Reducing **Low-Dose Pesticide Exposures** in **Infants** and **Children**

A Clinicians' Guide from

PSR®

PHYSICIANS FOR SOCIAL RESPONSIBILITY

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Introduction

THIS IS A GUIDE for health care professionals who care for children, families with children, and/or individuals planning to have children. It deals with pesticide exposures other than high dose, acute poisonings—these are well covered in standard texts and clinical training.[78] Physicians for Social Responsibility produced this guide because there is mounting evidence that lower dose exposures to a variety of pesticides may be associated with adverse effects, particularly when exposures occur during critical windows of development in early life. Pesticides are present in food, water, air, and soil, and in urban, suburban, and rural settings. Of all age groups, children are often the most highly exposed and vulnerable to harm. Increasingly, parents express concern about the potential health impacts of pesticide exposures to their children. Media attention has intensified in parallel. In contrast, clinicians often have little or no training on how to interpret or counsel patients on pesticide exposures other than overt poisonings.

This guide describes the pertinent scientific issues related to low-level pediatric pesticide exposures and provides practical, scientifically sound guidance to assist clinicians in counseling parents on why and how to reduce exposure to their children. It is not a comprehensive literature review. Rather, it is a synthesis of how the children's environmental health scientific community approaches these complex issues. We hope that this guide will provide quick access to basic knowledge, direct the reader to important literature, and suggest a framework for following the science as it develops.

There is mounting evidence that lower dose exposures to a variety of pesticides may be associated with adverse effects, particularly when exposures occur during critical windows of development in early life.

The first section gives background information including definitions, the scope of pesticide use in the United States, and documentation of exposures in U.S. children. The second section summarizes pediatric toxicities linked to pesticides using sentinel examples from the peer-reviewed literature, and includes a brief discussion of the weight-of-evidence approach to risk assessment. The third section is a case study of the organophosphate insecticide, chlorpyrifos (CPF), which illustrates the scientific issues and demonstrates the importance and success of reducing pediatric exposures through appropriate regulatory action. The final section offers a number of practical actions that clinicians can suggest to their patients and families to reduce pesticide exposures at home, and suggests advocacy approaches to reducing pesticide exposures in the broader community.

Background

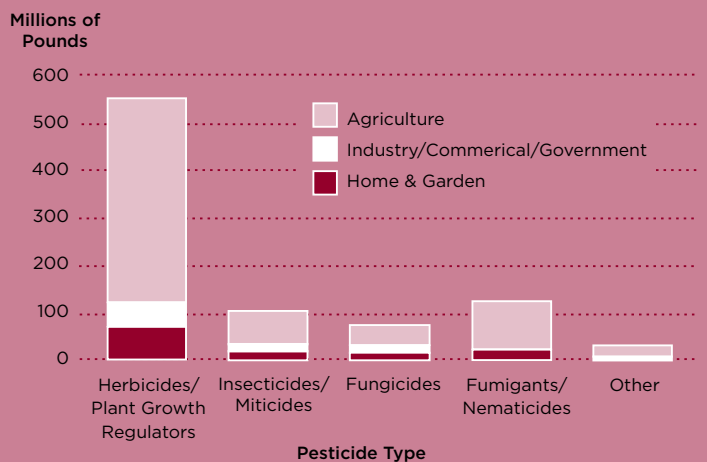
Definitions: As defined by the U.S. Environmental Protection Agency (U.S. EPA), pesticides are "substances intended to repel, kill, or control species designated as 'pests' including weeds, insects, rodents, fungi, bacteria, or other organisms."[99] They are intentional poisons. Usually pesticides are grouped according to target organism, (e.g., insecticides, fungicides, herbicides, rodenticides, bactericides), or classified by use (e.g., fumigants, repellents). Within these broad classifications, pesticides fall into specific chemical groups. Examples of common insecticides include organophosphates, which cause prolonged inhibition of acetylcholinesterase; carbamates, which cause reversible inhibition of acetylcholinesterase; and pyrethroids, which interfere with ion flux in nervous tissue. Common herbicides are chlorophenoxy compounds, which mimic plant hormones, and triazines, which inhibit photosynthesis. Conventional pesticides are "chemicals or other substances developed and produced primarily or only for use as pesticides."[99] Other substances, such as sulfur, hydrocarbons, petroleum distillates, and even sucrose may be classified as pesticides when used to control pests.

Currently there are close to 900 active-ingredient pesticides and over 18,000 preparations licensed for use in the United States.

