 7–15</td>
<td>Slight changes in learning ability as measured by simple two-choice maze. Effects on open-field activity.</td>
</tr>
<tr>
<td>Maslinska et al., 1981 (103)</td>
<td>Rabbit</td>
<td>Dichlorvos (0.0) Gavage</td>
<td>PND 6–16 or 16</td>
<td>Inhibited AChE activity in all brain regions tested; recovery slower in animals exposed over 10 days than after a single dose. Decreased serotoninin concentration in brainstem (22%), mesencephalon (26%), and hippocampus (59%) after prolonged exposure.</td>
</tr>
<tr>
<td>Gupta et al., 1985 (101)</td>
<td>Rat</td>
<td>Methyl parathion (1.0, 1.5) Oral</td>
<td>GD 6–12</td>
<td>Altered postnatal development of brain cholinergic neurons. Reduced AChE activity in all brain regions (1.5 mg/kg). Increased choline acetyltransferase activities in all brain regions (1.5 mg/kg). Subtle alterations in selected behaviors: impaired cage emergence, accommodated locomotor activity, and operant behavior in a mixed paradigm. No morphologic changes in hippocampal or cerebellar tissue.</td>
</tr>
<tr>
<td>Berge et al., 1986 (110)</td>
<td>Guinea pig</td>
<td>Trichlorfon (100) Gavage</td>
<td>GD 36–38 or 51–53</td>
<td>Doses of locomotion. Reduced brain weight, particularly cerebellum, hippocampus, thalamus, and colliculi.</td>
</tr>
<tr>
<td>Pope et al., 1986 (133)</td>
<td>Pig</td>
<td>Trichlorfon (60) Oral</td>
<td>GD 55 or 55 and 70</td>
<td>Dose-related cerebellar hypoplasia. Ataxia not observed in neonates.</td>
</tr>
<tr>
<td>Stamper et al., 1988 (96)</td>
<td>Rat</td>
<td>Parathion (1.3, 1.9) Subcutaneous</td>
<td>PND 5–20</td>
<td>Dose-dependent reductions in AChE activity and muscarinic receptor binding in the cortex. No differences in most reflex measures, eye opening, or incisor eruption during the preweaning period. Small deficits in tests of spatial memory in both the T-maze and the radial arm maze during the postweaning period.</td>
</tr>
<tr>
<td>Lehotzky et al., 1989 (113)</td>
<td>Rat</td>
<td>Sumithion (5, 10, 15) Gavage</td>
<td>GD 7–15</td>
<td>Dose-related decrease in open-field activity and motor coordination (rotorod). Alterations in acquisition and extinction of a conditioned escape response. Increased social interactions. No significant behavioral effects at lowest dose (5 mg/kg).</td>
</tr>
<tr>
<td>Clemens et al., 1990 (134)</td>
<td>Rat</td>
<td>METASYSTOX-R (Methyl demeton) (0.5, 1.5, 4.5) Oral</td>
<td>GD 6–15</td>
<td>No differences in fetal brain AChE. No differences in neonatal survival, growth, and development. No alteration of sensory or reflex functions, maze learning ability, or open-field activity.</td>
</tr>
<tr>
<td>Veronesi and Pope, 1990 (106)</td>
<td>Rat</td>
<td>Parathion (0.882) Subcutaneous</td>
<td>PND 5–20</td>
<td>Cellularr disruption and necrosis in the dentate gyrus and CA4 regions of the hippocampus. Depressed hippocampal AChE (73%) and muscarinic [H+] QNB binding (38%) at PND 12.</td>
</tr>
<tr>
<td>Muto et al., 1992 (86)</td>
<td>Rat</td>
<td>Chlorpyrifos (0.03, 0.1, 0.3) (0.1, 0.3) Intraperitoneal</td>
<td>GD 0–7 or 7–21 PND 3, 10 or 12, 6–10</td>
<td>Lower body weight. Balance effects (rotorod). Effects on open-field motor behavior. Effects early gestation &gt; late gestation &gt; postnatal. Inhibition of brain and plasma ChE activity in both neonate and adult. Good correlation between brain ChE (r = 0.93) or plasma ChE (r = 0.99) inhibitory potency and acute toxicity.</td>
</tr>
<tr>
<td>Pope and Chakraborti, 1992 (93)</td>
<td>Rat</td>
<td>Methyl parathion (&lt; 7.8) (adult: &lt; 18) Parathion (&lt; 2.1) (adult: &lt; 18) Chlorpyrifos (&lt; 45) (adult: &lt; 279) Subcutaneous</td>
<td>PND 7 and adult</td>
<td>(Continued)</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Species</td>
<td>Agent (dose mg/kg) Route</td>
<td>Exposure period</td>
<td>Neurodevelopmental effects</td>
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<tr>
<td>Srivastava et al., 1992 (102)</td>
<td>Rat</td>
<td>Quinalphos (0.5, 1.5) Gavage</td>
<td>GD 6–20</td>
<td>Reduced AChE activity in fetal brain (0.5–1.5 mg/kg) and placenta (1.5 mg/kg)</td>
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<td></td>
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<td></td>
<td></td>
<td>No differences in fetal weight or anomalies</td>
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<tr>
<td>Baldini et al., 1993 (104)</td>
<td>Rat</td>
<td>Diisopropylfluorophosphate (0.5–1.0) Subcutaneous</td>
<td>PND 4–9 or 4–20</td>
<td>Inhibition of AChE Downregulation of muscarinic receptor recognition sites</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>These alterations may delay the maturation of the cholinergic system and may account for some long-lasting neurotropic effects observed after developmental exposure</td>
