Pesticides

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ABSTRACT. Pesticides are a broad group of heterogeneous chemicals that have a significant public health benefit by increasing food production productivity and decreasing food-borne and vector-borne diseases. However, depending on the agent and the exposure, they may pose health risks. Because of their behavior, acute accidental toxic exposures occur more commonly in children. Because of the dietary habits and greater intake of foods per kilogram in children and because some infants are breastfed, there is also concern about the effects on them of low-level environmental exposures. In the absence of direct conclusive evidence, consistent and relevant observations have led some investigators to infer that chronic low-dose exposure to certain pesticides might pose a potential hazard to the health and development of infants and children. Other investigators have concluded that such inferences can be neither supported nor refuted at the present time. The pediatrician has a role to play in recognizing the symptoms of acute exposure and to be able to provide appropriate treatment. It is essential to study whether there are subtle neurologic effects that may result from low-level pesticide exposures in individual patients. ***Pediatrics*** **2004;113:1030–1036;** ***pesticides, brain development, neurotoxicity, behavior, endocrine disruption.***

ABBREVIATIONS. DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethylene; DES, diethylstilbestrol.

Pesticides are substances that are used to prevent, repel, or destroy pests—organisms that compete for food supply, adversely affect comfort, or endanger human health.[1] Several classes of compounds are used for this purpose. More than 20 000 pesticide products with nearly 900 active ingredients are registered for use as insecticides, miticides, herbicides, rodenticides, nematocides, fungicides, fumigants, wood preservatives, and plant growth regulators. Pesticides are ubiquitous in the environment. They are found in food, water, homes, schools, workplaces, lawns, and gardens.

Pesticides have significant economic, environmental, and public health impacts. Pesticide usage helps improve human nutrition through greater availability, longer storage life, and lower costs of food. It also reduces human labor requirements and attendant risks of injury. Pesticides also assist in the control of food-borne and vector-borne diseases, which affect millions of children and adults and kill thousands annually in the United States alone.[2,3] Pesticides also pose human health concerns because they are toxic substances and widely released into the environment. Although the toxic actions of pesticides are targeted at specific pest species, the potential for adverse health effects in humans and other nontargeted species is incompletely characterized. This article examines the potential for such effects in infants and young children.

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PESTICIDE USAGE AND EXPOSURE

A total of 4.5 billion pounds of chemicals are applied annually as pesticides in the United States. This total consists of 1.2 billion pounds of conventional pesticides (975 million pounds) and other pesticide chemicals such as sulfur (260 million pounds; Table 1),[4] plus wood preservatives (660 million pounds), specialty biocides (270 million pounds), and chlorine/hypochlorite compounds (2.4 billion pounds). Each year, nearly 1 million farms use an estimated 944 million pounds of active ingredient and nearly 74 million households (three fourths of all US households) use an estimated 76 million pounds of pesticides annually (Fig 1).[4] The overall use of conventional pesticides and other pesticide chemicals decreased 17.2% from 1979 to 1997.[4]

Because pesticides are used extensively and widely, they are commonly stored in considerable quantities in or near human dwellings. Unintentional exposure to pesticides is a common cause of acute poisoning, particularly among young children. More than half (57%) of all reported pesticide poisonings in the United States occur in children younger than 6 years—nearly 50 000 children per year.[5,6] A recent study estimated that nearly half of all households with a child younger than five years stored pesticide in an unlocked cabinet within reach of the child.[7]

CLASSES AND TOXICITY OF PESTICIDES

The most commonly used classes of pesticides are composed of different types of chemicals with different mechanisms of action (Table 2). Most insecticides work by interfering with nervous system function. Organophosphates, which account for approximately one half of the insecticides used in the United States, and carbamates, which are widely used in homes and gardens, inhibit the activity of acetylcholinesterase at nerve endings, resulting in an excess of the neurotransmitter acetylcholine and a depolariz-

TABLE 1. Estimated Pesticide Usage, 1997

Class of Pesticide	Target Pest	Millions of Pounds Sold	
		US	Worldwide
Herbicides and plant growth regulators	Unwanted plants, noncrop and hazardous plants	568	2254
Insecticides and miticides	Insects, spiders, and mites	129	1470
Fungicides	Fungi (molds, rots, and plant diseases)	81	539
Rodenticides, fumigants, and others*		453	1421
Total		1231	5684

* Includes nematicides, molluscicides, aquateic, fish and bird pesticides, other miscellaneous pesticides; and other chemicals used as pesticides, such as sulfur and petroleum. Does not cover industrial wood preservatives, specialty biocides, chlorine, and hypochlorites. Source: 1997 EPA estimates cited by Aspelin and Grube 1999.