The mechanism of action or toxicity of a pesticide is determined by the molecular target of the "active ingredient." It may be highly selective to the target pest (insect growth inhibitors, hormone mimetics, or plant antimetabolites)[86] or quite non-selective, affecting many organisms including humans (e.g., anticoagulant rodenticides such as warfarin and acetylcholinesterase-inhibiting insecticides, such as organophosphates and carbamates).[12] Potency and human safety margins can vary by several orders of magnitude.[78]

Pesticide preparations or formulations are composed of one or more active ingredient(s) and "inert" ingredients such as water, petroleum distillates, talc, corn meal, or soaps.[99] These so-called inert ingredients are intended as vehicles to convey the pesticide to the target organism. Many are chemically and biologically active and may cause health and environmental problems. Though sometimes toxic, inert ingredients may comprise up to 99% of a formulation by weight. At present, U.S. EPA does not have uniform labeling requirements that compel registrants to list all inert ingredients. This is problematic, because while toxicity evaluations are performed on the active ingredients, they are only occasionally performed on specific preparations or formulations (commercial products). In cases of accidental poisonings, the absence of labeling information on inert ingredients can pose problems for healthcare providers. Currently there are close to 900 active-ingredient pesticides and over 18,000 preparations licensed for use in the United States.[94]

FIGURE 1.[29] Amount of Conventional Pesticide Active Ingredient Used in United States by Pesticide Type and Market Sector: 2001 Estimates

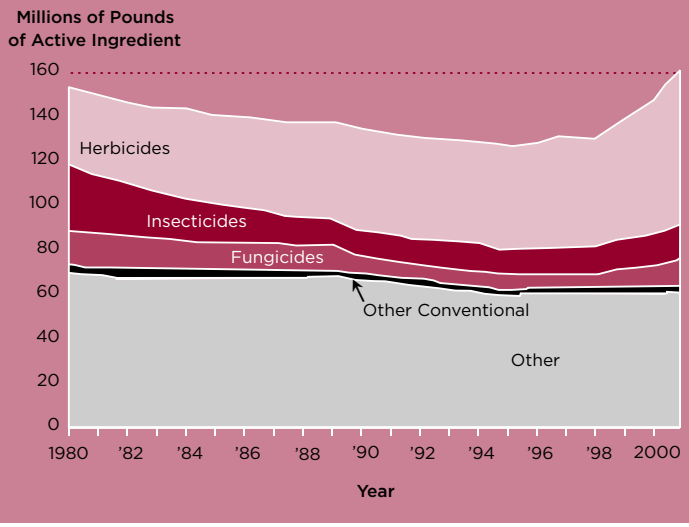


Annual Pesticide Use: The U.S. EPA estimates that in 2000–2001, the world community used over five billion pounds of pesticide active ingredient[28] of which the United States was responsible for almost 25%. The share of world pesticide use by the United States differs by category; for example, in 2001, the United States used 30% of world herbicides, 9% of

world insecticides, and 15% of world fungicides. Over three- fourths of all conventional pesticides used in the United States are used in agriculture, primarily as herbicides and plant growth regulators (Figure 1).

While home and garden usage is small compared to agricultural usage, it is still a common usage that is on the increase and frequently under the direct control of individual consumers (Figure 2). In 2000, 74% of households used at least one form of pesticide; 56% used insecticides; 50% used repellents; 39% used herbicides; and 13% used fungicides.[30] While herbicides represent the largest amount by weight used in homes and gardens, surveys show that insecticides and repellents are used by more households, albeit in smaller quantities.[31]

FIGURE 2.[32] Annual Amount of Pesticide Active Ingredient Used in the United States by Pesticide Type in Home and Garden Market Sector: 1982–2001 Estimates



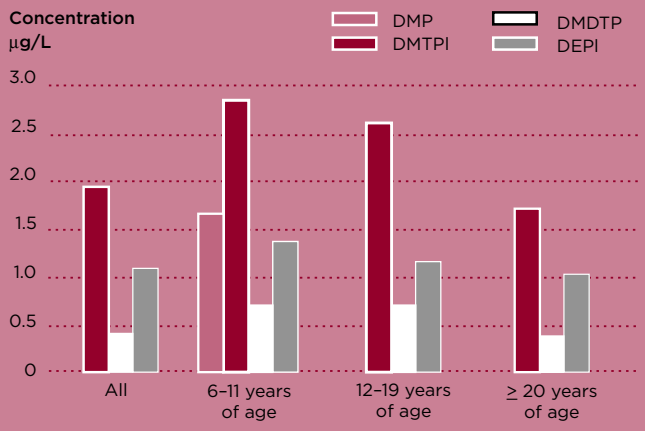
Other conventional pesticides include nematicides, fumigants, and other conventional pesticides. **Other** include sulfur, petroleum, and other chemicals used as pesticides (e.g., sulfuric acid and insect repellents).

Pesticides in the Environment: Pesticides may accumulate and persist in the environment, often reaching non-target organisms, including children. Some older pesticides, such as the organochlorine, dichlorodiphenyltrichloroethane (DDT), were designed to resist degradation and thus persist in the environment for decades. DDT metabolites are detected in a significant numbers of adults born 10 or more years after DDT was banned in 1973.[19] Several of these persistent pesticides have been banned by international treaty as "persistent organic pollutants" or POPs, because of the long residence time in the environment, global transport via winds and water cycles, and persistent toxicity to ecosystems and humans.

