

Putting it into Practice: Pediatric Environmental Health Training Resource

Pesticides and Children's Health User Guide



Children's
Environmental
Health
Network

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User Guide

I. Introduction

Pesticides have been used to control many kinds of pests. The primary classes recognized are insecticides, herbicides, rodenticides, and fungicides. Fumigants and pentachlorophenol are agents that are broad spectrum and do not fall neatly into any of these categories. USEPA also considers disinfectants as pesticides under its' regulatory framework. In agricultural use, the largest uses are herbicides, insecticides, and fungicides. There are several major groups of insecticides and herbicides which should be considered in evaluating use and toxicity of pesticides. The latest published data by USEPA from the years 2006, 2007 show that the largest categories of use are herbicides, insecticides and fungicides, with herbicides alone representing 25% of usage. In this estimate over 6 billion tons of pesticides were used worldwide in these years.¹

II. Pesticide Regulation

Pesticides are regulated under several statutes and their amendments. The primary laws governing pesticide regulation are the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). This law is administered by the USEPA. The second is the Federal Food Drug and Cosmetic Act (FFDCA) which is administered by the Food and Drug Administration (FDA). An important amendment to both these laws was unanimously approved by the US Congress in 1996. This amendment, known as the Food Quality Protection Act (FQPA), made some important changes in FIFRA and FFDCA.

The primary tool used in pesticide regulation is a risk assessment process that results in quantities of pesticide known as "tolerances". Tolerances may be loosely considered as an acceptable daily exposure. In order to register a pesticide for use, the manufacturer (known as the "registrant") is required to conduct a specific set of toxicity testing primarily in non-primate animals. This testing results in a No Observed Effect Level (NOEL) or No Observed Adverse Effect Level (NOAEL). Though FIFRA requires use of the NOEL in setting tolerances, USEPA routinely applies the NOAEL, after making a judgment as to what are "adverse" effects. In order to allow for variation within the test animal species, a "safety factor" divisor of 10 is applied to the NOAEL to account for intra-species variation. In addition another divisor of 10 is applied to the NOAEL to account for the extrapolation across species from animal to human (the interspecies safety factor). These two divisors result in a tolerance that is 1/100th of the NOAEL.



The USEPA is primarily responsible for determining and setting these tolerance standards, while FDA and the United States Department of Agriculture (USDA) have the primary responsibility for ensuring that foods actually are "safe" under these residue standards.

The FQPA made several important changes in this process. First, it removed the so-called Delaney Clause. The Delaney Clause had mandated that "processed foods", not raw agricultural commodities, have no detectible trace of carcinogens. As methods of detecting chemicals became more sensitive and specific this became a difficult, if not unattainable or enforceable standard. Furthermore, the exclusion of processed foods allowed known carcinogens to be introduced during processing. For agents which were not carcinogens a cost/benefit analysis was used to define tolerances. For carcinogens as well as other agents FQPA instituted the requirement that a standard should be set that ensured a "reasonable certainty of no harm" This removed, in theory, the use of a cost/benefit evaluation and provided consistency across all agents and applied to all foods. Second, FQPA required that "aggregate" and "cumulative" exposure be considered in setting and applying tolerances. Aggregate exposure refers to all sources of exposure, including all foods, residential use, and other sources of exposure. For this it is required to consider variation in levels in food and other media, as well as variation in exposure based, for instance, on dietary variation. Cumulative exposure refers to all pesticides with a common mechanism of toxicity. The most important of these in initial implementation of this law was consideration of all pesticides which inhibit cholinesterase, including organophosphate and anticholinergic carbamate insecticides. Finally FQPA required an additional divisor of 10 (safety factor) in tolerance setting where children might be more exposed or more susceptible to a pesticide. In practice this factor has rarely been applied by USEPA.

III. Acute Pesticide Poisoning

While management of acute pesticide poisonings is complex, and a complete discussion goes far beyond the intent of this discussion, some basic understanding of the more common and severe acute toxicities should be part of the knowledge of every pediatrician. There are hundreds of registered pesticides (as active ingredients) thousands of different formulations. There is little recent data on the incidence of acute poisonings or outcomes from these poisonings. However, most of the life-threatening poisoning events occur with a few common and highly toxic agents. In this context, it is useful to recognize and manage acute episodes with these agents by recognition of a few common toxic syndromes or "toxidromes". One of the very typical toxidromes is that associated with cholinesterase inhibition (cholinergic crisis).



