

# **Pesticides and Human Health**

## **A Resource for Health Care Professionals**



**Physicians for Social Responsibility**



A resource from Californians for Pesticide Reform

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Pesticides and Human Health: A Resource for  
Health Care Professionals

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## **A Resource for Health Care Professionals**

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The opinions expressed in this report are those of the authors and do not necessarily reflect the views of our reviewers.

# 1 Introduction

No one wants to miss a diagnosis, especially if it might mean significant morbidity or even mortality for the patient. Similarly, it can be frustrating, even embarrassing, when a patient has a reasonable health-related question and the clinician does not feel equipped to answer. Due to rapid growth of public awareness about the risks of pesticide exposure, it is increasingly common for clinicians to receive questions about these chemicals.

Heightened public awareness of pesticide health effects is certainly merited: nearly one of every four pounds of pesticide applied in agriculture in the U.S. is applied here in California. Every week, reports in the press and in scientific journals provide new information on pesticide health impacts. Organic food, meanwhile, is becoming increasingly popular as consumers seek to reduce their exposure to chemicals designed to be toxic to living organisms. Pesticide exposure is not confined to agricultural areas. In urban locations pesticides are used in homes, yards, public buildings, stores, schools, parks, and other settings, resulting in per-acre pesticide intensity in some urban areas that exceeds agricultural use.<sup>1</sup>

Pesticides affect sensitive groups to a disproportionate degree. Children, whose developmental patterns, physiology, and behavior make them more susceptible than adults; immune-compromised and chemically sensitive patients; and asthmatics may report pesticide-related symptoms that are different from or more pronounced than normal adults.

Unfortunately, clinicians on average receive fewer than four hours of training in the important field of occupational and environmental health. Although some health workers may be familiar with the management of acute pesticide poisoning, chronic effects of pesticide exposure are often overlooked.

With the large number of potential exposure “pathways”—pesticides can move from their intended target through air, water, food, and surface-contact—the physician’s role is critical. In some cases, the doctor must become the detective, identifying clues that could link symptoms to environmental health hazards.

Pesticides vary in their uptake, mode of action, metabolism, toxicity, and elimination from the body. Most pesticides in current use—even those approved by U.S. EPA for consumer use—are highly toxic to living organisms and have the capacity to affect biological systems in non-target organisms, including humans.<sup>2</sup> This Resource Kit utilizes and references over 150 studies that link pesticides with a variety of acute and chronic conditions, including cancer, neurological damage, reproductive and developmental hazards, and immune-system and endocrine disruption. The format covers pesticide health effects by toxic endpoint symptomatically and is referenced with endnotes.

Key elements of good preventive medicine include education, behavior change, and even social change aimed at prevention of future disease. Effective prevention may entail taking protective action despite scientific uncertainty. We already immunize children to prevent their serious illness should they by (statistically small) chance be exposed to certain infectious diseases; we ban smoking in many public places due to the increased risk of lung cancer and other diseases from environmental tobacco smoke. Similarly, health professionals dealing with pesticides must consider recommendations to protect public health. These might range from counseling children and pregnant women to avoid pesticide exposure, to recommendations to eliminate use of the most hazardous pesticides.

An important public health policy model is the precautionary principle—an approach based on the concept of limiting or preventing harm. The precautionary principle puts concern for public health and preventing further harm to the environment first. Simply

## Prevention and the Precautionary Principle

put, it suggests that “an ounce of prevention is worth a pound of cure.” Moreover, this approach shifts the burden of proof from government, the scientific community, and the public victims of environmental harm onto the chemical producers. It implements a policy more like FDA’s drug approval process, where the manufacturer must first demonstrate a product’s safety before it can be introduced into widespread use.

### **Wingspread Statement on the Precautionary Principle**

An international group of physicians, scientists, government officials, lawyers, and labor and environmental advocates met January 23–25, 1998, at Wingspread in Racine, Wisconsin, to define and discuss the precautionary principle. During this meeting the group developed this consensus statement.

“The release and use of toxic substances, the exploitation of resources, and physical alterations of the environment have had substantial unintended consequences affecting human health and the environment. Some of these concerns are high rates of learning deficiencies, asthma, cancer, birth defects, and species extinction, along with global climate change, stratospheric ozone depletion and worldwide contamination with toxic substances and nuclear materials.

“We believe existing environmental regulations and other decisions, particularly those based on risk assessment, have failed to protect adequately human health and the environment—the larger system of which humans are but a part.

“We believe there is compelling evidence that damage to humans and the worldwide environment is of such magnitude and seriousness, that new principles for conducting human activities are necessary.

“While we realize that human activities may involve hazards, people must proceed more carefully than has been the case in recent history. Corporations, government entities, organizations, communities, scientists, and other individuals must adopt a precautionary approach to all human endeavors.

“Therefore, it is necessary to implement the Precautionary Principle: When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof.

“The process of applying the Precautionary Principle must be open, informed, and democratic, and must include potentially affected parties. It must also involve an examination of the full range of alternatives, including no action.”<sup>3,4</sup>

### **Some Pesticide Definitions**

#### **Insecticides**

Pesticides are chemicals designed to kill a variety of pests, such as weeds, insects, rodents, and fungi. They can be characterized on the basis of function—insecticide, herbicide, rodenticide, fungicide, and others—and on the basis of chemical class—organophosphates, organochlorines, S-triazines, and pyrethroids, for example.

Insecticides accounted for nearly 25% of reported pesticide use in California in 1998. *Organochlorines*, such as DDT and dieldrin, are largely banned for use in the U.S., although some, such as lindane, endosulfan, methoxychlor, and dicofol, are still used. Widely used in the 1960s and 1970s, organochlorines are acutely toxic and very persistent in the environment. Many have been shown to be carcinogens, reproductive toxicants, or both.<sup>5</sup>

*Organophosphates* and *N-methyl carbamates* are often grouped together because they act similarly. They interfere with cholinergic transmission in the nervous system of their target, and affect human health because of the similarity between human and insect systems. Introduced to replace organochlorines, they are generally shorter-lived in the environment but more acutely toxic. Most are classified as highly or moderately toxic by U.S. EPA. Some commonly used organophosphates include malathion, methyl parathion, chlorpyrifos, azinphos methyl, and diazinon. Common N-methyl carbamates include aldicarb and carbaryl.<sup>6</sup>

*Synthetic pyrethroid* insecticides, used primarily in structural pest control and agriculture, function much like organochlorines, acting as contact and stomach poisons to insects. However they are fairly short-lived in the environment and are less acutely toxic to humans. Typical pyrethroids include permethrin, cypermethrin, cyfluthrin, and esfenvalerate.<sup>7</sup>

## Herbicides

Herbicides are used for weed control in agriculture, right-of-ways, and gardens. Designed to kill plants rather than animals, they are generally less acutely toxic to humans than insecticides, but many are classified as probable (e.g., alachlor) or possible (e.g., atrazine, simazine) carcinogens by U.S. EPA.<sup>8</sup> Research shows some may be endocrine disruptors.<sup>9</sup> Two widely used dipyrindyl compounds, paraquat and diquat, are non-selective contact herbicides highly toxic to humans.

## Fumigants

Used to sterilize soil and in structural pest control, fumigants have a high tendency to diffuse, and can frequently be carried off-site by volatilization and drift. They tend to be rapidly absorbed across the pulmonary membrane and through skin. Many are classified as carcinogens (e.g., metam sodium) by U.S. EPA and as reproductive and developmental toxicants (e.g., methyl bromide, metam sodium) by the state of California.<sup>10,11</sup> Most are acutely toxic to respiratory and dermal systems.

## Fungicides

Fungicides are used extensively in agriculture and around homes and structures to control mold and mildew. They vary greatly in their potential for adverse effects on human health. As a class they are disproportionately responsible for skin and mucous membrane irritation. Some (e.g., captan, maneb) are classified as probable carcinogens by U.S. EPA. Several may be endocrine disruptors.

## Health Effects of Pesticides

*A 3-year-old Latina girl is brought into the clinic by her parents. She has been vomiting for several hours and has now developed diarrhea. No one else in the family is sick. On physical exam she appears moderately ill and dehydrated. She is tachycardic, although normotensive and afebrile. Her skin is moist. She shows only mild abdominal tenderness, and scattered wheezes and ronchi on lung exam. The rest of the exam is unremarkable. You are about to diagnose a viral gastroenteritis and bronchitis, when you think to ask about possible pesticide exposure.*

*A 32-year-old pregnant woman comes in for her first prenatal visit. In the course of the visit, she asks whether pesticides may pose a risk to her fetus. She explains that her cat has fleas and that her usual routine is to send the pet for a flea dip and have the house flea-bombed to eliminate eggs in the carpets. The exterminator assures her that she runs no risk if she airs the house out sufficiently before returning. She wants your reassurance that this plan is indeed safe.*

## Acute Health Impacts

### Acute Toxicity

Acute toxicity refers to the immediate effects of a particular dose of pesticide on human health. Acute effects can present numerous symptoms, including respiratory problems, nervous system disorders, and aggravation of pre-existing conditions such as asthma. Symptoms range from mild irritations to death. Pesticides can cause irritation of the eyes, nose, and throat; burning, stinging, itches, rashes, and blistering of the skin; nausea, vomiting, and diarrhea; and coughing, wheezing, headache, and general malaise. Because these symptoms are similar or identical to those caused by other illnesses, acute pesticide poisoning is often misdiagnosed.

### Acute Toxicity Facts

- Between 1991 and 1996 California EPA reported 3,991 cases of occupational poisoning by agricultural pesticides.<sup>12</sup>
- In 1997, 88,255 pesticide exposure emergencies were reported to the national network of Poison Control Centers.<sup>13</sup> Fourteen fatalities were attributed to pesticide poisoning during the same period. Over 50% of all reported pesticide poisoning cases involved children under six years of age.<sup>14</sup>
- It is widely thought that many agricultural poisoning cases go unreported. The many barriers to accurate reporting include lack of access to medical care and fear of reprisal and job loss.<sup>15</sup>
- Acute dermatitis is the second most common occupational disease for all industrial sectors. The rates of dermatitis in the agricultural industry are the highest in any industrial sector. In California, pesticide-related skin conditions represent 15–25% of pesticide illness reports.<sup>16</sup>

## Chronic Effects

A substantial body of laboratory and epidemiological evidence suggests that certain pesticides are associated with carcinogenesis, immunotoxicity, neurotoxicity, behavioral impairment, reproductive dysfunction, endocrine disruption, developmental disabilities, skin conditions, and respiratory diseases such as asthma. Chronic health effects from pesticides are problematic to study in humans because most people are exposed to low doses of pesticide mixtures, and delayed health effects are difficult to link to past exposures. Pesticides are biologically active. Some are genotoxic, others disrupt normal neurotransmitter function, while still others mimic human hormones, any of which may create subtle health effects.

## Cancer Facts

- Forty pesticides are listed by the state of California as known to cause cancer in animals.<sup>17</sup>
- A number of human epidemiological studies have found associations between household or occupational pesticide exposure and childhood leukemia, brain tumors, Wilm's tumor, non-Hodgkin's lymphoma, sarcomas, prostate cancer, and other cancers.<sup>18 19 20 21 22 23</sup>
- Children with brain cancer are more than twice as likely to have been exposed to pesticides at home than are healthy children. The incidence of childhood brain cancer has increased 30% in the past 20 years.<sup>24 25 26</sup>

## Reproductive and Developmental Facts

- Forty-three pesticides registered for use in California, including the widely-used fumigants methyl bromide and metam sodium, are listed by the state as known to cause birth defects or other reproductive harm or to impair childhood development.<sup>27</sup>
- Occupational exposure to pesticides has been associated with increased risk of miscarriage and with a variety of birth defects, particularly of the musculoskeletal system.<sup>28 29 30</sup>
- There is often a period of heightened vulnerability to the effects of toxic chemicals, including pesticides, during fetal gestation and early childhood. Such susceptibility occurs during the development of various organ systems. Permanent structural birth defects or permanent functional changes may occur.<sup>31 32</sup>

## Endocrine Disruption

A condition appreciated relatively recently, endocrine disruption refers to the hormone-altering effects of certain chemicals on animal endocrine systems, impairing reproduction or development. Endocrine disrupting pesticides and other chemicals are currently the subject of intense study, the result of which may impact use.

- Numerous pesticides have been shown to mimic or block estrogen, while others have been shown to block androgens or thyroid hormones.<sup>33 34 35 36</sup>
- Health effects of endocrine disrupting pesticides in animals include altered circulating hormone levels, hypospadias, exaggerated nipple development in males, cryptorchidism, decreased semen quality, altered time to sexual maturity, and abnormal behavior.<sup>37 38 39</sup>
- Evidence that exposure to certain pesticides may compromise the immune system is based in part on animal studies that demonstrate damage to immune organs, suppression of immune-mediating cells, and increased susceptibility to infectious disease.<sup>40 41 42</sup>
- Evidence of pesticide-associated neuropsychological deficits is based primarily on studies of workers exposed to organophosphate or N-methyl carbamate pesticides.<sup>43</sup>
- Cognitive symptoms include impairment of memory and psychomotor speed, as well as affective symptoms such as anxiety, irritability, and depression.<sup>44</sup>
- Visuo-spatial deficits have also been linked to organophosphate exposure.<sup>45</sup> Long-term memory and language abilities are generally spared.<sup>46</sup>
- Neurological development in children is particularly at risk of disruption. Animal studies demonstrate periods of vulnerability, particularly to anticholinesterase, during early life.<sup>47 48</sup> Recent evidence that acetylcholinesterase may play a direct role in neuronal differentiation supports these findings.<sup>49</sup>

## Immunological and Neurological Facts

## Pesticide Use in California and the U.S.

Much information on pesticide use in California is available through a Pesticide Use Reporting system maintained by the state Department of Pesticide Regulation. Not all pesticide use is reported, including consumer use in homes and gardens and most institutional use.

- Reported use of pesticide active ingredients in California increased 40% between 1991 and 1998, from 153 million to 215 million pounds; approximately 90% of reported use occurs in production agriculture. It is estimated that total use is 20–25% higher than reported use.<sup>50</sup>
- An average of nearly 23 pounds of pesticide active ingredient is applied per planted acre in the state.<sup>51</sup>
- Viewed from another perspective, more than 6.5 pounds of pesticide active ingredient are used per person per year in California,<sup>52</sup> more than double the national rate of 3.1 pounds.<sup>53</sup>
- Use of known and probable carcinogens—as designated by U.S. EPA and the state of California—increased by 127% between 1991 and 1998.<sup>54</sup>
- Nationally, about 875 pesticide active ingredients are officially registered and marketed in more than 21,000 product formulations.<sup>55</sup>
- Large quantities of pesticides are also used in non-agricultural sectors, particularly in homes and landscape management, where the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) is the most widely employed.<sup>56</sup>
- In the U.S. a mixture of pesticide residues are detected in the blood and urine of nearly 100% of all persons sampled.<sup>57 58 59</sup>

## Preventing Adverse Health Effects of Pesticide Exposure

What can health professionals do to reduce pesticide exposure? They can

- Inform patients about the risks of pesticide exposure and discourage use of many pesticides in the home and garden and on pets, particularly in homes with small children or pregnant women.
- Learn about pesticides used in local schools, hospitals, day care centers, parks, and playgrounds, and push to eliminate use of hazardous pesticides in these environments.
- Work for strict regulation or phase-out of aerial spraying of chemical pesticides.
- Support phaseout of the most acutely toxic pesticides, as well as those that cause cancer or reproductive harm.
- Encourage conversion to organic food production by recommending and purchasing organic food.
- Support increased funding for independent research to identify pesticide exposure and potential consequent health effects.