The newer synthetic pesticides break down more quickly, but can still be found in water, air, and food weeks to months after application. The U.S. Geological Survey Pesticide National Synthesis Project tests surface water, ground water, and sediments for 76 pesticides and seven pesticide breakdown products throughout the country. A recent survey found that 90% of streams and 50% of wells had positive tests for at least one pesticide.[72] Levels often vary substantially depending on factors such as agricultural use patterns, surface water runoff, and season of the year.[71] While the water contaminant levels were often low, safe limits have not been determined for many pesticides, and conventional municipal water treatment does not remove them from public drinking water supplies. Concentrations of agricultural pesticides in the air may exceed both acute and chronic health standards depending on season, weather, local climate, and geographic location.[56] Finally, pesticides registered for outdoor use on crops or in gardens, where the sun and rain promote rapid degradation, may be tracked indoors on shoes, clothes, pets, or people. In the protected environment of the home, degradation is inhibited and exposures may persist for weeks or months.

Food is also a major source of exposure to pesticides. The U.S. Department of Agriculture (USDA) tests commercially available foods in the United States. In 2002, of the 2,122 domestic foods sampled, 65.5% had no detectable pesticide residues; 33.7% had residues within regulatory limits; and 0.8% had residues in excess of regulatory limits. Of the 4,644 imported samples analyzed, 70.4% had no residues detected, 25.3% had residues within regulatory limits, and 4.3% had residues in excess of regulatory limits. Most residues were detected on fruits and vegetables in both the domestic and imported categories.[101]

FIGURE 3.[7] Organophosphate Metabolites in Urine from Second National Exposure Study



Exposures to American Children: Children are likely to have higher exposures than adults to many chemicals, including pesticides, for a variety of reasons. Contact with pesticides is increased in children because they spend time close to the ground where pesticides are often applied and stored, and where concentrations in indoor air are more persistent and higher than in the adult breathing zones.[51] Exposures are often increased through children's normal exploratory behaviors, including hand-to-mouth and object-to-mouth activities, compounded by immature cognition, decreased ability to perceive danger, and inability to read or understand warning labels. Because of rapid growth, a child's metabolic rate is high, resulting in a higher breathing rate and greater nutrient requirements than that of an adult. Consequently, pesticides in air and food will be absorbed in greater quantities in children versus adults. Fruits and vegetables, which are the food most likely to have pesticide residues, comprise a larger proportion of the diets of children compared to adults.[70] Children have a larger surface-area-to-volume ratio than adults, often have more exposed skin, and are more likely to have rashes, cuts, and abrasions, leading to potentially higher transdermal absorption. Finally, children may also be exposed to pesticides that traverse the placenta or are secreted in breast milk. So, by all routes of exposure, oral (including via breast milk), inhalational, dermal, and transplacental, children are often exposed to the highest levels of pesticides of any age group.

For many pesticides, higher childhood exposures have been confirmed by measuring blood and urine levels of pesticide compounds and/or their metabolites (an approach known as "biomonitoring"). For some pesticides, metabolites measured in blood or urine of children exceed levels found in adults by two fold or more. The U.S. Centers for Disease Control and Prevention began an expanded evaluation of environmental chemical exposures in 1999. The first survey of environmental chemical exposures using a nationally representative sample of the U.S. population was published in early 2003.[19] A total of 40 pesticides and pesticide metabolites were measured in the urine of children ages 6–11 years, adolescents 12–19 years, and adults 20–59 years. Notably, organophosphate pesticide metabolites were consistently highest in the youngest age groups tested (Figure 3). Metabolites of the herbicides studied were rarely found above the level of detection in this survey, but when found, were highest in children or adolescents. Other biomonitoring studies that evaluated children as young as one year have shown that, in general,

FOOD QUALITY PROTECTION ACT OF 1996

The Food Quality Protection Act of 1996 (FQPA)(Pub. L. 104-170) was passed unanimously by Congress in response to recognition of children's higher exposures to pesticides and greater vulnerability to toxic effects.[a] This law replaced several different standards mandated by a series of previous laws with a single standard of "reasonable certainty of no harm" to the most vulnerable individuals, specifically infants and children. FQPA requires that both aggregate exposures from food, water, and other sources, and cumulative toxicities from pesticides sharing a common mechanism of toxicity be considered when setting allowable residue limits of pesticides on foods. Further, it requires that in the absence of complete scientific information, an extra uncertainty factor be applied when calculating allowable limits in order to protect infants and children.[b]

[a] National Research Council. 1993. Pesticides in the Diets of Infants and Children. Washington, D.C.: National Academy Press.

[b] Goldman LR, Koduru S. 2000. Chemicals in the environment and developmental toxicity to children: a public health and policy perspective. Environmental Health Perspectives 108 (Suppl 3):443–448.

the younger the child, the higher the levels of pesticide metabolite found.[39]

Pesticides and their metabolites have also been measured in amniotic fluid, meconium, and cord blood indicating *in utero* exposures,[14,20,103] as well as in breast milk.[89] Where trend data are available, it appears that strict control of pesticides can consistently reduce children's exposures throughout all life stages (see Case Study).[89]

Pesticide Regulations: Pesticides are regulated by U.S. EPA and individual states. States may be more restrictive than federal regulations require. A suite of federal laws applies to pesticide licensure, registration, use, and disposal.[100] The Food Quality Protection Act of 1996 was passed to help unify the approach to pesticide regulations and make them more health protective for the most vulnerable members of the population—infants and children.

