American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

FROM THE AMERICAN ACADEMY OF PEDIATRICS

TECHNICAL REPORT

# Pesticide Exposure in Children

James R. Roberts, MD, MPH, Catherine J. Karr, MD, PhD, and COUNCIL ON ENVIRONMENTAL HEALTH

**KEY WORDS**
pesticides, toxicity, children, pest control, integrated pest management

**ABBREVIATIONS**
CDC—Centers for Disease Control and Prevention
CI—confidence interval
2,4-D—2,4-dichlorophenoxyacetic acid
DDE—*p,p'*-dichlorodiphenyldichloroethylene
EPA—Environmental Protection Agency
ES—Ewing sarcoma
GI—gastrointestinal
INR—international normalized ratio
IPM—integrated pest management
NPDS—National Poison Data System
OP—organophosphate
OR—odds ratio
PT—prothrombin time
RR—relative risk
SGA—small for gestational age
Th2—T helper 2



www.pediatrics.org/cgi/doi/10.1542/peds.2012-2758

doi:10.1542/peds.2012-2758

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).



## abstract

FREE

Pesticides are a collective term for a wide array of chemicals intended to kill unwanted insects, plants, molds, and rodents. Food, water, and treatment in the home, yard, and school are all potential sources of children's exposure. Exposures to pesticides may be overt or subacute, and effects range from acute to chronic toxicity. In 2008, pesticides were the ninth most common substance reported to poison control centers, and approximately 45% of all reports of pesticide poisoning were for children. Organophosphate and carbamate poisoning are perhaps the most widely known acute poisoning syndromes, can be diagnosed by depressed red blood cell cholinesterase levels, and have available antidotal therapy. However, numerous other pesticides that may cause acute toxicity, such as pyrethroid and neonicotinoid insecticides, herbicides, fungicides, and rodenticides, also have specific toxic effects; recognition of these effects may help identify acute exposures. Evidence is increasingly emerging about chronic health implications from both acute and chronic exposure. A growing body of epidemiological evidence demonstrates associations between parental use of pesticides, particularly insecticides, with acute lymphocytic leukemia and brain tumors. Prenatal, household, and occupational exposures (maternal and paternal) appear to be the largest risks. Prospective cohort studies link early-life exposure to organophosphates and organochlorine pesticides (primarily DDT) with adverse effects on neurodevelopment and behavior. Among the findings associated with increased pesticide levels are poorer mental development by using the Bayley index and increased scores on measures assessing pervasive developmental disorder, inattention, and attention-deficit/hyperactivity disorder. Related animal toxicology studies provide supportive biological plausibility for these findings. Additional data suggest that there may also be an association between parental pesticide use and adverse birth outcomes including physical birth defects, low birth weight, and fetal death, although the data are less robust than for cancer and neurodevelopmental effects. Children's exposures to pesticides should be limited as much as possible. *Pediatrics* 2012;130:e1765–e1788

## INTRODUCTION

Pesticides represent a broad classification of chemicals that are applied to kill or control insects, unwanted plants, molds, or unwanted animals (eg, rodents). "Pesticide" is a collective term for a wide array of products but is often inappropriately used in reference to only insecticides. The universe of pesticide types and products is broad, and

a comprehensive review of all active ingredients is beyond the scope of this report. This review focuses on select insecticides, herbicides, and rodenticides and specific chemical classes within these groups that have the greatest acute and chronic toxicity for children on the basis of historical experience and/or emerging evidence (Table 1).

Several types of pesticides are not discussed in this report. Fumigants and fungicides, although potentially toxic, are less commonly involved in acute childhood exposure and poisoning, in general, so these are not included. Wood preservatives containing arsenic are also not included in this report. The specific compound containing arsenic, copper chromium arsenate, has been removed from the market since January 2004. Older wood structures treated with copper chromium arsenate may still be found in homes, on playgrounds, and in yards and should be treated yearly with a waterproof sealant.[1] Insect repellents, including *N, N*-diethyl-meta-toluamide and picaridin, are different from most pesticides in that they are a product purposefully applied to human skin to prevent insect bites and are, in fact, not insecticides. These compounds are unique and have been reviewed recently.[2]

Although the severity of pesticide exposures and toxicity may be greater in developing countries where regulatory oversight and information is limited, the content of this technical report is oriented toward exposures most relevant to children residing in the United States. Commonly used insecticides, including the organophosphates (OPs), carbamate, and pyrethroid classes, are discussed, as are the relatively new neonicotinoids. Other pesticides that will be discussed in some detail include the phosphonate herbicides (eg, glyphosate), chlorophenoxy herbicides, and long-acting anticoagulants (rodenticides). For a more comprehensive survey of the acute toxicity from the spectrum of pesticide active ingredients and products, see other sources.[1,3]

## CHILDREN'S EXPOSURE: VULNERABILITY, MECHANISMS, AND SOURCES OF EXPOSURE

### Children's Unique Vulnerabilities

Children are uniquely vulnerable to uptake and adverse effects of pesticides because of developmental, dietary, and physiologic factors. Exposure occurs through ingestion, inhalation, or dermal contact. Unintentional ingestion by children may be at a considerably higher dose than an adult because of the greater intake of food or fluids per pound of body weight. Children exhibit frequent hand-to-mouth activity, and this is an important source of increased exposure in comparison with adults.[4,5]

### Residential Factors

Fortunately, acute toxicity attributable to pesticide poisoning is relatively uncommon in US children, and a pediatrician in general practice may not encounter such an event. However, subacute and chronic low-level exposure is common. Residential factors that influence chronic exposure include the use of insecticides and rodenticides in the home, and herbicide and fungicide use on lawns, as well. Indoors, broadcast applications including sprays, "flea bombs," and foggers can leave lingering residues in the air, carpet, toys, and house dust.[6–9] Typical exploratory behavior, including playing on and crawling across the floor, increases the risk of dermal, inhalation, and oral exposure to residues on surfaces or the air as it settles.[10] Repeated and cumulative incidental exposure can also occur. Pesticides can be measured in indoor air samples and persist in dust vacuumed from carpeted areas, upholstered objects, and children's toys, such as stuffed animals, and can also be brought home from the workplace.[11–14] Herbicides applied on the lawn or garden can be tracked into the home, with residues building up over time.[15] Applications of diazinon to lawns have been demonstrated to be carried indoors via the paws of pet dogs.[16] Residential pesticide residue levels also vary geographically according to the specific pesticide needs in the area. In Los Angeles, high levels of chlorpyrifos and other insecticides were found because of the large numbers of crawling insects, fleas, and termites. Conversely, in Iowa, there were high levels of the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and dicamba because of weed-control applications.[17]

Residentially related sources may be relevant in other settings where children spend time, including school, child care, a relative's home, etc, depending on indoor and outdoor pesticide use patterns and proximity to pesticide use. In a North Carolina study of 142 urban homes and preschools, chlorpyrifos was detected in all indoor air and dust samples.[18]

### Biomonitoring Data for Exposure Assessment

The Centers for Disease Control and Prevention (CDC) conducts a population-based biomonitoring program associated with the NHANES.[19] The most recent report includes biomarker data for many organochlorine, OP, and carbamate insecticides; herbicides; pyrethroid insecticides; and some other pesticides. Testing of 44 pesticide metabolites revealed that 29 were detectable in most people from whom samples were analyzed (ages 6–59 years), with OP and organochlorine insecticides reported to be most prevalent in the US population.[19] Although the health implications of these "snapshot" sampling data are largely unknown, they do

**TABLE 1** Major Pesticide Classes and Selected Examples

| Pesticide Class | Examples | Toxicity | Comment, Uses |
|---|---|---|---|
| Organochlorines | DDT, endrin, aldrin, chlordane, lindane | • High toxicity | • Many organochlorines now banned in the United States<br>• Lindane has been banned in California, elsewhere used for control of lice and scabies<br>• DDT and other organochlorines have long metabolic disposition and are stored in fatty tissues and can persist in the environment |
| Organophosphates | Parathion, chlorpyrifos, dichlorvos, acephate, methyl-parathion, malathion, phorate | • Most OPs are highly toxic<br>• Malathion is considered relatively less toxic than other OPs | • Parathion is banned for use in the United States<br>• Chlorpyrifos is no longer approved for residential use<br>• Most others are used for insect control in both agricultural and home settings<br>• Malathion is an approved treatment of head lice |
| *N*-Methyl carbamates | Aldicarb, carbaryl, carbofuran, pirimicarb, propoxur | • Aldicarb and carbaryl are both highly toxic<br>• Other carbamates have a relatively moderate toxicity | • Insect control in agricultural and home settings |
| Pyrethrins and pyrethroids | Permethrin, cyano-pyrethroids: deltamethrin, cypermethrin, fenvalerate | • Permethrin has relatively low toxicity<br>• Other pyrethroids have moderate toxicity | • Permethrin is a common pediculicide<br>• Most other pyrethroids are commonly used to control insects, often used in home and garden |
| Neonicotinoids | Imidacloprid | • Relatively newer class of insecticides | • Selective affinity toward insect nicotinic acetylcholine receptors compared with mammalian nicotinic acetylcholine receptors |
| | | • Have relatively lower toxicity than OPs and carbamates | • Often used as spot-on flea control for domestic animals |
| *N*-Phenylpyrazole insecticides | Fipronil | • Relatively newer class of insecticides | • Often used as spot-on flea control for domestic animals<br>• Yard treatments for insect control |
| Phosphonate herbicides | Glyphosate | • Because of primary mechanism of action, has relatively low toxicity from active ingredient.<br>• Toxicity often due to the accompanying organic solvent | • Acts on plant cell wall<br>• Commercially available in many products |
| Chlorophenoxy herbicides | 2,4-D, 2,4,5-T | • Moderate toxicity | • Weed control |
| Dipyridyl herbicides | Paraquat, diquat | • Highly toxic | • Infrequently used<br>• Paraquat toxicity often requires lung transplant |
| Long-acting anticoagulants | Brodifacoum (superwarfarins) | | • Rodenticides<br>• Longer-acting than warfarin<br>• Recently eliminated packaging as loose pellets |

2,4,5-T, 2,4,5-trichlorophenoxy acetic acid.

provide a reference point on pesticide metabolite distributions. Periodic reassessment also allows for evaluations of population-level exposure trends.

As noted previously, children's unique behaviors and metabolic rate often place them at risk for absorption of higher doses from contaminated environments in comparison with adults. One example evident from the biomonitoring data is chlorpyrifos, a nonpersistent OP insecticide. Although banned in 2000 for use inside the home, it continues to be used in agriculture, including orchard fruits, such as apples and pears, and other dietary staples of children. In the CDC biomonitoring data, chlorpyrifos-specific urinary metabolites were highest for the youngest age group assessed (6–11 years) compared with older children and adults.[19] In contrast, biomonitoring of serum markers of organochlorine insecticides and their metabolites, such as DDT, dieldrin, and chlordane, many of which were banned from use in the United States in the 1970s and 1980s, revealed lower concentrations in the youngest age group monitored (12–19 years). Despite relatively lower concentrations, the ongoing detection and the higher levels with increasing age likely reflect the influence of the accumulation of these fat-soluble, persistent compounds over a lifetime.

## Exposures From the Food Supply

In the general population, the food supply represents the most important source of exposure for organochlorines and OPs. For pyrethroids, both food residues and household pest control products are important sources.[20] The US Environmental Protection Agency (EPA) regulates exposure to pesticides in food by setting "tolerances," which are the maximum amount of pesticides that may legally remain in or on food

and animal feed. The US Food and Drug Administration is responsible for enforcement of these tolerances, which includes a modest monitoring program, which analyzed 7234 total samples in 2003. Among the domestically produced samples, 49% of fruit, 29% of vegetables, 26% of grain products, 24% of fish/shellfish, and 0% of milk/dairy tested had detectable but legally allowable pesticide residues. Only fruit and vegetables had residues above the legal tolerance (approximately 2% each). Overall, the detection of residues in the samples from imported fruits and vegetables tested were less, but the exceedances of legal tolerances were greater (5%–7% of imported fruits/vegetables sampled).[21] Consumption of organic food may lower pesticide exposure, as demonstrated by a study in which children were placed on an organic diet for a period of 5 consecutive days. A rapid and dramatic drop in their urinary excretion of metabolites of malathion and chlorpyrifos OP insecticides during the organic diet phase was observed.[22]

### Agriculturally Related Exposures

Proximity to pesticide-treated agricultural areas or household members that work with pesticides presents another opportunity for contamination of the residential environment for some children. In a Washington State study of children of agricultural workers and nonagricultural workers in an agricultural setting, pesticide levels in carpet dust and pesticide metabolites in urine of residents increased with self-reported proximity of homes to orchard fields and during the pesticide application season.[9,23] Similarly, in an agriculture center in California, pesticide residues of 3 chemicals used recently on crops were significantly correlated with house dust samples in nearby homes and urine samples among their inhabitants. The findings were noted in both farmworkers and nonfarmworkers.[24] The presence of an agricultural worker in the home also increases pesticide levels through "take-home" exposures.[23] Children living on a farm had higher urinary pesticide metabolite levels than children not living on a farm.[25] Children themselves may participate in agricultural work that involves the use of pesticides or contact with pesticide-treated foliage.[26–28]

### Exposures From Drinking Water

Contamination of drinking water presents another potential source of exposure, particularly for herbicides. A 10-year study (1992–2001) by the US Geological Survey's National Water-Quality Assessment program provided a national-scale view of pesticide occurrence in streams and groundwater. Overall, pesticides were detected in more than 50% of sampled wells from shallow groundwater tapped beneath agricultural and urban areas as well as in 33% of the deeper wells that tap major aquifers used for water supply. The concentrations associated with these detections rarely exceeded water quality health reference levels (approximately 1% of the 2356 domestic and 364 public-supply wells that were sampled). Herbicides, particularly the triazine class, were the most frequently detected pesticide group in agricultural areas. (It should be noted that atrazine and other triazine herbicides were monitored from surface water.) In urban areas, both herbicides and insecticides (particularly diazinon and carbaryl) were frequently detected. The greatest proportion of wells exceeding a health reference level was for those tapping shallow groundwater beneath urban areas. It is noteworthy that the detection of pesticides usually occurred as mixtures, and health reference levels reflected exposure to a single agent.[29]