Cholinergic crisis. A commonly used mnemonic SLUD (salivation, lacrimation, urination and defecation) misses the most critical and essentially pathognomonic symptoms. These are the respiratory symptoms of bronchorrhea and bronchospasm, associated with bradycardia (usually) and meiosis as key muscarinic symptoms. Muscular paralysis and fasciculation including respiratory paralysis represent the key nicotinic symptoms. Though central nervous system depression with coma, seizures, confusion, etc., is commonly observed, the syndrome is not considered unique enough to assist in diagnosis.^{2,3} Diagnosis is established by response to atropine. **Atropine refractoriness** is diagnostic of these poisonings. Patients with acute toxicity with these agents require very large doses of atropine to reverse the muscarinic symptoms.

Along with recognition of toxidromes, assessment of possible exposures is important to the process of diagnosis and management of acute poisonings. Inquiries should be made as to what agents are in or around the home. If a pest control operator (PCO) has been used, parents should be aware of the agents used. PCO's are required to leave a record of agents and quantities applied at each application. Likewise, it is important to know other possible sites of exposure for the child, such as school, playgrounds, neighbors, or agricultural operations. Parental occupation may also be important with the possibility of take home exposures as well as direct exposure of children working in agriculture.

Whenever possible, the original container for the pesticide should be obtained. The label will identify the active ingredient(s) as well as the manufacturer or formulator. Trade names are not useful as many companies market many formulations and active ingredients with the same trade name. The labels do not reveal "inert" ingredients which are commonly hydrocarbon solvents, some of which are highly toxic by ingestion or inhalation. Dilution of these agents for application with water results in a "milky" emulsion, which may be very attractive to children. The only available source to identify these inert ingredients is the formulator and it may be necessary in some cases to directly contact the formulator.

The laboratory is very limited in the diagnosis of acute pesticide poisonings. The toxin screens in most hospital laboratories are only designed for detection of drugs of abuse. Some of the broader spectrum screens are only qualitative and will not quantify exposure. Evaluation of interlaboratory variation in Mass Spectroscopy and High Pressure Liquid Chromatography has shown marked variation in ability to detect and quantify toxic exposures. The history of exposure, evaluation of sources, review of label, and recognition of toxidromes remain the most reliable methods for diagnosis. However, the laboratory is very useful in management of acute poisonings after diagnosis, as management is most often supportive and responsive to organ injury. On pages 26-27 of the 6th edition of *Recognition and Management of Pesticide Poisoning*, a text from the US EPA, there is a detailed list of the information and biological



samples that should be collected in the event of an acute poisoning. The book is in print from the US EPA and also available on line at www2.epa.gov/pesticide-worker-safety/recognition-and-management-pesticide-poisonings.

Due to shifts in formulations, developments of new pesticides, and changes in management, textbooks of toxicology are of very limited value in the diagnosis and management of pesticides poisoning. In addition to *Recognition and Management of Pesticide Poisonings 6th Edition* resource, Micromedex Systems (Poisondex) is another useful proprietary system that is relatively frequently updated and available in many Medical Libraries. Note that many poison control centers use this as a primary source and it may be useful to access it directly, rather than relying on staff of the poison control center to interpret it for the medical provider. Another useful and reliable source is the National Pesticide Information Center available by toll free phone or online at <http://npic.orst.edu/>.

IV. Chronic Pesticide Effects

In some cases, there may be lingering effects following an acute poisoning, while in other situations, chronic low level or sub-acute pesticide exposure may be associated with persistent symptoms or demonstrable physiological alteration. Evidence for links to chronic health conditions rely on observational epidemiological studies or standard chronic toxicity testing using animal models. For obvious ethical reasons, experimental studies with purposeful dosing of pesticides are not conducted in humans. Therefore, while cause and effect is not proven with any one epidemiology study, several well designed studies in different study populations can strongly support the likelihood that a given association is in fact causal in nature. Since direct experimental evidence is lacking for pesticide exposures in humans, evidence must be drawn from inferential evidence from animal exposures and from human epidemiological studies.

Multiple chronic health conditions may have an association with pesticide exposure. Neurological effects, particularly neurodevelopmental abnormalities in children, have been implicated with exposure to insecticides that have toxicological activity on the central nervous system. Numerous studies have examined the effects of pesticides on the development of cancer in children and adults. Several classes of pesticides have properties that mimic endocrine hormones and may affect multiple organ systems and functions including reproductive health and cancer risk. Recently, data are emerging that there may be a potential relationship between certain pesticides and asthma.