Pediatric Toxicities

Basic Toxicology: The basic tenets of toxicology date from the middle ages when Paracelsus said, *"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy."*[a] In the case of acute poisonings, pesticides adhere to this simple principle. In general, it takes a larger amount or "dose" to harm a human than an insect or a weed, even for those pesticides that target cellular systems shared across species. Depending upon the potency, the mechanisms of toxicity, and the pest, there may be a large or a very narrow margin of safety between lethal doses to pests and toxic doses to humans. (See sidebar on acute poisonings.)

The case with non-acute childhood exposures is much more complex. While the amount or dose of the exposure is still important in the non-acute setting, the timing of the exposure may be even more important. Timing can refer to characteristics such as continuous or intermittent exposures; short-term (days or weeks) or long-term (months or lifetime) exposure; as well as to exposures occurring during critical periods of differentiation, growth, and development of physiological systems, called lifestages.[85] The sentinel examples of ionizing radiation, methylmercury, and diethylstilbestrol (DES) show that toxicity can be remarkably different depending upon when exposure occurs in the lifestage. In part, this is due to differences in an agent's mechanism of toxicity in tissues and systems during differentiation and maturation (see chlorpyrifos case study). Even when the toxic endpoints are the same, the incidence of disease may be dramatically different when exposure occurs early, and may require much lower doses than those causing disease in adults.

For many pesticides, higher childhood exposures have been confirmed by measuring blood and urine levels of pesticide compounds and/or their metabolites (an approach known as "biomonitoring").

[a] Paracelsus, circa 1500 AD as quoted by the National Library of Medicine. Toxicology Tutorials http://sis.nlm.nih.gov/Tox/ToxTutor.html

Historically, toxicological research of non-acute exposures has emphasized adult onset cancers as the major endpoint.[43] The gold-standard approach has been chronic exposure studies designed to identify excess cancer rates in mature laboratory animals. Gradually, this emphasis has shifted to include additional toxic endpoints including toxicities that are immediately relevant to children.[70] A lifestage approach is evolving that considers lower-dose exposures during critical periods and adverse effects on growth and development from pre-conception through adolescence.[51,54]

Epidemiology studies are often the most useful in identifying potential human health risks since they deal with "real world" human exposures and human disease. In the case of environmental exposures, however, they are rarely sufficient to define a direct cause-and-effect relationship. It is usually difficult to measure exposures precisely and accurately, and most of the diseases or conditions of concern are complex and multi-causal.[58] Nonetheless, low-level pesticide exposure has been implicated as a modifiable risk factor in a wide range of adverse health effects specifically affecting children. The studies cited below are illustrative only and do not represent a comprehensive review of the literature. Recent reviews of the literature on pesticides and human health highlight the need for studies specifically evaluating pediatric toxicity from low-dose pesticide exposures. [54, 81]

Adverse Birth Outcomes: A number of studies have found that pesticide exposures to mothers, fathers, or both parents increase the risk of congenital anomalies,[8,44,46,47,52,83,102] preterm birth,[82,91] and fetal growth retardation.[10,67,75] Infertility and pregnancy loss may also be increased with some types of exposures and are reviewed elsewhere.[81] Conclusions from these and other studies are mixed, however, largely due to methodological problems common to environmental epidemiology research.

Childhood Cancer: Childhood cancers are rare, but in the United States they are the third

leading cause of death between the ages of 1–19 and the second leading cause between 5–14 years.[6] While it is clear that cancer mortality is decreasing in U.S. children, there is some suggestion that incidences of certain childhood cancers such as acute lymphocitic leukemia and total brain tumors have been increasing slightly over the past several decades.[68] Pesticide exposures to parents have been linked to some forms of childhood cancer, including those cancers which seem to be on the increase.[13,40,79,108] Early lifestage exposure to pesticides has been linked to an increased risk of both childhood and adult onset cancers.[25,57,63,74]

Developmental Neurotoxicity: Pesticides, particularly insecticides, often work by interfering with neuronal function in target organisms. Many of these functions are conserved (shared) across species, and humans are susceptible to toxicity at higher doses by the same mechanisms that kill smaller pest organisms. Of increasing concern is the potential damage from pesticide exposures to the immature nervous system and possible increased risk of neurodevelopmental disabilities and behavioral problems in children. One observational study from Mexico found multiple cognitive and motor deficits in preschool children chronically exposed to pesticides used in their agricultural community compared to similar children raised in an agricultural community where pesticides were not used.[49] Growing evidence supports an association between early lifestage pesticide exposures and increased risk of Parkinson's Disease later in life.[59,90]

These concerns are supported by animal experiments showing that the developing nervous system is one of the most sensitive and critical targets of pesticide damage. Exposures to the immature nervous system can disrupt normal differentiation, migration, organization, and multiplication of nervous tissue before and after birth. Several pesticide classes are known to cause damage to the developing nervous system in animals, some by mechanisms different from the primary mechanisms of toxicity that define their utility in controlling pests.[4] Animal studies also confirm narrow pre- and postnatal windows of neurodevelopmental vulnerability with persistent damage.[4]

ACUTE POISONING

Children are at highest risk of acute poisonings, including from pesticides, compared to any other age group. Of the almost 2.4 million reports of poison exposures made to US poison control centers in 2003, 52% concerned children under six years of age. Pesticides were involved in more than 97,600 of these reports, and over 52% of these involved children under six years. Even with these numbers, true pesticide poisonings are likely under-diagnosed and under-reported. Nonetheless, when acute poisonings are identified in children, health care professionals have ready access to diagnostic and therapeutic tools. Of the pesticide exposure events reported to the poison control centers in 2003, only three children under six years died and the vast majority had no sequelae at all.[a]

a Watson WA, et al. 2004. 2003 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. American Journal of Emergency Medicine 22:. http://www.aapcc.org/Annual%20Reports/03report/Annual%20Report%202003.pdf .