</tr>
<tr>
<td>Wurpel et al., 1993 (89)</td>
<td>Rat</td>
<td>Chlorpyrifos (0.3–10) Subcutaneous</td>
<td>PND 16 or 17</td>
<td>More rapid amygdala kindling in treated animals Proconvulsant effect was dose related</td>
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<td></td>
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<td>Increased excitability of the amygdala</td>
</tr>
<tr>
<td>Chakraborti et al., 1993 (94)</td>
<td>Rat</td>
<td>Chlorpyrifos (40) Subcutaneous</td>
<td>PND 7–10</td>
<td>AChE activity 55–60% controls Less inhibition of AChE in neonate relative to adult</td>
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<td></td>
<td>Muscarinic [3H] QNB receptor binding in cortex, hippocampus, and striatum marginally affected (5–11% reduction) in neonate Basal motor activity levels not affected</td>
</tr>
<tr>
<td>Mehl et al., 1994 (129)</td>
<td>Guinea pig</td>
<td>Dichlorvos (15–30) Trichlorfon (125) Subcutaneous</td>
<td>GD 42–46</td>
<td>Reduction in brain weight Most pronounced in cerebellum, medulla, thalamus, hypothalamus, and quadrigeminal plate</td>
</tr>
<tr>
<td>Santhoshkumar and Shivananandappa, 1994 (38)</td>
<td>Rat</td>
<td>Bromophos (500) Gavage</td>
<td>GD 18</td>
<td>AChE inhibition in fetal brain started at 2 hr and reached a maximum at 16 hr postexposure (transient) Recovery almost complete by PND 1 Sensitivity of ChE inhibition in vivo: maternal serum &gt; maternal brain &gt; fetal brain</td>
</tr>
<tr>
<td>Stanton et al., 1994 (91)</td>
<td>Rat</td>
<td>Chlorpyrifos (90, 120, 240) Subcutaneous</td>
<td>PND 21</td>
<td>Signs of severe poisoning prevented behavioral testing at highest dose Transient memory impairment on maze (120 mg/kg) Dose-related inhibition of brain AChE but transient Reduced muscarinic binding of [3H]QNB in frontal cortex (240 mg/kg)</td>
</tr>
<tr>
<td>Ahlborn et al., 1995 (107)</td>
<td>Mouse</td>
<td>Diisopropylfluorophosphate (1.5) Gavage</td>
<td>PND 3, 10, or 19</td>
<td>Altered spontaneous motor behavior (increased locomotion, rearing, and total activity) observed at adult age of 4 months Decreased muscarinic receptor density at adult age Persistent effects found in adult mice exposed to single subsymptomatic dose on PND 3 or 10, not in animals exposed on PND 19</td>
</tr>
<tr>
<td>Chanda et al., 1995 (87)</td>
<td>Rat</td>
<td>Chlorpyrifos (200) Subcutaneous</td>
<td>GD 12</td>
<td>Decreased brain AChE activity in both dams (85–88%) and fetuses (42–44%) By PND 3, brain AChE still inhibited in pups (30%), less than for dams (62%) In vitro inhibition of maternal and fetal brain AChE activity indicated that prenatal AChE activity was somewhat more sensitive Righting reflex time was increased in PND 1 pups No differences in righting reflex at PND 3</td>
</tr>
<tr>
<td>Nagmajtenyi et al., 1995 (135)</td>
<td>Rat</td>
<td>Dimethoate (7, 10.5, 14, 28) Dichlorvos (1, 1.5, 2, 3.9) Methyl parathion (0.2, 0.3, 0.4, 0.9) Gavage</td>
<td>Three generations</td>
<td>Males and non-pregnant females: 5 days/week Pregnant females throughout gestation and lactation</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Altered electrophysiological function in primary somatosensory, visual, and auditory cortex Increased mean frequency and EEG index, and decreased mean amplitude dose dependent Changes more expressed in second and third generations AChE inhibition in brain (significant at highest dosages)</td>
</tr>
<tr>
<td>Schulz et al., 1995 (89)</td>
<td>Rat</td>
<td>Dichlorvos (0.97–3.88) Oral</td>
<td>Throughout gestation and lactation</td>
<td>Increased maze running time and errors AChE in brain 40–65% control Changes were dose related Inhibition of DNA synthesis within 4 hr of treatment and at 8 days of age in all brain regions Concluded that low doses target the developing brain during critical period in which cell division is occurring, effects that may produce eventual cellular, synaptic, and behavioral aberrations after repeated or prolonged subtoxic exposures</td>
</tr>
<tr>
<td>Whitney et al., 1995 (97)</td>
<td>Rat</td>
<td>Chlorpyrifos (2.0) Subcutaneous</td>
<td>PND 1</td>
<td>No teratogenic effects found in animals exposed on gestational days 6–15 Two generation study: AChE inhibition in brain (52% control) and decreased body weight in F1 litters (5 mg/kg)</td>
</tr>
<tr>
<td>Brezlin et al., 1996 (115)</td>
<td>Rat</td>
<td>Chlorpyrifos (0.1, 3, 15) gavage (0.1, 1, 5) oral</td>
<td>GD 6–15</td>
<td>Two generations: AChE inhibition in brain (52% control) and decreased body weight in F1 litters (5 mg/kg)</td>
</tr>
</tbody>
</table>