## NATIONAL DATA ON ACUTE EXPOSURE, MORBIDITY, AND MORTALITY

Although some states (eg, California and Washington) mandate the reporting of pesticide-related illness, there is no national surveillance system for pesticide exposure and poisoning. The American Association of Poison Control Centers' National Poison Data System (NPDS [formerly known as the Toxic Exposure Surveillance System]) compiles annual data on pesticide exposures. Incidents reported by the NPDS are categorized by age (<6 years, 6–19 years, and >19 years), reason (unintentional, intentional, other, adverse reaction), and outcome (none [no morbidity], minor, moderate, major, or death). However, these data represent self-reports from patients and/or family members and calls from medical treatment facilities. Although they are useful to describe trends, they do not indicate true prevalence or incidence. Data are reported annually and, since 2005, have been published in *Clinical Toxicology*.[30]

In 2009, pesticides were the tenth most frequently involved substance in human exposure (3.9% of all NPDS reports) and the ninth most common substance encountered in children (3.3% of pediatric NPDS reports). Nearly 55.8% of all single-substance pesticide exposures involved children ≤19 years of age, and 94% of all pesticide ingestions were unintentional. Twenty-one of the reports from pesticide exposure resulted in death; however, these were not categorized by age.[30] Rates (calculated by using US census data for the catchment area served by the poison control center as the denominator) of reported pesticide poisonings described as moderate, major, and fatal declined from 1995 to 2004 by approximately 42%. The sharpest declines in poisonings were from OP and carbamate insecticides,

likely reflecting EPA regulatory action to discontinue residential use of several previously widely available OP and carbamate insecticides on the basis of child health concerns.[31]

## ACUTE TOXICITY MECHANISMS AND CLINICAL MANIFESTATIONS

### OP and Carbamate Insecticides

OP and carbamates insecticides have been widely used for insect control in the home and in agriculture since the 1960s. During this period, OP and carbamates usage largely replaced the use of organochlorines because of environmental and human health concerns of the latter class. In the past 10 years, chemical products in the OP and carbamate group have come under scrutiny, with subsequent regulatory action based on human health concerns. Examples include 2 commonly used OPs with high acute toxicity: parathion (banned) and chlorpyrifos (no longer allowed for residential use). Other OPs that remain widely used include dichlorvos, acephate, methyl-parathion, and malathion. Malathion has relatively lower acute toxicity among the OPs and is registered for the treatment of head lice (Ovide). A well-known example of a carbamate is aldicarb, although use has largely been curtailed by regulatory action because of its high toxicity. Commonly used carbamates include carbaryl and pirimicarb.[1,3]

#### *Toxicity, Clinical Signs, and Symptoms*

OPs and carbamates exert a common mechanism of action by inhibiting the acetylcholinesterase enzyme, thereby producing accumulation of acetylcholine at the synapses, neuromuscular junction, and end organs, which results in excessive stimulation at those sites. The reaction is generally an irreversible binding by OPs and a reversible binding by carbamates, and it influences treatment approaches for each class of insecticides. Consequently, acute poisoning by OPs tends to be more severe and refractory than that of carbamates; however, variations are observed in each class. There are some notable carbamates (such as aldicarb) that have equal if not greater toxicity than some OPs.[1,3]

Acute clinical manifestations reflect the development of cholinergic crisis and can arise from stimulation of muscarinic, nicotinic, and/or central nervous system receptors (Table 2). Early findings can often mimic a flu-like illness and include hypersecretion. Miosis is a helpful diagnostic sign. The classic cardiovascular sign is bradycardia, although early on, tachycardia may be present initially because of nicotinic stimulation. Progressive symptoms lead to muscle and respiratory problems. The central nervous system may also be affected, signifying severe poisoning, particularly in children.[1,3,32–34] Reviews of case series indicate that between 20% and 30% will have seizures, and between 50% and 100% of children will have lethargy, stupor, or coma.[32–34] A high clinical suspicion plus directed and persistent environmental history taking to identify potential exposures are necessary to identify these poisonings. Reviews of pediatric poisonings note that, historically, most children were transferred to a referral center with the wrong preliminary diagnosis and parents initially denied any exposure history.[33,34]

#### *Laboratory Evaluation and Treatment*

Poisoning with OPs and carbamates can be detected on the basis of clinical findings and history of exposure. Laboratory confirmation can assist in the diagnosis by using red blood cell and plasma cholinesterase levels; both are typically depressed with acute poisoning, although there is some variation among active ingredients as well as variation in levels by severity of poisoning.[35] Measurement techniques and resultant levels vary among laboratories; therefore, clinicians will need to check with their own laboratory for reference values. Red blood cell cholinesterase levels typically are more specific for acute poisoning and will be depressed longer than plasma cholinesterase levels (often 1–3 months) until enzyme is replaced.[3] Interpretation of results can be discussed with a pediatric environmental health specialist or clinical toxicologist.

The parent active ingredient cannot typically be measured in biological specimens. These compounds undergo metabolic transformation in the liver and are excreted in the urine mostly in their metabolized form, most of which are nonspecific metabolites for all OPs.[19] Exceptions include parathion, methyl-parathion, and chlorpyrifos, all of which have their own specific metabolite in addition to the nonspecific metabolites. Urinary metabolites can be measured, and human data are available from the CDC on a nationally representative sample.[19] However, an evidence base to support clinical interpretation of urinary concentrations is lacking.

Treatment of OP poisoning (and this applies to the acute treatment of any other pesticide as well) begins with the basics of advanced life support, with any necessary airway or breathing support as needed. Gastrointestinal (GI) decontamination is controversial. The American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists issued a joint statement on the use of single-dose charcoal for poisoned patients (inclusive of all types of poisonings). They stated that activated charcoal is most effective when given within 1 hour after the ingestion of a poison, but routine administration in all poisonings is not recommended.

**TABLE 2** Clinical Signs and Symptoms

| Class of Compounds | Signs and Symptoms | Special Notes, Laboratory Evaluations, Specific Treatments, or Antidote |
|---|---|---|
| Organophosphate and carbamate insecticides | • Nonspecific early symptoms: headache, nausea, vomiting, abdominal pain, and dizziness | • Red blood cell and plasma cholinesterase levels |
| | • Sometimes hypersecretion: sweating, salivation, lacrimation, rhinorrhea, diarrhea, and bronchorrhea | • Measure nonspecific metabolites for most OPs |
| | • Progressive symptoms: muscle fasciculation, muscle weakness, and respiratory symptoms (bronchospasm, cough, wheezing, and respiratory depression) | • Specific metabolites can be measured for chlorpyrifos and parathion |
| | • Bradycardia is typical, although early in acute poisoning, tachycardia may be present | • Atropine is primary antidote |
| | • Miosis | • Pralidoxime is also an antidote for OP and acts as a cholinesterase reactivator |
| | • Central nervous system: respiratory depression, lethargy, coma, and seizures | • Because carbamates generally produce a reversible cholinesterase inhibition, pralidoxime is not indicated in these poisonings |
| Pyrethroids | • Dermal: skin irritation and paresthesia | • At times have been mistaken for acute OP or carbamate poisoning and treated with atropine with potentially adverse or disastrous results |
| | • Nonspecific symptoms including headache, fatigue, vomiting, diarrhea, and irritability | • Symptomatic treatment |
| | • Similar findings found in OPs, including hypersecretion, muscle fasciculation, pulmonary symptoms and seizures | • Vitamin E oil for dermal symptoms |
| Neonicotinoids | • Disorientation, agitation—severe enough to require sedation, drowsiness, dizziness, weakness, and, in some situations, loss of consciousness | • Supportive care |
| | • Vomiting, sore throat, abdominal pain | • No available antidote |
| | • Ulcerations in upper GI tract | • No available diagnostic test |
| Fipronil (*N*-phenylpyrazole insecticides) | • Nausea and vomiting | • Supportive care |
| | • Aphthous ulcers | • No available antidote |
| | • Altered mental status and coma | • No available diagnostic test |
| | • Seizures | |
| Organochlorines | • Central nervous system: mental status changes and seizures | • Control acute seizures with lorazepam |
| | • Paresthesia, tremor, ataxia, and hyperreflexia | |
| Glyphosate (phosphonate herbicides) | • Nausea and vomiting | • Supportive care |
| | • Aspiration pneumonia type syndrome | |
| | • Hypotension, altered mental status, and oliguria in severe cases | |
| | • Aspiration pneumonia type syndrome | |
| | • Pulmonary effects may in fact be secondary to organic solvent | |
| Chlorophenoxy herbicides | • Skin and mucous membrane irritation | • Consider forced alkaline diuresis with sodium bicarbonate in IV fluids |
| | • Vomiting, diarrhea, headache, confusion | |
| | • Metabolic acidosis is the hallmark | |
| | • Renal failure, hyperkalemia, and hypocalcemia | |
| Long-acting anticoagulants (rodenticides) | • Bleeding: gums, nose, and other mucous membrane sites | • Consider PT (INR) or observation |
| | • Bruising | • Vitamin K indicated for bleeding (IV vitamin K) or for elevated PT (INR) (oral vitamin K) |

IV, intravenous.

Activated charcoal is contraindicated if the patient does not have a protected or intact airway.[36] A randomized controlled trial evaluating the effect of multiple-dose charcoal for pesticide-poisoned patients in Asia found no benefit, as measured by a reduction in mortality.[37] Skin decontamination also is critically important, and clothing should be removed. Medical personnel should take measures to protect themselves from contaminated skin and clothing, because numerous cases of hospital-acquired OP poisoning have been documented.[38] Parents or other family caregivers may also be at risk for skin contamination. Seizures should be controlled with intravenous lorazepam.[3]

Atropine can be given as a nonspecific antidote in both OP and carbamate poisoning. It will reverse the muscarinic effects of the poisoning; however, it is less effective on central nervous system effects. It is given as a dose of

0.05 to 0.1 mg/kg per dose and may be given as often as every 15 minutes until respiratory secretions are controlled.[3] Notably, this dose is 10 times the usual dose given during a resuscitation situation, because the purpose is to overcome complete blockade of the muscarinic channel. Pralidoxime is also given as a specific antidote to reverse the acetylcholinesterase inhibitor complex. The use of pralidoxime continues to be of interest, particularly in developing countries, although most studies have been performed with adult patients.[39,40] The World Health Organization recommends its use for all patients who require atropine.[41] Its use is indicated for OP poisoning, because cholinesterase inhibition usually is permanent in OP poisoning. Use of pralidoxime usually is not necessary or recommended for carbamate poisoning, because this inhibition is reversible.[3]

## Pyrethrins and Pyrethroid Insecticides

Pyrethrins and pyrethroids are a relatively more recent class of insecticides that have been largely replacing the use of cholinesterase-inhibiting insecticides, especially in the consumer market. These insecticides are used for structural pest control in urban areas, in gardening or agriculture for row crops and orchards, and in the home for pet sprays and shampoo.

The pyrethrins are botanically derived from pyrethrum, an extract of the chrysanthemum plant. For these consumer products, pyrethrins are usually combined with another active ingredient: either a longer-acting synthetically derived pyrethroid or one of the cholinesterase inhibitors. Pyrethrins are not stable in heat or sunlight and, therefore, are usually used more for indoor application. Permethrin is the most widely known example of a pyrethrin and is one of the few products licensed for use to apply to human skin, because it is commonly used as a pediculicide.[3,42,43]

Pyrethroids are synthetically derived compounds that have been modified to be more stable in sunlight and heat and are, therefore, used more widely for insect control, especially outdoors. Toxicity varies widely among pyrethrins and pyrethroids, and, although they are less acutely toxic as a class than the cholinesterase insecticides, there is a subgroup of these compounds that has been modified with a cyano side chain. This modification creates a compound that is significantly more resistant to degradation and potentially more acutely toxic than other pyrethroids. Commonly used chemicals in this subgroup include deltamethrin, cypermethrin, and fenvalerate—these are the insecticides to which the majority of toxic signs and symptoms in the next section apply.[43]

### *Toxicology, Clinical Signs, and Symptoms*

Pyrethroids exert their toxic effect by blocking the sodium channel at the level of the cell membrane. Most clinical reports of poisoning occur either through excessive skin contact or through ingestion or inhalation. The result is continued hyperpolarization, effectively inhibiting cell function. Some types of pyrethroids also work at other sites, including voltage-dependent chloride channels and γ-aminobutyric acid–gated chloride channels. This appears to be one of the reasons for a variety of toxicity found among pyrethroid insecticides.[42,43] Pyrethroids with a cyano group, also known as type II pyrethroids, constitute most cases of human poisoning.[42,43] Pyrethroids are well absorbed across the GI tract, but limited penetration occurs across the skin barrier, which can limit acute toxicity.[42,44] Some pyrethroids have a high acute toxicity, usually after ingestion.[42,45] Pyrethroids are metabolized by the liver and excreted in their metabolic forms.

Pyrethroids have adverse effects on the nervous system, GI tract, and skin. Specific signs and symptoms are found in Table 2. Similar to OPs, muscle fasciculation, weakness, an altered level of consciousness, and seizures can develop after exposures to some pyrethroids.[42–45] Of note, paresthesias, including burning, tingling, stinging, and eventually numbness, are characteristic of pyrethroid exposure.[46,47] The paresthesias appear to be dose-dependent and occur at pyrethroid dosages lower than what would cause systemic toxicity, thereby acting as a warning of exposure. The paresthesias are self-limiting once exposure is eliminated.[48]

### *Laboratory Evaluation and Treatment*

Pyrethroid toxicity is identified through clinical history and knowledge of exposure to the agent. There are no rapidly available diagnostic laboratory tests. Most pyrethroids are metabolized to 3-phenoxybenzoic acid, which can be recovered in the urine. CDC national surveys provide biomonitoring information on pyrethroid urinary metabolites and can act as comparison for background measures of exposure in the general population. However, in the clinical setting, results of metabolite levels are usually obtained from specialty laboratories and are not immediately available; therefore, these results not useful in acute clinical management.

Paresthesias are generally self-limiting and resolve within 24 hours.[46,48] If exposure is interrupted after the onset of paresthesias and other dermal findings, no additional treatment is necessary. Vitamin E oil or cream has been shown to improve the

symptoms associated with the paresthesias.[47] The mechanism is not completely clear; however, in experimental studies, vitamin E (α-tocopherol) blocked tetramethrin-modified sodium channels.[49]

Treatment of systemic pyrethroid poisoning is supportive, in general, and there are no specific antidotes. Because of the similar features of cholinesterase inhibitor poisoning, some patients have been treated erroneously with high atropine, sometimes with disastrous results.[45] Efforts have been aimed at antagonizing the sodium current resulting from the pyrethroid blockade. Several medications have been tested in the animal model, but, to date, none have been considered effective antidotes for systemic pyrethroid poisoning in humans. For significant neurologic effects, patients should have standard decontamination, including GI tract decontamination, supportive respiratory care, seizure control with diazepam or lorazepam, and careful dosing of atropine for excessive salivation.[42] Proper identification of the offending agent is imperative to distinguish these poisonings from OPs and often requires a high index of suspicion and a thorough exposure history.