Other Toxicities: The endocrine, immune, and respiratory systems are among the critical systems that continue to develop throughout childhood. Pesticides, because of their ubiquitous presence in multiple media, are of interest as potential toxic agents to these developing systems.

Some environmental chemicals can mimic, modulate, or block hormonal signals in the body. This form of toxicity is called "endocrine disruption." For example, some neurodevelopmental toxicities may be mediated through disruption of thyroid homeostasis. There is limited evidence in humans that pesticides may cause damage via these mechanisms.[24]

Perturbations of the immune system, either before or after birth, can make children more vulnerable to infection, less responsive to immunizations, and more likely to develop chronic illness, including cancer. Currently, there are very limited tools to investigate immune toxicity from pesticides or other environmental chemicals.[26,76]

Asthma is the one of the top chronic illnesses in U.S. children, and a major cause of lost school days and health care costs.[27] Environmental exposures to chemical and biological agents, particularly before the age of one, are linked to increased risk of both asthma

and allergies. Pesticides may be among the early exposures that can increase the risk of asthma in some individuals.[80]

RISK ASSESSMENT AND ANIMAL TOXICOLOGY

The gold standard of toxicology is the placebo-controlled, multi-dose exposure animal study. Protocols have been standardized for a variety of toxicological endpoints including acute, sub-chronic, and chronic toxicity; carcinogenesis and genetic toxicity; dermal and ocular toxicity; reproductive toxicity; developmental toxicity; and neurotoxicity. Protocols for other endpoints such as endocrine disruption and immune toxicity remain areas of active development. Proper interpretation of animal studies requires extrapolating results across species differences (e.g., from rodent to human); age differences (e.g., adult to fetus); dose ranges (e.g., from high dose to low dose); differences in route (e.g., oral to inhalation); and timing of exposures (e.g., critical windows of development). Standard approaches to these extrapolations include the application of uncertainty factors[a] to the slope of the dose-response curve or to the no or lowest observable affect level and/or the use of physiologically based pharmacokinetic models.[b]

[a] Uncertainty Factor: Factors used in the calculation of acceptable humans or environmental exposures. They are applied to data from laboratory experiments or epidemiology studies. Factors of 10 are normally used to account for such uncertainties as animal to human data, acute to chronic exposure data, or lowest observable adverse dose level rather than no observable adverse dose level. For further explanation see http://www.sis.nlm.nih.gov/Tox/ToxTutor.html.

[b] Physiologically Based Pharmacokinetic Model: A risk assessment model that quantitates risk using biological data on the absorption of a foreign substance, its distribution, metabolism, storage in tissues, and elimination. For further explanation see http://www.sis.nlm.nih.gov/Tox/ToxTutor.html (Suppl 3):443-448.

Pesticides are among the most intensively studied chemical use groups, but there are still more questions than answers about specific risks to children from low- dose exposures. Associations from epidemiological studies must be confirmed using appropriate animal testing and/or a variety of in vitro techniques.[1,42,69] All lines of evidence must then be assembled using a "weight-of-evidence" approach to estimate human risk. Evaluating the risks of pesticides to children throughout all developmental lifestages is particularly challenging. The mechanism of toxicity of the active ingredient(s) may be different at different stages of physiological development, and the harmful dose may be much lower for immature systems than for fully mature adult systems. Additional toxicities may be associated with specific formulations using more than one active ingredient and/or related to the inert ingredients, which may not be disclosed or studied. The routes of exposure may vary with age and the timing of an exposure may be critical. The complexity of the developing system increases the uncertainty of toxicological evaluation and requires additional regulatory approaches to achieve reasonable protections.

The case study below uses the rich data set now available on pediatric exposure to and toxicity from the organophosphate insecticide, chlorpyrifos. It illustrates both why it is critical to consider children as a highly vulnerable group and how effective a child-protective approach can be.

Case Study—Chlorpyrifos

Chlorpyrifos (CPF) is a broad-spectrum, chlorinated organophosphate (OP) insecticide, acaricide, and nematicide, which was first registered in the United States in 1965. Originally approved for use on soil, foliage, food, and feed crops, CPF eventually became a major pesticide used in households. Between 1987–1998, 21–24 million pounds of CPF were used annually. Close to half of this amount was used in non-agricultural settings. At one point, over 400 products containing CPF were on the market in the United States.[95] This very high use coupled with mounting evidence of excess childhood exposures and developmental toxicities made CPF one of the first pesticides to be regulated specifically to protect infant and child health.