### Screening Questions for Occupational and Environmental Exposures

For an adult patient:

*(After establishing the chief complaint and history of the present illness)*

- What kind of work do you do?
- Do you think your health problems are related to your home or other location?
- (If employed)* Do you think your health problems are related to your work? Are your symptoms better or worse when you are at home or at work?
- Are you now or have you previously been exposed to pesticides, solvents, or other chemicals, dusts, fumes, radiation, or loud noise?

For a pediatric patient:

*(Questions asked of parent or guardian)*

- Do you think the patient's health problems are related to the home, daycare, school, or other location?
- Has there been any exposure to pesticides, solvents, or other chemicals, dusts, fumes, radiation, or loud noise?
- What kind of work do the parents or other household members engage in?

Note: A full screening protocol developed by U.S. EPA is in Chapter 11 of this Kit.

## Chapter 1 Notes

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## 2 Acute Effects of Pesticide Exposure

*Three farmworkers were transported to the emergency room by their supervisor. They had been working in a vineyard when a nearby cotton field was aerially sprayed with pesticides. The spray had drifted downwind into the vineyard where about a dozen people were working. Many of the workers began to complain of a variety of symptoms, including difficulty breathing, irritation of the eyes and throat, and nausea. The sickest workers were taken to the emergency room, while others were being seen in a local clinic. There was no information available yet about what the workers were exposed to.*

### Overview

Acute pesticide poisonings present with rapid onset of symptoms—such as those in the case above—stemming from exposures generally within the past several hours or days. Acute pesticide poisonings are the pesticide-related health effect that practitioners are most likely to recognize and treat. However, large numbers of acute pesticide poisonings each year go undiagnosed and unreported, according to pesticide researchers.<sup>1</sup> The available reporting data indicate that each year between 2000 and 5000 individuals require hospitalization as a result of pesticide poisoning in the United States.<sup>2</sup> Children under six years of age represent more than half of acute reported pesticide poisoning incidents, usually via accidental ingestion or dermal exposure.<sup>3</sup> An estimated 10,000-20,000 farmworkers in the United States suffer from acute pesticide poisonings each year.<sup>4</sup> In California the state's Pesticide Illness Surveillance Program reported nearly 4000 farmworker pesticide poisonings from 1991 to 1996.<sup>5</sup>

Physicians should be aware of the pesticide poisoning reporting requirements under the California Health and Safety Code.<sup>6</sup> The state Pesticide Illness Surveillance Program (PISP) requires that "any physician or surgeon who knows, or has reasonable cause to believe, that a patient is suffering from pesticide poisoning or any disease or condition caused by a pesticide shall promptly report that fact to the local health officer by telephone within 24 hours and by a copy of the report within seven days." Failure to report can result in civil penalties of up to \$250. County health officers must then report to county agricultural commissioners, who determine whether the cases are potentially related to pesticides. The state Department of Pesticide Regulation (DPR) administers the program. Pesticide illness records are useful for assessing the public health implications of pesticide use and the effectiveness of current regulations. DPR reports, however, that most pesticide illness data are obtained from workers compensation reports rather than through the PISP.<sup>7</sup>

Careful diagnosis is critical. An EPA model screening protocol is included in the appendix of this resource kit. For a comprehensive guide to protocols for diagnosis, treatment, and follow-up of acute pesticide poisoning, refer to the U.S. EPA handbook on Recognition and Management of Pesticide Poisonings.<sup>8</sup>

Organophosphate and carbamate pesticides are among the most common causes of pesticide poisonings and hospitalizations in the United States.<sup>9</sup>

Organophosphate (OP) insecticides irreversibly deactivate the enzyme acetylcholinesterase, thereby destabilizing neurotransmission at synaptic junctions. This leads to overstimulation of both the sympathetic and parasympathetic nervous systems.<sup>10,11</sup> Specific antidotes and therapeutic protocols are available for organophosphate and carbamate poisonings.

One of the most frequently used OP pesticides is chlorpyrifos (Dursban or Lorsban). It is widely used to kill insects in agriculture, as well as in home insect sprays and in dips to kill fleas. Other common OP insecticides include malathion, azinphos-methyl (Guthion),

### Acute Organophosphate and n-methyl-Carbamate Toxicity

## Signs and Symptoms

methyl parathion, diazinon, demeton, and phosmet. These pesticides are often used in agriculture, homes and gardens.

The N-methyl-carbamate insecticides also deactivate acetylcholinesterase, but the inhibition is reversible rather than permanent. Thus, while the symptoms of carbamate and organophosphate poisoning are identical and may be equally severe, carbamate poisoning generally runs a shorter course.<sup>12</sup> Common N-methyl-carbamate pesticides include carbaryl (Sevin), aldicarb (Temik), fenoxycarb, propoxur, and methomyl.

The symptoms of OP or carbamate poisoning include bradycardia, dyspnea, wheezing, nausea, vomiting, diarrhea, ocular meiosis, fasciculations, muscle weakness, and hypersecretion, (e.g., lacrimation, perspiration, rhinorrhea, and salivation). Central nervous system signs and symptoms are also prominent, including headache, dizziness, restlessness, and anxiety. Severe intoxication may result in psychosis, seizures, and coma.<sup>13</sup>

Children may present with a different clinical picture from adults. Hypotonia, lethargy, seizures, and coma were more common presenting symptoms in children than in adults, and children rarely present with the classic cholinergic signs of salivation, lacrimation, diaphoresis, bradycardia, or fasciculations.<sup>14</sup>

Theoretically, acute symptoms of organophosphate or carbamate poisoning are classic and easily recognized, but in practice diagnosis can be difficult. Pesticide poisoning can easily be misdiagnosed as gastroenteritis, influenza, bronchitis, or a wide range of other illnesses. Even severe pesticide poisoning requiring intensive care unit admission was misdiagnosed 80% of the time in one series, with diagnoses including pneumonia, meningitis, and epilepsy.<sup>15</sup>

The only way to be sure to correctly diagnose acute pesticide poisoning is to maintain a high index of suspicion and take a screening occupational and environmental history from any patient that presents with suggestive symptoms. Brief questions about occupation, household exposures, and any other potential exposures to fumes, dusts, or gases will allow a rapid assessment of the likelihood that an illness could be related to pesticides or other toxic chemicals.

## Diagnosis and Treatment

Plasma or red blood cell cholinesterase levels can be useful in OP or carbamate poisoning, and are readily available through most labs. However, treatment should not be delayed pending results of the laboratory test. Baseline cholinesterase levels, particularly in plasma, are subject to wide variability. As a result, interpretation of the results can be difficult without a baseline for the individual, and a result within the normal range may still represent clinically-significant suppression of cholinesterase for a particular individual.<sup>16</sup> Urinary alkyl phosphates and phenols can be useful for documenting exposure within the first 48 hours, and are more sensitive to low-level exposure than cholinesterase levels.

Therapy for any pesticide poisoning begins with removal of all potential sources of ongoing exposure including gloves and clothing (every effort should be made to ensure privacy when removing clothes in field situations). If residues may be on skin or hair, the patient should be decontaminated with ample soap and water. Supportive care, including continuous cardiac monitoring, oxygenation, airway preservation and aggressive hydration, are all generally indicated.<sup>17</sup>

For many ingested pesticides gastric lavage and cathartics may be indicated. Be aware, however, that gastric lavage is contraindicated with hydrocarbon ingestion (a common vehicle in pesticide preparations), and cathartics may not be needed after ingestion of pesticides such as the OPs and carbamates, which often result in diarrhea.<sup>18</sup> Consultation with a Poison Control Center is highly advisable at this stage.<sup>19</sup>

Atropine sulfate IV or IM is used to control muscarinic symptoms of OP or carbamate poisoning, including lacrimation, salivation, vomiting, diarrhea, and bronchorrhea. This treatment does not affect nicotinic symptoms such as muscle weakness, fasciculations, and

## Other Pesticides Associated with Acute Poisoning

## Preventing Acute Pesticide Poisoning Advice for Patients

respiratory depression. An atropine challenge can be useful for diagnostic purposes. Atropine is generally administered in repeated doses of 2–4 mg q 15 minutes in adults, or 0.05–0.1 mg/kg q 15 minutes in children until secretory symptoms have reversed. Consult a Poison Control Center or EPA's Recognition and Management of Pesticide Poisonings for current treatment protocols. Repeated doses may be needed for hours, particularly in the case of OP poisoning, and severe poisoning can require very large doses, up to 300 mg/day.<sup>20</sup>

Pralidoxime IV is used to reactivate cholinesterase only in severe cases of OP poisoning. A blood sample for cholinesterase must be drawn prior to administration of pralidoxime. This medication is generally contraindicated in carbamate poisoning. The adult dose of pralidoxime is up to two grams in a slow IV drip, while for children the dose should not exceed 50 mg/kg. Blood pressure and heart rate must be carefully monitored during dosing.<sup>21</sup>

Acute symptoms associated with other major pesticide categories are presented in Table 2-1. It is noteworthy that clinical manifestations of acute poisoning have only been studied for a small fraction of pesticides in current use.

Patients who have suffered acute pesticide poisoning require close medical follow-up because certain health effects, particularly neurological impairment, can emerge after apparently successful treatment and recovery.<sup>22</sup>

- Avoid using pesticides unless absolutely necessary. Select less toxic alternatives whenever possible. For example, insect baits and traps are almost always safer than broadcast sprays, and non-pesticide alternatives include sealing cracks, cleaning up food scraps, and using soap products to eradicate scents.
- If there are children in the home, make sure that all pesticides are stored out of reach. Do not store any highly toxic pesticides in the home, especially agricultural pesticides or OP pesticides.
- Never store pesticides in containers other than the original, labeled container. In particular, never store pesticides in soft-drink bottles or other food containers.
- If any object, including clothing, containers, or equipment, becomes contaminated with pesticides, discard it or clean it thoroughly and separately. Do not leave any pesticide-contaminated objects in areas where children might come into contact with them.
- Never apply pesticides without following label directions. Always wear protective gloves, long sleeves, and protective clothing. Do not re-enter an area where pesticides were applied until well after any time interval specified on the label.
- If you suspect pesticide poisoning, seek emergency medical care as quickly as possible. Bring along any containers associated with the incident.

**Table 2-1: Acute Symptoms Associated With Some Major Pesticide Categories**

| Pesticide Category            | Chemical Examples   | Physiological Target  | Acute Symptoms   | Diagnosis/Treatment   |
|-------------------------------|---|---|--|---|
| Organophosphates              | Chlorpyrifos, diazinon, methyl parathion, malathion, azinphos-methyl, naled | Irreversibly inhibits acetylcholinesterase resulting in muscarinic and nicotinic effects                                      | Vomiting, diarrhea, hypersecretion, bronchoconstriction, headache, weakness  | Cholinesterase levels/ Supportive care, atropine, pralidoxime   |
| n-methyl Carbamates           | Carbaryl, aldicarb, fenoxycarb, methomyl, bendiocarb                        | Reversibly inhibits acetylcholinesterase resulting in muscarinic and nicotinic effects  | Vomiting, diarrhea, hypersecretion, bronchoconstriction, headache, weakness  | Cholinesterase levels/ Supportive care, atropine  |
| Pyrethrins                    | Pyrethrum   | Neuronal paralysis, sensitization   | Allergic reactions, anaphylaxis. Tremor, ataxia at very high doses   | No diagnostic test/ Treat allergic reactions with antihistamines or steroids, as needed   |
| Pyrethroids Type I            | Allethrin, permethrin, tetramethrin   | Interference with sodium channel in neuronal cell membranes — repetitive neuronal discharge                                   | Dizziness, irritability to sound or touch, headache, vomiting, diarrhea  | No diagnostic test/ Decontamination, supportive care, symptomatic treatment   |
| Type II (cyano-pyrethroids)   | Deltamethrin, cypermethrin, fenvalerate                                     | Interference with sodium channel and inhibition of gamma-aminobutyric acid (GABA)   | Seizures, dizziness, irritability to sound or touch, headache, vomiting, diarrhea                                    | Note: Skin contact may cause highly unpleasant, temporary paresthesias, best treated with Vitamin E oil preparations                                |
| Organochlorines               | Lindane, endosulfan, dicofol, methoxychlor                                  | Blockade of chloride channel in the GABA receptor complex   | Incoordination, tremors, paresthesia, hyperesthesia, headache, dizziness, nausea, seizures                           | Detectable in blood/ Decontamination, supportive care, cholestyramine to clear enterohepatic recirculation  |
| Chlorophenoxy compounds       | 2,4-Dichlorophenoxyacetic acid (2,4-D), 2,4-DB, 2,4-DP                      | Peripheral neuropathy, myopathy, metabolic acidosis, skin and mucus membrane irritant, uncoupler of oxidative phosphorylation | Nausea and vomiting, headache, confusion, myotonia, low fever, acidosis, EKG changes, CPK elevation, myoglobinuria   | Detectable in urine and blood/ Decontamination, hydration, forced alkaline diuresis   |
| Dipyridyl compounds           | Paraquat, diquat  | Oxidative, free radical formation, lipid peroxidation, selective damage to pneumocytes  | Pain, diarrhea, headache, myalgias, acute tubular necrosis, delayed pulmonary edema. Neurologic toxicity from diquat | Urine dithionite test (colorimetric), detectable in urine and blood/ Decontamination, do not administer oxygen, aggressive hydration, hemoperfusion |
| Anticoagulant Rodenticides    | Warfarin, brodifacoum, difenacoum, coumatchlor, bromadiolone                | Antagonize vitamin K, inhibition of clotting factors  | Nosebleeds, hematuria, melena, ecchymoses  | Elevated PT and INR/ Vitamin K administration   |
| Chlorophenols                 | Pentachlorophenol (PCP, Penta)  | Uncouples oxidative phosphorylation, skin and mucus membrane irritant   | Fever, tremor, thirst, sweating, tachycardia, hypercapnia, chest constriction, abdominal pain                        | Detectable in blood and urine/ Decontamination, supportive care, control hyperthermia   |
| Nitrophenols and Nitroacetals | Dinocap   | Uncoupler of oxidative phosphorylation  | Hyperthermia, tachycardia, anxiety, confusion, headache, diaphoresis   | Detectable in serum, bright yellow staining of skin and urine/ Supportive care, control hyperthermia  |
| Fumigants                     | Methyl bromide  | Irritant, inhibits sulfhydryl enzymes and reversibly breaks down ATP  | Headache, ataxia, tremor, agitation, visual disturbances, vomiting, seizures, pulmonary edema                        | Blood or urine bromide levels/ Supportive care, benzodiazepines, dimercaprol  |
| Fumigants                     | Metan sodium  | Decomposes in water to methyl isothiocyanate, severely irritant gas   | Mucus membrane irritation, pulmonary edema   | No diagnostic test/ Supportive care   |

Source: J.R. Reigart and J.R. Roberts, *Recognition and Management of Pesticide Poisoning*, Fifth Ed. U.S. Environmental Protection Agency, EPA 735-R-98-003, 1999. Online at <http://www.epa.gov/pesticides/safety/healthcare>

## Chapter 2 Notes

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- 22 See note 8 above.