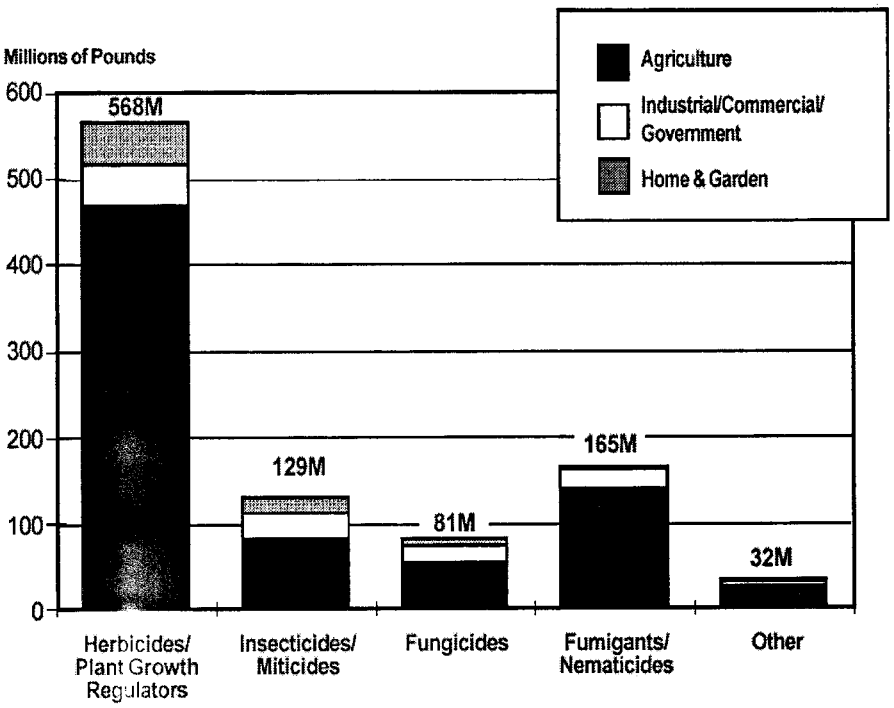

Fig 1. US volume of pesticide use, 1997 (www.epa.gov/oppbead1/pestsales/97pestsales/tables_charts1997_2.html).

TABLE 2. Commonly Used Pesticides by Chemical Classification and Mechanisms of Action

Chemical Classification	Mechanism of Action	Examples
Carbamates	Inhibition of acetylcholinesterase impairs nervous system function	Carbaryl Aldicarb Maneb
Organochlorines	Depolarization of nerve membranes impairs nervous system function	DDT Lindane Chlordane Chlordecone
Organophosphates	Inhibition of acetylcholinesterase impairs nervous system function	Parathion Malathion Diazinon Chlorpyrifos
Pyrethroids	Disruption of nerve membrane permeability to sodium ions impairs nervous system function	Deltametrin Permethrin Fenvalerate

ing blockade of neural transmission. The effects of carbamates are more readily reversible and of shorter duration. Organochlorines, such as dichlorodiphenyltrichloroethane (DDT) and lindane, interfere with nerve cell membrane cation transport, resulting in neural irritability and excitation of the central nervous system. Lindane is available by physician's prescription as a topical cream for scabies, but a pyrethrin (permethrin) is now preferred for infants, for young children, and during pregnancy because of the risk of toxicity. Pyrethrins, which are emitted naturally by plants, are rapidly metabolized by mammals and less neurotoxic but sometimes cause allergic reactions. They are commonly used as ingredients in anti-lice shampoos and as topical treatment for scabies (noted previously). Repellants, such as diethyltoluamide, are used in varying concentrations to reduce the risk of insect stings and vector-borne diseases such as Lyme disease, West Nile disease, and Rocky Mountain spotted fever. Toxic encephalopathy and seizures can result from ingestion or, less common, from dermal absorption,

which is more likely in the very young and in people with conditions of impaired skin integrity.[8–14]