Evidence of Excess Exposure: Several independent research programs have studied the patterns of childhood exposure to OPs in general and to CPF in particular. Most of the studies used a combination of questionnaire data, environmental sampling, and biomonitoring to define the extent of individual exposure.[33] These reports document important exposure pathways for children including "take home" exposures to children by occupationally exposed parents,[21,23,60,61] dermal and non-nutritive ingestion exposures from contaminated surfaces,[35,38] toys,[50] pets,[62] and children's hands,[38] and exposures from fruits, vegetables, and grains favored by children.[96] Children have higher levels of urinary OP metabolites than adults, and younger children have higher levels than older children.[2,37] These exposure differences are robust across urban, suburban, rural, and agricultural populations[62] and have been confirmed in a nationally representative sample from the National Health and Nutrition Examination Survey.[7]

Investigations of potential exposures in utero find additional cause for alarm. OP metabolites are found in meconium[103] and amniotic fluid,[14] in paired plasma of mothers and newborns,[104] and in urine of pregnant women.[9] Measurement of chlorpyrifos in personal air samples of pregnant women is correlated with levels in maternal urine[103] and use patterns of CPF and other pesticides.[105]

Evidence of Neurodevelopmental Toxicity: Acute toxicity from CPF results from inhibition of acetyl cholinesterase (AChE) in the central nervous system, the cardiovascular system, and the respiratory system.[73] Acute toxicity can be quantified by the level of enzyme inhibition in peripheral blood samples. A threshold of acute toxicity exists for humans, which allows CPF and other OP pesticides to be useful at levels below acute human toxicity, but above lethal toxicity to smaller organisms such as insects. While some data suggest that very small infants may be more likely to have symptoms of acute toxicity at doses below those causing acute toxicity in adults,[16,70] the strong and growing evidence that neurodevelopmental toxicity occurs below the level of acute toxicity is even more worrisome.[33]

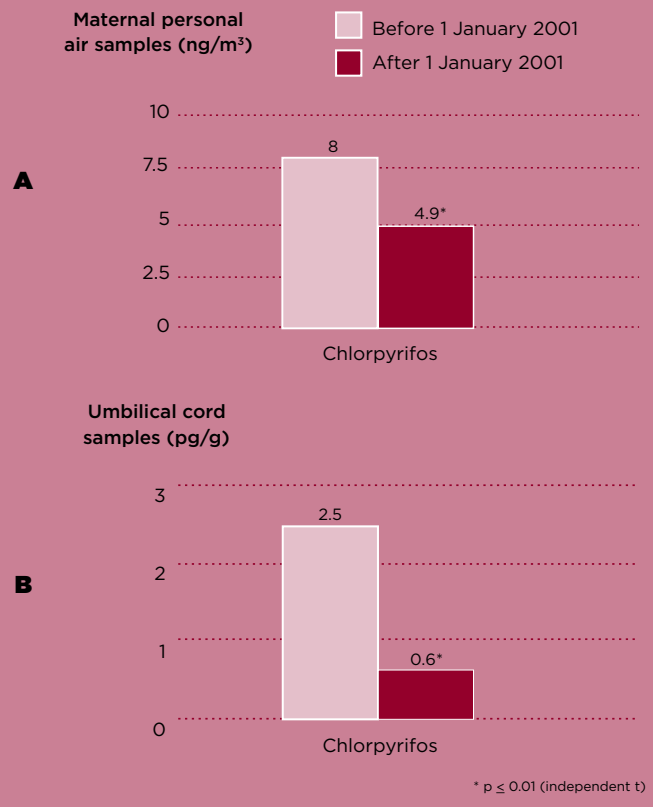
Low-level pesticide exposure has been implicated as a modifiable risk factor in a wide range of adverse health effects specifically affecting children.

Animal studies show with increasing certainty that CPF interferes with cell signaling, DNA synthesis, axonal outgrowth, and organization of structural brain architecture during neurodevelopment through both cholinergic and non-cholinergic mechanisms.[11,16,84,88] Damage to the fetal brain occurs at exposures well below the levels that cause symptoms or biochemical evidence of AChE inhibition in pregnant animals.[16,48,84] These experimental levels are equivalent to the exposure levels in humans created by routine use of CPF in residential settings. Furthermore, in animal experiments, there are narrow, critical windows of a few days of development, during which exposures can disrupt structure and/or function of the brain,[4,65] resulting in damage persisting into adulthood.[64,77] Exposure during some time windows results in gender-specific damage.[5] Finally, emerging animal data suggest that other developing systems, such as the heart

and liver, may be damaged by fetal and neonatal exposure to CPF.[66]

In humans, CPF was implicated as the cause of structural anomalies of brain and genitals in a report of four cases in 1996.[87] More recent epidemiological studies link maternal exposure to CPF to changes in birth outcomes including decreases in gestational age, birth weight, birth length, and head circumference.[10,34,75] While these studies are not always in agreement,[34,107] the complex nature of real-world exposures, population variability, and gene-environment interactions make it unlikely that the consistency of results achieved in controlled animal experiments would be achievable in human epidemiological studies. For example, Berkowitz et al. found that exposed mothers with genetically determined lower levels of a specific detoxifying enzyme for CPF were more likely to have babies with a smaller head circumference than mothers with higher enzyme levels and similar exposures.[10] The fact that many of the observations made in human populations corroborate the animal studies strengthens the concerns that developing humans are at risk from low-dose exposures experienced during routine use of CPF and other pesticides.