## Developmental Abnormalities: Growth Retardation and Spontaneous Abortion

- A study of over eight hundred couples undergoing *in-vitro* fertilization revealed that men moderately or highly exposed to pesticides at work had significantly decreased fertilization rates compared with unexposed males, with only one-third the likelihood of successful *in-vitro* fertilization. These effects persisted after adjustment for all other known exposures, including smoking, alcohol, caffeine, and other chemical use.<sup>16</sup>
- Wives of male fruit growers in the Netherlands have shown an increased time-to-pregnancy, particularly during the spring and summer growing season when pesticides are applied. During that season, time-to-pregnancy more than doubled. Twenty-eight percent of farm couples sought medical attention for infertility, compared with only 8% in the control (unexposed) population.<sup>17</sup>
- Increased time-to-pregnancy was also found to be significant in Canadian farm families. During periods when both husbands and wives applied pesticides, fecundability dropped to between 50% and 80% of expected, whereas when only the husband or neither partner applied, fecundability was within normal ranges. There was no clear link to particular pesticides or pesticide classes.<sup>18</sup>
- Numerous studies report an increased rate of spontaneous abortions and stillbirths among female agricultural workers. These studies are limited by potential recall bias, and by difficulties in exposure assessment since workers are exposed to a complex mixture of chemicals and doses are unknown. Some studies of wives of agricultural workers also show an increased risk of spontaneous abortion and stillbirth.<sup>19,20,21,22,23,24</sup>
- A California study demonstrated an association between pesticide exposure at work or in the home and stillbirths, particularly those with congenital anomalies. Elevated risks ranged from a 70% increased risk of stillbirth for home exposure to pesticides, to a 240% increased risk for occupational exposure.<sup>25</sup>
- Higher levels of organochlorine pesticides have been found in abortuses and pre-term infants than in full-term babies.<sup>26</sup>
- Women living in communities supplied with drinking water contaminated by a variety of herbicides, including atrazine, cyanazine, and metolachlor, had an 80% increased risk of intra-uterine growth retardation compared with similar communities with uncontaminated water.<sup>27</sup>
- Teachers working in day care centers in Germany where wood was treated with the pesticides and wood preservatives pentachlorophenol and lindane were significantly more likely to give birth to lower birthweight and smaller size infants. These preservatives are known to volatilize off wood for years and become entrained in air or dust particles.<sup>28</sup>

## Pesticides and Birth Defects

Numerous epidemiological studies and case reports associate pesticide exposure at work or home with increased risk of various types of congenital malformations.<sup>29</sup>

Particular birth defects associated with pesticides include

- Cleft lip and palate—a doubling of risk with exposure during the first trimester.<sup>30,31,32</sup>
- Limb defects—a 3–4-fold increased risk for garden or workplace exposure, and greater than doubling of risk with household exposure, particularly if pesticides were applied by a professional pest eradication service.<sup>33,34,35,36</sup>
- Cardiovascular malformations, particularly Total Anomalous Pulmonary Venous Return—a 2–3-fold greater risk found in the Baltimore-Washington Infant Study.<sup>37</sup>
- Spina bifida and hydrocephaly—a 2.7- and 3.5-fold increased risk respectively in one study, and a 50% increased risk with residence within a quarter-mile of an agricultural field in another.<sup>38,39</sup>

- Cryptorchidism and hypospadias—2–3-fold greater rates of orchidopexy in highly agricultural areas; a 50% increase in hypospadias also reported.<sup>40,41</sup>
- A California study using the state birth defects monitoring program found that infants with limb reduction defects along with other anomalies were 60% more likely to have parents involved in agricultural work and 2.4 times more likely to live in an agricultural county compared with unafflicted infants.<sup>42</sup>
- One Minnesota study of pesticide applicators revealed that their children were at higher risk of a variety of birth defects, including circulatory/respiratory anomalies, and urogenital, musculoskeletal, and integumental defects. These same trends and birth defects, although less marked, were paralleled among the general population in heavily agricultural regions of the state. Defects were most significantly associated with use of

**Table 7-1. Developmental and Reproductive Toxins**

| Chemical Name                       | Chemical Use                               | Developmental Toxin | Female Repro. Toxin | Male Repro. Toxin |
|-------------------------------------|--|---------------------|---------------------|-------------------|
| 1080                                | Rodenticide                                |                     |                     | Y                 |
| 2,4-Db acid                         | Herbicide                                  | Y                   |                     | Y                 |
| Amitraz                             | Insecticide                                | Y                   |                     |                   |
| Arsenic acid                        | Herbicide                                  | Y                   |                     |                   |
| Arsenic pentoxide                   | Multiple uses, insecticide, wood treatment | Y                   |                     |                   |
| Arsenic trioxide                    | Rodenticide                                | Y                   |                     |                   |
| Benomyl                             | Fungicide                                  | Y                   |                     |                   |
| Bromacil, Lithium salt              | Herbicide                                  | Y                   |                     | Y                 |
| Bromoxynil octanoate                | Herbicide                                  | Y                   |                     |                   |
| Chlorsulfuron                       | Herbicide                                  | Y                   | Y                   | Y                 |
| Cyanazine                           | Herbicide                                  | Y                   |                     |                   |
| Cycloate                            | Herbicide                                  | Y                   |                     |                   |
| Diclofop-methyl                     | Herbicide                                  | Y                   |                     |                   |
| Disodium cyanodithioimido carbonate | Microbiocide                               | Y                   |                     |                   |
| Eptc                                | Herbicide                                  | Y                   |                     |                   |
| Ethylene oxide                      | Fumigant                                   |                     | Y                   |                   |
| Fenoxaprop ethyl                    | Herbicide                                  | Y                   |                     |                   |
| Fluazifop-butyl                     | Herbicide                                  | Y                   |                     |                   |
| Hydramethylnon                      | Insecticide                                | Y                   |                     | Y                 |
| Linuron                             | Herbicide                                  | Y                   |                     |                   |
| Metam-sodium                        | Fumigant                                   | Y                   |                     |                   |
| Methyl bromide                      | Fumigant                                   | Y                   |                     |                   |
| Metiram                             | Fungicide                                  | Y                   |                     |                   |
| Myclobutanil                        | Fungicide                                  | Y                   |                     | Y                 |
| Nabam                               | Fungicide                                  | Y                   |                     |                   |
| Nicotine                            | Insecticide                                | Y                   |                     |                   |
| Nitrapyrin                          | Microbiocide                               | Y                   |                     |                   |
| Oxadiazon                           | Herbicide                                  | Y                   |                     |                   |
| Oxydemeton-methyl                   | Insecticide                                |                     | Y                   | Y                 |
| Oxythioquinox                       | Insecticide, fungicide, fumigant           | Y                   |                     |                   |
| Potassium dimethyl dithio carbamate | Microbiocide                               | Y                   |                     |                   |
| Propargite                          | Insecticide                                | Y                   |                     |                   |
| Resmethrin                          | Insecticide                                | Y                   |                     |                   |
| Sodium dimethyl dithio carbamate    | Microbiocide                               | Y                   |                     |                   |
| Streptomycin sulfate                | Fungicide                                  | Y                   |                     |                   |
| Tau-fluvalinate                     | Insecticide                                | Y                   |                     |                   |
| Thiophanate-methyl                  | Fungicide                                  |                     | Y                   | Y                 |
| Triadimefon                         | Fungicide                                  | Y                   | Y                   | Y                 |
| Tributyltin methacrylate            | Antifoulant, microbiocide                  | Y                   |                     |                   |
| Triforine                           | Fungicide                                  | Y                   |                     |                   |
| Vinclozolin                         | Fungicide                                  | Y                   |                     |                   |
| Warfarin                            | Rodenticide                                | Y                   |                     |                   |

Source: Proposition 65 List of Chemicals Known to the State of California to Cause Cancer and Reproductive Harm (Sacramento: California Office of Environmental Health Hazard Assessment, 29 December 1999), United States Environmental Protection Agency Toxic Release Inventory database.



## Disruption of Hormone Function

2,4-D and various fungicides. Risks for children of both pesticide applicators and the general public in the agricultural region were greatest among those conceived in the spring, a time of greater pesticide use.<sup>43</sup>

- Communities in Iowa with elevated levels of the herbicide atrazine in their drinking water showed a 2–3-fold increase in all birth defects—specifically, a 3-fold increase in cardiac defects, a 3–4-fold increase in urogenital defects, and a nearly 7-fold increase in limb reduction defects.<sup>44</sup>
- Numerous case reports and case series present various combined severe congenital anomalies following occupational or accidental exposure of pregnant women to pesticides.<sup>45,46,47</sup>
- Many pesticides are reported to cause birth defects in animals. Pesticides listed as reproductive or developmental toxicants by the State of California or by U.S. EPA are listed in Table 7-1.

Various pesticides mimic estrogen, while others block androgens or thyroid hormone.<sup>48</sup>

- Estrogenic pesticides that have been studied in some detail include numerous banned and still used organochlorine pesticides, such as DDT, chlordecone, dicofol, methoxychlor, endosulfan, and lindane.<sup>49</sup> Fungicides such as vinclozolin and iprodione are anti-androgens.<sup>50</sup> In addition, some triazine herbicides such as atrazine interfere with estrogen via indirect pathways.<sup>51</sup>

**Table 7-2: Endocrine-Disrupting Pesticides**

| Chemical Name            | Chemical Use              |
|--------------------------|---------------------------|
| Alachlor                 | Herbicide                 |
| Aldicarb                 | Insecticide               |
| Atrazine                 | Herbicide                 |
| Benomyl                  | Fungicide                 |
| Carbaryl                 | Insecticide               |
| Chlorpyrifos             | Insecticide               |
| Cyanazine                | Herbicide                 |
| Endosulfan               | Insecticide               |
| Lindane                  | Insecticide               |
| Malathion                | Insecticide               |
| Mancozeb                 | Fungicide                 |
| Maneb                    | Fungicide                 |
| Methomyl                 | Insecticide               |
| Methyl parathion         | Insecticide               |
| Metiram                  | Fungicide                 |
| Metolachlor              | Herbicide                 |
| PCNB                     | Fungicide                 |
| PCP                      | Wood preservative         |
| Pyrethrins               | Insecticide               |
| Resmethrin               | Insecticide               |
| Simazine                 | Herbicide                 |
| Tributyltin methacrylate | Antifoulant, Microbiocide |
| Tributyltin oxide        | Antifoulant, Microbiocide |
| Vinclozolin              | Fungicide                 |

Sources: L. Keith, *Environmental endocrine disruptors* (New York: Wiley Interscience, 1997); J. Liebman, *Rising toxic tide* (San Francisco: Pesticide Action Network/Californians for Pesticide Reform, 1997); Illinois EPA, *Report on endocrine disrupting chemicals* (Illinois EPA, 1997); T. Colborn, D. Dumanoski, and J.R. Myers, *Our stolen future* (New York: Penguin Books, 1996), 253; C.M. Benbrook, *Growing doubt: A primer on pesticides identified as endocrine disruptors and/or reproductive toxicants* (The National Campaign for Pesticide Policy Reform, September 1996).

- Pentachlorophenol (PCP), a pesticidal wood preservative, binds to human transthyretin and may directly reduce uptake of thyroxine (T4) into the brain.<sup>52,53</sup> Other currently used pesticides, including dicofol and bromoxynil, have similar effects on thyroxine binding, as does dinoseb, now banned.<sup>54</sup>
- Health effects of endocrine disrupting pesticides in animals include altered circulating hormone levels, hypospadias, nipple development in males, cryptorchidism, decreased semen quality, altered time to sexual maturity, and abnormal behavior.<sup>55,56,57</sup>
- Male pesticide factory workers in China exposed to the organophosphate pesticides ethyl parathion and methamidophos had significant abnormalities in their reproductive hormone profiles. Increased pesticide exposure correlated positively with serum LH and FSH levels, and negatively with serum testosterone. In addition, workers with higher exposure tended to show greater risk of abnormal semen parameters.<sup>58</sup>
- Workers applying ethylene bisdithiocarbamate fungicides (such as Maneb or Zineb) in Mexico developed elevated levels of TSH without changes in thyroid hormone levels. Although findings were subclinical in these healthy adult males, they could be relevant to a developing fetus were a pregnant woman exposed.<sup>59</sup>
- In the fetus or neonate, disruption of endocrine homeostasis can result in permanent alterations in sexual development, whereas disturbance in adulthood is less likely to create lasting health effects.<sup>60</sup>

## Chapter 7 Notes

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# 8 Effects of Pesticides on the Immune System

*A family comes into a local clinic because the state health department recently informed them of pesticide contamination in the well water in their small town. They want to know whether their children's persistent respiratory infections and skin rashes might be associated with the water contamination problem. They are particularly concerned about immune problems and want to have their immune functions tested. They also want to know whether switching to bottled water is sufficient to protect them.*

## Overview

There is limited evidence that exposure to certain pesticides may compromise the immune system. Findings are based primarily on animal studies that demonstrate damage to immune organs, suppression of immune-mediating cells, and increased susceptibility to infectious disease.<sup>1,2,3,4,5,6</sup>

The intrinsic variability of immune parameters between and within individuals makes study of the effects of environmental or occupational exposure on human immune function extremely difficult.