(Continued)
signaling cascade, which would disrupt cell development in all areas of the body, not only those cholinergically regulated (82).

Muto et al. (86) reported lower body weight in rats exposed during the first 7 days of gestation to chlorpyrifos (0.03 mg/kg); with higher doses they found a decrease in the length of the limbs (0.1 and 0.3 mg/kg) and head circumference (0.3 mg/kg). Other studies have reported a decrease in pup weight (115) and a decrease in weight gain postnatally following exposure to chlorpyrifos (88) or diazinon (112) during gestation.

Spyker and Avery (112) also reported lower birth weight and a slower rate of postnatal weight gain in mice exposed to diazinon (9 mg/kg) throughout gestation. In rats, low levels of two carbamates and a triazine herbicide administered postnatally interacted to increase thyroxine levels and alter levels of somatotropin, hormones that regulate growth (116).

**Potential Respiratory Health Effects**

Much of the animal literature reviewed here has focused on the central nervous system effects of organophosphate exposure. Because OP pesticides exert their pharmacologic effects through inhibition of AChE, both short- and long-term effects on autonomic regulation are prominent features in the toxicology of this class of pesticides (76,117). No previous work has addressed the autonomic sequelae of pesticide exposure per se, yet disorders of autonomic regulation may be one of the earliest and most sensitive measures of long-term physiologic effects of exposures in infants and young children.
Similarly, the parasympathetic nervous system provides the principal neural control of lung airway tone. There are considerable data indicating that dysregulation of both parasympathetic (cholinergic) and sympathetic autonomic control of airways, such as by pesticide exposure, may be important in the occurrence of asthma and its severity (118). Dysregulation of parasympathetic function, as measured by respiratory sinus arrhythmia, predicts the onset of wheezing in adults (119). Although there are few direct studies of the effects of OP and carbamate pesticide exposure on asthma risk, farmworkers’ exposure to carbamate pesticides has been associated with the occurrence of asthma after adjustment for other relevant factors (120). Professional fumigators reportedly have an increased occurrence of allergy and asthma in parallel with a higher risk of a > 20% decrease in red blood cell AChE (121). Exposure to chlorpyrifos has also been associated with an increase in the occurrence of atopic conditions (122). Although none of these studies involved children, they raise the prospect that pesticide exposure could be important etiologic and morbidity-modifying factors in the occurrence of childhood asthma.