FIGURE 4.[106] Geometric mean chlorpyrifos levels in (A) maternal personal air samples collected over 48 hr during the third trimester of pregnancy and (B) in umbilical cord blood samples at delivery stratified by whether the delivery took place before or after 1 January 2001.



Regulatory Response: Because of the high use, and the rapidly accumulating evidence of developmental neurotoxicity and high childhood exposures to CPF and other OPs, CPF was the first individual pesticide, and OPs were the first class of pesticides to be re-evaluated under the Food Quality Protection Act of 1996. At the same time the U.S. EPA began revising risk assessments, it also entered into discussions with registrants of products containing CPF and negotiated a voluntary Memorandum of Agreement to withdraw most uses of CPF that could result in excess pediatric exposures.[17] The Interim Reregistration Eligibility Decision on CPF, finalized in February 2002, further reduced use by decreasing allowable residuals on foods in accordance with providing "a reasonable certainty of no harm" to infants and children.[95]

CPF is now banned from use in all indoor and outdoor home settings except for limited use in baits that have child-resistant packaging. Many other indoor and outdoor uses where children may be present (e.g., schools and parks) have also been cancelled. Registration has been cancelled or severely limited for most agricultural and many construction uses as well. Implementation of these bans and limits began in 2000 and will be complete by the end of 2005.[93]

Evidence of Success: In July 2004, Whyatt, et al. published data from New York City describing the effects of prenatal exposure to CPF on fetal growth.[105] They found a dose-response relationship between increasing prenatal exposure (as measured in cord blood) to CPF and several other insectides, and decreasing birth weight and length, which was "similar in magnitude to those observed with maternal smoking during pregnancy."[106] Furthermore, their data span the

time before and after the phase-out of domestic use of CPF in 2000. They were able to document significant changes in maternal personal air samples and umbilical cord blood levels of CPF collected before and after January 2001 (Figure 4). After the ban, exposure levels fell, and the significant negative correlation between exposure and birth length ($p=0.04$) and birth weight ($p=0.03$) was no longer demonstrable. This suggests rapid success following the implementation of regulatory action to protect child health.

Conclusions and Implications: The "take home message" from the CPF story is powerful; babies benefit from reduced exposures. We can say this with confidence based on strong data showing:

1) CPF was heavily used in agriculture and homes.
2) Children were highly exposed (including prenatally) compared to the general population.
3) Toxicity to the developing nervous system has been documented in animals, by more than one mechanism of action, and at doses below those causing overt symptoms.
4) Prenatal exposure in humans resulting from ordinary use of CPF has been linked to reduced birth weight and birth length.
5) Adverse effects on fetal growth reversed when household use bans took effect and prenatal exposures fell.

The "take home message" from the CPF story is powerful; babies benefit from reduced exposures.

Pesticide use in the home is often elective and amenable to individual control. It is much more difficult for individuals to control environmental exposures; however, pesticides are subject to strigent regulation and use restrictions, which can dramatically reduce human exposures. Pesticides are intentional poisons. They have no positive role in the human body and have a considerable potential to cause serious damage. It makes sense to minimize exposures, especially to the most vulnerable members of our population, developing children.[b]

[b] prenatal and postnatal

Clinical Response

Advice to Parents and Patients

Despite persistent uncertainties about the precise nature of threats to children's health from individual pesticides, the data available suggest that precaution is needed. We know that children are exposed to numerous pesticides and often at higher levels than adults. We know that children can experience different toxicities than adults, which may result in permanent adverse effects on health. Current experience suggests that as other individual chemicals undergo careful scrutiny similar to that given to CPF, "safe" exposure levels for children are likely to fall below current standards for conventional pesticides. Further, little attention has been given to the effects of specific pesticide products which can include up to 99% inert—and potentially toxic—ingredients. Even more uncertainty surrounds the effects of exposures to chemical mixtures.[18] It is reasonable, therefore, for clinicians to encourage their patients to minimize pesticide exposures as much as possible, particularly to pregnant women, infants, and small children, and to support community-based and legislative activities that will reduce pesticide use whenever possible.