Pesticide exposure has been associated with

- Hypersensitivity reactions ranging from dermatitis to asthma or anaphylaxis.
- Suppression of immune function and consequent susceptibility to infectious pathogens.
- Autoimmune responses.
- Cancers of immune cell lines (*see Section 2. Pesticides and Cancer*).
- Some pesticides may cause immediate hypersensitivity symptoms such as rhinitis, asthma, or anaphylaxis.<sup>7,8</sup> Pesticides reported to cause hypersensitivity reactions in humans include atrazine, parathion, dichlorvos, captafol, folpet, captan, naled, maneb, zineb, dithianone, and dinitrochlorobenzene.<sup>9,10</sup>
- Adults occupationally exposed to organophosphate or organochlorine pesticides were found to have increased frequency and severity of respiratory infections such as tonsillitis, pharyngitis, and bronchitis. These workers also showed diminished neutrophil response—related to duration of exposure to pesticides—including impaired phagocytosis, respiratory burst, and adhesion.<sup>11,12</sup>
- In humans, one now—banned organochlorine pesticide, chlordane, was associated with abnormal T-cell and B-cell subsets, decreased proliferation response to mitogen, and suppressed antibody-dependent cell cytotoxicity. These findings were statistically significant among people whose homes were sprayed with this pesticide for termite control.<sup>13</sup>
- A study of Nebraska farmers showed slight but significant reductions in serum complement activity in the most highly pesticide-exposed group. No consistent differences in total leukocyte count, mitogen-stimulation of T-cell or B-cell proliferation, or serum IgG and IgM concentration among the groups were detected.<sup>14</sup>
- Women who consumed aldicarb contaminated groundwater in a potato farming area had significantly decreased CD8 cell subsets when compared with women drinking uncontaminated groundwater.<sup>15</sup>
- The environmentally persistent wood preservative pentachlorophenol (PCP) is consistently associated with a range of abnormal immune parameters, from increased levels of serum IgM and increased immature leukocytes to greater incidence of infection and

## Allergic Responses

## Immune Suppression

## Chapter 8 Notes

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# 9

## Pesticide Laws and Regulations

### Overview

Pesticides are regulated at both the state and federal levels. These regulatory systems designate a process for determining the health and environmental impacts of pesticides before they can be registered in the United States and California, and provide guidance for pesticide use and disposal. Registration does not necessarily mean the material is safe. In fact, a series of state and federal laws and guidelines prohibit claims such as "safe," "non-poisonous," "non-injurious," "harmless," or "nontoxic to humans and pets" on pesticide labels and in advertisements.<sup>1</sup>

Regulations at both the federal and state levels of government allow use of dangerous pesticides; they attempt to reduce the potential for significant human and environmental harm by mitigating exposure and assessing risk of use. Exposure, however, is very difficult to measure and risk-assessment procedures have severe limitations. Ongoing federal and state efforts to reassess pesticide registrations may find some pesticides currently in use too harmful to human health and the environment for continued use. In April 2000, for example, U.S. EPA proposed drastic curtailment of chlorpyrifos use in homes, schools, daycare centers, and other non-agricultural sectors, as well as some agricultural uses.

"Risk assessment" does not take into account a number of critical factors that make for a high degree of uncertainty. For example, California permits the use of hazardous pesticides on the basis of a risk assessment methodology that does not generally take into account the following crucial measures of harm: 1) subtle and delayed toxicity, 2) interactive effects resulting from mixing pesticides, 3) unique risks to children, and 4) multiple exposures to the same chemical in food, water, and air.

While there is significant regulation of pesticides in California, there is cause for concern. Many dangerous pesticides remain registered for legal use in California. As of 1998, the State of California was permitting the use of 40 pesticides known by the state to cause cancer,<sup>2</sup> 43 known to cause reproductive and developmental harm,<sup>3</sup> and 17 identified as known groundwater contaminants.<sup>4</sup> More than 215 million pounds of pesticide active ingredient were reported used in California in 1998, nearly 30% of which is on federal and state lists of hazardous materials.<sup>5</sup>

### Federal Law

On the federal level, the primary law regulating pesticides is the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). This act requires pesticide manufacturers to register pesticides by first submitting results from toxicity testing. U.S. EPA then balances the projected health impacts of pesticide use with the economic benefits of use. Many dangerous pesticides registered prior to implementation of FIFRA remain on the market even as they undergo re-registration evaluation.

### State Law

Any pesticide for sale or use in California must also be registered by the State. The state Department of Pesticide Regulation (DPR) is empowered to restrict the use or cancel the registration of pesticides found to cause "significant adverse health effects." Unlike federal practices, DPR does not employ a cost-benefit analysis. However, DPR has cancelled very few applications, despite the fact that many pesticides currently in use are known to cause harm to human health and the environment.

## **Additional State and Federal Regulations**

### **The California Birth Defects Prevention Act**

### **California Toxic Air Contaminant (TAC) Program**

### **Regulation of Pesticides in Water**

### **Farmworker Pesticide Regulations**

### **The Federal Food Quality Protection Act**

In addition to registration requirements, several laws regulate pesticide use. The California legislature enacted the California Birth Defects Prevention Act in 1984 with the purpose of preventing pesticide-induced abortions, birth defects, and infertility. Mandatory health effect studies are required to determine a pesticide's chronic toxicity, mutagenicity, neurotoxicity, oncogenicity, and teratogenicity. These studies are required for registration and licensing of a pesticide in California. The law requires the Director of DPR to take cancellation or suspension action against products containing an active ingredient with significant adverse health effects, including reproductive abnormalities, birth defects, or infertility.<sup>6</sup> DPR has only taken cancellation action against one pesticide under this law—DDVP. However, use of reproductive and developmental toxicant pesticides increased from 25.8 to 31.0 million pounds, an increase of 20%, from 1991 to 1998.<sup>7</sup>

The California Toxic Air Contaminant Program (TAC), created in 1983 and 1984, mandates DPR to nominate potentially harmful pesticides for inclusion on an official list of "toxic air contaminants" and to regulate them to the point "at which no significant adverse health effects are anticipated." However, among 57 pesticides identified as possible TAC chemicals, DPR has completed the TAC process for only two pesticides through 1999. One of those chemicals, ethyl parathion, was banned only after it was first deregistered by U.S. EPA.<sup>8</sup>

Pesticides have been detected in water serving 16.5 million people in 46 California counties over the past ten years.<sup>9</sup> Many of these pesticides in drinking water are at levels that may impact public health. The Pesticide Contamination and Prevention Act (1985) requires DPR to maintain a statewide database of wells sampled for pesticides and to report annually on detections and follow-up actions. This activity was intended to prevent pesticides from migrating to groundwater, but DPR has not implemented an adequate groundwater protection program. Two pesticides, DBCP and EDB, have repeatedly been detected throughout the state at concentrations higher than state safety levels. Many others are found at levels believed to pose significant health risk, but below the maximum allowed by law. In addition, numerous pesticides have not been officially assessed for their health risk in drinking water.<sup>10</sup> Both DPR and California Department of Health Services have regulatory responsibilities under this law.

From 1991 to 1996, DPR reported 3991 cases of occupational poisoning by agricultural pesticides, an annual average of 665.<sup>11</sup> Pesticide exposure incidents are under-reported because many farmworkers fear incurring medical bills and employer retaliation and/or do not recognize their illness as related to pesticide encounters.<sup>12</sup> The two most common sources of exposure leading to illness are pesticide drift from nearby applications and pesticide residues remaining in the field after application.<sup>13</sup>

Unfortunately, regulations that prohibit workers from re-entering fields before residues have dissipated and state rules that mandate protective clothing are often not observed in real-world situations.<sup>14</sup> Protection measures are frequently ignored and enforcement of pesticide law is virtually non-existent. Counties reporting the highest rates of pesticide use and, correspondingly, the greatest number of reported pesticide illnesses also account for the lowest number of fines for pesticide violations.<sup>15</sup> When fines are issued, they are generally very low: less than 5% of fines statewide exceed \$1,000.<sup>16</sup>

In 1996, Congress passed the Food Quality Protection Act (FQPA), which altered regulations governing pesticide residues on food. FQPA currently requires EPA to assess cumulative effects from multiple exposures to a particular pesticide or to similarly acting pesticides. Risk is calculated by combining cumulative exposure from all sources. Food, water, occupational, and residential "pathways" are considered, and children have significant additional protective standards. In addition, provisions require that EPA design tests to detect endocrine disrupting effects. Over the past six years overall implementation of the

law has become increasingly politicized, leading to concern that its benefits could be indefinitely delayed.

Many state and federal laws and regulations managing pesticides do not adequately protect public health. Existing statutes *a priori* assume that dangerous pesticides can be managed with negligible impact on health. However, such faith appears unfounded, given current acute and chronic pesticide-illness data, continued increase in use of many hazardous pesticides, and persistence of these toxins in air and water.

Widespread pesticide use and consequent health effects will likely remain until a precautionary approach to pesticide use is utilized widely and existing laws are enforced. The challenge to medicine is to reduce health risks by identifying the wide variety of pesticide-related diseases and by improving diagnostic and therapeutic strategies for acute and chronic pesticide poisoning. Just as important, health professionals can add their voices to the growing number of scientists and doctors who advocate a precautionary approach to achieve the goal of reducing negative health impacts of pesticide use. (See Section 1: Introduction, for more on the Precautionary Principle.)

## Chapter 9 Notes

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# 10

## General Sources of Information

Books, articles

## Government Sources of Information

# Resources

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EPA. March 1999. *Recognition and Management of Pesticide Poisonings*. 735-3-984823. 9th ed. Clinical descriptions of acute pesticide intoxication symptoms and treatment approaches. Free by contacting 703-305-7666 or <http://www.epa.gov/pesticides/safety/healthcare>.

American Academy of Pediatrics. 1999. *Committee on Environmental Health: Handbook of Pediatric Environmental Health*. Also known as *The Green Book*, a comprehensive guide for clinicians on children's environmental health. Order from <http://www.aap.org/pubserv>.

### California Department of Pesticide Regulation

Information on the status of pest management, pesticide use, and related health and environmental hazards in California.

830 K Street

Sacramento, CA 95814

Ph: 916-445-4000

Web: [www.cdpr.ca.gov](http://www.cdpr.ca.gov)

#### Worker Health and Safety Branch

<http://www.cdpr.ca.gov/docs/whs/services/whsmenu.htm>

### EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS)

Office of Pesticide Programs

Aerial Rios Building

1200 Pennsylvania Avenue NW

Washington, DC 20460

Ph: 202-260-2902

#### Pesticide program

Web: [www.epa.gov/pesticides](http://www.epa.gov/pesticides)

#### Pesticides and food

Web: [www.epa.gov/pesticides/food/](http://www.epa.gov/pesticides/food/)

### Integrated Risk Information System (IRIS)

Electronic database maintained by EPA on human health effects that may result from exposure to various chemicals in the environment. Hazard identification and dose-response assessment information.

Web: [www.epa.gov/ngispgm3/iris](http://www.epa.gov/ngispgm3/iris)

### California Office of Environmental Health Hazard Assessment

Pesticide and Environmental Toxicology Section (PETS)

1515 Clay Street, 16th Floor

Oakland, CA 94612

Ph: 510-622-3200

Web: [www.oehha.org/pesticides/programs/services.html](http://www.oehha.org/pesticides/programs/services.html)

### California Department of Health Services

#### Occupational Health Branch

The Occupational Health Branch is in the Division of Environmental and Occupational Disease Control, California Department of Health Services, located in Oakland, California. It is responsible for surveillance, evaluation, and public education about occupational disease and injury among California workers. Programs include

- Hazard Evaluation System and Information Service (HESIS)
- SHARPS Injury Control Program (SHARPS)

## Pesticide Organizations and Information

- Occupational Lead Poisoning Prevention Program (OLPPP)
- Occupational Health Surveillance and Evaluation Program (OHSEP)
- Agricultural Injury and Illness Prevention Program

1515 Clay Street, Suite 1901  
Oakland, CA 94612  
Ph: 510-622-4300 or 510-622-4328 for free publications  
Fx: 510-622-4310  
Web: [www.ohb.org/OHB.HTM](http://www.ohb.org/OHB.HTM)

### **National Pesticide Telecommunications Network (NPTN)**

Based at Oregon State University, NPTN is cooperatively sponsored by the university and U.S. EPA. It serves as source of objective, science-based pesticide information on a wide range of pesticide-related topics—for example, recognition and management of pesticide poisonings, safety information, health and environmental effects, referrals for investigation of pesticide incidents, and emergency treatment for both humans and animals.  
Hotline: 800-858-7378, 6:30 a.m. to 4:30 p.m. daily except holidays  
Email: [nptn@ace.orst.edu](mailto:nptn@ace.orst.edu)  
Web: [ace.orst.edu/info/nptn/](http://ace.orst.edu/info/nptn/)

### **Physicians for Social Responsibility (PSR)**

PSR is a national organization of over 18,000 health care professionals founded in 1961. PSR works to address the public health effects of weapons of mass destruction, environmental degradation and community violence. With its international affiliate, International Physicians for the Prevention of Nuclear War, PSR received the 1985 Nobel Peace Prize for its efforts to eliminate nuclear weapons. The Greater San Francisco Bay Area and Los Angeles Chapters work to educate the medical community and the public about the linkages between environmental toxic exposures and human health. PSR also works to encourage health professionals to participate in creating a sustainable and healthy environment. Members provide technical assistance and information on human health and environmental issues to citizens groups, health care providers, educational institutions, and public policy makers.

#### **PSR-LA**

1316 Third Street Promenade, #B-1  
Santa Monica, CA 90401  
Ph: 310-458-2694  
Fx: 310-458-7925  
Email: [psrsm@psr.org](mailto:psrsm@psr.org)  
Web: [www.labridge.com/PSR](http://www.labridge.com/PSR)

#### **PSR-Greater Bay Area**

2288 Fulton Street, Suite 307  
Berkeley, CA 94704-1449  
Ph: 415-845-8395  
Fx: 415-845-8476  
Email: [info@SFbaypsr.org](mailto:info@SFbaypsr.org)

### **Californians for Pesticide Reform (CPR)**

A coalition of more than 140 public health, consumer, sustainable agriculture, labor, rural assistance, and public interest organizations, CPR's goals are to protect public health and the environment from dangerous pesticides. CPR works to eliminate use of the most toxic pesticides, reduce total pesticide use, promote safer, ecologically sound pest-management in agriculture and other settings, and expand the public's right-to-know.  
49 Powell Street, Suite 530  
San Francisco, CA 94102  
Ph: 415-981-3939 or 888-CPR-4880 in California  
Email: [pests@igc.org](mailto:pests@igc.org)  
Web: [www.igc.org/cpr](http://www.igc.org/cpr)

**Pesticide Action Network North America (PANNA)**

PANNA has campaigned to replace pesticides with ecologically sound alternatives since 1982. It has a comprehensive database on pesticides accessible on the web that includes information for each pesticide on ingredients, health effects, regulatory status, environmental impacts, and more. PANNA also publishes a pesticides and health research update three times per year. In addition, it links more than 100 affiliated health, consumer, labor, environmental, progressive agriculture, and public interest groups in Canada, Mexico, and the U.S. with thousands of supporters worldwide to promote healthier, more effective pest management through research, policy development, education, media, demonstrations of alternatives, and international advocacy campaigns.