### Organochlorine Insecticide (Lindane)

The discussion of acute toxicity for organochlorines is focused on lindane, because most other organochlorine compounds have been banned for use in the United States. Other organochlorines, including DDT and some of the cyclodienes, including chlordane and dieldrin, are important compounds, because they can still persist in human and environmental samples. These chronic exposures are of continuing concern for developmental health effects, including immunotoxicity, endocrine disruption, and neurodevelopmental insults (see Chronic Health Effects of Pesticide Exposure).

Lindane, also known technically as the γ-isomer of hexachlorocyclohexane, is still approved in some states for control of lice and scabies. However, in a comparison of in vitro activity against lice with other pediculicides, it was the least effective.[50] It is efficiently absorbed across the skin (approximately 9%) and even more so across abraded skin, such as with severe excoriations from scabies.[51,52] Signs and symptoms are noted in Table 2. Treatment is supportive and includes decontamination and the control of seizures with lorazepam. There is no specific antidote. Lindane has been banned in California because of high levels found in the water supply.[53]

### Neonicotinoids

Neonicotinoids are a new class of insecticides based on metabolic alterations of nicotine. They are used primarily in agriculture and are gaining widespread use for flea control on domestic animals. They act on the nicotinic *N*-acetylcholine receptors and selectively displace acetylcholine. They do have a relatively selective affinity for insects as opposed to mammals, although there have been a few reports of human poisoning.[54–56] The most commonly used neonicotinoid in the United States is imidacloprid. Information about toxicity and signs and symptoms can be found in Tables 1 and 2.

### *N*-Phenylpyrazoles

Fipronil is the primary representative of this class and was developed in the mid-1990s. It is widely used in flea control on domestic pets. It is also used in ant and roach bait stations, agriculture crops, and lawn treatments. It acts by inhibiting γ-aminobutyric acid–gated chlorine channels. The inhibition will block chloride passage and result in hyperexcitability of the cell.[57–59] Signs and symptoms are reported in Table 2.

## HERBICIDES

### Chlorophenoxy Herbicides

Chlorophenoxy herbicide compounds are often mixed with fertilizers and are used both in agriculture and on residential lawns. These compounds are well absorbed from the GI tract but are not well absorbed after inhalational or dermal exposure.[60] Examples of commonly used chlorophenoxy herbicides are 2,4-D and 2,4,5-trichlorophenoxy acetic acid. The half-lives of these compounds range between 13 and 39 hours. They are mostly excreted unchanged in the urine; excretion can be greatly enhanced in an alkaline environment.[3,61,62] More toxic substances that can be produced during the manufacture of these herbicides include dioxins, which were contaminants of the herbicide Agent Orange and were found in the Love Canal chemical dump site.[63]

Primary initial effects are on the skin and mucous membranes. Severe poisoning will result in metabolic acidosis and possibly renal failure.[3,61,64] Specific symptoms are discussed in Tables 1 and 2. The compounds can be measured in the urine, although similar to pyrethroid insecticides, analyses are generally performed at specialty laboratories, so results are usually not immediately available to clinicians. Treatment is primarily supportive and may also include forced alkaline diuresis by adding sodium bicarbonate to the fluids and establishing a high urine pH and high urine flow.[3,61,65]

### Phosphonate Herbicides (Glyphosate)

Glyphosate is a commonly used herbicide and is commercially available in

many products. Glyphosate acts on the cell wall of plants, so, theoretically, it should have no effect on human cells, at least by way of its primary mechanism of action. Despite this, there are numerous reports in the medical literature of adverse events after human exposure, particularly unintentional ingestions. Patients have presented with signs and symptoms consistent with an aspiration pneumonia–like syndrome, and the offending agent may be the hydrocarbon solvent with which the glyphosate is mixed. Treatment is primarily supportive, and providers should be vigilant for aspiration pneumonia.

## RODENTICIDES (LONG-ACTING ANTICOAGULANTS)

Most currently used rodenticides belong to the class of warfarin-type anticoagulants. Unlike warfarin, the superwarfarin agents, such as brodifacoum, have a much longer half-life. Although they have traditionally been available as pellets that can be spread around or in a box that the rat can consume, the EPA has recently changed the type of products that are available to consumers. Since 2008, superwarfarins can only be sold as a child-resistant bait station instead of loose pellets.[66]

The mechanism of action is inhibition of the synthesis of vitamin K–dependent clotting factors. As such, the primary manifestations of toxicity are bleeding and easy bruisability. In severe cases, bleeding may be life-threatening. Clinicians who suspect that their patients may have ingested a superwarfarin should consider obtaining a prothrombin time (PT; also known as the international normalized ratio [INR]).[3] However, several studies that have analyzed cohorts of exposed children have found very few subjects with an elevated PT (INR) or active bleeding. Therefore, in situations in which it is unclear whether a child ingested more than a few pellets, it is reasonable to simply observe the child.[67–70] Most patients can be managed in the outpatient setting as long as the ingestion has been recognized early.[71]

Treatment is vitamin K and should be reserved for patients with elevated PT (INR) levels or active bleeding. With severe bleeding or shock, a transfusion of blood or plasma is indicated as well.[3]

## CHRONIC HEALTH EFFECTS OF PESTICIDE EXPOSURE

The health implications of the nonacute, relatively low, but often repetitive and combined exposures encountered routinely by children are an ongoing focus of concern and inquiry for scientists, regulators, and parents.[72,73] Pediatricians are well placed to provide guidance to parents about potential long-term or subtle health effects from pesticide residues on food, in water, or used in homes or schools and on exposure-reduction strategies. However, surveys suggest pediatricians often feel ill-prepared with training in this topic, underscoring the importance of improving educational opportunities for clinical providers.[74–76]

The associated health effects of chronic pesticide exposure in children vary, reflecting the diversity of toxicological properties of this broad group of differing chemicals. Some of the important end points of concern include an increased risk of cancer, abnormal neurodevelopment, asthma, perturbation of gestational growth, and endocrine-mimicking effects. Health effects of pesticides and the current relative strength of the evidence base are reviewed in subsequent sections for each of these health outcomes.

### Childhood Cancer

All pesticides undergo in vitro and animal testing to determine their likelihood of causing cancer. The EPA maintains a list and classification of all active ingredients in pesticides and their potential for carcinogenicity. The method of identifying potential carcinogenicity has changed. Before 1996, pesticides were assigned a letter classification (eg, pesticides with the "C" classification were considered "possibly carcinogenic"). Subsequently, pesticides have been assigned a category such as "likely to be carcinogenic to humans," "suggestive evidence of carcinogenic potential," "inadequate evidence," and "not likely." These categories are not directly comparable, so both classifications (before 1996) and categories (after 1996) continue to exist.

The pesticides that are categorized as "possibly carcinogenic" or "likely to be carcinogenic to humans" are available from the EPA via an e-mailed report.[77] Included in this report are some well-known and widely used OPs, carbamates, pyrethroids, and fungicides. Within classes of pesticides, variation in carcinogenicity potential exists. Note that a pesticide, such as cypermethrin, that has "replaced" use of cancer-causing OPs has cancer-causing potential.

A substantial amount of observational epidemiological data demonstrate a link between pesticide exposure and childhood cancers.[78–87] However, the evidence base includes studies that found no association between childhood cancers and pesticides or few associations that cannot be ruled out as a chance finding.[88,89] Overall, the most comprehensive reviews of the existing literature implicate an association of pesticides with leukemia and brain tumors.[78,79]

#### *Leukemia*

In 1998, Zahm and Ward[79] reviewed 18 studies assessing the relationship between pesticide exposure and leukemia; 13 studies found an elevated risk, and,

for 6 of those studies, the association was statistically significant. The most frequently occurring associations among the studies were between pesticide exposure and acute lymphocytic leukemia.

A 2007 review by Infante-Rivard and Weichenthal[78] summarized the 1998 review of Zahm and Ward and updated findings from recent studies. Although it was previously postulated that childhood exposure to agricultural products or proximity to an agricultural setting would present the highest risks, the most commonly associated pesticide exposure in childhood acute lymphocytic leukemia studies was household insecticide use. Cases were more likely to have had preconception exposure and/or exposures in utero in most studies. The main limitations with the studies in the 1998 review included crude exposure assessment, concern for recall bias, small numbers of exposed cases, and mixing of different leukemia types.[78]

In the updated review, 5 of 6 recent case-control studies found a statistically significant relationship between pesticide exposure and leukemia.[84,85,90–92] In particular, 2 studies included the most detailed exposure assessment to date and reported findings related to a dose/exposure–response gradient.[84,85] The primary risk factors were maternal exposure to pesticide between the periods of preconception through pregnancy. The largest of the 2 studies had 491 cases and an equal number of controls, focused only on acute lymphocytic leukemia, included a measure of frequency of use, and considered genetic susceptibility. For maternal use of herbicides, plant insecticides, and pesticides for trees during pregnancy, the odds ratio (OR) was 1.84 (95% confidence interval [CI], 1.32–2.57), 1.97 (95% CI, 1.32–2.94), and 1.70 (95% CI, 1.12–3.59), respectively. For parental use during the child's postnatal life, OR was 1.41 (95% CI, 1.06–1.86), 1.82 (95% CI, 1.31–2.52), and 1.41 (95% CI, 1.01–1.97) after exposure to herbicides, plant insecticides, and pesticides for trees, respectively.[84]

To further explore associations between pesticides and leukemia, a group of authors conducted 2 meta-analyses. They provided similar and additional support to the associations described previously. One examined studies that included parental occupational exposure (prenatally and in early childhood) and leukemia in their offspring. Maternal occupational exposure, but not paternal occupational exposure, was found to be associated with leukemia. The reported OR was 2.09 (95% CI, 1.51–2.88) for overall pesticide exposure, 2.38 (95% CI, 1.56–3.62) for insecticide exposure, and 3.62 (95% CI, 1.28–10.3) for herbicide exposure.[93] The second meta-analysis assessed pesticide exposure in the home and garden setting. In this meta-analysis, 15 studies were included, and exposures during pregnancy to unspecified pesticides, insecticides, and herbicides were all associated with leukemia (OR, 1.54 [95% CI, 1.13–2.11], 2.05 [95% CI, 1.80–2.32], and 1.61 [95% CI, 1.2–2.16], respectively).[94]

### *Brain Tumors*

Zahm and Ward's 1998 review included 16 case-control studies examining associations between brain tumors and pesticide exposures. Of these, 12 found an increased risk estimate of brain tumors after pesticide exposure; 7 of these findings reached statistical significance. Associated exposures were most often from parental use of pesticides in the home, in the garden, and on pets. Interpretation of these studies is difficult given the inadequate exposure assessments, small numbers because of a relatively rare childhood outcome, and a mixture of brain tumor types among cases.[79]

Since 1998, 10 additional studies have been published, all but one of which demonstrated an increased risk estimate of cancer with maternal and/or paternal exposure, although not all studies demonstrated statistical significance. Some of the more robust findings come from a case-control study with 321 cases of astrocytomas. The risk estimate from maternal occupational exposure to insecticides before or during pregnancy was 1.9 (95% CI, 1.1–3.3). The risk estimates for paternal exposure for insecticides, herbicides, and fungicides were 1.5, 1.6, and 1.6, respectively. These risk estimates were just short of reaching statistical significance.[87] In a cohort study of more than 200 000 patients, paternal exposure in any occupation and in agricultural/forestry preceding conception was associated with an increased risk of central nervous system tumors (relative risk [RR], 2.36 [95% CI, 1.27–4.39] and RR, 2.12 [95% CI, 1.08–4.39], respectively).[83] For all studies, it appears that prenatal exposure to insecticides, particularly in the household, as well as both maternal and paternal occupational exposure before conception through birth represent the most consistent risk factors.[83,86,87,95–100]

### *Ewing Sarcoma*

Two case-control studies were performed to evaluate potential parental occupational exposures and the development of Ewing sarcoma (ES). One study of 196 cases and matched controls found an association between ES in boys age 15 years or younger and household pesticide extermination (OR, 3.0; 95% CI, 1.1–9.2). There was no association between parental occupational exposure to pesticides and ES.[101] A study in Australia compared 106 cases of either ES or peripheral primitive neuroectodermal tumor with 344 population-based controls. Exposures

included prenatal exposure from conception through pregnancy and also included parental exposures through the time of the child's diagnosis. Notable elevated risks were observed for mothers who worked on farms (OR, 2.3; 95% CI, 0.5–12.0), mothers who handled pesticides (OR, 2.3; 95% CI, 0.6–8.5), patients who ever lived on a farm (OR, 2.0; 95% CI, 1.0–3.9), and farming fathers at the time of conception and/or pregnancy (OR, 3.5; 95% CI, 1.0–11.9).[102] Of note in this study, all 95% CIs include 1.0, so they did not reach statistical significance, although some ORs approached it.

In summary, there is some evidence of increased risk of developing several childhood cancers after preconception and/or prenatal exposure to pesticides. The strongest evidence appears to be for leukemia, which is a relatively more common type of childhood cancer than brain tumors. Maternal exposure to insecticides and paternal occupational exposure appear to carry the greatest risk.