Herbicides, including the chlorophenoxy compounds 2,4-D and 2,4,5-T, are primarily irritative to the skin and respiratory tract during acute exposures and work by different mechanisms. Some substances, such as paraquat, are highly corrosive and can cause multisystem injury and progressive pulmonary failure.[8,10]

Arsenical pesticides, such as copper chromium arsenate, have been used, until recently, as wood preservatives to prolong the useful life of exterior wooden structures, including residential decks and playground equipment. These compounds cause central nervous system depression at sufficient doses.[10]

EXPOSURE OF CHILDREN

Environmental Pathways

The unique behaviors and activities of children place them at greater risk for heavier exposure to contaminants such as pesticides present in air, water, and soil, compared with adults who live in the same environment. Outdoor play activities of children often result in hand contact with the lawn, soil, or objects on the ground. Children are less likely than adults to wash their hands before eating, and they often eat without utensils. Their breathing zones are closer to the ground, where pesticide residues accumulate, increasing inhalation exposure to heavier-than-air toxicants and low-lying particulates.[15,16] For example, higher chlorpyrifos concentrations have been demonstrated closer to the floor (25 cm vs 100 cm above the carpet) after the indoor broadcasting of Dursban.[17]

The deposition of pesticides on toys and other objects takes on greater significance for children who frequently place their fingers and other objects in their mouth. In a study of residential treatment with chlorpyrifos, peak levels on surfaces such as toys and furniture were measured 36 hours after the original application. These peaks were the result of a 2-phase physical process during which the pesticide was released from its initial contact site as a vapor and then adsorbed by toys or furniture in the home. This process lasted up to 2 weeks after the home was treated. The total dose of chlorpyrifos for a 3- to 6-year-old child whose home was treated depended on the frequency of that child's hand-to-mouth activity and far exceeded the Environmental Protection Agency's reference dose of 3 μg/kg/day.[18]

Dermal absorption is an active exposure pathway for some agricultural pesticides, according to data from farm workers.[17] There are no comparable studies of children. However, a study of newborn piglets found that chlorpyrifos, an organophosphate, was more lethal when sprayed on the youngest animals, possibly because it penetrated their skin more easily than the older pigs.[19]

Children may also ingest pesticides through contaminated nonfood items, such as pica behavior (eg, soil ingestion). Children with developmental delays and those younger than 6 years are at increased risk of this behavior and the attendant heightened exposures to toxicants.[20]

Dietary Pathways

Breastfeeding infants may ingest pesticides or pesticide metabolites present in the breast milk,[21] because its fat content allows for the accumulation of substances with high lipid solubility. For example, a mother's breast milk level of dichlorodiphenyldichloroethylene (DDE; a metabolite of DDT), which is lipophilic, may be 6 to 7 times higher than that found in her blood.[22] Pesticides in breast milk are not limited to those used locally near the mother's residence or workplace. For example, the breast milk of mothers in Finland contained chlordane in a 1980s study, although chlordane was not used in Finland. The maternal exposures were attributed to the consumption of chlordane-contaminated fish from the Baltic Sea.[23] In another investigation, similar breast milk DDE/DDT ratios were found in Saudi mothers who lived in regions with different usage patterns of DDT: Riyadh, where DDT use was banned; and Al-Ehssa, where DDT was used regularly to control leishmaniasis. The study estimated that 97.2% from the Riyadh region and 99.2% of the infants who resided in the Al-Ehssa region had DDE levels >20 μg/kg of body weight per day, suggesting that DDT intake was similar in both regions.[24]

Multiple pesticides may be present at the same time in breast milk. Aldrin, lindane, endosulfan, methoxychlor, dieldrin, and DDT and its metabolites were detected in milk specimens from women in southern Spain.[25] The quantity of pesticide that is passed to the infant via breast milk is influenced by many variables such as maternal age and parity, maternal body burden of the chemical, and breastfeeding patterns.

As infants are weaned and progress to solid foods, they consume, per unit of body weight, proportionally more fruit and more fruit juice than adults. For example, the typical 1-year-old infant drinks, per unit of body weight, 16 times as much apple juice as an adult.[26] The National Academy of Sciences in 1993 reported that children's dietary exposures to pesticides differed from adults both quantitatively and qualitatively and questioned the protection afforded infants and children from pesticide tolerances in effect at the time. The report noted that they experienced higher exposure to pesticides from agricultural crop residues because of their higher intake of fruits and vegetables, per body weight, relative to adults. The report estimated that 50% of lifetime pesticide exposure occurs during the first 5 years of life.[27]

Children also tend to have less variety in their diets. The amount of pesticide contamination varies throughout all food. Although pesticide residues on a particular food item may be low, the cumulative exposure by ingestion will sometimes be high if the item constitutes a disproportionately high percentage of a child's diet.