49 Powell Street, Suite 500

San Francisco, CA 94102

Ph: 415-981-1771

Email: [panna@panna.org](mailto:panna@panna.org)

Web: [www.panna.org](http://www.panna.org)

**Beyond Pesticides/National Coalition Against the Misuse of Pesticides (NCAMP)**

In 1981 Beyond Pesticides/NCAMP formed to serve as a national network of organizations committed to pesticide safety and adoption of alternative pest management strategies that reduce or eliminate dependency on toxic chemicals.

701 E Street SE, Suite 200

Washington, DC 20003

Ph: 202-543-5451

Web: [www.ncamp.org](http://www.ncamp.org)

**Pesticide Watch and the Pesticide Watch Education Fund**

Providing California communities the tools they need to protect themselves and the environment from the hazards of pesticides, Pesticide Watch Education Fund assists community groups and activists by offering information, organizing assistance, networking, and lobbying assistance.

450 Geary Street, Suite 500

San Francisco, CA 94102

Ph: 415-292-1486

Email: [info@pesticidewatch.org](mailto:info@pesticidewatch.org)

Web: [www.pesticidewatch.org/](http://www.pesticidewatch.org/)

**Environmental Working Group (EWG)**

A leading content provider for public interest groups and concerned citizens campaigning to protect the environment, EWG offers reports, articles, technical assistance, and development of computer databases and internet resources.

1904 Franklin Street, Suite 515

Oakland, CA 94612

Ph: 510-444-0973

Web: [www.ewg.org](http://www.ewg.org)

**Northwest Coalition for Alternatives to Pesticides (NCAP)**

NCAP provides assistance in developing model policies to protect our groundwater, food supply, and forest watersheds from pesticide contamination. They also offer information on hundreds of pesticides and alternatives for many pest problems, and updates on citizen reform efforts and policy initiatives from across North America through the *Journal of Pesticide Reform*.

PO Box 1393

Eugene, OR 97440

Ph: 541-344-5044

Email: [info@pesticide.org](mailto:info@pesticide.org)

Web: [www.pesticide.org](http://www.pesticide.org)

## Reporting a Pesticide Poisoning

### **California Public Interest Research Group (CALPIRG)**

CALPIRG is a non-profit, non-partisan research and advocacy organization acting on behalf of consumers and the environment. They work for a clean and healthy environment, preservation of natural resources, strong protections for consumers, and government accountability. Recent campaigns have included reforming school pesticide use and ending pesticide contamination of drinking water.

450 Geary Street, Suite 500  
San Francisco, CA 94102  
Ph: 415-292-1487  
Web: [www.pirg.org/calpirg](http://www.pirg.org/calpirg)

### **Pesticide Education Center (PEC)**

Founded in 1988 to educate workers and the public about hazards and health effects of pesticides, PEC makes presentations, develops curricular materials, and provides other services targeted to the needs of average citizens and workers concerned about pesticide exposure throughout the country.

PO Box 420870  
San Francisco, CA 94142  
Ph: 415-391-8511  
Web: [www.igc.apc.org/pesticides](http://www.igc.apc.org/pesticides)

### **National Agricultural Health and Safety Center**

#### **University of California Agricultural Health and Safety Center**

One of eight centers throughout the US that involve clinicians and other health specialists in the area of pesticide-related illness and injury.

Old Davis Road  
University of California  
Davis, CA 95616  
Ph: 916-752-4050

### **Enviro Health Information Clearinghouse**

Sponsored by Information Ventures, Inc., to provide substantive information and key documents on a variety of environmental health issues.

100 Capitola Drive, Suite 108  
Durham, NC 27713  
Ph: 800-643-4794  
Web: [infoventures.com/e-hlth](http://infoventures.com/e-hlth)

### **CALIFORNIA CODES: HEALTH AND SAFETY CODE (Section 105200)**

Any physician or surgeon who knows, or has reasonable cause to believe, that a patient is suffering from pesticide poisoning or any disease or condition caused by a pesticide shall promptly report that fact to the local health officer by telephone within 24 hours. The reporting requirement includes all types of pesticide cases: skin and eye injuries, systemic poisonings, suicides, homicides, home cases, and occupational cases. Failure to comply with the reporting requirement renders the physician liable for a civil penalty of \$250.00.

Pesticides include any substance or mixture of substances intended for defoliating plants, regulating plant growth, or preventing, destroying, or mitigating any pest. Pesticides include sanitizers and disinfectants.

A case seen as a pesticide poisoning, or suspected as a pesticide poisoning, may not be categorized as "first-aid" and must be reported.

For occupational cases, there is the additional requirement to send a copy of the "Doctor's First Report of Occupational Injury or Illness" (DFR) to the local health officer within seven days and also to send the DFR to the State Department of Industrial Relations.

**Clinics offering  
diagnosis and  
treatment for  
exposures to  
pesticides**

The Pesticide Illness Report form or Doctor's First Report of Occupational Injury or Illness form are available from the Office of Environmental Health Hazard Assessment, PETS  
1515 Clay Street, 16th Floor  
Oakland, CA 94512  
Ph: 510-622-3170  
Fx: 510-622-3218

For more information on the pursuant health and safety codes call OEHHA at the number above or see <http://www.legend.ca.gov/calaw.html>.

**Occupational and Environmental Health Clinic  
University of California at Davis**

IIEH  
Davis, CA 95616  
Ph: 916-734-5620  
Ph: 916-34-2715 (Clinic appointments)  
Fx: 916-752-3956

**Occupational and Environmental Clinic  
University of California, Irvine  
Center for Occupational and Environmental Health**

19722 MacArthur Blvd. Clinic  
Irvine, CA 92715  
Ph: 714-824-8641  
Fx: 714-824-2345

**Occupational and Environmental Medicine Clinic  
University of California at San Francisco/SFGH**

Building 30, 5th Floor, 1001 Potrero Avenue  
San Francisco, CA 94110  
Ph: 415-206-4320  
Fx: 415-206-8949

**UCSF Occupational Health Services  
University of California at San Francisco**

2186 Geary Boulevard, Suite 103  
San Francisco, CA 94115  
Ph: 415-885-7580  
Fx: 415-771-4472

**California Poison Control Center**

Ph: 800-876-4766 which is 1-800-8-POISON (in California)  
Web: [www.calpoison.org](http://www.calpoison.org)

# 11

## Detailed Interview for Occupational and Environmental Exposures

### Occupational Exposures

### Environmental Exposure History

### Symptoms and Medical Conditions

# Exposure History

- What is your occupation? (*If unemployed, go to next section*)
- How long have you been doing this job?
- Describe your work and what hazards you are exposed to (e.g., pesticides, solvents or other chemicals, dust, fumes, metals, fibers, radiation, biologic agents, noise, heat, cold, vibration)  
Under what circumstances do you use protective equipment? (e.g., work clothes, safety glasses, respirator, gloves, and hearing protection)
- Do you smoke or eat at the worksite?
- List previous jobs in chronological order, include full and part-time, temporary, second jobs  
Summer jobs, and military experience. (*Because this question can take a long time to answer, one option is to ask the patient to fill out a form with this question on it prior to the formal history taking by the clinician. Another option is to take a shorter history by asking the patient to list only the prior jobs that involved the agents of interest. For example, one could ask for all current and past jobs involving pesticide exposure.*)
- Are pesticides (e.g., bug or weed killers, flea and tick sprays, pet collars, powders, or shampoos) used in your home or garden or on your pet?
- If pesticides are used:
  - What is the name of the product(s) you use?
  - Do you contract with a service?
  - How often do you or your service apply pesticides?
  - Where do you apply the pesticides?
  - Are children allowed to play in areas treated with pesticides? How soon after the application
  - Where are the pesticides stored?
- Do you purchase mainly conventionally grown or organic food?
- Do you or any household member have a hobby with exposure to any hazardous materials (e.g., pesticides, paints, ceramics, solvents, metals, glues)?
- Did you ever live near a facility that could have contaminated the surrounding area (e.g., mine, plant, smelter, dump site)?
- Have you ever changed your residence because of a health problem?
- Does your drinking water come from a private well, city water supply, and/or grocery store?
- Do you work on your car?
- Which of the following do you have in your home: ( air conditioner/purifier, central heating (gas or oil), gas stove, electric stove, fireplace, wood stove, or humidifier?
- Have you recently acquired new furniture or carpet, or remodeled your home?
- Have you weatherized your home recently?
- Approximately what year was your home built?

### *(If employed)*

- Does the timing of your symptoms have any relationship to your work hours?
- Has anyone else at work suffered the same or similar problems?
- Does the timing of your symptoms have any relationship to environmental activities listed above?
- Has any other household member or nearby neighbor suffered similar health problems?

**Non-occupational  
Exposures  
Potentially Related  
to Illness or Injury**

- Are there tobacco smokers/users in the home? If yes, who and in what forms (cigarettes, pipe, cigar, chewing tobacco)?
- What medications or drugs is the patient taking? (Include prescription and non-prescription uses)
- Has anyone in the family worked with hazardous materials that they might have brought home? (e.g. pesticides, asbestos, lead)? (If yes, inquire about household members potentially exposed.)

Source: J.R. Reigart and J.R. Roberts. Recognition and Management of Pesticide Poisonings, Fifth Edition. U.S. Environmental Protection Agency, EPA 735-R-98-003, 1999. Online at <http://www.epa.gov/pesticides/safety/healthcare>.

# Pesticides and Human Health

A Resource for Health Care Professionals



Physicians for Social Responsibility (PSR) is a national organization of over 18,000 health care professionals founded in 1961. PSR works to address the public health effects of weapons of mass destruction, environmental degradation, and community violence. With its international affiliate, International Physicians for the Prevention of Nuclear War, PSR received the 1985 Nobel Peace Prize for its efforts to eliminate nuclear weapons. The Greater San Francisco Bay Area and Los Angeles Chapters work to educate the medical community and the public about the linkages between environmental toxic exposures and human health. PSR also works to encourage health professionals to participate in creating a sustainable and healthy environment. Members provide technical assistance and information on human health and environmental issues to citizens groups, health care providers, educational institutions, and public policy makers.

PSR-LA  
1316 Third Street Promenade, #B-1  
Santa Monica, CA 90401  
ph 310.458.2694  
fx 310.458.7925  
email psrsm@psr.org

PSR-Greater Bay Area  
2288 Fulton Street, Suite 307  
Berkeley, CA 94704-1449  
ph 415.845.8395  
fx 415.845.8476  
email info@SFbaypsr.org



Californians for Pesticide Reform (CPR) is a coalition of over 140 public interest organizations committed to protecting public health and the environment from pesticide proliferation. CPR's mission is to:

- educate Californians about health and environmental risks posed by pesticides;
- eliminate the use of the most dangerous pesticides in California and reduce overall pesticide use;
- promote sustainable pest control solutions for our farms, communities, forests, homes and yards; and
- hold government agencies accountable for protecting public health and Californians' right to know about pesticide use and exposure.

For more information, contact CPR:  
49 Powell St., Suite 530  
San Francisco, CA 94102  
ph 415.981.3939 or in California, 888.CPR.4880  
fx 415.981.2727  
email pests@igc.org  
website [www.igc.org/cpr](http://www.igc.org/cpr)



# 3 Dermatologic Effects of Pesticide Exposure

*An agricultural worker comes in with a rash on her hands and arms. It appeared three days ago, the day after she went into some recently sprayed strawberry fields to pick fruit. She reports that many co-workers have similar rashes but have not sought medical attention: They fear losing their jobs if they report the problem. She does not know the name of the pesticide sprayed, but thinks it is used to control mold. She mentions that she is pregnant and wonders whether the chemical could harm her baby.*

## Overview

Many pesticides penetrate the skin and cause systemic exposure.<sup>1</sup> Acute illness and death have been reported from percutaneous absorption of pesticides, particularly through damaged skin.<sup>2</sup>

Dermatitis is the second most common occupational disease. Rates in the agricultural industry are the highest of any industrial sector.<sup>3</sup> In California, pesticide-related skin conditions represent between 15% and 25% of pesticide illness reports.<sup>4</sup>

Skin reactions can involve any skin area, including areas covered by clothing, particularly if the pesticide contacts the clothing and soaks through. However, exposed areas, such as arms, hands, face, and neck, are most commonly affected.<sup>5</sup>

Pesticides are reported to cause irritant dermatitis, allergic contact dermatitis, and other skin conditions, including photodermatitis, porphyria cutanea tarda, and chloracne.<sup>6</sup>

Plants alone can also cause dermatitis. Strawberries, mangoes, and some nursery plants are common causes of allergic contact dermatitis. Parsley and limes can cause photodermatitis.<sup>7,8</sup>

## Irritant Dermatitis

- Soil fumigators can get irritant dermatitis and chemical burns of the lower extremities from methyl bromide, dichloropropene (Telone), and metam sodium. These can be prevented by use of chemical-resistant boots.<sup>9,10</sup>
- Other pesticides frequently associated with irritant dermatitis include the herbicides paraquat and diquat, the miticide propargite, and the fungicides sulfur, ziram, benomyl, and captan. Reactions are generally more severe in the setting of pre-existing skin abrasions, such as those produced by picking or weeding prickly or rough crops.<sup>11</sup>

## Allergic Dermatitis

- Fungicides are particularly known as potential skin sensitizers. The ethylene bisdithiocarbamate (EBDC) fungicides such as maneb, mancozeb, zineb, and ziram break down to ethylene thiourea, a known sensitizer.<sup>12,13,14</sup>
- Sulfur is one of the most commonly reported causes of skin reactions among agricultural workers. This compound is a skin irritant, but can also cause allergic dermatitis.<sup>15,16</sup>

**Table 3-1: Pesticides Reported To Be Associated with Allergic Contact Dermatitis**

|                |                  |             |             |
|----------------|------------------|-------------|-------------|
| Acephate       | Diazinon         | Malathion   | Pyrethrum   |
| Benomyl        | Dienochlor       | Mancozeb    | Sulfur      |
| Captan         | Dimethoate       | Maneb       | Thiram      |
| Carbaryl       | Ethoxyquin       | Norflurazon | Vinclozolin |
| Chlorothalonil | Fenbutatin-oxide | Omethoate   | Zineb       |
| Chlorpyrifos   | Fluvalinate      | PCNB        | Ziram       |
| DCNA           | Folpet           | Permethrin  |             |

Source: M.A. O'Malley. Skin reactions to pesticides, *Occup Med State Art Rev* 12 (1997)2: 327-45.

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| Captan         | Dimethoate       | Maneb       | Thiram      |
| Carbaryl       | Ethoxyquin       | Norflurazon | Vinclazolin |
| Chlorothalonil | Fenbutatin-oxide | Omethoate   | Zineb       |
| Chlorpyrifos   | Fluvalinate      | PCNB        | Ziram       |
| DCNA           | Folpet           | Permethrin  |             |

Source: M.A. O'Malley, Skin reactions to pesticides, *Occup Med State Arts Rev* 12 (1997)2: 327-45.