## Neurodevelopment/ Neurobehavioral Effects

Many pesticides have well-described acute neurotoxicant properties that have been described previously in this report in relation to human poisoning episodes and acute toxic mechanisms. However, information on the potential neurodevelopmental toxicity arising from chronic, low-level exposure in gestational or postnatal life is inadequate or lacking for most pesticides in use. There is a growing available evidence base supporting an adverse effect on neurodevelopment from 2 classes of insecticides, the organochlorines (specifically DDT and its metabolite *p,p′*-dichlorodiphenyldichloroethylene [DDE]) and, most recently, OPs. Several recent reviews of the evidence base are now available.[103–105]

Although chronic neurologic sequelae after acute OP poisoning have been observed in multiple adult studies, the epidemiological data on children are limited.[106,107] A recent neuropsychological evaluation of healthy school-aged children who had experienced hospitalization for acute OP poisoning before the age of 3 years found subtle but significant deficits in their ability to restrain and control their motor behaviors compared with both children who had no history of poisoning and children who had a history of early life poisoning with kerosene.[108]

Of greater public health concern is the potential neurotoxicity from routinely encountered chronic exposures. This is the subject of study in ongoing, large National Institutes of Health/EPA-sponsored prospective birth cohorts. Studies in 2 urban settings and a rural farmworker community have enrolled women during pregnancy with an objective assessment of exposure by the use of environmental measurements and biological monitoring.[104,109,110] Follow-up assessment of neurodevelopment and neurobehavior in their children with the use of validated tools such as the Brazelton Neonatal Assessment Scales, the Bayley Scales of Infant Development, the Child Behavior Checklist, and IQ testing at comparable intervals is being conducted. To date, remarkably similar findings relating adverse neurodevelopmental and neurobehavioral outcomes associated with prenatal OP exposure have been made in these distinct cohort studies. For example, in 2 cohorts, the Brazelton Neonatal Behavioral Assessment Scale was administered in the first weeks of life. In both, deficits in the primitive reflex domain were noted with the other 6 of 7 Brazelton Neonatal Behavioral Assessment Scale domains not associated with prenatal OP exposure.[111,112] Two of the cohorts have published their Bayley Mental and Psychomotor Developmental Index results conducted during the toddler years (ages 2–3).[113,114] Significantly poorer mental development was associated with higher OP exposure in both, whereas one of the cohorts also observed OP-associated deficits in the motor scale at 3 years of age. Results of Child Behavior Checklist assessments are also available for 2 cohorts, conducted at 2 years of age in one and 3 to 4 years of age in the other. Significantly increased scores representative of pervasive developmental disorder were associated with higher OP exposure in both.[113,114] One cohort also had increased scores for inattention and attention-deficit/hyperactivity disorder subscales.[114] All 3 cohorts have found decrements in IQ testing associated with higher prenatal exposures at the time of follow-up at 7 years of age.[115–117]

In one of the cohorts, postnatal exposure effects in the child have been investigated and reported. Interestingly, improved mental development based on Bayley's Index at 12 and 24 months of age is associated with higher contemporary child excretion of OP urinary metabolites. Explanations for this are debated but include theories that children with higher cognitive abilities may explore their environments more thoroughly and, as such, experience higher exposure.

Recently, a US-based cross-sectional analysis demonstrated that children with high urinary concentrations of OP metabolites were more likely to have a diagnosis of attention-deficit/hyperactivity disorder. This study used data from a representative sample of 8- to 15-year-old children collected as part of the NHANES conducted by the CDC.[118]

One study based in Ecuador has examined the relationship of OP exposure on neurodevelopment in school-aged children.[119] Prenatal exposure (based

on mother occupational history questionnaire) was associated with a decrease on the Stanford-Binet copying test among the study subjects at 7 years of age. Their concurrent exposure (on the basis of OP urinary metabolites) was associated with an increase in simple reaction time.

The toxicological mechanisms that underlie the adverse neurodevelopmental observations are also under investigation. Interestingly, noncholinergic mechanisms are being deciphered in animal models and in vitro studies, distinct from the well-described mechanism of acute OP toxicity (cholinesterase inhibition) and occurring at doses much lower than required to inhibit cholinesterase.[120]

Well-designed recent cohort studies and previous work including animal models suggest that OP exposures that are being experienced by US children may have adverse neurodevelopmental consequences. The plasticity of these effects and clinical implications are as yet unclear, although continued assessments as these cohorts age and enter school age are planned and may add clarity. The potential modification of these effects on the basis of genetic factors, specifically metabolic enzymes involved in pesticide detoxification pathways, are also being explored in these cohorts. For example, preliminary analyses indicate that children with a particular variant of the paraoxonase I gene, which is associated with lower levels of this OP-metabolizing enzyme, may be at higher risk of health consequences from OP exposure.[121,122]

Although DDT has not been used since the early 1970s, its persistence in the environment and fat solubility results in ongoing detection of the parent compound and breakdown product (DDE) in contemporary US populations.[19] The potential adverse neurodevelopmental consequences of prenatal DDT (2 studies) and DDE (several studies) was studied in one of the recent cohorts described previously in this report, which was a predominately Mexican American farmworker population. In this cohort, maternal serum DDT levels were negatively associated with mental development and psychomotor development at 12 and 24 months.[123] Maternal serum DDE was associated with reduced psychomotor development at 6 months and mental development at 24 months. A review of the overall evidence base reveals that studies of in utero DDE exposure and neurodevelopment are mixed, with at least 2 studies showing decrements in psychomotor function. Both of the 2 studies that have evaluated effects of DDT exposure observed cognitive deficits.[103]

In summary, the existing and recently emerging evidence base suggests that organochlorine and OP exposure in early life, particularly prenatally, may have adverse consequences on child neurodevelopment.

## Physical Developmental Effects

In addition to neurodevelopmental toxicity, there is also considerable concern of physical developmental toxicity to the embryo and fetus from pesticide exposure. These concerns arise from multiple epidemiological studies that have investigated their relationship to adverse pregnancy outcomes including intrauterine growth retardation, preterm birth, fetal death, and congenital anomalies. The available studies are heterogeneous in design, are conflicting in results, and often have an insufficient exposure assessment. Nonetheless, pesticides remain one of the most common environmental exposures of concern cited in relation to adverse pregnancy outcomes and have been the focus of recent reviews on the topic, which include weight of the evidence evaluations.[124–126]

Among studies that are able to address specific types of pesticide exposures, there are more data focused on the organochlorine and OP insecticides or phenoxy or triazine herbicides. These represent the currently or historically (eg, organochlorine) most heavily used pesticides. This review summarizes the highlights of the existing evidence base with a focus on studies that incorporate direct measures of exposure for individual study subjects.

### *Fetal Death and Birth Defects*

A California-based case-control study found an increased risk of fetal death attributable to congenital anomalies when OP application occurred in the residential area of the mother during weeks 3 through 8 of pregnancy—consistent with organogenesis.[127] One other study found an elevated risk of spontaneous abortion associated with chlorophenoxy herbicides. However, as with some studies of birth defects discussed previously, this study also relied on self-report and less reliable means of exposure assessment.[128] Results are not consistent, because other studies have not found association of parental exposure to OPs with spontaneous abortion or stillbirth.[129–131]

Birth defects will be discussed first, followed by other adverse birth outcomes. The more common birth defects include orofacial clefts, limb defects, and neural tube defects, which are generally the defects studied in relationship to pesticide exposures. Although several studies have found associations of maternal or paternal exposures with a wide variety of birth defect categories, all of the studies used indirect measures of exposure and most were ecological study designs, making interpretation of the adverse birth outcome evidence base inadequate and unreliable.[125]

A 1995 review article discussed the available evidence for associations between birth defects and potential

pesticide exposure.[132] Five studies were included that assessed various birth defects (central nervous system, oral cleft, limb defects) compared with maternal agricultural occupation. Four of those 5 reported an elevated RR or an OR ranging from 1.6 to 5.0; however, only 2 were statistically significant.[133–137] Of note, in these studies, there was not an assessment to any single pesticide; rather, the "exposure" was maternal occupation.

Six additional studies from this period evaluated maternal pesticide exposure at work and the development of birth defects. Of the 5 studies with an elevated OR or RR, ranging from 1.3 to 7.5,[138–142] 3 were statistically significant. Unfortunately, some of these studies included small numbers of cases, and others were likely to have significant exposure misclassification. The conclusion of this review was that there are some indications of elevated risk but no clearly convincing evidence.[143]

Two studies from Minnesota have reported a relationship between physical defects in children and paternal occupation of pesticide applicator. The first study compared data from a birth registry between 1989 and 1992. A geographic section of Minnesota that had the highest agriculture activity and highest frequency of use of chlorophenoxy herbicides and fungicides was also found to have the highest rate of birth defects (30.0/1000). By comparison, the general population in this same region had a birth defect rate of 26.9/1000. Interestingly, there was a seasonal effect, with the highest frequency occurring in infants who were conceived in the spring, the same time as most herbicide and some fungicide application (OR, 1.36; CI, 1.10–1.69).[144] The second study is a cross-sectional study that used a survey of licensed applicators and subsequently more in-depth interviews of either/both the applicator and female partners of licensed applicators when possible. The study eventually included live births fathered by 536 applicators. The birth defect rate in this study was 31.3/1000, which is statistically significantly higher than what the previous study found for the general population. Again, there was a significant difference in season of conception (7.6% in spring versus 3.7% in other seasons).[145]

Studies of birth defects often include all types within the analysis because of insufficient numbers of individual defects to allow adequate power of statistical analyses. A meta-analysis used 19 studies that had sufficient data to be included to estimate the effects of pesticides on orofacial clefting. Maternal occupational exposure to pesticides was associated with orofacial clefts (OR, 1.37; 95% CI, 1.04–1.81). There was a weaker association for paternal occupation (OR, 1.16; 95% CI, 0.94–1.44).[146] Studies on 3 other birth defects—cryptorchidism, hypospadias, and polythelia—will be discussed in the section on endocrine effects.

In summary, a small risk elevation is noted for birth defects and pesticide exposure, but the findings are not robust, and the data specific to pesticide subtypes are not adequate.

### *Adverse Birth Outcomes (Low Birth Weight, Decreased Gestational Age)*

DDT (and its major metabolite DDE) is the organochlorine that has been most extensively examined in relation to birth defects, fetal death, and fetal growth, with mixed findings. Fetal exposures, as determined by maternal serum or umbilical cord blood levels, have been associated with preterm birth, decreased birth weight, and intrauterine growth retardation.[147–151] However, not all studies reported significant associations between exposure with infant birth weight or preterm birth, including a relatively recent study of Mexican American farmworking women in the United States with higher exposures in comparison with a similar group of a national sample of nonfarmworking Mexican American women.[142,152] In the largest cohort study to date (a US cohort of births between 1959 and 1966), DDE concentrations in maternal serum during pregnancy demonstrated a dose–response relationship to risk of preterm delivery and delivering small for gestational age (SGA) infants.[147]

Exposure to pesticides is associated with risk of decreased birth weight. In a study conducted before recent regulatory actions that reduced their residential use, exposure to the OPs chlorpyrifos and diazinon were associated with decreased birth weight in a New York City cohort.[110] In another New York City cohort, birth weight was reduced among mothers with higher OP exposure levels in pregnancy, but only among those with a genetic polymorphism of an OP detoxification enzyme (paraoxonase 1 or PON1).[150] In a similar longitudinal pregnancy cohort conducted among Latina farmworkers in agricultural California, no association of maternal pregnancy exposure to OPs and birth weight was determined, but a reduction in gestational age was associated.[153]

An ecological study determined that women in a rural region of Iowa with increased levels of triazine, metolachlor, and cyanazine herbicides in the drinking water had an elevated risk of delivering an infant with intrauterine growth retardation compared with women in other parts of the state.[154] A study based in France reported that atrazine levels in municipal drinking water throughout pregnancy were not associated with increased risk of delivering an SGA infant but that the

risk of delivering an SGA infant increased when the third trimester occurred in whole or in part during the period of May through September, when atrazine levels typically peak.[155]

### Summary: Physical Developmental Defects

In summary, the true extent and nature of pesticide exposure on adverse fetal growth and birth outcomes is unknown despite suggestive epidemiological studies that link some of the most widely used pesticides to reduced intrauterine growth, fetal death, preterm birth, and congenital anomalies. Very little is known about many pesticide types in current use, including synthetic pyrethroids and carbamate insecticides, rodenticides, and fungicides. Studies that examine the timing and extent of exposure to pesticides and exposure to pesticide mixtures with validated exposure assessment techniques including biological markers are needed. The potential for differential vulnerabilities because of genetic polymorphisms that influence the toxicological properties of these exposures must also be explored.

## ENDOCRINE EFFECTS

An emerging concern, although less well studied in humans, is the potential effects that some chemicals including pesticides may have on the endocrine system. Some of the most notable pesticides thought to have such effects are the organochlorine pesticides, such as DDT, endosulfan, methoxychlor, chlordecone, chlordane, and dieldrin. Other herbicides (atrazine, 2,4-D, and glyphosate) and fungicides (vinclozolin) also have some endocrine activity.[156–159] The associations are very complex and are primarily based on in vitro and animal studies. Estrogen-mimicking properties tend to be the most commonly reported, although effects on androgen and thyroid hormones, among others, are also reported. Feminization has been noted in alligators found in lakes highly contaminated by organochlorine pesticides.[160] Hayes et al[161] have studied the effects of atrazine on amphibians and have noted a 10-fold decrease in testosterone from exposure to 25 ppb of atrazine in mature male frogs. The mechanism of the latter appears to be activation of the enzyme aromatase, which promotes conversion of testosterone to estrogen.[162]

The human epidemiology literature is limited on endocrine effects from pesticides. One report from Macedonia noted some degree of early pubertal findings, primarily premature thelarche, which was hypothesized to be related to organochlorine pesticide exposure.[163] A study in 2000 with 48 patients, 18 of which had cryptorchidism, first raised the hypothesis about an association with organochlorine pesticides. An association between cryptorchidism and organochlorine pesticide levels has been hypothesized.[164] Since then, additional case-control studies have been conducted to examine the effects of organochlorines on endocrine-related birth outcomes, cryptorchidism, hypospadias, and/or polythelia. Two focused on fetal exposures from maternal levels of DDE alone and development of cryptorchidism and hypospadias.[165,166] Bhatia et al[165] calculated an OR of 1.34 (95% CI, 0.51–3.48) for the association of cryptorchidism and DDE and 1.18 (95% CI, 0.46–3.02) for the association of hypospadias and DDE. Longnecker et al[166] estimated an OR of 1.3 (95% CI, 0.6–2.4) for the association between DDE and cryptorchidism and an OR of 1.2 (95% CI, 0.6–2.4) the association between DDE and hypospadias. The modest association is felt to be inconclusive with the imprecision in risk estimates and suggests that a larger sample size may be needed. A third case-control study found inconclusive results on the effect of heptachlor and β-hexachlorocyclohexane levels in pregnant women on cryptorchidism. For heptachlor, the OR was 1.2 (95% CI, 0.6–2.6), and for β-hexachlorocyclohexane, the OR was 1.6 (95% CI, 0.7–3.6). The sample size in this study was 219 cases, compared with 564 controls.[167]

Two nested case-control studies have examined the possibility that multiple organochlorine compounds will have a cumulative effect on the development of urogenital abnormalities in boys.[168,169] Fernandez et al[168] reported that total xenoestrogens as well as detectable pesticide levels were associated with cryptorchidism and/or hypospadias. They found elevated ORs in the range of 2.19 for endosulfan to 3.38 for lindane. All 95% CIs were noted to be statistically significant. The study in Finland and Denmark reported a significant relationship between chlordane and cryptorchidism but no other relationships between 7 other individual organochlorines. However, combined analysis of the 8 persistent pesticides did demonstrate a statistically significant increase in cryptorchidism in exposed boys.[169]

Testing chemicals is an important and necessary step for the EPA to determine potential long-term risks from pesticide during the registration or re-registration process. There has been progress in the development of appropriate biomarkers to evaluate chemicals for the presence of endocrine-disruption qualities. The ability to measure DDE and dioxins from human milk has been developed.[170] More recently, a biomarker for xenoestrogen mixtures was developed in Spain.[171]

In summary, there is compelling basic science evidence for endocrine-mimicking effects of several pesticide chemicals that is sound and scientifically plausible. Human data

are slowly emerging but not yet conclusive.[172]

### Asthma

Given the widespread use of pesticides and the high morbidity of asthma in children, questions have been raised regarding pesticides as triggers as well as risk factors for incident disease. Concern is raised by a mounting adult occupational literature associating pesticides with asthma or other measures of respiratory health. In addition, preliminary toxicological data provide mechanisms that link pesticides and asthma. An important limitation of most epidemiological studies to date is the lack of exposure specificity regarding pesticide chemicals or chemical classes. In addition, studies regarding children are few.