Intake and Body Burden

Infants and children are physiologically different from adults. Because infants and small children are

growing rapidly, they have greater energy demands than adults, resulting in greater caloric and oxygen requirements (higher basal metabolic rate). For example, the energy requirement of a premature newborn infant is 140 kcal/kg versus 43 kcal/kg for a man.[27] Infants drink more water, eat more food, and breathe more air relative to body weight than adults, resulting in a higher dose when exposed to substances present in the air, water, soil, and food.[27] Infants younger than 6 months drink >7 times as much water[28] and children younger than 5 years consume 3 to 4 times more food, per unit body weight, than adults.[12] An alert newborn infant breathes an average of 64 times per minute versus 35 per minute in a child 1 to 4 years of age.[29] However, this greater minute ventilation rate must be balanced with the smaller size and number of alveoli (decreased surface area for gas exchange) when considering the potential difference in risk that inhalation of toxicants poses to children versus adults.

Consumption of low residual levels of pesticide must also be viewed in light of their cumulative effects. A study done by Soto et al[30] revealed that estrogenic chemicals used in combination cumulatively induced estrogenic responses in human breast cells at lower individual concentrations than when administered alone.

Infants have a 2.7-fold greater ratio of surface area to body mass compared with adults.[31] This difference, combined with infants' crawling behavior, accounts for a greater potential, versus adults, for dermal exposure to contaminants on carpets, floors, lawns, and soil.[15]

Infants and young children may distribute and metabolize certain toxicants differently from adults. Compared with adults, they have a higher proportion of total body water and less body fat in which to store lipophilic substances. This lesser ability to store toxicants in fat can lead to higher circulating levels. Renal clearance rates and activities of hepatic enzymes vary considerably during infancy and early childhood; as a result, a xenobiotic may exert greater or lesser toxicity. For example, a reduced capacity to metabolize organophosphate or carbamate insecticides might be beneficial because the metabolites are more toxic than the parent substances. Conversely, if metabolism of a toxicant typically converts it to a less active and more readily excreted metabolite, then reduced metabolism would result in a greater toxic effect. For example, permethrin is almost 5 times more acutely toxic in 8-day-old rats than in adult rats because the neonates lack permethrin-specific esterases.[32]

During infancy, the brain grows rapidly and there is continuing neuronal migration. Myelination of the brain in not completed until the second year of life. The blood-brain barrier of infants is immature and "leaky," allowing increased concentration of some chemicals to accumulate in the brain.[33] Exposure to toxicants during these times of rapid cell growth when the blood-brain barrier is immature may disrupt essential elements of development. The endocrine system offers an excellent example. Endocrine disruptors may alter cell differentiation during critical windows of development by mimicking hormones or altering their action. The result may be permanent endocrine, growth, or reproductive dysfunction.

In addition, children have more future potential years of life. This allows more time in which to develop diseases triggered by early exposure to environmental toxicants, some with latency periods for certain effects extending into decades.

The Centers for Disease Control and Prevention in 2003 published a national survey of human exposure to environmental chemicals based on laboratory analysis of blood and urine specimens obtained in 1999–2000. The report provides reference ranges for 116 chemicals, including selected pesticides, measured in a randomly selected subsample of participants in the National Health and Nutrition Examination Survey, 6 through 59 years of age. Urine levels of dimethylthiophosphate (a major metabolite of many organophosphate pesticides) were approximately twice as high in children 6 through 11 years of age as in adults 20 through 59 years of age.[34] This finding suggests that children in the United State have had higher levels of exposure to organophosphates than adults.