## Other Skin Manifestations of Pesticide Exposure

### Chapter 3 Notes

- The organic pesticide *Bacillus thuringiensis* has recently been shown to induce skin sensitization in exposed workers,<sup>17</sup> as have the fungicide triforine and the organophosphate insecticide dichlorvos (DDVP).<sup>18</sup>
- Patch testing with standardized concentrations of certain pesticides can be used to confirm sensitization.<sup>19</sup>
- Paraquat and diquat, herbicides that can cause skin burns, are also known to severely damage fingernails.<sup>20,21</sup>
- Various herbicides have been associated with chloracne, potentially due to contamination with dioxins. The principal herbicide that has been associated with chloracne is 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), the now-banned primary constituent of Agent Orange. Other herbicides potentially associated with chloracne include 2,4-D, diuron, and linuron.<sup>22</sup>
- Porphyria cutanea tarda has been reported following exposure to hexachlorobenzene and diazinon.<sup>23</sup>

- 1 R.C. Wester, D. Quan, and H.I. Maibach, In vitro percutaneous absorption of model compounds glyphosate and malathion from cotton fabric into and through human skin, *Food Chem Toxicol* 34 (1996)8: 731-35.
- 2 F. Jaros, Acute percutaneous paraquat poisoning, *Lancet* 1(1978): 275.
- 3 M.A. O'Malley, Skin reactions to pesticides, *Occup Med State Art Rev* 12 (1997)2: 327-45.
- 4 Ibid.
- 5 Ibid.
- 6 Ibid.
- 7 Ibid.
- 8 E. Paulsen, Occupational dermatitis in Danish gardeners and greenhouse workers (II): Etiological factors, *Contact Dermatitis* 38 (1998)1: 14-19.
- 9 M. Hezemans-Boer, J. Toonstra, J. Meulenbelt, et al., Skin lesions due to exposure to methyl bromide, *Arch Dermatol* 124 (1988): 917-21.
- 10 D. Koo, L. Goldman, and R. Baron, Irritant dermatitis among workers cleaning up a pesticide spill: California 1991, *Am J Ind Med* 27 (1995)4: 545-53.
- 11 See note 3 above.
- 12 M. Bruze and S. Fregert, Allergic contact dermatitis from ethylene thiourea, *Contact Dermatitis* 9 (1983): 208-12.
- 13 M. Johnsson, M. Buhagen, H.L. Leira, and S. Solvang, Fungicide-induced contact dermatitis, *Contact Dermatitis* 9 (1983): 285-88.
- 14 P. Koch, Occupational allergic contact dermatitis and airborne contact dermatitis from 5 fungicides in a vineyard worker: Cross-reactions between fungicides of the dithiocarbamate group, *Contact Dermatitis* 34 (1996)5: 324-29.
- 15 D.S. Wilkinson, Sulphur sensitivity, *Contact Dermatitis* 1 (1975): 58.
- 16 See note 3 above.
- 17 I.L. Bernstein, J.A. Bernstein, M. Miller, et al. Immune responses in farm workers after exposure to *Bacillus thuringiensis* pesticides, *Env Hlth Persp* 107 (1999)7:575-82.
- 18 A. Ueda, K. Aoyama, F. Manda, et al., Delayed-type allergenicity of triforine (Saprol), *Contact Dermatitis* 31 (1994)3: 140-45.
- 19 K.A. Mark, R.R. Brancaccio, N.A. Soter, and D.E. Cohen, Allergic contact and photoallergic contact dermatitis to plant and pesticide allergen, *Arch Dermatol* 135 (1999)1: 67-70.
- 20 R.L. Baran, Nail damage caused by weed killers and insecticides, *Arch Dermatol* 110 (1974): 467.
- 21 C.E. Hearn and W. Keir, Nail damage in spray operators exposed to paraquat, *Br J Ind Med* 28 (1971): 399-403.
- 22 A.J. McDonagh, D.J. Gawkrödger, and A.E. Walker, Chloracne—study of an outbreak with new clinical observations, *Clin Exp Dermatol* 18 (1993): 523-25.
- 23 A.G. Collins, A.W. Nichol, and S. Elsbury, Porphyria cutanea tarda and agricultural pesticides, *Australia J Dermatol* 23 (1982): 70-75.

# 4 Pesticides and Cancer

*A 41-year-old farmworker comes into your office complaining of fatigue and bone pain. Since teenagers, he and his sister have worked in fields harvesting crops and mixing pesticides. His work-up reveals multiple lytic bone lesions, pancytopenia, and a monoclonal immunoglobulin spike. A bone marrow aspirate confirms a diagnosis of multiple myeloma. He responds well to treatment. He later tells you that his sister was treated for a soft-tissue sarcoma a few years ago at age 36. Both siblings are motivated to encourage co-workers to participate in a study of farmworker health that is being proposed by the Public Health Department. They ask if their diseases could be related to pesticide exposure. How do you respond?*

## Overview

A wealth of research explores connections between pesticide exposure and neoplasia. Collected clues from the fields of molecular biology, toxicology, biochemistry, and epidemiology may help us chart a course for cancer prevention.

Numerous pesticides are implicated in causing or promoting many types of cancers, leukemias, and lymphomas. Some of these diseases are relatively common, others quite rare. Many of the neoplasms for which association with pesticides is most well-established are among those cancers increasing in incidence in industrialized countries. It is unclear whether exposure to pesticides is causally related to the rising rates of these cancers.

The mechanisms by which pesticides contribute to cancer causation vary, and one pesticide may operate by more than one of the major mechanisms, which include

- Genotoxic effects—producing direct changes in DNA.
- Promotion—causing fixation and proliferation of abnormal clones. This process includes endocrine effects that may stimulate otherwise quiescent but hormonally sensitive cells to carcinogenesis.
- Immunotoxic effects—disturbing the body's normal cancer surveillance mechanisms.

Whereas the usual concept of toxicity follows the principle that “the dose makes the poison,” genotoxic chemicals and hormone disruptors may have effects at very low doses without a true threshold below which no risk exists (the stochastic or probabilistic model). Current understanding of carcinogenesis favors the conclusion that even a tiny dose of a genotoxic agent can initiate the process of converting a normal cell to a malignant one.<sup>1,2,3,4,5</sup>

In the field of endocrine disruption, some scientists argue that because background levels of endogenous hormones such as estrogen are known to promote cancer, any additional external hormonally active agents add to an already established risk.<sup>6</sup> For these reasons, at least in theory, even rather low-dose exposure to certain carcinogens may pose a health risk.

Three major lines of evidence relate cancer to pesticide exposure:

1. Cell-culture studies that demonstrate effects such as chromosomal damage or estrogenicity.
2. Laboratory animal studies (see Table 4-1).
3. Human epidemiological investigations.

This section focuses primarily on human epidemiological evidence linking pesticide exposure and cancer.

Abundant in vitro and animal research on the potential carcinogenic effects of pesticides is available and often leads to important advances in understanding human carcinogenesis. However, to eliminate the variable of cross-species interpretation of tests, we confine

## Overview of the Epidemiological Evidence

**Pesticides and  
Cancers of  
Adulthood**  
**Hematological  
Malignancies**  
Non-Hodgkins  
Lymphoma (NHL)

Multiple Myeloma (MM)

discussion to the study of exposed humans. In the case of pesticides, a number of occupational, home, and other environmental studies illustrate the risks of exposure.

For many human studies of pesticides and cancer, the pesticide specifically responsible for carcinogenesis has not been determined. Because occupations in agriculture involve use of multiple agents (including non-pesticidal chemicals), it is often difficult to determine what agent is linked to a specific endpoint. The same problem occurs with home and environmental exposures, where multiple products may be used, their doses unmeasured, their names long forgotten by those exposed. In this document, whenever studies are specific enough, the class or type of implicated pesticide will be provided.

It is scientifically difficult to prove that something causes cancer. For example, it took a decade of research to confirm the causative link between cigarettes and lung cancer, despite the fact that smoking causes more than 90% of all lung cancers<sup>7</sup> and one third of all cancers in the U.S.<sup>8</sup>

When we refer to the risk of developing various cancers, it should be understood that pesticides are not the only possible cause of any given disease (e.g., leukemia may be caused by some pesticides and also by other chemicals such as benzene). It is usually not possible to know, on an individual basis, all factors that have contributed to carcinogenesis. The following information summarizes those substances that should stimulate suspicion and rigorous study if we are to progress toward prevention.

Sometimes called the "silent epidemic," over the last several decades Non-Hodgkins Lymphoma (NHL) incidence has been increasing by 3–4% per year throughout most of the world.<sup>9,10</sup> In some studies annual increases in incidence are as high as 4.2–8.0%.<sup>11,12,13</sup> These reported increases are corrected for known viral causes of NHL, such as human immunodeficiency virus (HIV), and therefore largely exclude AIDS-related lymphomas.<sup>14,15</sup> Some research on pesticide workers demonstrates associations between occupational exposures (in agriculture or exterminator work) and NHL.<sup>16,17,18</sup> A large number of studies find more specific correlation, especially to phenoxy herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D).<sup>19,20,21,22</sup> Other research on pesticide workers implicates furan and dioxin contaminants (2,3,7,8-tetrachlorodibenzo-p-dioxin) of the phenoxy herbicides.<sup>23</sup> Although the phenoxy herbicides and their contaminants are the most consistently NHL-associated chemicals, investigators raise concern about other pesticides, including lindane (used in some head and body lice-treatments),<sup>24</sup> organophosphate pesticides,<sup>25</sup> and a variety of others, such as carbaryl, chlordane, dichlorodiphenyltrichlorethane (DDT), diazinon, dichlorvos, malathion, nicotine, and toxaphene.<sup>26</sup> Evidence shows that some fungicides may also be lymphomagens.<sup>27</sup>

Other epidemiologists have studied exposure of persons who are not pesticide workers but live in areas of pesticide use or drift. Herbicide spraying doubled the risk of fatal NHL in a study of persons living in agricultural regions in Canada.<sup>28</sup> The phenoxy herbicides were associated with increased risk of NHL among residents of rice-growing areas in northern Italy.<sup>29</sup> In the U.S., a cluster of NHL and other B cell malignancies has been reported in a Midwestern farming community.<sup>30</sup>

Humans and their dogs live in close proximity, and a study of canine cancer reinforces the above data. Increased risk of canine malignant lymphoma has been associated with pets' exposure to 2,4-D on lawns.<sup>31</sup>

Multiple Myeloma (MM) is another hematological malignancy for which age-adjusted incidence seems to have increased during the last several decades. Rates vary, even among industrialized countries: U.S. investigators found an increased incidence of 4% per year from the late 1940s to the early 1980s among white men and women.<sup>32</sup> In contrast, epidemiologists in Spain observed a greater than 10% annual rise from the 1960s to the

|   |   |
|---|---|
| Hairy Cell Leukemia (HCL)   | <p>mid-1980s.<sup>33</sup> A number of reports cite intermediate increases in several other nations.<sup>34</sup> Many epidemiological studies reveal an association between employment in farming and the chance of contracting MM, with risks as high as 5-fold.<sup>35,36,37,38,39</sup></p> <p>Some investigators have more specifically identified possible causative agents. One study of herbicide applicators reports an 8-fold increase in risk of succumbing to MM.<sup>40</sup> The phenoxy herbicides are implicated in this excess risk,<sup>41</sup> an association that should not be surprising since the malignancy is closely related to lymphoma. Chlorinated insecticides are also associated with increased risk for MM in another study.<sup>42</sup></p>   |
| Myelodysplastic Syndrome (MDS)  | <p>Increased occurrence of a rare disease is often more obvious to researchers than a similar rise in the rate of a common illness. The latter tends to get "washed out" among the large numbers of expected cases. Hairy Cell Leukemia (HCL) is so rare that multiple recent reports linking it with pesticide exposure raise great interest.<sup>43,44</sup> One study specifically associates organophosphates with HCL.<sup>45</sup></p> <p>Myeloid leukemia and Myelodysplastic Syndrome (MDS) have been associated with occupational exposure to pesticides.<sup>46,47</sup> One case-control study finds significant associations between occupational exposure to pesticides and both acute myeloid and lymphoid leukemia.<sup>48</sup> Review of recent Cancer Registry of Central California data shows correlation of the herbicides 2,4-D and atrazine and the pesticide captan with leukemia among Hispanic males.<sup>49</sup> One cohort study of a group of gardeners known to have been highly exposed to pesticides reveals a nearly 3-fold increased risk for chronic lymphocytic leukemia,<sup>50</sup> an illness for which few possible causes have been proposed.</p>  |
| Soft Tissue Sarcomas (STS) in Adults  | <p>As with NHL, development of Soft Tissue Sarcomas (STS) as a function of pesticide exposure is widely studied and frequently correlated. While some studies reveal a simple association with gardening or farming,<sup>51,52</sup> many show a more specific association with the phenoxy herbicides<sup>53,54</sup> or with a combination of exposure to phenoxy herbicides and the pesticide contaminant TCDD.<sup>55</sup></p> <p>Occupational exposure to phenoxy herbicides and/or chlorophenol is repeatedly linked to STS.<sup>56,57,58</sup> In one of the most detailed investigations of any tumor/pesticide association, one case-control study of workers with STS derived odds ratios for exposure to three major pesticide-classes—phenoxy herbicides, chlorophenols, and dioxins. The odds of contracting STS after exposure to any phenoxy herbicide was approximately ten times higher than for non-exposed controls; to the class comprising 2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, and 4-chloro-2-methylphenoxyacetic acid and to any chlorinated dibenzodioxin or furan, nearly six; and to 2,3,7,8-tetrachlorodibenzo-p-dioxin, greater than five.<sup>59</sup></p>  |
| <p><b>Carcinomas and Central Nervous System (CNS) Malignancies in Adults</b></p> <p>Skin Cancer and Cancer of the Lip</p> <p>Brain Tumors</p> | <p>While elevated risk for skin cancer and cancer of the lip is repeatedly associated with farming,<sup>60,61,62,63</sup> ultraviolet light exposure may be a more likely causative factor than pesticides. Therefore, observation of an association between one specific type of skin cancer—Bowen's disease—and the manufacture of paraquat<sup>64</sup> is of interest because the paraquat-associated skin cancers demonstrate DNA abnormalities which differ from sunlight-induced skin cancers.</p> <p>The age-adjusted incidence of primary tumors of the Central Nervous System (CNS) (particularly astrocytomas, including the rapidly progressive glioblastoma multiforme as well as the benign meningiomas) appears to have increased by 50–100% over the past several decades, with greatest increase among the elderly.<sup>65,66,67</sup> Studies also show increased occurrence of high-grade neuroepithelial tumors, lymphoma, and other primary CNS tumors of 5–13%<sup>68,69</sup> per annum in the elderly. Some observers attribute the apparent increase to the availability of computerized tomography,<sup>70</sup> but disproportionate increase in certain histologic types,<sup>71</sup> parallel increases in mortality,<sup>72</sup> and studies that show diagnostic</p> |

imaging only contributes about 20% to case ascertainment all suggest the rise is probably real.<sup>73</sup>

Several studies of workers in farming,<sup>74</sup> gardening and orchard work,<sup>75</sup> pesticide application,<sup>76</sup> and golf-course superintendence<sup>77</sup> show increased risk for primary tumors of the brain. Research analyzing risk of brain cancer among many occupational groups indicates that workers in occupations likely to involve pesticide exposure heighten their liability to brain tumors.<sup>78,79</sup> No studies yet connect specific pesticides to these observed increases.