**Biologic Plausibility for the Effects of Low-Level Chronic Pesticide Exposure in Children**

Tests on young rodents demonstrate a progressive decrease in susceptibility to OP pesticides with increasing age (13,123–125). In some cases, the lethal dose in immature animals is only 1% of the adult lethal dose (92,93,97). A study of rats found that animals 1 and 7 days of age tolerated only 4% and 17% of the adult dose, respectively (92,93,97). Seven-day-old rats were 2.3, 8.6, and 6.2 times more sensitive than adults to the acute toxicity of methyl parathion, parathion, and chlorpyrifos, respectively (92). In humans, children have had higher fatality rates than adults in several cases of OP poisoning (13).

Young animals may be more susceptible to the toxic effects of organophosphates due to lower activity of detoxifying enzymes such as paraoxonase that deactivate active OP metabolites (e.g., paraoxon, chlorpyrifos–oxon) (123,126–131). For example, Mortensen et al. (126) reported markedly lower plasma and liver chlorpyrifos–oxonase levels in neonates compared to adult rat tissue. They concluded that the higher sensitivity of young rats to acute chlorpyrifos toxicity may not be explained by increased sensitivity of the target enzyme, brain AChE, but it may be partially explained by a deficiency of chlorpyrifos–oxonase activity (126).

Although young animals are more sensitive than adults to the acute toxic effects of chlorpyrifos, some researchers have suggested that lower level chlorpyrifos exposures may produce more extensive neurobehavioral effects in the adult rat than in the neonate (94). In addition, more extensive changes have been found in cholinergic parameters in the maternal brain compared to the fetus or neonate (88). Developing animals also appear to recover more quickly from cholinesterase inhibition than the adult (92,98), and may be less susceptible to developing OPIDN (71). However, repeated low-dose chlorpyrifos exposure during gestation has been associated with persistent neurochemical and neurobehavioral changes in developing rodents (88).

In summary, young children may be especially vulnerable to pesticides because of the sensitivity of their developing organ systems combined with a limited ability to enzymatically detoxify these chemicals (13,123,126–131). According to the National Academy of Sciences (13), children’s OP exposures are of special concern because “exposure to neurotoxic compounds at levels believed to be safe for adults could result in permanent loss of brain function if it occurred during the prenatal and early childhood period of brain development” (13). Because there is so little information available on the levels and routes of children’s pesticide exposure, it is not feasible to conduct a risk assessment predicting the likelihood of adverse effects based on animal studies. Thus far, there are no data in children to support or refute the hypothesized health effects of chronic low-level pesticide exposure.

**Future Directions**

There is clearly a lack of information on the sources, pathways, and levels of pesticide exposures of children, and in particular, of those children at highest risk because they live in agricultural communities. Similarly, there is a dearth of information on whether low-level chronic exposure to pesticides is associated with adverse health effects. The goal of the Center for Children’s Environmental Health Research at the University of California, Berkeley is to address these questions by conducting a longitudinal cohort study of approximately 500 pregnant women and their children who live in a rural agricultural community in the Salinas Valley of Monterey County, California. The specific aims of this Center for the Health Assessment of Mothers and Children of Salinas, or CHAMACOS (which means “little child” in Chicano Spanish), are to a) characterize OP exposure levels and pathways in pregnant women and their children; b) determine the predictors of OP levels in the body and home; c) describe the exposure-prone behavior of children at different developmental stages using time–activity analysis; and d) follow up the children to 3 years of age to determine whether exposure in utero and/or during the postnatal period is associated with poor neurodevelopment (assessed by tests of the central and autonomic nervous system), slower and stunted growth, and increased prevalence of respiratory symptoms and disease. Our ultimate goal is to involve community partners in planning, coordinating, and conducting an intervention to reduce pesticide exposures to young children in this agricultural community and to evaluate the efficacy and sustainability of the intervention. To accomplish our goals, we have established a multidisciplinary partnership comprised of farmworkers, health care providers, growers, journalists, scientists, educators, and representatives of community groups and state and county health and agricultural departments. We are hopeful that the results of this study will benefit this community and agricultural communities, in general, and will directly contribute to the information necessary for the implementation of the Food Quality Protection Act.

**References and Notes**


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