V. Neurological and Neurodevelopmental Injury in Childhood

Research on insecticide toxicity to the developing brain and neurodevelopmental outcomes has been reviewed.⁴ Most studies focus on exposure to organophosphates and organochlorines. Since these insecticides have historically and/or currently been in wide usage for household or agricultural pest control, exposures to the child and pregnant mother have been common. The recognized important developmental events in the growth and maturation of the nervous system are likely involved in the pathogenesis of pesticide injury to the nervous system of children. The candidate events, supported to some degree in animal models, are cell proliferation, synaptogenesis, synaptic maturation and myelination.⁵ Much of the existing evidence of injury to children, derived commonly from longitudinal studies, seems related to intrauterine and early life exposure, supporting this assessment. These studies have been assisted by the ability to relate outcomes to exposure by use of laboratory measurements of organochlorine metabolites and of organophosphate metabolites.

Organochlorines (such as DDT, chlordane, etc.) have been linked to a variety of adverse outcomes with prenatal exposure.^{6,7} These agents have been associated with decreased scores on the Brazelton Neonatal Behavior Assessment Scale, the California Preschool Social Competence Scale and the Psychomotor Development Index. These very early life outcomes have been followed by observation of increased rates of Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) in school age children.^{8,9}

Organophosphates have been linked to several adverse outcomes related to prenatal and early childhood exposure.^{10,11} These outcomes include lower scores on the Brazelton Neonatal Behavior Assessment Scale, and the preschool measures the Bayley Scales of Infant Development and the Mental Development Index. Longitudinal studies extending to school age have suggested effects on performance at school age from intrauterine and early childhood exposure to organophosphate compounds.^{12,13,14}

VI. Carcinogenesis in Childhood

Several meta-analyses and systematic reviews have been published on the association between pesticide exposure and cancer. In most instances, these analyses and reviews serve as the primary source of information for childhood cancers.

Relationships between childhood cancers and pesticides have been summarized in two review articles.^{15,16} The pediatric cancer types with the most compelling evidence for an association with pesticides are leukemia and brain tumors. Of note, in most of the studies reviewed, all



forms of leukemia were combined due to insufficient numbers in any group of specific types of leukemia (i.e. acute lymphocytic leukemia (ALL) or acute myelocytic leukemia (AML). The more recent review reported improved studies of leukemia in children.¹⁶ Most of these studies were larger and used higher quality exposure assessment methodologies compared to earlier studies. Five studies found statistically significant associations between leukemia and pesticide exposure. Two included a detailed exposure assessment and were able to demonstrate a dose-response effect.

Brain tumors are also combined in studies rather than by individual tumor types as they are even rarer than childhood leukemia. The body of evidence estimating an association between brain tumors and pesticides since the earlier review (1999) is more robust with larger studies and improved exposure assessment. Nine of 10 studies in a later review (2007) suggested an increased risk of brain tumors following maternal and/or paternal exposure, with three of the studies reaching statistical significance.¹⁶ For all studies, it appeared that prenatal exposure to insecticides, particularly in the household, as well as both maternal and paternal occupational exposure before conception through birth represented the most consistent risk factors.

Two meta-analyses have been conducted which further explore associations between pesticides and leukemia and support previously described associations. The first meta-analysis examined parental occupational exposure to pesticides and leukemia and the second focused on studies of pesticide use in the home and garden.¹⁷ Maternal occupational exposure was found to be associated with leukemia. No associations were found for paternal occupational exposure. In another meta-analysis focused on exposure through home and garden uses of pesticides, 15 studies were included and exposure during pregnancy to unspecified pesticides, insecticides, and herbicides were all associated with leukemia.¹⁷

VII. Endocrine Disruption

Over the last fifteen years there has been increasing interest in the ability of environmental chemicals to disrupt endocrine systems. Many pesticides and pesticide vehicle and contaminants have endocrine disrupting properties based on *in vitro* and animal studies. While data on human effects remains somewhat fragmentary and inconclusive, the weight of evidence from multiple lines of investigation appears to support the concern for human effects. It is important to consider *in vitro* studies as well as *in vivo* animal studies in order to understand the biological plausibility of the human epidemiologic evidence.

The cellular biology of endocrine disruption is very complex and has been extensively reviewed.¹⁸ As a group, exogenous agents including pesticides that affect the endocrine system



have been labeled endocrine disruptive chemicals (EDC). Several basic mechanisms have been identified, including direct interaction with nuclear receptors (NR), disturbance of NR signaling, and changes in hormone availability. In vitro evidence of the hormone availability exists for several pesticides occurring by alteration of P450 enzyme activity that influences the availability of steroid hormones either by increasing or decreasing rates of metabolism.