#### Respiratory Tract Cancer

Modest increase in cancers of the nose and nasal cavity is reported among workers exposed to phenoxy herbicides and chlorophenols.<sup>80,81</sup> A greater than 2-fold increase in lung cancer (adjusted for smoking) has been observed among structural pest-control workers.<sup>82</sup> Excess cancer of the sinonasal cavities and lungs has been found among women working in agricultural settings.<sup>83</sup>

#### Gastrointestinal Cancers

Gastric cancer has been associated with work as a farmer,<sup>84</sup> as has colorectal cancer.<sup>85,86</sup> In one retrospective cohort study, colorectal cancer specifically correlated with working in a plant that manufactured the herbicide alachlor. For all exposed workers, risk for developing leukemia or colorectal cancer was 50% higher than for a comparable non-exposed population, while incidence of colorectal cancer among workers with five or more years of the highest alachlor exposure was more than five times greater.<sup>87</sup>

One study finds that biliary and liver cancer correlate highly with work as a pesticide applicator.<sup>88,89</sup> Another study strongly implicates exposure to DDT.<sup>90</sup> Research on workers in plants that manufacture organochlorines shows a nearly 4-fold increased risk from exposure to chlordane, heptachlor, endrin, aldrin, and dieldrin.<sup>91</sup> These pesticides are no longer used in the U.S., but persist in the environment—including termite-protected homes—so exposure may still occur.

A number of studies implicate pesticides in pancreatic cancer. They show that occupational pesticide-exposure increases the risk of pancreatic cancer.<sup>92,93,94</sup> Workers exposed to DDT and related compounds suffer more than a 7-fold increased incidence of pancreatic cancer compared with non-exposed workers.<sup>95</sup> In short, organochlorine exposure appears to be consistently linked with a variety of gastrointestinal malignancies.

#### Urinary Tract Cancer

The U.S. has recently experienced increased incidence of and mortality from renal cancers. According to the Surveillance, Epidemiology and End Results (SEER) national cancer-monitoring program, the last 25 years have witnessed dramatic increases in disease and death from kidney cancer among black and white Americans of both sexes. During the last 20 years, all white men saw increased incidence at 3.1% per year; white women at 3.9%; and African-American men and women, the steepest at 3.9% and 4.3%.<sup>96</sup> Such rates over a 20-year period cannot be explained by early detection, especially given that screening tests are not routinely employed. An environmental cause is likely.

Occupational exposure to pesticides (work in agriculture) has been correlated with increased risk for kidney cancer (or hypernephroma).<sup>97,98,99</sup> One study shows specific risk associated with pentachlorophenol.<sup>100</sup> Among women occupationally exposed to pesticides, one study observed increased incidence of bladder cancer.<sup>101</sup>

#### Testicular Cancer

Testicular cancer is another malignancy rising in occurrence for the last several decades in virtually all developed nations. Annual incidence increases range from 2.3% to 5.2% in Europe since the 1940s.<sup>102</sup> In Miyagi, Japan, growth is among the highest, with 6.6% per annum.<sup>103</sup> U.S. data suggest similar trends: The nation's oldest on-going statewide tumor registry finds a mean annual increase in testicular cancer incidence of more than 5.5% over the last 60 years.<sup>104</sup>

Studies of offspring of parents who work in agricultural activities reveal higher rates of testicular cancer, with occurrence manifesting in childhood as well as young adulthood.<sup>105</sup>

Prostate Cancer

Another study shows excess risk of testicular cancer among workers exposed to phenoxy herbicides and chlorophenols.<sup>106</sup>

Numerous studies demonstrate small but significant correlations between prostate cancer and occupational settings likely to lead to pesticide exposure,<sup>107,108</sup> as well as jobs involving direct pesticide or herbicide application.<sup>109</sup>

Breast Cancer

Age-adjusted incidence of breast cancer in industrialized countries has increased 1–2% per year for several decades, both before and after introduction of mammography.<sup>110,111</sup> This observation suggests environmental factors may play a role in this common disease.

Recent years have witnessed great controversy over the possibility of attributing increased breast cancer incidence to hormonally active environmental contaminants, including some pesticides. The organochlorines have received special attention due to their estrogenic effects *in vitro*, lab animals, and wildlife. While we cite studies that seem to support that some pesticides contribute to breast cancer causation, it should be noted that there are negative findings as well, so the precise contribution of pesticides to breast carcinogenesis is not settled.

A case-control study of postmenopausal breast cancer measured serum levels of certain organochlorine compounds (DDE, hexachlorobenzene, mirex, and several polychlorinated biphenyls or PCBs). Some increased risk appeared for women with certain types of PCBs and mirex detectable in their serum, but this effect was predominantly restricted to postmenopausal women who had never breast-fed.<sup>112</sup> It should be observed that PCBs, although organochlorines, are not expected pesticide-components.

Another case-control study analyzed breast tissue from patients with invasive cancer for the presence of organochlorines and compared it with control measurements from women with benign breast biopsies. Some, but not all, classes of PCBs were associated with breast cancer, especially among postmenopausal women with estrogen-receptor positive tumors. Hexachlorobenzene levels were also associated with increased risk of malignancy.<sup>113</sup>

Case-control research from Colombia showed an association between serum dichlorodiphenyl-dichloroethane (DDE, a metabolite of DDT) levels and risk for breast cancer.<sup>114</sup> Another study found serum dieldrin levels associated with dose-related, significantly elevated risk of breast cancer, but other organochlorines appeared not to affect risk.<sup>115</sup>

In an ecological study of breast cancer incidence in an agricultural district heavily contaminated with organochlorine and triazine herbicides, a very modest but statistically significant increased risk of breast cancer is evident.<sup>116</sup>

In summary, organochlorine pesticides may disrupt some actions of estrogens. However, the actual effect on breast cancer risk is likely to vary from compound to compound and even change with different endocrine states of the host.<sup>117</sup>

Thyroid

A large cohort study of workers exposed to phenoxy herbicides and chlorophenols reveals increased risk of thyroid cancer among exposed persons.<sup>118</sup>

In a community exposed to unusually high levels of the organochlorine hexachlorobenzene, excess incidence of thyroid cancer was observed.<sup>119</sup> An agricultural region of Minnesota with heavy use of ethylene bis-dithiocarbamate fungicides (such as maneb, mancozeb, and zineb) suffered a nearly 3-fold increased risk. These fungicides are metabolized to ethylene thiourea, a known thyroid carcinogen in animals.<sup>120</sup>

Every year approximately 8000 children under age fifteen are diagnosed with a malignant disease, most frequently leukemia and brain tumors. Environmental exposure such as to ionizing radiation, hormones, and antineoplastic agents are accepted to be contributors to these diseases. Some childhood tumors such as gliomas, leukemia, and Wilms' tumor seem



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Childhood Leukemia

Non-Hodgkin's  
Lymphoma

Brain and Nervous  
System Tumors

Sarcomas

Wilms' Tumor

#### Chapter 4 Notes

to be increasing in incidence, but the cause for most of these illnesses remains unknown.<sup>121</sup> The clues pertaining to pesticides and children should be treated seriously given pesticides' ubiquitous presence, the tendency of children (especially toddlers) to experience their world by tasting it, and the possible increased sensitivity of children to carcinogens.

Parental occupational exposure to pesticides as well as home and garden pesticide use may increase risk of childhood leukemia.<sup>122,123,124</sup> Home use of pest strips has been strongly associated with risk.<sup>125</sup>

Pesticides have been linked to childhood NHL.<sup>126</sup> Children of parents engaged in agricultural work show higher than expected risk.<sup>127</sup>

A multicenter case-control study finds home use of pesticides increases risk of childhood brain cancers.<sup>128</sup> Other research on home pesticide deployment demonstrates highly significant correlation between pediatric brain tumors and use of sprays or foggers to dispense flea and/or tick pet-treatments.<sup>129</sup> Other pesticides implicated include pest strips, termite-control pesticides, lindane shampoo, flea collars, yard and orchard herbicides, home pesticide bombs, and carbaryl for outdoor use.<sup>130</sup> Occupational pesticide use by parents has been associated with increased risk of childhood neuroblastoma.<sup>131</sup>

A study of parental occupation and childhood cancer shows a strong association between fathers' employment in agricultural work (from six months prior to conception up to the time of diagnosis) and Ewings' sarcoma in offspring.<sup>132</sup> Yard pesticide treatments have been linked to an increased rate of childhood soft-tissue sarcomas.<sup>133</sup>

Paternal employment in agriculture has been associated with increased risk of Wilms' tumor.<sup>134</sup> In other studies, both paternal and maternal exposures to pesticides correlates with increased risk.<sup>135,136</sup>

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Table 4-1: Carcinogenic Pesticides

| Chemical Name                      | Chemical Use                     |
|------------------------------------|----------------------------------|
| Arsenic acid                       | Herbicide                        |
| Arsenic pentoxide                  | Insecticide, wood preservative   |
| Arsenic trioxide                   | Rodenticide                      |
| Cacodylic acid                     | Herbicide, defoliant             |
| Captan                             | Fungicide                        |
| Chlorothalonil                     | Fungicide                        |
| Chromic acid                       | Wood preservative                |
| Creosote                           | Wood preservative                |
| Daminozide                         | Plant growth regulator           |
| Ddvp                               | Insecticide                      |
| Dipropyl isocinchomeronate         | Insecticide                      |
| Diuron                             | Herbicide                        |
| Ethoprop                           | Insecticide                      |
| Ethylene sodium                    | Fumigant                         |
| Fenoxycarb                         | Insecticide                      |
| Folpet                             | Fungicide                        |
| Formaldehyde                       | Microbiocide                     |
| Iprodione                          | Fungicide                        |
| Lindane                            | Insecticide                      |
| Mancozeb                           | Fungicide                        |
| Maneb                              | Fungicide                        |
| Metam-sodium                       | Fumigant                         |
| Metiram                            | Fungicide                        |
| Ortho-phenylphenol                 | Microbiocide                     |
| Ortho-phenylphenol, Sodium salt    | Microbiocide                     |
| Oxadiazon                          | Herbicide                        |
| Oxythioquinox                      | Insecticide, fungicide, fumigant |
| Para-dichlorobenzene               | Insecticide                      |
| Pentachlorophenol                  | Wood preservative                |
| Potassium dichromate               | Wood preservative                |
| Propargite                         | Insecticide                      |
| Propoxur                           | Insecticide                      |
| Propylene oxide                    | Fumigant                         |
| Propyzamide                        | Herbicide                        |
| Pyrethrins                         | Insecticide                      |
| S,S,S-tributyl phosphorotrithioate | Defoliant                        |
| Silica aeroge                      | Insecticide                      |
| Sodium dichromate                  | Wood preservative                |
| Thiodicarb                         | Insecticide                      |
| Thiophanate-methyl                 | Fungicide                        |
| Trichlorfon                        | Insecticide                      |
| Vinclozolin                        | Fungicide                        |

Source: Pesticides listed as known, likely, or probable carcinogens by U.S. EPA Office of Pesticides Programs as of August 1999, or by the state of California under Proposition 65 and the Safe Drinking Water and Toxic Enforcement Act of 1986.

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# 5 Pesticides and Respiratory Disease

*A 24-year-old man comes into an occupational health clinic with a three year history of chest tightness, wheezing, and episodic dyspnea. The patient works in a chemical plant that manufactures pesticides. His symptoms began shortly after his transfer to a captafol production line, are worst in the evening and at night, but resolve on weekends and vacations. There is no personal or family history of allergies or asthma. Review of systems reveals rashes on his wrists above his gloves, chronic burning eyes, and rhinitis. Specific bronchial challenge testing reveals a marked and persistent fall in FEV1.<sup>1</sup>*

## Overview

Acute organophosphate or N-methyl carbamate overexposure is well known to cause cholinesterase inhibition, resulting in bronchoconstriction, increased airway secretions, and respiratory distress.<sup>2</sup>

A few pesticides are known sensitizers and can result in allergic reactions including asthma.<sup>3,4</sup> An association between low-level pesticide exposure and asthma is controversial, and confounded by the fact that animal, plant, and other antigens cannot be completely ruled out.