There is indirect evidence that pesticides skew the immune response toward the T helper 2 (Th2) phenotype associated with atopic disease. The National Institutes of Health/EPA-sponsored rural birth cohort described above regarding evaluation of neurodevelopmental effects has also observed that maternal agricultural work was associated with a 26% increase in proportion of Th2 cells in their 24-month-old infants' blood samples.[173] The percentage of Th2 cells was associated with both physician-diagnosed asthma and maternal report of wheeze in these infants. This population of largely Mexican American farmworkers was selected for study on the basis of the relatively high use of OP pesticides in this agricultural area.

Animal-based toxicological mechanistic models include OP-induced airway hyperreactivity via alteration in muscarinic receptor function in airway smooth muscle and oxidative stress induced by OP-related lipid peroxidation.[174–177]

The few epidemiological data on pesticides and respiratory health in children have mixed results. In a cohort of rural Iowan children, any pesticide use indoors or any outdoor use in the previous year was not significantly associated with asthma symptoms and prevalence.[178] Contrarily, a cross-sectional analysis of Lebanese children identified increased risk of chronic respiratory symptoms, including wheeze, among those with any pesticide exposure in the home, exposure related to parent's occupation, and use outside the home. The highest risk was observed for children whose parents had occupational exposure to pesticides (OR, 4.61; 95% CI, 2.06–10.29).[179] However, given this study's cross-sectional design, it is not possible to discern whether the pesticide exposure preceded the diagnosis of asthma.

Among exposures in the first year of life explored in a nested case-control study of the Southern California Children's Health Study, both herbicides and pesticides/insecticides had a strong association with asthma diagnosis before 5 years of age (OR, 4.58 [95% CI, 1.36–15.43] and OR, 2.39 [95% CI, 1.17–4.89], respectively).[180]

More published data are available regarding adult farmers and adult rural residents. These studies more consistently support a link between pesticides and respiratory symptoms or chronic respiratory disease, such as asthma.[181,182] For example, use of multiple individual pesticides was evaluated in relation to self-reported episodes of wheeze in the previous year in a large cohort of commercial pesticide applicators (adults) and farmers enrolled in the Agricultural Health Study.[182] Among the pesticides classes, several OPs showed associations with wheeze, including several that demonstrated a dose–response trend. Chlorpyrifos, malathion, and parathion were positively associated with wheeze among the farmers; for the commercial applicators, the OPs chlorpyrifos, dichlorvos, and phorate were positively associated with wheeze. Among commercial applicators, the strongest OR was for applying chlorpyrifos on more than 40 days per year (OR, 2.40; 95% CI, 1.24–4.65). Elevated risk for wheeze related to herbicide use was almost exclusively associated with chlorimuron-ethyl (urea-derivative class).

Similar studies addressing the respiratory health implications for children for specific pesticide chemical types or groups are rare. However, for DDT, there is some emerging evidence for a link between metabolites of DDT and asthma risk.[183,184] In a prospective cohort study of children in Spain, wheezing at 4 years of age increased with increasing levels of DDE at birth. The adjusted RR for the children with exposure in the highest quartile was 2.63 (95% CI, 1.19–4.69). The use of physician-diagnosed asthma (occurring in 1.9% of children) instead of wheezing as the outcome variable also resulted in a positive association, although it was not statistically significant.[184]

In summary, the available data regarding chronic exposure to pesticides and children's respiratory health remain limited. Studies that incorporate pesticide-specific exposure assessment and markers of biological mechanisms and consider the influence of timing of exposure across the life span are needed.

## THE PESTICIDE LABEL

Pesticides for sale or use in the United States must be registered with the EPA, and this includes approval of the product label, which contains the EPA registration number. The pesticide label contains several types of information that may be important in understanding and preventing acute health consequences associated with their use.[185]

The product label identifies the active ingredient and provides the manufacturer's

contact information. The label does not specify the particular class of pesticide for the active ingredient, which may make it difficult for a physician to identify potential toxic effects. Information about "other" or "inert" ingredients, which may account for up to 99% of the product, is not required to be disclosed on the label. These constituents include chemicals with known toxicity. The physician treating a patient may request this from the manufacturer; however, delay in information may compromise optimal clinical care. The local or regional poison control center plays an important role as a resource for any suspected pesticide poisoning. The EPA is currently considering rulemaking changes that would expand the disclosure of information on inert ingredients. One of the options under consideration includes labeling 100% of the ingredients.[186]

The "directions for use" section on the label explains when, how, and where the pesticide may be applied. The label is considered the law; therefore, any use of the product in a manner inconsistent with the label is a violation of the Federal Insecticide, Fungicide, and Rodenticide Act (Pub L No. 80-104).[187] Information on recommended storage of the product and disposal of the container is also printed on the label.

The label will contain a signal word and symbol to identify acute toxicity potential: "danger" along with the word poison and the skull and crossbones symbol signifies high acute toxicity; "warning" signifies moderate acute toxicity; and "caution" represents slight acute toxicity. There is a section for precautionary statements regarding the potential hazards to people or pets and the actions that can be taken to reduce these hazards, such as wearing gloves or other protective equipment. Basic first aid advice for responding to dermal, inhalational, and/or oral exposure is provided. Some labels contain a "note for physicians" that includes specific medical information. The label does not provide any information or warnings about the potential for chronic toxicity arising from normal use or misuse of the pesticide. An example of an interactive pesticide label can be found at the EPA Web site.[188] It includes "pop-up" features that define each of the components on the pesticide label.

## STATE OF PESTICIDE KNOWLEDGE AMONG PEDIATRICIANS

Self-reported medical education and self-efficacy suggests pediatricians are not well prepared to identify pesticide exposure and illness, including taking a relevant environmental history or discussing pesticide risks with their patients.[189–191] Even in agricultural areas of the Pacific Northwest, where pesticide use is heavy, a survey of health care providers who serve high volumes of agricultural farmworkers and their families found that 61% did not feel comfortable responding to patient/client questions regarding pesticides on the basis of their training, background, and experience.[75] Among academic pediatricians with an interest in pediatric environmental health, pesticides were among the topics they felt least prepared to teach to their trainees.[192] Given the widespread use of pesticides and concerns for child health, opportunities to increase pesticide competency in pediatric medical education are likely to prevent missed diagnoses and reduce exposure because of improved anticipatory guidance.

Clinicians must have a high index of suspicion to identify pesticide poisoning. Identification and treatment of acute pesticide poisoning requires familiarity with the toxic mechanisms and related signs and symptoms of the pesticide classes. For example, when evaluating a patient with status epilepticus or mental status changes, certain insecticides belong in the differential among the numerous and more common etiologies. Eliciting an environmental history will help decipher the relative importance of pesticides in further clinical decision-making. The environmental history is a general tool for addressing potentially hazardous environmental exposures and is discussed in detail in the Pediatric Environmental Health manual from the AAP.[193]

## EFFORTS TO REDUCE PESTICIDE EXPOSURE

### Dietary Considerations

Dietary modifications can help reduce pesticide exposure. As mentioned previously, consuming organic produce has shown a reduced amount of urinary pesticide levels in comparison with a conventional diet.[22] Because many food-based pesticide residues occur on the surface of food crops, other practical approaches may be used to reduce exposures by washing produce, peeling off outer layers of leafy vegetables, and removing peels from fruits and vegetables. Trimming fat from meat and fat and skin from poultry and fish may reduce residues of persistent pesticides, such as the organochlorines, that concentrate in animal fat.

Efforts to address and reduce chronic pesticide exposure via the food supply in children have included regulatory approaches that consider the unique vulnerability of the developing child in policy decision-making. For example, the 1996 Food Quality Protection Act (Pub L No. 104-170, Section 405) required that the EPA use an additional 10-fold margin of safety regarding limits of pesticide residues on food (unless there are data that show a less stringent residue level is safe for

prenatal and postnatal development; for description, see http://www.epa.gov/opp00001/factsheets/riskassess.htm).

### Integrated Pest Management

In addition to food residues, use of pesticides in and around the home and other settings where children spend time (child care, school, and playgrounds and sports fields) is an important influence on the chronic and cumulative exposure to pesticides among US children. Most of the pest problems that occur indoors as well as control of lawn and garden pests can be addressed with least toxic approaches, including integrated pest management (IPM) techniques. IPM focuses on nontoxic and least toxic control methods to address pest problems have been promoted and adopted for residential, school, and agricultural settings (fact sheets available at http://www.epa.gov/opp00001/factsheets/ipm.htm).

"Integrated" refers to employment of complementary strategies of pest control, which may include mechanical devices; physical devices; genetic, biological, and cultural management; and chemical management. For example, to control cockroaches, a family could be counseled to keep garbage and trash in containers with well-fitted lids, eliminate plumbing leaks or other sources of moisture, store food in insect-proof containers, vacuum cracks and crevices, clean up spills immediately, and use the least-toxic insecticides, such as boric acid, in cracks and crevices or bait stations. The goal is to target the pest and limit the effect on other organisms and the environment. Although developed with a focus on agricultural insect pests, IPM programs and knowledge have extended to address weeds and pest control in residential settings and schools, commercial structures, lawn and turf, and community gardens.

Within agriculture, IPM has been recognized and promoted for decades; however, inadequate leadership, coordination, and management of US Department of Agriculture IPM programs were identified as impediments to adequate progress in a 2001 report.[194] The report provided the basis for an ongoing national roadmap effort to improve ongoing development of increased IPM in agriculture.

To protect children, IPM in schools has been recommended by the US Department of Agriculture, EPA, American Public Health Association, and National Parent Teacher Association. Many states and local municipalities have adopted programs and resources to encourage IPM in public places, in addition to homes and schools (see Table 3). IPM strategies seek to minimize insecticide use by applying strategies such as cleaning up food and water, sealing cracks and crevices, and using pesticides that are contained in baits or traps, which are far less likely to pose a health concern compared with any type of broadcast spray application. Avoiding combination products with pesticides and fertilizers (ie, "weed and feed" preparations) is advised for lawn maintenance, because these tend to result in overapplication of pesticides. Hand weeding is always a reasonable alternative to herbicides. However, if an herbicide is to be used, some (such as glyphosate) have better acute human toxicity profiles than others (such as 2,4-D). Even so, glyphosate is not without its risks. Most cases of moderate to severe toxicity have occurred after intentional (suicidal) ingestion.[195] Using safe storage practices (in a locked cabinet or building) and not reusing pesticide containers are important components toward the prevention of acute poisonings after unintentional ingestion by small children. Reliable resources for useful information on pest-control alternatives and safe use of pesticides are available from the EPA and University of California-Davis (Table 3).

### Spraying in the Community: Right to Know

Although there is no federal mandate for notification of pesticide use in communities, many states, locales, or schools have implemented requirements for posting warning signs or developing registries to alert individuals of planned pesticide application (see Table 3). These are designed to allow the public to make decisions to avoid exposures during application or soon after from residues. Other local policies that have been developed include restricting spray zones that create buffers from schools or other areas or restrict specific types of pesticide products in schools. Pediatricians can play a role in the promotion of development of model programs and practices in the communities and schools of their patients. For example, in some communities, pediatricians have participated in local organizations that have successfully advocated for no pesticide application in schools.

## SUMMARY

Pesticides are a complex group of chemicals with a wide range of acute and chronic toxicity. Poison control centers report lower rates of more severe poisonings but continue to report similar total numbers of acute exposures among children. There is a growing body of literature that suggests that pesticides may induce chronic health complications in children, including neurodevelopmental or behavioral problems, birth defects, asthma, and cancer. Pediatricians are a trusted source of information for families and communities, although current training focused on pesticide toxicity and environmental health, in

**TABLE 3** Pesticide and Child Health Resources for the Pediatrician

| | | |
|---|---|---|
| **Management of Acute Pesticide Poisoning** | | |
| *Recognition and Management of Pesticide Poisonings* | | Print: fifth (1999) is available in Spanish, English (6th edition available 2013)<br>http://www.epa.gov/pesticides/safety/healthcare/handbook/handbook.htm |
| Regional Poison Control Centers | | 1-800-222-1222 |
| **Chronic Exposure Information/Specialty Consultation** | | |
| The National Pesticide Medical Monitoring Program (NPMMP) | Cooperative agreement between Oregon State University and the EPA<br>NPMMP provides informational assistance by e-mail in the assessment of human exposure to pesticides | npmmp@oregonstate.edu<br>or by fax at 541-737-9047 |
| Pediatric Environmental Health Specialty Units (PEHSUs) | Coordinated by the Association of Occupational and Environmental Clinics to provide regional academically based free consultation for health care providers | http://www.aoec.org/PEHSU.htm<br>Toll-free telephone number 888-347-AOEC (2632) |
| **Resources for Safer Approaches to Pest Control** | | |
| EPA | Consumer information documents | http://www.epa.gov/oppfead1/Publications/Cit_Guide/citguide.pdf |
| *Citizens Guide to Pest Control and Pesticide Safety* | • Household pest control<br>• Alternatives to chemical pesticides<br>• How to choose pesticides<br>• How to use, store, and dispose of them safely<br>• How to prevent pesticide poisoning<br>• How to choose a pest-control company | |
| Controlling pests | Recommended safest approaches and examples of programs | http://www.epa.gov/pesticides/controlling/index.htm |
| The University of California Integrative Pest Management Program | Information on IPM approaches for common home and garden pests | http://www.ipm.ucdavis.edu |
| **Other Resources** | | |
| National research programs addressing children's health and pesticides | NIEHS/EPA Centers for Children's Environmental Health & Disease Prevention Research<br>The National Children's Study | www.niehs.nih.gov/research/supported/centers/prevention<br>www.nationalchildrensstudy.gov/Pages/default.aspx |
| EPA | Pesticide product labels | www.epa.gov/pesticides/regulating/labels/product-labels.htm#projects |
| The National Library of Medicine "Tox Town" | Section on pesticides that includes a comprehensive and well-organized list of Web link resources on pesticides | http://toxtown.nlm.nih.gov/text_version/chemicals.php?id=23 |

NIEHS, National Institute of Environmental Health Sciences.

general, is limited. Pediatricians should be familiar with the common pesticide types, signs and symptoms of acute toxicity, and chronic health implications. Efforts should be made to limit children's exposure as much as possible and to ensure that products released to the marketplace have been appropriately tested for safety to protect fetuses, infants, and children from adverse effects.