Actions to Take at the Individual Level

- Eliminate all pesticide use for cosmetic purposes in the home and yard. In particular, eliminate all calendar-based pesticide use, including weed killers.
- Practice integrated pest management at home. Integrated pest management is a comprehensive, common-sense, and inexpensive approach to pest management that emphasizes preventing pest infestations and minimizes use of toxic chemicals.
  - Prevent infestations by carefully maintaining household structures such as screens, foundations, doors, faucets, and drains.
    - Trim plants and shrubs to keep them at least one foot away from buildings.
    - Remove piles of scrap wood, mulch, or leaves from around the outside of the house.
  - Drain standing water and wear protective clothing to avoid mosquitoes.[98]
  - Limit food to kitchen and dining areas.
  - Clean cooking and eating areas often and store foods in pest-proof containers.
  - Dispose of trash regularly and often.
  - Use chemical pesticides ONLY as a last resort for serious infestations.
    - Never use foggers or broadcast methods.
    - Never use outdoor or agricultural chemicals in the home.
    - Avoid use of no-pest strips, crack-and-crevice treatments,[53] and other forms of chemical pesticides that can present ongoing exposure sources.
    - Always use the least toxic chemical available in the most contained form, such as bait stations in child-resistant packaging.
    - Always follow directions on the package completely.
- Wash all fruits and vegetables before cooking or eating. Studies show that up to 90% or more of many pesticide residues on the surface of foods can be removed by peeling or discarding outer leaves and carefully washing with clean water and a scrub brush.[41,55] Some foods, however, have been treated with systemic pesticides that cannot be removed by washing.
- When available, consider choosing USDA-certified organic foods.[92] This program was launched in October 2002. In order to use the official USDA seal, food must be produced without conventional pesticides in addition to several other restrictions and pass government certification. A $10,000 fine can be assessed for each violation by people selling or labeling products as "USDA organic" without satisfying USDA standards. Children eating substantial amounts of organic fruits and vegetables have been shown to have measurably lower pesticide exposures than children eating conventionally grown foods.[22]

Actions to Support at the Community Level

- Advocate for integrated pest management in all school buildings, pre-kindergarten through university, as well as daycare centers, playgrounds and parks, and public buildings.[97]
- Develop programs to reward landlords for practicing integrated pest management with local recognition, free advertising, or certificates of merit.[15]
- Insist on prior notification of pesticide use in or around public schools, public buildings, utility easements, etc. Support mandatory neighborhood notification laws at the city, county, and state level.
- Encourage institutions that feed children to offer organic foods, especially fruits and vegetables.
- Lobby local grocers to carry organic foods.

Actions to Advocate at the State/Federal Level

- Advocate for child-protective pesticide laws and regulations.
  - Support strict implementation of the Food Quality Protection Act.
  - Support a federal School Environmental Protection Act.
  - Support international treaties to limit persistent organic pollutants.
- Advocate for strong biomonitoring and environmental public health tracking programs.

INTEGRATED PEST MANAGEMENT

Integrated pest management (IPM) combines several types of pest management and control techniques. The goal of IPM is to employ strategies that are more efficient, healthier, and more environmentally sustainable in the long run. Unlike conventional pest management practices, IPM does not turn to chemical applications first. Managing pests is the first step in establishing a safe and practical pest control system. The EPA suggests the following:

1) Set an action threshold
Establishing the point at which a pest population becomes economically or environmentally detrimental is the first step in an IPM system. Mere cosmetic damage to fruits, vegetables, ornamental plants, or home lawns may not be serious enough to warrant control.

2) Monitor and Identify pests
Not all pests need to be controlled. Many organisms pose no threat to your home or garden, and some can be helpful in fostering plant growth or controlling other pest populations.

3) Prevent pest populations
Prevention is different depending upon the setting. In the house, preventing access and eliminating food and water sources are key. In the yard or garden, supporting a plant community that is not susceptible to harmful pests is an easy way to prevent pests from appearing in the first place. Know what plants are in your garden. Investigate the suitability of plants to your area. Look into planting varieties of plants that resistant to typically harmful pests.

4) Control
When prevention fails and dangerous pests reach the action threshold, control measures need to be taken. IPM can involve the use of chemicals, but always the least risky, most targeted to the pest, timed for the most effect in the pest lifecycle, and by the most contained distribution method. (See Resources for details.)

Selected Resources

General information on special vulnerabilities of children to environmental exposures.

Agency for Toxic Substances and Disease Registry
- Taking an Exposure History http://www.atsdr.cdc.gov/HEC/CSEM/exphistory/index.html
- Pediatric Environmental Health http://www.atsdr.cdc.gov/HEC/CSEM/pediatric/index.html

Etzel RA, Balk SJ, eds. 2003. Pediatric Environmental Health Handbook. 2nd Ed. Elk Grove Village, IL: American Academy of Pediatrics.

Greater Boston Physicians for Social Responsibility
- In Harm's Way http://psr.igc.org/ihw-project.htm

U.S. EPA Office of Children's Health Protection
- Publications on Children's Health and the Environment http://yosemite.epa.gov/ochp/ochpweb.nsf/content/publications.htm#2

Explore these sites for reliable information on pesticide hazards, strategies to minimize exposures, integrated pest management, and alternatives to pesticide use.

Agency for Toxic Substances and Disease Registry
- ToxFAQs http://www.atsdr.cdc.gov/toxfaq.html

National Environmental Education & Training Foundation
- The Implementation Plan for the National Strategies for Health Care Providers: Pesticides Initiative http://www.neetf.org/Health/providers/implplan.htm

National Pesticide Information Center
- 1-800-858-7378 or http://npic.orst.edu/index.html

Pesticide Action Network of North America
- Pesticide Database http://www.pesticideinfo.org/Index.html

USDA Regional IPM Centers
- http://www.ipmcenters.org/Producers/

U.S. EPA Office of Pesticides
- Recognition and Management of Pesticide Poisonings. 5th Edition, 1999 http://www.epa.gov/pesticides/safety/healthcare/handbook/handbook.htm

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