Animal studies conducted in the laboratory environment suggest that some pesticides may disrupt the endocrine systems of a variety of animals. Vinclozolin, a fungicide with low acute toxicity, has been shown to be strong antiandrogen in rats when exposure occurs *in utero*.¹⁹ An androgenic response to chlordane (an organochlorines insecticide) during gestation has been shown in male and female rodent offspring.²⁰ A systematic review by the Endocrine Society has led to a scientific statement on endocrine disrupting environmental toxicants and notes potential for a variety of human effects, including alteration in mammary gland development and possible carcinogenesis, alteration in male fertility and testicular cancer, male urogenital malformations, prostate cancer, thyroid disruption, and obesity, among others.¹⁸ The most relevant to childhood are precocious puberty, altered sexual behaviors, hypospadias and cryptorchidism, and thyroid dysfunction. This is a rapidly evolving field of investigation.

Of importance to the understanding of the regulation of endocrine disrupting chemicals is the increasing evidence that the effects of such chemicals may be non-linear and may occur at very low levels as well as high levels. These effects may also differ depending on whether a low dose or high dose exposure has occurred. To the extent that this is true, the present risk paradigm, which requires determining a NOEL or NOAEL, cannot be applied to such pesticides and a new method for risk assessment and tolerance setting is necessary. A recent extensive review of this issue has recently been published.²¹

VIII. Asthma and Pesticides in Childhood

There is considerable interest in the relationship between pesticides and asthma. Much of the investigation of this relationship has occurred in farm families or has been related to occupations of adults. The role of pesticides in the development of and/or exacerbation of asthma has been hypothesized and is under investigation. Pyrethrin insecticides have some potential as an allergic sensitizing agent, with reports of contact dermatitis, asthma, and anaphylactic reactions occurring following exposure.^{22,23} There also appears to be some possible mechanisms for organophosphates to impact the development or exacerbation of asthma.



The few epidemiologic studies on the association between pesticide exposure and respiratory health in children have reported mixed results. In a cohort of rural lowan children, multiple farm-related exposures were studied for any associations with several asthma related outcomes ranging from doctor-diagnosed asthma to cough with exercise. Any pesticide use in the previous year was not significantly associated with asthma symptoms and prevalence.²⁴

A nested-case control study of the Southern California Children's Health Study was conducted to evaluate the relationship between multiple environmental exposures and early life experiences and the occurrence of asthma. Among environmental exposures in the first year of life, "herbicides" and "pesticides" both had a strong association with asthma diagnosis before age 5 years.²⁵ Specific evidence for individual pesticides is limited but subject to considerable interest at this time.

IX. Advice for Parents

Since there is considerable evidence that prenatal, infant, and childhood exposure has effects in all the areas discussed, including neurodevelopmental, carcinogenesis, endocrine disruption, and asthma, parents should be advised to limit children's exposure to these toxic chemicals.

Some specific actions include:

1. Choice of USDA certified organic foods to the extent possible and affordable.²⁶
2. Limiting or eliminating indoor use of indoor pesticides and garden use of pesticides in their homes. There are multiple sources of information regarding integrated pest management a tool that can remove most need for such use.^{27,28}
3. Promoting policies in their communities that limit use of pesticides. In particular, oppose use of pesticides in playing fields and other areas where children spend considerable time.
4. Promoting integrated pest management in community schools.
5. If pesticides are used in the home, they should always be stored out of the reach of children in their original containers to limit the risk of accidental acute poisoning.
6. Always using pesticides, if they choose to, in accordance with all package instructions and precautions.



KEY RESOURCES FOR FURTHER READING

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

Roberts JR, Karr CJ, and American Academy of Pediatrics Council on Environmental Health. Pesticide Exposure in Children: Technical Report. *Pediatrics* 2012; 130:e1765-1788.

Roberts JR, Reigart JR. Recognition and Management of Pesticide Poisonings: 6th Edition: 2013, Environmental Protection Agency, Washington DC. <http://www2.epa.gov/pesticide-worker-safety/recognition-and-management-pesticide-poisonings>

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Note: This User Guide is intended to accompany the PowerPoint module of the same name. It elaborates on some studies which may require more in-depth information than what is provided on the slides. However, the contents of all slides in the module are equally important to present.

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