## LEAD AUTHORS

James R. Roberts, MD, MPH
Catherine J. Karr, MD, PhD

## COUNCIL ON ENVIRONMENTAL HEALTH EXECUTIVE COMMITTEE, 2012–2013

Jerome A. Paulson, MD, Chairperson
Alice C. Brock-Utne, MD
Heather L. Brumberg, MD, MPH
Carla C. Campbell, MD
Bruce P. Lanphear, MD, MPH
Kevin C. Osterhoudt, MD, MSCE
Megan T. Sandel, MD
Leonardo Trasande, MD, MPP
Robert O. Wright, MD, MPH

## FORMER EXECUTIVE COMMITTEE MEMBERS

Helen J. Binns, MD, MPH
James R. Roberts, MD, MPH
Catherine J. Karr, MD, PhD
Joel A. Forman, MD
James M. Seltzer, MD

## LIAISONS

Mary Mortensen, MD – *Centers for Disease Control and Prevention/National Center for Environmental Health*
Walter J. Rogan, MD – *National Institute of Environmental Health Sciences*
Sharon Savage, MD – *National Cancer Institute*

## STAFF

Paul Spire

## REFERENCES


1. American Academy of Pediatrics, Committee on Environmental Health. Pesticides. In: Etzel RA, Balk SJ, eds. *Pediatric Environmental Health*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003
2. Katz TM, Miller JH, Hebert AA. Insect repellents: historical perspectives and new developments. *J Am Acad Dermatol*. 2008;58(5):865–871
3. Reigart JR, Roberts JR. *Recognition and Management of Pesticide Poisoning*. 5th ed. Washington, DC: US Environmental Protection Agency; 1999
4. Freeman NC, Hore P, Black K, et al. Contributions of children's activities to pesticide hand loadings following residential pesticide application. *J Expo Anal Environ Epidemiol*. 2005;15(1):81–88
5. Freeman NC, Jimenez M, Reed KJ, et al. Quantitative analysis of children's microactivity patterns: The Minnesota Children's Pesticide Exposure Study. *J Expo Anal Environ Epidemiol*. 2001;11(6):501–509
6. Lewis RG, Fortune CR, Blanchard FT, Camann DE. Movement and deposition of two organophosphorus pesticides within a residence after interior and exterior applications. *J Air Waste Manag Assoc*. 2001;51(3):339–351
7. Hore P, Robson M, Freeman N, et al. Chlorpyrifos accumulation patterns for child-accessible surfaces and objects and urinary metabolite excretion by children for 2 weeks after crack-and-crevice application. *Environ Health Perspect*. 2005;113(2):211–219
8. Curwin BD, Hein MJ, Sanderson WT, et al. Pesticide contamination inside farm and nonfarm homes. *J Occup Environ Hyg*. 2005;2(7):357–367
9. Lu C, Fenske RA, Simcox NJ, Kalman D. Pesticide exposure of children in an agricultural community: evidence of household proximity to farmland and take home exposure pathways. *Environ Res*. 2000;84(3):290–302
10. Fenske RA, Black KG, Elkner KP, Lee CL, Methner MM, Soto R. Potential exposure and health risks of infants following indoor residential pesticide applications. *Am J Public Health*. 1990;80(6):689–693
11. Whyatt RM, Garfinkel R, Hoepner LA, et al. Within- and between-home variability in indoor air insecticide levels during pregnancy among an inner-city cohort from New York City. *Environ Health Perspect*. 2007;15(3):383–389
12. Gurunathan S, Robson M, Freeman N, et al. Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. *Environ Health Perspect*. 1998;106(1):9–16
13. Coronado GD, Vigoren EM, Thompson B, Griffith WC, Faustman EM. Organophosphate pesticide exposure and work in pome fruit: evidence for the take-home pesticide pathway. *Environ Health Perspect*. 2006;114(7):999–1006
14. Julien R, Adamkiewicz G, Levy JI, Bennett D, Nishioka M, Spengler JD. Pesticide loadings of select organophosphate and pyrethroid pesticides in urban public housing. *J Expo Sci Environ Epidemiol*. 2008;18(2):167–174
15. Nishioka MG, Lewis RG, Brinkman MC, Burkholder HM, Hines CE, Menkedick JR. Distribution of 2,4-D in air and on surfaces inside residences after lawn applications: comparing exposure estimates from various media for young children. *Environ Health Perspect*. 2001;109(11):1185–1191
16. Morgan MK, Stout DM, Jones PA, Barr DB. An observational study of the potential for human exposures to pet-borne diazinon residues following lawn applications. *Environ Res*. 2008;107(3):336–342
17. Colt JS, Lubin J, Camann D, et al. Comparison of pesticide levels in carpet dust and self-reported pest treatment practices in four US sites. *J Expo Anal Environ Epidemiol*. 2004;14(1):74–83
18. Morgan MK, Sheldon LS, Croghan CW, et al. Exposures of preschool children to chlorpyrifos and its degradation product 3,5,6-trichloro-2-pyridinol in their everyday environments. *J Expo Anal Environ Epidemiol*. 2005;15(4):297–309
19. Centers for Disease Control and Prevention, National Center for Environmental Health Division of Laboratory Sciences. *National Report on Human Exposure to Environmental Chemicals*. Atlanta, GA: Centers for Disease Control and Prevention; 2005. NCEH Pub. No. 05-0570. Available at: www.cdc.gov/exposurereport/. Accessed June 8, 2011
20. Riederer AM, Bartell SM, Barr DB, Ryan PB. Diet and nondiet predictors of urinary 3-phenoxybenzoic acid in NHANES 1999-2002. *Environ Health Perspect*. 2008;116(8):1015–1022
21. US Food and Drug Administration. Center for Food Safety and Applied Nutrition. Pesticide Residue Monitoring Program 2003. Available at: www.cfsan.fda.gov/~dms/pes03rep.html. Accessed June 8, 2011
22. Lu C, Toepel K, Irish R, Fenske RA, Barr DB, Bravo R. Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. *Environ Health Perspect*. 2006;114(2):260–263
23. Curl CL, Fenske RA, Kissel JC, et al. Evaluation of take-home organophosphorus pesticide exposure among agricultural workers and their children. *Environ Health Perspect*. 2002;110(12):A787–A792
24. Harnly ME, Bradman A, Nishioka M, et al. Pesticides in dust from homes in an agricultural area. *Environ Sci Technol*. 2009;43(23):8767–8774
25. Curwin BD, Hein MJ, Sanderson WT, et al. Pesticide dose estimates for children of Iowa farmers and non-farmers. *Environ Res*. 2007;105(3):307–315
26. Shipp EM, Cooper SP, del Junco DJ, Bolin JN, Whitworth RE, Cooper CJ. Pesticide safety training among farmworker adolescents from Starr County, Texas. *J Agric Saf Health*. 2007;13(3):311–321
27. Gamlin J, Diaz Romo P, Hesketh T. Exposure of young children working on Mexican tobacco plantations to organophosphorous and carbamic pesticides, indicated by cholinesterase depression. *Child Care Health Dev*. 2007;33(3):246–248
28. Eckerman DA, Gimenes LS, de Souza RC, Galvão PR, Sarcinelli PN, Chrisman JR. Age related effects of pesticide exposure on neurobehavioral performance of adolescent farm workers in Brazil. *Neurotoxicol Teratol*. 2007;29(1):164–175
29. Gilliom RJ. Pesticides in U.S. streams and groundwater. *Environ Sci Technol*. 2007;41(10):3408–3414
30. Bronstein AC, Spyker DA, Cantilena LR, Jr; Green JL, Rumack BH, Giffin SL. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)*. 2010;48(10):979–1178
31. Blondell JM. Decline in pesticide poisonings in the United States from 1995 to 2004. *Clin Toxicol*. 2007;45(5):589–592
32. Lifshitz M, Shahak E, Sofer S. Carbamate and organophosphate poisoning in young children. *Pediatr Emerg Care*. 1999;15(2):102–103
33. Zwiener RJ, Ginsburg CM. Organophosphate and carbamate poisoning in infants and children. *Pediatrics*. 1988;81(1):121–126
34. Sofer S, Tal A, Shahak E. Carbamate and organophosphate poisoning in early

childhood. *Pediatr Emerg Care*. 1989;5(4):222–225

35. Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. *BMJ*. 2007;334(7594):629–634
36. Chyka PA, Seger D, Krenzelok EP, Vale JA; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement: single-dose activated charcoal. *Clin Toxicol (Phila)*. 2005;43(2):61–87
37. Eddleston M, Juszczak E, Buckley NA, et al; Ox-Col Poisoning Study collaborators. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet*. 2008;371(9612):579–587
38. Geller RJ, Singleton KL, Tarantino ML, et al; Centers for Disease Control and Prevention (CDC). Nosocomial poisoning associated with emergency department treatment of organophosphate toxicity—Georgia, 2000. *MMWR Morb Mortal Wkly Rep*. 2001;49(51-52):1156–1158
39. Pawar KS, Bhoite RR, Pillay CP, Chavan SC, Malshikare DS, Garad SG. Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. *Lancet*. 2006;368(9553):2136–2141
40. Eddleston M, Eyer P, Worek F, et al. Pralidoxime in acute organophosphorus insecticide poisoning—a randomised controlled trial. *PLoS Med*. 2009;6(6):e1000104
41. World Health Organization, International Programme on Chemical Safety. *Poisons Information Monograph G001. Organophosphorus Pesticides*. Geneva, Switzerland: World Health Organization; 1999
42. Ray DE, Forshaw PJ. Pyrethroid insecticides: poisoning syndromes, synergies, and therapy. *J Toxicol Clin Toxicol*. 2000;38(2):95–101
43. Ray DE, Fry JR. A reassessment of the neurotoxicity of pyrethroid insecticides. *Pharmacol Ther*. 2006;111(1):174–193
44. Dorman DC, Beasley VR. Neurotoxicology of pyrethrin and the pyrethroid insecticides. *Vet Hum Toxicol*. 1991;33(3):238–243
45. He F, Wang S, Liu L, Chen S, Zhang Z, Sun J. Clinical manifestations and diagnosis of acute pyrethroid poisoning. *Arch Toxicol*. 1989;63(1):54–58
46. Tucker SB, Flannigan SA. Cutaneous effects from occupational exposure to fenvalerate. *Arch Toxicol*. 1983;54(3):195–202
47. Tucker SB, Flannigan SA, Ross CE. Inhibition of cutaneous paresthesia resulting from synthetic pyrethroid exposure. *Int J Dermatol*. 1984;23(10):686–689
48. Wilks MF. Pyrethroid-induced paresthesia—a central or local toxic effect? *Clin Toxicol (Phila)*. 2000;38(2):103–105
49. Song JH, Narahashi T. Selective block of tetramethrin-modified sodium channels by (+/-)-alpha-tocopherol (vitamin E). *J Pharmacol Exp Ther*. 1995;275(3):1402–1411
50. Meinking TL, Serrano L, Hard B, et al. Comparative in vitro pediculicidal efficacy of treatments in a resistant head lice population in the United States. *Arch Dermatol*. 2002;138(2):220–224
51. Feldmann RJ, Maibach HI. Percutaneous penetration of some pesticides and herbicides in man. *Toxicol Appl Pharmacol*. 1974;28(1):126–132
52. Ginsburg CM, Lowry W, Reisch JS. Absorption of lindane (gamma benzene hexachloride) in infants and children. *J Pediatr*. 1997;91(6):998–1000
53. US Environmental Protection Agency. Lindane; Cancellation order. *Fed Regist*. 2006;71(239):74905–74907. Available at: www.epa.gov/fedrgstr/EPA-PEST/2006/December/Day-13/p21101.htm. Accessed June 28, 2011
54. Tomizawa M, Casida JE. Neonicotinoid insecticide toxicology: mechanisms of selective action. *Annu Rev Pharmacol Toxicol*. 2005;45(7):247–268
55. Matsuda K, Buckingham SD, Kleier D, Rauh JJ, Grauso M, Sattelle DB. Neonicotinoids: insecticides acting on insect nicotinic acetylcholine receptors. *Trends Pharmacol Sci*. 2001;22(11):573–580
56. David D, George IA, Peter JV. Toxicology of the newer neonicotinoid insecticides: imidacloprid poisoning in a human. *Clin Toxicol (Phila)*. 2007;45(5):485–486
57. Bloomquist JR. Ion channels as targets for insecticides. *Annu Rev Entomol*. 1996;41:163–190
58. Ratra GS, Casida JE. GABA receptor subunit composition relative to insecticide potency and selectivity. *Toxicol Lett*. 2001;122(3):215–222
59. Hainzl D, Cole LM, Casida JE. Mechanisms for selective toxicity of fipronil insecticide and its sulfone metabolite and desulfinyl photoproduct. *Chem Res Toxicol*. 1998;11(12):1529–1535
60. Arnold EK, Beasley VR. The pharmacokinetics of chlorinated phenoxy acid herbicides: a literature review. *Vet Hum Toxicol*. 1989;31(2):121–125
61. Friesen EG, Jones GR, Vaughan D. Clinical presentation and management of acute 2,4-D oral ingestion. *Drug Saf*. 1990;5(2):155–159
62. Prescott LF, Park J, Darrien I. Treatment of severe 2,4-D and mecoprop intoxication with alkaline diuresis. *Br J Clin Pharmacol*. 1979;7(1):111–116
63. Schecter A, Birnbaum L, Ryan JJ, Constable JD. Dioxins: an overview. *Environ Res*. 2006;101(3):419–428
64. Keller T, Skopp G, Wu M, Aderjan R. Fatal overdose of 2,4-dichlorophenoxyacetic acid (2,4-D). *Forensic Sci Int*. 1994;65(1):13–18
65. Proudfoot AT, Krenzelok EP, Vale JA. Position Paper on urine alkalinization. *J Toxicol Clin Toxicol*. 2004;42(1):1–26
66. US Environmental Protection Agency. Final risk mitigation decision for ten rodenticides. Available at: www.epa.gov/fedrgstr/EPA-PEST/2006/December/Day-13/p21101.htm. Accessed June 28, 2011
67. Ingels M, Lai C, Tai W, et al. A prospective study of acute, unintentional, pediatric superwarfarin ingestions managed without decontamination. *Ann Emerg Med*. 2002;40(1):73–78
68. Smolinske SC, Scherger DL, Kearns PS, Wruk KM, Kulig KW, Rumack BH. Superwarfarin poisoning in children: a prospective study. *Pediatrics*. 1989;84(3):490–494
69. Shepherd G, Klein-Schwartz W, Anderson BD. Acute, unintentional pediatric brodifacoum ingestions. *Pediatr Emerg Care*. 2002;18(3):174–178
70. Mullins ME, Brands CL, Daya MR. Unintentional pediatric superwarfarin exposures: do we really need a prothrombin time? *Pediatrics*. 2000;105(2):402–404
71. Caravati EM, Erdman AR, Scharman EJ, et al. Long-acting anticoagulant rodenticide poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*. 2007;45(1):1–22
72. US Environmental Protection Agency. Food Quality Protection Act of 1996. Pub L No. 104-170 (1996)
73. Karr CJ, Solomon GM, Brock-Utne AC. Health effects of common home, lawn, and garden pesticides. *Pediatr Clin North Am*. 2007;54(1):63–80, viii
74. Roberts JR, Balk SJ, Forman J, Shannon M. Teaching about pediatric environmental health [letter]. *Ambul Pediatr*. 2009;9(2):129–130
75. Karr C, Murphy H, Glew G, Keifer MC, Fenske RA. Pacific Northwest health professionals survey on pesticides and children. *J Agromed*. 2006;11(3-4):113–120
76. McCurdy LE, Roberts JR, Rogers B, et al. Incorporating environmental health into pediatric medical and nursing education. *Environ Health Perspect*. 2004;112(17):1755–1760