NEUROBEHAVIORAL EFFECTS IN CHILDREN

Animal studies suggest that exposure to pesticides such as DDT and its metabolites DDE and dichlorodiphenyldichloroethane at the levels found in the environment affect the developing brain. Ten-day-old mice that were treated once with DDT demonstrated behavioral changes, compared with controls, in horizontal and vertical movement as well as total activity when tested at 4 months of age. These effects occur only after DDT dosing at 10 days of age and not after similar dosing at 3 or 19 days of age.[35–37]

Acute pesticide poisonings in children are commonly encountered and well described. Clinical management of such episodes is also well described and beyond the scope of this article.[10,38,39]

Evidence of subacute and chronic adverse health effects of pesticides in children is shallow despite the considerable extent of exposure and in contrast to the weight of evidence on developmental toxicity of lead and methylmercury.[40] The experimental and epidemiologic evidence is surprisingly sparse given the immense amount of data available about mechanisms of pesticide toxicity, in particular neurotransmitter metabolism and electrophysiologic actions.[41] One exception is a study that compared growth and development of preschool children in 2 agricultural communities in Mexico. They came from the same ethnic stock, but one had adopted pesticide-based agriculture, whereas the other had not. Various indices of neuropsychological development used in the study by Guillette et al[42] suggested that children from the traditional community performed better on several measures, such as coordination and the ability to draw a human figure. However, pesticide levels were not reported for the individual children who received neuropsychological testing.

In the absence of direct conclusive evidence, consistent and relevant observations in the following 3

TABLE 3. Neuropsychological Test Score Means in a Matched-Pair Analysis Studying Chronic Effects of Acute Organophosphate Pesticide Poisoning (Savage et al. 1988)

Variable	Mean Scores		SE	*P**
	n = 100 Cases	*n* = 100 Controls		
Neuropsychological Summary Scores				
WAIS Verbal IQ	105.40	111.86	0.05	<.001
WAIS Performance IQ	108.41	110.13	1.46	.242
WAIS Full Scale IQ	107.50	111.77	1.32	<.001
Average Impairment Rating	1.07	0.91	0.05	<.001
Halstead Impairment Rating	0.30	0.23	0.03	.020
Individual tests†				
Grooved Pegboard	148.34	137.96	3.26	.002
Wisconsin Card Sorting Test	17.07	12.91	1.18	.001

IQ indicates intelligence quotient; SE, standard error; WAIS, Wechsler Adult Intelligence Scale.
* Effect size may or may not be clinically meaningful.
† Results selected from 34 individual tests administered "blind" to matched cases and controls.
Source: Savage et al. 1988.

areas have led some investigators to infer that chronic low-dose exposure to certain pesticides might pose a potential hazard to the health and development of infants and children. Other investigations have concluded that such inferences can be neither supported nor refuted at the present time.[43]

1. Adult farm workers who experienced clinically toxic exposures have demonstrated subclinical latent deficits in some neuropsychological tests.[44–47] For example, some mild latent neuropsychological deficits were reported in farm workers who had previously experienced acute organophosphate pesticide poisoning (Table 3).[48] The deficits were not clinically evident but were detectable with standardized neuropsychological tests.[48]
2. Adults who experienced clinically silent exposures have demonstrated subtle latent deficits in some neuropsychological tests.[49–51] Neurobehavioral deficits are detectable in exposed workers who show no evidence of clinical toxicity.[52,53] Several studies[44,48] demonstrate that episodes of organophosphate intoxication can leave residual neuropsychological deficits a year later, although measures of blood cholinesterase, the predominant marker of exposure, may have returned to normal several weeks after the episode. Additional findings suggest that the standard biomarker of organophosphate or carbamate exposure, blood cholinesterase, is not sufficiently sensitive for protection of the young child.[54] The fetal and neonatal brain are more sensitive than the adult brain to at least some classes of organophosphates; levels presumed to be nontoxic in adults may not be adequately protective of developing organisms. The rat detoxifies chlorpyrifos through the action of 2 esterases. The young rat is deficient in both of these detoxification enzymes, which may explain the increased sensitivity of young rats to chlorpyrifos toxicity.[54] More recently, Slotkin et al[55] administered chlorpyrifos to neonatal rats at dose levels that do not elicit systemic toxicity and that allow acetylcholinesterase levels to return rapidly to normal levels. Such a regimen induced abnormalities in catecholamine function during the rats' puberty and adulthood. The rats also displayed an enduring lack of sensitivity to nicotine, indicating impaired cholinergic function. These findings further suggest that chlorpyrifos acts as a behavioral teratogen.
3. The developing brain and central nervous system have pronounced vulnerability to neurotoxicants (eg, lead, mercury, alcohol) other than pesticides. As this special issue of *Pediatrics* confirms, threats to neurobehavioral development arising from chemicals in the environment must be a serious concern of pediatricians. The articles on lead, mercury, alcohol, and polychlorinated biphenyls all emphasize the special vulnerability of the developing brain to toxic challenges and, especially, how such vulnerability may be expressed in subtle disorders of function. The progression from encephalopathy to lowered IQ scores as criteria for excessive lead exposure or the similar progression from the overt signs of fetal alcohol syndrome to the subtle deficits of fetal alcohol effects offer a prototype for assessing the hazards of pesticides.