A few studies report other respiratory effects from pesticides, including pulmonary hemosiderosis, pneumonia-like infiltrates, chronic bronchitis, pulmonary fibrosis, Wegener's granulomatosis, and respiratory muscle impairment.<sup>5,6,7,8,9</sup>

The main target organ for the herbicide paraquat is the lung. This pesticide is selectively taken up by the lung from peripheral blood, and causes oxidative damage presenting as acute pulmonary edema and hemorrhage or as delayed pulmonary fibrosis. Respiratory failure has occurred following exclusively dermal exposure to this chemical.<sup>10</sup>

## Pesticides and Asthma

- Case reports and specific bronchial-challenge testing link several pesticides with occupational asthma. These pesticides include captafol,<sup>11</sup> sulfur,<sup>12</sup> pyrethrins and pyrethroids,<sup>13</sup> tetrachloroisophthalonitrile,<sup>14</sup> and several organophosphate and N-methyl carbamate insecticides that appear to have a methacholine-like effect on the lung.<sup>15,16</sup>
- A cross-sectional study of nearly two thousand farmers in Saskatchewan revealed a significant association between physician diagnosed asthma and reported use of cholinesterase inhibiting pesticides. Potential confounding from exposure to fungi and pollen cannot be completely ruled out.<sup>17</sup>
- Plantation workers in India showed a potential association between pesticide exposure and respiratory impairment. Although overall prevalence of asthma was lower among workers than among controls (perhaps due to the well known "healthy worker effect," in which the working population, on average, enjoys a better health status than the overall population),<sup>18</sup> the pesticide exposed workers revealed an exposure-related increase in both obstructive and restrictive deficits on pulmonary function testing.<sup>19</sup>
- Vineyard and orchard workers in Eastern Europe had significantly higher overall prevalence of dyspnea, chest tightness, chronic cough, and chronic phlegm compared with non-pesticide-exposed controls. Among both smoking and non-smoking workers employed for greater than ten years, FEV<sub>1</sub>, FEF<sub>25</sub>, and FEF<sub>50</sub> were significantly reduced. Exposed workers also had significantly reduced FVC compared to controls. It was not possible to determine whether findings were due to pesticide exposure or to occupational exposure to dust, pollen, or mold. However, the workers were exposed to a variety of organochlorines, organophosphates, sulfur, and inorganic copper compounds.<sup>20</sup>

### Other Respiratory Diseases Related to Pesticide Exposure

- Worldwide population trends indicate that the prevalence of asthma is increasing in the general population, particularly among children and young adults. Severity of asthma, as measured by emergency room visits, hospitalizations, and deaths, is also increasing despite treatment advances.<sup>21</sup> Causes of these trends are not well understood, but it is possible that increasing exposure to pesticides may play a role.<sup>22</sup>
- Children are more susceptible to airborne health hazards than adults for several reasons, such as more rapid respiratory rate and greater volume per unit of body weight, and greater average activity level with faster respiratory rates. Furthermore, very young children are naturally closer to the ground or floor, where chemicals denser than air tend to accumulate. The fact that terminal airways of the lung are not fully developed until several years after birth is also significant.<sup>23</sup>
- An interesting case report describes a young woman who developed diffuse pulmonary hemosiderosis four days after she applied a combination of three synthetic pyrethroids (deltamethrin, cyhalothrin, and bensultap) to a strawberry field. The patient developed sudden onset of dyspnea and severe hemoptysis requiring transfusion. Her chest x-ray showed bilateral cloudy infiltrates, and bronchoalveolar lavage revealed hemosiderin-loaded macrophages. All antibodies were negative. The syndrome responded well to cyclophosphamide.<sup>24</sup>
- One group of researchers proposes the existence of a "biocide lung" following prolonged exposure to pesticides. This syndrome is characterized by intermittent pulmonary infiltrates followed by chronic progressive fibrosis.<sup>25</sup>
- In a survey of about 200 Danish fruit-growers, individuals reported using an average of 13 different pesticides. The most commonly used pesticides comprised captan, paraquat, parathion, azinphos-methyl, diquat, amitrol, benomyl, and simazine. Approximately 40% of the growers reported at least one significant respiratory symptom in connection with pesticide spraying, and nearly 20% had diminished peak flow. These findings were more common among workers who did not wear respiratory protection when applying pesticides. X-ray revealed pulmonary infiltrates or fibrotic changes in nearly one quarter of the subjects.<sup>26</sup>
- A case-control study of 101 patients with Wegener's granulomatosis found that cases reported significantly greater occupational exposure to pesticides compared with both healthy controls and controls with other pulmonary diseases.<sup>27</sup>
- A study questionnaire administered to 54 workers in an Eastern European pesticide plant revealed a 50% prevalence of chronic bronchitis. Approximately two-thirds of the workers had significantly decreased peak expiratory flow. Exposed workers also showed significantly diminished maximum inspiratory and expiratory pressures, potentially indicating respiratory muscle weakness.<sup>28</sup>



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# 6 Neurological and Behavioral Effects of Pesticides

*A 52-year-old patient draws your attention to a tremor that has become increasingly bothersome over the past year. On examination, the tremor is pill-rolling and resolves with intention; the patient also has a positive Romberg Sign and an unstable tandem gait. You make a preliminary diagnosis of early Parkinson's Disease. The patient's wife mentions that she recently read in the newspaper that most Parkinson's is from environmental causes, and asks if the fact that her husband is a farmer and has used pesticides for years could be related to his early-onset disease.*

## Overview

Pesticides have been shown to affect both the central nervous system (CNS), and the peripheral nervous system (PNS) in animals and humans via a variety of mechanisms.

The effects of neurotoxic pesticides can be assessed by measuring changes in neurochemistry, neuropathology, and behavior, including subtle effects on visuospatial function, concentration, reaction-time, learning, and short-term memory.<sup>1,2</sup>

Certain pesticides, for example, the organophosphates and N-methyl carbamates, are designed specifically to damage neurological function in insects and are neurotoxic in humans because of similarities in nervous system function between insects and humans.

Human neurotoxic effects may be acute, may represent the chronic sequelae of an acute poisoning, or may result from chronic exposures in the absence of an acute episode of poisoning.<sup>3</sup> This section focuses on the chronic neurotoxic effects of pesticide exposure.

## Pesticides and Parkinson's Disease (PD)

There is increasing evidence that a high proportion of Parkinson's Disease (PD) may be associated with environmental factors.<sup>4</sup>

- Specific pesticides and pesticide classes implicated in PD include paraquat, the organophosphates, dieldrin, and the manganese-based fungicides maneb and mancozeb.<sup>5,6,7</sup>
- The designer heroin-like drug MPTP, known to cause a Parkinsonian syndrome in addicts via the neurotoxic effect of its major metabolite, is chemically related to the herbicide paraquat.<sup>8</sup>
- Numerous studies identify a higher incidence of PD in industrialized countries. Within these countries, people who live in rural areas, live or work on farms, or report a history of pesticide use have the highest risk.<sup>9,10</sup>
- Several population-based case control studies identify a 4-fold increased likelihood of past herbicide exposure among patients with PD, and a 3–4-fold increased likelihood of prior exposure to insecticides.<sup>11,12</sup>
- Several recent studies indicate a possible role for gene-pesticide interactions in the etiology of PD. In particular, higher than expected rates of certain glutathione transferase polymorphisms, the slow acetylator genotype of N-acetyltransferase-2, and the slow 4-hydroxylation of debrisoquine (the CYP 2D6 29B+ allele) have all been reported in patients with PD.<sup>13,14,15</sup> These genetic variants may increase risk from environmental exposure by slowing detoxification of exogenous compounds.<sup>16</sup>
- The cholinesterase inhibiting pesticides (organophosphates and N-methyl carbamates) interfere with impulse transmission in the PNS. Chronic effects of exposure can include sensory, motor, and autonomic neuropathies.<sup>17</sup>

## Peripheral Neurotoxicity

## Neurocognitive Effects of Pesticide Exposure

- Organophosphate pesticides can rarely cause a distinct syndrome known as organophosphate-induced delayed polyneuropathy (OPIDP), which occurs within five weeks after an acute intoxication.<sup>18</sup> OPIDP is characterized by axonal degeneration and secondary demyelination of long tract neurons.<sup>19</sup> Symptoms of OPIDP include paresthesias of the limbs, leg cramping, motor weakness of the wrist and ankle, and, in severe cases, paralysis.<sup>20</sup> Permanent residua include weakness, loss of reflexes, and sensory impairment.<sup>21</sup>
- In some cases, a so-called "intermediate syndrome" may develop 24 to 96 hours following acute organophosphate pesticide poisoning. The main symptoms consist of proximal muscle weakness, profound weakness of the neck flexors, and weakness or paralysis of the muscles involved in respiration.<sup>22</sup> Sensory function is completely spared.<sup>23</sup> This syndrome may or may not be followed by OPIDP.<sup>24</sup> Neither OPIDP nor the intermediate syndrome respond to therapy with atropine or pralidoxime.<sup>25</sup>
- PNS impairment may also occur following chronic occupational exposure to pesticide mixtures, even in the absence of acute poisoning or frank OPIDP. Several studies report an increased prevalence of neurological abnormalities in exposed workers compared with controls. Abnormalities include hyporeflexia, dysequilibrium, reduced vibration sensitivity, and nerve conduction delays.<sup>26,27</sup> Other studies fail to find peripheral nerve conduction delays in workers who have not suffered high level exposure.<sup>28</sup>
- Workers exposed to mixed pesticides, particularly to the dithiocarbamate fungicides maneb and zineb, have been shown to have slowed peripheral nerve conduction. Motor and sensory conduction were affected equally, with some indication of autonomic dysfunction as measured by reduced respiratory variability.<sup>29</sup>
- Many pesticides are able to penetrate the blood brain barrier, while others exert indirect effects on the brain via disruption of oxygen supply, nutrients, hormones, or neurotransmitters.<sup>30</sup>
- Areas of the brain most commonly affected by pesticides include the limbic system, hippocampus, basal ganglia, and cerebellum.<sup>31</sup>
- Evidence of pesticide-associated neuropsychological deficits is based primarily on studies of workers acutely or chronically exposed to organophosphate pesticides, although some case reports also implicate N-methyl carbamate pesticides in the appearance of similar effects.<sup>32</sup>
- Cognitive symptoms in these populations include impairment of memory and psychomotor speed, and affective symptoms such as anxiety, irritability, and depression.<sup>33</sup> Visuospatial deficits have also been linked to organophosphate exposure.<sup>34</sup> Standardized neuropsychiatric testing batteries confirm these deficits in exposed groups compared with unexposed controls. Long-term memory and language abilities are generally spared.<sup>35</sup>
- The fumigants methyl bromide, sulfuryl fluoride, and dichloropropene (Telone) have been reported to cause personality changes and shortened attention span following exposure. Methyl bromide exposure was related to decreased touch sensitivity and reduced cognitive ability; Telone exposure, to increased depression and anxiety reflected in standardized test batteries; and sulfuryl fluoride, to a range of behavioral and cognitive deficits.<sup>36,37</sup>
- Many pesticides are known to increase CNS excitability and to produce seizures with acute high-dose exposure.<sup>38</sup>
- Recent animal studies indicate that some pesticides can cause an electrical kindling response after repeated sub-threshold dosing. Low doses repeated three times a week for ten weeks of the pesticide lindane (used to treat head lice) resulted in enhanced myo-

## Pesticides and Seizures

## Effects of Pesticides on Neurological Development in Children

clonic jerks and seizures at normally subconvulsant doses. Other organochlorine pesticides, such as endosulfan and dieldrin, are reported to have similar effects.<sup>39</sup>

Neurological development in children is particularly vulnerable to disruption. Although there is some plasticity inherent in the development of the nervous system, even low-level exposure during the brain-growth spurt have been shown to exert subtle, permanent effects on the structure and function of the brain.

- Animal studies have demonstrated periods of vulnerability, particularly to anticholinesterases, during early life.<sup>40</sup> Recent evidence supports the finding that acetylcholinesterase may play a direct role in neuronal differentiation.<sup>41</sup>
- Children from a region in Mexico with intensive pesticide use were found to have a variety of developmental delays compared with otherwise similar children living where fewer pesticides were used. Although the children were similar in growth and physical development, significant delays were noted among the exposed children in physical stamina, gross and fine hand-eye coordination, and short-term memory.<sup>42</sup>

**Table 6-1: Chronic or Delayed Neurotoxic Effects of Pesticides**

| Pesticide Category   | Effects on Central Nervous System   | Effects on Peripheral Nervous System                  |
|--|---|---|
| <i>Organophosphates</i><br>e.g., malathion, chlorpyrifos                         | Cognitive, affective and perceptive effects                                   | OPIDP; sensorimotor neuropathy; intermediate syndrome |
| <i>Carbamates</i><br>e.g., carbaryl  | Memory deficits; visual impairment; lassitude                                 | Sensorimotor neuropathy                               |
| <i>Organochlorines</i><br>e.g., kepone   | Impairment of cognitive function and personality; seizure kindling            | Tremor (Kepone shakes)                                |
| <i>Metals</i><br>e.g., monosodium methyl arsenate, lead arsenate, zinc phosphide | Impaired visuospatial abilities; deficits in short-term verbal memory         | Painful, burning dysesthesias                         |
| <i>Fumigants</i><br>e.g., carbon disulfide, dichloropropene, methyl bromide      | Cognitive impairment; mood changes; difficulty concentrating; pyramidal signs | Loss of reflexes and distal motor strength            |
| <i>Fungicides</i><br>e.g., dithiocarbamates—zineb, maneb, mancozeb               | Reduction of physiologic respiratory arrhythmia; possibly Parkinson's         | Reduced nerve conduction                              |
| <i>Pyrethroids</i><br>e.g., fenvalerate, cypermethrin                            | Reduction of spontaneous motor activity; altered startle response             | Cutaneous paresthesia; numbness                       |
| <i>Rodenticides</i><br>e.g., vacor<br>(N-3-pyridylmethyl-N-p-nitrophenyl urea)   | Minimal data on cognitive impairment  | Autonomic incompetence                                |

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# 7 Reproductive and Developmental Effects of Pesticides

## Overview

*A 32-year-old man comes in with concerns about fertility. He has been married four years and his wife has not become pregnant despite regular attempts for the past several years. The man reports that he works at a chemical company that manufactures pesticides and that several other men are having similar problems. The men complained to the union steward; all would be coming in for medical evaluation over the next few weeks. Semen analysis reveals azospermia.*

Pesticides may affect human reproduction by direct toxicity to the reproductive organs or by interference with hormonal function.<sup>1,2,3,4</sup> Effects of pesticides on reproduction may include menstrual abnormalities, male or female infertility, or hormonal disturbances.

The developing fetus and infant are disproportionately susceptible to the health effects of pesticides.<sup>5</sup> Developmental toxicity of pesticides may result in spontaneous abortion, growth retardation, structural birth defects, or functional deficits.<sup>6</sup>

There is often a period of vulnerability to the effects of toxic chemicals—including pesticides—during fetal development and early childhood. This vulnerability occurs during the period of development of various organ systems. Permanent structural birth defects or permanent functional changes may occur.<sup>7,8,9</sup>

## Male Infertility: The Example of DBCP

The most thoroughly studied human epidemic of pesticide-induced reproductive dysfunction began in the 1970s when men at an Occidental chemical plant in Southern California sought medical care for infertility. Many were sterile, and subsequent investigation found that a fumigant manufactured in the plant, dibromochloropropane (DBCP), was responsible for effects on spermatogenesis and for germ-cell mutations.<sup>10</sup> In many cases, effects were permanent. Rodent studies performed decades earlier found dramatic testicular toxicity in animals, yet this evidence was disregarded until the human outbreak occurred.

Although use of DBCP has been discontinued in the U.S., it is persistent in soil and still present in groundwater in some parts of California. Thus there is potential for ongoing low-level human exposure.<sup>11</sup> The long-term effects of such exposures over the reproductive life-span are unknown. DBCP was still used until recently in Central American banana plantations, resulting in epidemics of sterility in agricultural workers.<sup>12</sup>

## Effects of Pesticides on Fertility

Use of chlordane (Kepone) was discontinued in the U.S. after incontrovertible evidence that it causes decreased sperm mobility and viability, in addition to serious neurological effects in workers.<sup>13</sup>

Exposure to carbaryl has been associated with increased frequency of morphologically deformed sperm, but longitudinal studies have not been conducted to confirm adverse reproductive outcomes.<sup>14</sup>

- The herbicide 2,4-Dichlorophenoxyacetic acid (2,4-D) is spermatotoxic in laboratory animals. A correlation between increased exposure to 2,4-D and decreased sperm density along with increased percentage of abnormal sperm was reported in agricultural pesticide applicators.<sup>15</sup>