77. US Environmental Protection Agency, Office of Pesticide Programs. Chemicals evaluated for carcinogenic potential. Available at: www.epa.gov/pesticides/carlist. Accessed June 8, 2011
78. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. *J Toxicol Environ Health B Crit Rev.* 2007;10(1-2):81–99
79. Zahm SH, Ward MH. Pesticides and childhood cancer. *Environ Health Perspect.* 1998;106(suppl 3):893–908
80. Buckley JD, Robison LL, Swotinsky R, et al. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. *Cancer Res.* 1989;49(14): 4030–4037
81. Cordier S, Iglesias MJ, Le Goaster C, Guyot MM, Mandereau L, Hemon D. Incidence and risk factors for childhood brain tumors in the Ile de France. *Int J Cancer.* 1994;59(6):776–782
82. Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer. *Arch Environ Contam Toxicol.* 1993;24(1):87–92
83. Feychting M, Plato N, Nise G, Ahlbom A. Paternal occupational exposures and childhood cancer. *Environ Health Perspect.* 2001;109(2):193–196
84. Infante-Rivard C, Labuda D, Krajinovic M, Sinnett D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology.* 1999;10(5):481–487
85. Ma X, Buffler PA, Gunier RB, et al. Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ Health Perspect.* 2002;110(9):955–960
86. Schüz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol.* 2001;36(2):274–282
87. van Wijngaarden E, Stewart PA, Olshan AF, Savitz DA, Bunin GR. Parental occupational exposure to pesticides and childhood brain cancer. *Am J Epidemiol.* 2003;157 (11):989–997
88. Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Harnly ME. Childhood cancer and agricultural pesticide use: an ecologic study in California. *Environ Health Perspect.* 2002;110(3):319–324
89. Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Harnly M, Hertz A. Agricultural pesticide use and childhood cancer in California. *Epidemiology.* 2005;16(1):93–100
90. Infante-Rivard C, Sinnett D. Preconceptional paternal exposure to pesticides and increased risk of childhood leukaemia. *Lancet.* 1999;354(9192):1819–1820
91. Meinert R, Schüz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. *Am J Epidemiol.* 2000;151(7):639–646, discussion 647–650
92. Alexander FE, Patheal SL, Biondi A, et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. *Cancer Res.* 2001;61(6):2542–2546
93. Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. *Environ Health Perspect.* 2009;117(10):1505–1513
94. Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukemia: a systematic review and meta-analysis. *Environ Health Perspect.* 2010;118(1):33–41
95. Flower KB, Hoppin JA, Lynch CF, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. *Environ Health Perspect.* 2004;112(5):631–635
96. Cordier S, Mandereau L, Preston-Martin S, et al. Parental occupations and childhood brain tumors: results of an international case-control study. *Cancer Causes Control.* 2001;12(9):865–874
97. McKinney PA, Fear NT, Stockton D; UK Childhood Cancer Study Investigators. Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. *Occup Environ Med.* 2003;60(12):901–909
98. Heacock H, Hertzman C, Demers PA, et al. Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenate fungicides. *Environ Health Perspect.* 2000;108(6):499–503
99. Rodvall Y, Dich J, Wiklund K. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. *Occup Environ Med.* 2003;60(10):798–801
100. Schreinemachers DM. Cancer mortality in four northern wheat-producing states. *Environ Health Perspect.* 2000;108(9):873–881
101. Moore LE, Gold L, Stewart PA, Gridley G, Prince JR, Zahm SH. Parental occupational exposures and Ewing's sarcoma. *Int J Cancer.* 2005;114(3):472–478
102. Valery PC, McWhirter W, Sleigh A, Williams G, Bain C. Farm exposures, parental occupation, and risk of Ewing's sarcoma in Australia: a national case-control study. *Cancer Causes Control.* 2002;13(3):263–270
103. Rosas LG, Eskenazi B. Pesticides and child neurodevelopment. *Curr Opin Pediatr.* 2008;20(2):191–197
104. Eskenazi B, Rosas LG, Marks AR, et al. Pesticide toxicity and the developing brain. *Basic Clin Pharmacol Toxicol.* 2008; 102(2):228–236
105. Jurewicz J, Hanke W. Prenatal and childhood exposure to pesticides and neurobehavioral development: review of epidemiological studies. *Int J Occup Med Environ Health.* 2008;21(2):121–132
106. Keifer MC, Mahurin RK. Chronic neurologic effects of pesticide overexposure. *Occup Med.* 1997;12(2):291–304
107. 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
108. Kofman O, Berger A, Massarwa A, Friedman A, Jaffar AA. Motor inhibition and learning impairments in school-aged children following exposure to organophosphate pesticides in infancy. *Pediatr Res.* 2006;60 (1):88–92
109. Berkowitz GS, Obel J, Deych E, et al. Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort. *Environ Health Perspect.* 2003;111(1):79–84
110. Perera FP, Rauh VA, Tsai WY, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environ Health Perspect.* 2003;111(2):201–205
111. Young JG, Eskenazi B, Gladstone EA, et al. Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates. *Neurotoxicology.* 2005; 26(2):199–209
112. 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 (12):1397–1404
113. Eskenazi B, Marks AR, Bradman A, et al. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. *Environ Health Perspect.* 2007;115(5):792–798
114. 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(6). Available at: www.pediatrics.org/cgi/content/full/118/6/e1845

115. Rauh V, Arunajadai S, Horton M, et al. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environ Health Perspect*. 2011;119(8):1196–1201
116. Bouchard MF, Chevrier J, Harley KG, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ Health Perspect*. 2011;119(8):1189–1195
117. Engel SM, Wetmur J, Chen J, et al. Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. *Environ Health Perspect*. 2011;119(8):1182–1188
118. Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. *Pediatrics*. 2010;125(6). Available at: www.pediatrics.org/cgi/content/full/125/6/e1270
119. Grandjean P, Harari R, Barr DB, Debes F. Pesticide exposure and stunting as independent predictors of neurobehavioral deficits in Ecuadorian school children. *Pediatrics*. 2006;117(3). Available at: www.pediatrics.org/cgi/content/full/117/3/e546
120. 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(5):746–751
121. Holland N, Furlong C, Bastaki M, et al. Paraoxonase polymorphisms, haplotypes, and enzyme activity in Latino mothers and newborns. *Environ Health Perspect*. 2006;114(7):985–991
122. Furlong CE, Holland N, Richter RJ, Bradman A, Ho A, Eskenazi B. PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity. *Pharmacogenet Genomics*. 2006;16(3):183–190
123. 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(1):233–241
124. Windham G, Fenster L. Environmental contaminants and pregnancy outcomes. *Fertil Steril*. 2008;89(suppl 2):e111–e116, discussion e117
125. Weselak M, Arbuckle TE, Foster W. Pesticide exposures and developmental outcomes: the epidemiological evidence. *J Toxicol Environ Health B Crit Rev*. 2007;10(1-2):41–80
126. Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. Environmental exposures and adverse pregnancy outcomes: a review of the science. *Reprod Sci*. 2008;15(7):631–650
127. Bell EM, Hertz-Picciotto I, Beaumont JJ. A case-control study of pesticides and fetal death due to congenital anomalies. *Epidemiology*. 2001;12(2):148–156
128. Arbuckle TE, Savitz DA, Mery LS, Curtis KM. Exposure to phenoxy herbicides and the risk of spontaneous abortion. *Epidemiology*. 1999;10(6):752–760
129. Salazar-García F, Gallardo-Díaz E, Cerón-Mireles P, Loomis D, Borja-Aburto VH. Reproductive effects of occupational DDT exposure among male malaria control workers. *Environ Health Perspect*. 2004;112(5):542–547
130. Arbuckle TE, Lin Z, Mery LS. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ Health Perspect*. 2001;109(8):851–857
131. Savitz DA, Arbuckle T, Kaczor D, Curtis KM. Male pesticide exposure and pregnancy outcome. *Am J Epidemiol*. 1997;146(12):1025–1036
132. Nurminen T. Maternal pesticide exposure and pregnancy outcome. *J Occup Environ Med*. 1995;37(8):935–940
133. Schwartz DA, LoGerfo JP. Congenital limb reduction defects in the agricultural setting. *Am J Public Health*. 1988;78(6):654–658
134. Bjerkedal T. Use of medical registration of birth in the study of occupational hazards to human reproduction. In: Hemminki K, Sorsa M, Vainio H, eds. *Occupational Hazards and Reproduction*. Washington, DC: Hemisphere Publishing Corporation; 1985:313–321
135. Hemminki K, Mutanen P, Luoma K, Saloniemi I. Congenital malformations by the parental occupation in Finland. *Int Arch Occup Environ Health*. 1980;46(2):93–98
136. McDonald AD, McDonald JC, Armstrong B, et al. Congenital defects and work in pregnancy. *Br J Ind Med*. 1988;45(9):581–588
137. Schwartz DA, Newsum LA, Heifetz RM. Parental occupation and birth outcome in an agricultural community. *Scand J Work Environ Health*. 1986;12(1):51–54
138. Restrepo M, Muñoz N, Day NE, Parra JE, de Romero L, Nguyen-Dinh X. Prevalence of adverse reproductive outcomes in a population occupationally exposed to pesticides in Colombia. *Scand J Work Environ Health*. 1990;16(4):232–238
139. Restrepo M, Muñoz N, Day N, et al. Birth defects among children born to a population occupationally exposed to pesticides in Colombia. *Scand J Work Environ Health*. 1990;16(4):239–246
140. McDonald JC, Lavoie J, Côté R, McDonald AD. Chemical exposures at work in early pregnancy and congenital defect: a case-referent study. *Br J Ind Med*. 1987;44(8):527–533
141. Lin S, Marshall EG, Davidson GK. Potential parental exposure to pesticides and limb reduction defects. *Scand J Work Environ Health*. 1994;20(3):166–179
142. Zhang J, Cai WW, Lee DJ. Occupational hazards and pregnancy outcomes. *Am J Ind Med*. 1992;21(3):397–408
143. Nurminen T, Rantala K, Kurppa K, Holmberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. *Epidemiology*. 1995;6(1):23–30
144. Garry VF, Schreinemachers D, Harkins ME, Griffith J. Pesticide appliers, biocides, and birth defects in rural Minnesota. *Environ Health Perspect*. 1996;104(4):394–399
145. Garry VF, Harkins ME, Erickson LL, Long-Simpson LK, Holland SE, Burroughs BL. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. *Environ Health Perspect*. 2002;110(suppl 3):441–449
146. Romitti PA, Herring AM, Dennis LK, Wong-Gibbons DL. Meta-analysis: pesticides and orofacial clefts. *Cleft Palate Craniofac J*. 2007;44(4):358–365
147. Longnecker MP, Klebanoff MA, Zhou H, Brock JW. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. *Lancet*. 2001;358(9276):110–114
148. Ribas-Fitó N, Sala M, Cardo E, et al. Association of hexachlorobenzene and other organochlorine compounds with anthropometric measures at birth. *Pediatr Res*. 2002;52(2):163–167
149. Weisskopf MG, Anderson HA, Hanrahan LP, et al; Great Lakes Consortium. Maternal exposure to Great Lakes sport-caught fish and dichlorodiphenyl dichloroethylene, but not polychlorinated biphenyls, is associated with reduced birth weight. *Environ Res*. 2005;97(2):149–162
150. Wolff MS, Engel S, Berkowitz G, et al. Prenatal pesticide and PCB exposures and birth outcomes. *Pediatr Res*. 2007;61(2):243–250
151. Siddiqui MK, Srivastava S, Srivastava SP, Mehrotra PK, Mathur N, Tandon I. Persistent chlorinated pesticides and intrauterine foetal growth retardation:

a possible association. *Int Arch Occup Environ Health*. 2003;76(1):75–80

152. Fenster L, Eskenazi B, Anderson M, et al. Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect*. 2006; 114(4):597–602
153. Eskenazi B, Harley K, Bradman A, et al. Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect*. 2004; 112(10):1116–1124
154. Munger R, Isacson P, Hu S, et al. Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. *Environ Health Perspect*. 1997;105(3):308–314
155. Villanueva CM, Durand G, Coutté MB, Chevrier C, Cordier S. Atrazine in municipal drinking water and risk of low birth weight, preterm delivery, and small-for-gestational-age status. *Occup Environ Med*. 2005;62(6):400–405
156. Reigart JR, Roberts JR. Pesticides in children. *Pediatr Clin North Am*. 2001;48 (5):1185–1198, ix
157. Gasnier C, Dumont C, Benachour N, Clair E, Chagnon MC, Séralini GE. Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. *Toxicology*. 2009;262(3):184–191
158. Silva MH, Gammon D. An assessment of the developmental, reproductive, and neurotoxicity of endosulfan. *Birth Defects Res B Dev Reprod Toxicol*. 2009; 86(1):1–28
159. Molina-Molina JM, Hillenweck A, Jouanin I, et al. Steroid receptor profiling of vinclozolin and its primary metabolites. *Toxicol Appl Pharmacol*. 2006;216(1):44–54
160. Guilette LJ JrCrain DA, Gunderson MP, et al. Alligators and endocrine disrupting contaminants: a current perspective. *Am Zool*. 2000;40:438–452
161. Hayes TB, Collins A, Lee M, et al. Hermaphroditic, demasculinized frogs after exposure to the herbicide atrazine at low ecologically relevant doses. *Proc Natl Acad Sci USA*. 2002;99(8):5476–5480
162. Fan W, Yanase T, Morinaga H, et al. Atrazine-induced aromatase expression is SF-1 dependent: implications for endocrine disruption in wildlife and reproductive cancers in humans. *Environ Health Perspect*. 2007;115(5):720–727
163. Krstevska-Konstantinova M, Charlier C, Craen M, et al. Sexual precocity after immigration from developing countries to Belgium: evidence of previous exposure to organochlorine pesticides. *Hum Reprod*. 2001;16(5):1020–1026
164. Hosie S, Loff S, Witt K, Niessen K, Waag KL. Is there a correlation between organochlorine compounds and undescended testes? *Eur J Pediatr Surg*. 2000;10(5): 304–309
165. Bhatia R, Shiau R, Petreas M, Weintraub JM, Farhang L, Eskenazi B. Organochlorine pesticides and male genital anomalies in the child health and development studies. *Environ Health Perspect*. 2005;113(2):220–224
166. Longnecker MP, Klebanoff MA, Brock JW, et al. Maternal serum level of 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene and risk of cryptorchidism, hypospadias, and polythelia among male offspring. *Am J Epidemiol*. 2002;155(4):313–322
167. Pierik FH, Klebanoff MA, Brock JW, Longnecker MP. Maternal pregnancy serum level of heptachlor epoxide, hexachlorobenzene, and beta-hexachlorocyclohexane and risk of cryptorchidism in offspring. *Environ Res*. 2007; 105(3):364–369
168. Fernandez MF, Olmos B, Granada A, et al. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case-control study. *Environ Health Perspect*. 2007;115(suppl 1):8–14
169. Damgaard IN, Skakkebaek NE, Toppari J, et al; Nordic Cryptorchidism Study Group. Persistent pesticides in human breast milk and cryptorchidism. *Environ Health Perspect*. 2006;114(7):1133–1138
170. LaKind JS, Berlin CM, Park CN, Naiman DQ, Gudka NJ. Methodology for characterizing distributions of incremental body burdens of 2,3,7,8-TCDD and DDE from breast milk in North American nursing infants. *J Toxicol Environ Health A*. 2000;59(8):605–639
171. Fernandez MF, Aguilar-Garduño C, Molina-Molina JM, Arrebola JP, Olea N. The total effective xenoestrogen burden, a biomarker of exposure to xenoestrogen mixtures, is predicted by the (anti)estrogenicity of its components. *Reprod Toxicol*. 2008;26(1):8–12
172. Rogan WJ, Ragan NB. Some evidence of effects of environmental chemicals on the endocrine system in children. *Int J Hyg Environ Health*. 2007;210(5):659–667
173. Duramad P, Harley K, Lipsett M, et al. Early environmental exposures and intracellular Th1/Th2 cytokine profiles in 24-month-old children living in an agricultural area. *Environ Health Perspect*. 2006;114(12):1916–1922
174. Fryer AD, Lein PJ, Howard AS, Yost BL, Beckles RA, Jett DA. Mechanisms of organophosphate insecticide-induced airway hyperreactivity. *Am J Physiol Lung Cell Mol Physiol*. 2004;286(5):L963–L969
175. Lein PJ, Fryer AD. Organophosphorus insecticides induce airway hyperreactivity by decreasing neuronal M2 muscarinic receptor function independent of acetylcholinesterase inhibition. *Toxicol Sci*. 2005; 83(1):166–176
176. Gultekin F, Ozturk M, Akdogan M. The effect of organophosphate insecticide chlorpyrifos-ethyl on lipid peroxidation and antioxidant enzymes (in vitro). *Arch Toxicol*. 2000;74(9):533–538
177. Ranjbar A, Pasalar P, Abdollahi M. Induction of oxidative stress and acetylcholinesterase inhibition in organophosphorous pesticide manufacturing workers. *Hum Exp Toxicol*. 2002;21(4):179–182
178. Merchant JA, Naleway AL, Svendsen ER, et al. Asthma and farm exposures in a cohort of rural Iowa children. *Environ Health Perspect*. 2005;113(3):350–356
179. Salameh PR, Baldi I, Brochard P, Raherison C, Abi Saleh B, Salamon R. Respiratory symptoms in children and exposure to pesticides. *Eur Respir J*. 2003;22 (3):507–512
180. Salam MT, Li YF, Langholz B, Gilliland FD; Children's Health Study. Early-life environmental risk factors for asthma: findings from the Children's Health Study. *Environ Health Perspect*. 2004;112(6):760–765
181. Hoppin JA, Umbach DM, London SJ, Lynch CF, Alavanja MC, Sandler DP. Pesticides and adult respiratory outcomes in the agricultural health study. *Ann N Y Acad Sci*. 2006;1076:343–354
182. Hoppin JA, Umbach DM, London SJ, Lynch CF, Alavanja MC, Sandler DP. Pesticides associated with wheeze among commercial pesticide applicators in the Agricultural Health Study. *Am J Epidemiol*. 2006; 163(12):1129–1137
183. Karmaus W, Kuehr J, Kruse H. Infections and atopic disorders in childhood and organochlorine exposure. *Arch Environ Health*. 2001;56(6):485–492
184. Sunyer J, Torrent M, Muñoz-Ortiz L, et al. Prenatal dichlorodiphenyldichloroethylene (DDE) and asthma in children. *Environ Health Perspect*. 2005;113(12):1787–1790
185. US Environmental Protection Agency. Pesticide product labels. Available at: www.epa.gov/pesticides/regulating/labels/product-labels.htm#projects. Accessed June 6, 2011

186. Weinhold B. Mystery in a bottle: will the EPA require public disclosure of inert pesticide ingredients? *Environ Health Perspect*. 2010;118(4):A168–A171
187. US Environmental Protection Agency. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Available at: www.epa.gov/oecaagct/lfra.html. Accessed May 4, 2011
188. US Environmental Protection Agency. "Read the Label First" interactive pesticide label. Available at: www.epa.gov/pesticides/kids/hometour/label/read.htm. Accessed June 6, 2011
189. Balbus JM, Harvey CE, McCurdy LE. Educational needs assessment for pediatric health care providers on pesticide toxicity. *J Agromed*. 2006;11(1):27–38
190. Kilpatrick N, Frumkin H, Trowbridge J, et al. The environmental history in pediatric practice: a study of pediatricians' attitudes, beliefs, and practices. *Environ Health Perspect*. 2002;110(8):823–827
191. Trasande L, Schapiro ML, Falk R, et al. Pediatrician attitudes, clinical activities, and knowledge of environmental health in Wisconsin. *WMJ*. 2006;105(2):45–49
192. Roberts JR, Balk SJ, Forman J, Shannon M. Teaching about pediatric environmental health. *Acad Pediatr*. 2009;9(2):129–130
193. American Academy of Pediatrics, Committee on Environmental Health. Taking an environmental history and giving anticipatory guidance. In: Etzel RA, Balk SJ, eds. *Pediatric Environmental Health*. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:39–56
194. US General Accounting Office. Agricultural pesticides: management improvements needed to further promote integrated pest management. Available at: www.gao.gov/new.items/d01815.pdf. Accessed June 12, 2012
195. Roberts DM, Buckley NA, Mohamed F, et al. A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning. *Clin Toxicol (Phila)*. 2010;48(2):129–136

# ERRATA

**Spooner. We Are Still Waiting for Fully Supportive Electronic Health Records in Pediatrics. *Pediatrics*. 2012;130(6):e1674–e1676.**

An error occurred in this article by Spooner, titled "We Are Still Waiting for Fully Supportive Electronic Health Records in Pediatrics" published in the December 2012 issue of *Pediatrics* (2012;130[6]:e1674–e1676; originally published online November 19, 2012; doi:10.1542/peds.2012-2724). On page e1674, on line 33, this reads: "The alarming result from the survey was that only 3% of AAP Fellows reported that they had a system that provided all of the items listed by Leu and colleagues." This should have read: "The alarming result from the survey was that only 9.6% of AAP Fellows reported that they had or planned to adopt within 12 months a system that provided all of the five "pediatric-supportive" items listed by Leu and colleagues."

doi:10.1542/peds.2013-0134

**Auger et al. Medical Home Quality and Readmission Risk for Children Hospitalized With Asthma Exacerbations. *Pediatrics*. 2013;131(1):64–70**

An error occurred in this article by Auger et al, titled "Medical Home Quality and Readmission Risk for Children Hospitalized With Asthma Exacerbations" published in the January 2013 issue of *Pediatrics* (2013;131[1]:64–70; doi:10.1542/2012-1055). On page 69, in Table 2 under the heading Adjusted HR, on the line Medicaid, this reads: "0.28 (0.51–1.34)." This should have read: "0.82 (0.51–1.34)."

doi:10.1542/peds.2013-0187

**Council on Environmental Health. Policy Statement: Pesticide Exposure in Children. *Pediatrics*. 2012;130(6):e1757–e1763**

A couple of errors occurred in this AAP Policy Statement titled "Pesticide Exposure in Children" published in the December 2012 issue of *Pediatrics* (2012;130[6]:e1757–e1763; originally published online November 26, 2012; doi:10.1542/peds.2012-2757). In Table 2, in the second and third columns where glyphosate is discussed, the words "organic solvent" should be replaced with the word "surfactant." On page e1758, in the first paragraph of the left-hand column, immediately beneath Table 1, the first full sentence should be amended to read: "For many children, diet may be the most influential source, as illustrated by an intervention study that placed children on an organic diet (produced without most conventional pesticides) and observed drastic and immediate decrease in urinary excretion of organophosphate pesticide metabolites."

doi:10.1542/peds.2013-0576

**Robert JR, Karr CJ; Council on Environmental Health. Technical Report: Pesticide Exposure in Children. *Pediatrics*. 2012;130(6):e1765–e1788**

Several inaccuracies occurred in this AAP Technical Report titled "Pesticide Exposure in Children" published in the December 2012 issue of *Pediatrics* (2012;130[6]:e1765–e1788; originally published online November 26, 2012; doi:10.1542/peds.2012-2758). On page e1773 and in Tables 1 and 2 where the phosphonate herbicide glyphosate is discussed, changes should be noted. In the first paragraph of the first column on page e1773 about acute glyphosate poisoning, the word "intentional" should be substituted for the word "unintentional." In this same paragraph as well as in Tables 1 and 2, the word "surfactant" should replace the words "hydrocarbon solvent" and "organic solvent, respectively." The

mechanism of action for glyphosate should be changed from "acts on cell wall" to "inhibits a critical enzyme pathway for amino acid synthesis that is found only in plants" (Bradberry SM, Proudfoot AT, Vale JA. Glyphosate poisoning. *Toxicol Rev.* 2004;23[3]:159–167).

doi:10.1542/peds.2013-0577

**Copeland et al. Clinical Practice Guideline: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents. *Pediatrics*. 2013;131(2):364–382**

Several inaccuracies occurred in the American Academy of Pediatrics "Clinical Practice Guideline: Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents" published in the February 2013 issue of *Pediatrics* (2013;131[2]:364–382).

On page 366 in the table of definitions, "Prediabetes" should be defined as "Fasting plasma glucose ≥100–125 mg/dL or 2-hour glucose concentration during an oral glucose tolerance test of ≥140 but <200 mg/dL or an HbA1c of 5.7% to 6.4%."

On page 378, middle column, under "Reducing Screen Time," the second sentence should read as follows: "The US Department of Health and Human Services reflects the American Academy of Pediatrics policies by recommending that individuals limit "screen time" spent watching television and/or using computers and handheld devices to <2 hours per day unless the use is related to work or homework."[79–81,83]

Also on page 378, middle column, in the second paragraph under "Reducing Screen Time," the fourth sentence should read: "Pending new data, the committee suggests that clinicians follow the policy statement 'Children, Adolescents, and Television' from the AAP Council on Communications and Media (formerly the Committee on Public Education)." The references cited in the next sentence should be 80–83.

Reference 82 should be replaced with the following reference: Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007;120(suppl 4):S164–S192

Finally, a new reference 83 should be added: American Academy of Pediatrics, Council on Communications and Media. Policy statement: children, adolescents, obesity, and the media. *Pediatrics*. 2011;128(1):201–208

doi:10.1542/peds.2013-0666

**Springer et al. Technical Report: Management of Type 2 Diabetes Mellitus in Children and Adolescents. *Pediatrics*. 2013;131(2):e648–e664.**

An error occurred in the American Academy of Pediatrics "Technical Report: Management of Type 2 Diabetes Mellitus in Children and Adolescents" published in the February 2013 issue of *Pediatrics* (2013;131[2]:e648–e664).

On page e651, third column, under "Definitions," the first sentence should read as follows: "Children and adolescents: children <10 years of age; adolescents ≥10 years but ≤18 years of age."

doi:10.1542/peds.2013-0667

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

# Pesticide Exposure in Children

James R. Roberts, Catherine J. Karr and COUNCIL ON ENVIRONMENTAL HEALTH

*Pediatrics*; originally published online November 26, 2012;
DOI: 10.1542/peds.2012-2758





American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™