ENDOCRINE EFFECTS

A human reproductive study in Canada suggested a critical window of vulnerability to pesticide, from up to 3 months before conception through the first month after conception.[56] Another study suggested an increase in urogenital anomalies and limb reduction deformities in offspring born to pesticide applicators and the general population exposed to high agricultural pesticide usage in Minnesota.[57,58] The effect sizes in both studies were small (odds ratios <2).

Perhaps the best known example of endocrine-disrupting activity in early embryonic and fetal development is that of the synthetic estrogen diethylstilbestrol (DES). DES was used extensively in the 1950s to 1970s to maintain pregnancy in women threatening spontaneous premature delivery.[59] Only decades later was it discovered that daughters born to DES-treated mothers experienced increased rates of vaginal clear cell adenocarcinoma, genital tract abnormalities, and abnormal pregnancies. Although not a pesticide, the DES model provides evidence for

the effects of estrogen receptor agonists on the developing human reproductive system. Animal studies and cell-culture studies have shown that a variety of pesticides such as DDT/DDE, mirex, aldrin, dieldrin, atrazine, hexachlorocyclohexane, toxaphene, alachlor, chlordane, vinclozolin, and chlorpyrifos can interact with endocrine system components such as the estrogen, androgen, and thyroid receptors during critical periods of development and produce an equally varied spectrum of adverse developmental effects such as altered social skills, decreased intelligence, and reproductive difficulties or failures.[60–67] Thyroid function in pregnant women is a critical determinant of offspring IQ,[68] and contaminants such as polychlorinated biphenyls and dioxins are known to disrupt thyroid function.[69] Such findings demonstrate the special sensitivities of developing embryos and fetuses to chemical exposure levels that are safe and without effect in mature adults.

RELEVANCE FOR PEDIATRIC PRIMARY CARE PROVIDERS

The clinician has dual responsibilities in the management of pesticide exposures. First, acute poisonings must be recognized and promptly addressed. Such events are often misdiagnosed because nonspecific clinical signs and symptoms are more common than classic "toxidromes."[70] Clinicians misdiagnosed acute poisonings with methyl parathion, an organophosphate, in a family cluster in 1984 and again in a 7-state outbreak in 1997–1998.[71,72] In many instances, the clinicians treated the presenting complaints (reactive airway disease, seizures, intractable vomiting, or diarrhea) without considering organophosphate poisoning as the underlying cause. Increasingly, pediatric primary care providers are learning that a thorough medical history includes questions about possible environmental exposures, including exposures to pesticides. Topics covered include chemical products used in the home, garden, lawn, school, and child care and how and where pesticides are used and stored.[8,38] Clinical management of acute pesticide poisoning is beyond the scope of this article, as noted previously, and covered elsewhere.[10,38,39]

The second responsibility of clinicians is to prevent exposure of infants and children to pesticides. Clinicians can encourage parents to be prudent when using pesticides in the home and adjacent areas. They can instruct parents on the appropriate use of insect repellant such as applying the products only as directed by the product label. For example, there are some new permethrin insect repellants that are designed for application directly to clothing and not skin. When insect repellants are applied directly to skin, they should be applied only to exposed skin, using the smallest amount that will adequately cover the skin, and washed off with soap and water as soon as the outdoor activity has ended. Parents can be reminded of the hazards of improperly stored or labeled pesticides; storing pesticides in any container other than the product's original container can result in unintentional ingestions. Simple washing of fresh fruits and other fresh produce can reduce ingestion of pesticide residues. Educational programs are available to help families and communities learn about integrated pest management techniques, and community-level programs exist to promote the prudent use of pesticides in schools and neighborhoods.

OTHER RESOURCES

National Pesticide Information Center, 1–800-858–7378 (toll-free to any caller in the United States, Puerto Rico, or the Virgin Islands)

Agency for Toxic Substances and Disease Registry, www.atsdr.cdc.gov

Pesticides and Child Safety, www.epa.gov/pesticides/factsheets/childsaf.htm

US Environmental Protection Agency, www.epa.gov/pesticides

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