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The Clinical Laboratory in the Diagnosis of Overexposure to Agrochemicals

ABSTRACT *Pesticides are the most toxic agrochemicals, and the World Health Organization estimates that 3 million acute pesticide poisonings occur yearly worldwide, with about 220,000 deaths. Others estimate the annual global toll of poisonings at 25 million. The cholinesterase inhibitors (organophosphates and N-methyl carbamates) are the chemical pesticides most commonly implicated in poisonings, but other pesticides, including herbicides, fungicides, and fumigants, may cause illness. Despite these numbers, even rural clinicians rarely see agrochemical poisonings. While many assays are available only at specialty laboratories, the informed laboratory specialist can help enormously in solving puzzling cases, obtaining important legal evidence, and ruling out exposure when not present.*

This is the final article in a two-part series on hazards to agricultural workers. The series discusses the diagnosis of overexposure to agrochemicals and other farming hazards, such as zoonotic infections. On completion of this series, the reader will be able to identify the laboratory methods appropriate for assisting in the diagnosis of exposure to major agrochemical groups, name common farm hazards, and list major zoonotic infections in the United States.

This article informs laboratory professionals about agrochemical overexposure and the role of laboratories in the diagnosis of clinical cases of overexposure. Because it would be impractical to discuss all agrochemicals individually, the focus is on groups of chemicals. It describes the nature of each group's toxicity and identifies the types of laboratory tests a clinician might request. Specific information on testing procedures, anticoagulant rodenticides, and pesticides containing metals such as mercury, lead, arsenic, and copper, are not discussed.

Epidemiologic Considerations

Estimating the number of agrochemical overexposures worldwide or even in the United States is difficult. First, most countries and most of the 50 states do not systematically collect information on poisoning by pesticides or other agrochemicals. Second, the chemicals used in agriculture are numerous and diverse. Third, most frontline clinicians lack training in clinical toxicology and occupational medicine. Consequently, there is probably substantial underdiagnosis and underreporting of the incidence of agrochemical overexposure.

The World Health Organization estimates that 3 million acute pesticide poisonings occur yearly worldwide and that these result in about 220,000 deaths,[1] although a report based on surveys of agricultural workers in developing countries suggested that the annual number of pesticide poisonings was closer to 25 million.[2] In the United States, the poison control centers compile statistics annually and show pesticide exposures as a separate category, but they do not separate agricultural and nonagricultural exposures. The summarized reports for the period 1991–1995 show that pesticides were responsible for about 4% of all reported poisonings, and fertilizers were implicated in 8,000 to 10,000 reported exposures per year.[3]

One study published in 1997 found that, during a 6-year period, 338,170 poisonings involving herbicides, insecticides, rodenticides, and fungicides had been recorded and that 25,418 of these poisonings resulted in hospitalization.[4] Another study estimated that between 20,000 and 40,000 occupational poisonings per year may occur in the United States (this estimate includes, in line with Environmental Protection Agency [EPA] definitions, poisonings from disinfectants, but not fertilizers).[5]

Agrochemical Groups

Total US use of all agrichemicals is difficult to estimate because nonagricultural use is poorly quantified. Pesticide usage is quantified annually by the US EPA. About 1.2 billion lbs of conventional pesticides

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is used annually in the United States. Seventy-seven percent of this is used in agriculture.[6]

Insecticides

Insecticides are among the most acutely toxic of the pesticides and are responsible for most pesticide poisonings. The two insecticide groups that represent the greatest hazard are the organophosphates and the carbamates. The pyrethroids are commonly used but have a low toxicity, and the organochlorines are used relatively rarely today.

Organophosphates and Carbamates

These chemicals cause acute toxic effects through their inhibition of acetylcholinesterase. The inhibition of this enzyme results in the accumulation of acetylcholine and the overstimulation of muscarinic and nicotinic receptors. The clinical symptoms include miosis, diaphoreses, salivation, lacrimation, urination, diarrhea, gastroenteric cramping, and emesis. Also included in the complex of symptoms and signs characteristic of an acute cholinergic inhibitor overexposure are bronchorrhea, bronchospasm, weakness, fasciculations, lightheadedness, headache, and, often, anxiety. Severe intoxication can lead to loss of consciousness and even death if central respiratory depression, worsened by mechanical factors, such as brochospasm, muscle weakness, and secretory obstruction, occurs.

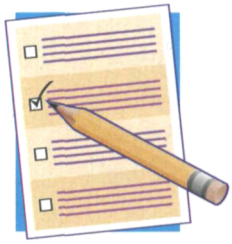
The initial diagnosis of overexposure must frequently depend on clinical assessment, because tests for cholinesterase—the enzyme used as an indicator of organophosphate and carbamate toxicity—are not available from most clinical laboratories on a nonmedical basis and so cannot be used to guide first contact therapy. Nevertheless, the laboratory may be asked to measure the level of cholinesterase activity and test for traces of the parent chemical or metabolic end products in various body fluids. Plasma and erythrocyte cholinesterase can be measured in blood samples.

In organophosphate overexposure, the enzyme toxin complex undergoes "aging" and is transformed into an irreversibly inhibited enzyme. While some reactivation of unaged complex can occur in sample processing and cause the estimate of the degree of inhibition to be inaccurately low, the test will frequently confirm that overexposure occurred. Note, however, that the normal ranges for erythrocyte cholinesterase and serum cholinesterase are wide and that symptoms of toxicity can occur in patients with values within the normal range. Consequently, calculating the percentage of enzyme activity inhibition for a particular person requires the availability of a preexposure or postrecovery level for that person. In most cases, a preexposure measurement will not exist, so comparing tests done some months apart will be necessary (acetylcholinesterase recovers at the rate of RBC replacement, and plasma cholinesterase recovers at a rate of roughly 1.2% per day). For the comparison to be valid, the test methods must be comparable (and they will preferably be identical).

Urinary metabolites of organophosphates (the di-alkyl-phosphates) can be measured in urine up to several days after exposure has ceased by use of gas chromatography (GC). Some organophosphates have unique metabolites, but determining the occurrence of exposure to others may require the measurement of multiple metabolites. Furthermore, the amount of a pesticide metabolite in urine correlates only rarely with the severity of the toxic effects.

N-methyl carbamates, like organophosphates, inhibit erythrocyte and serum cholinesterase. Unlike organophosphates, *N*-methyl carbamates do not go through an aging process and are considered competitive and reversible inhibitors of the enzyme. In workers with overexposure to *N*-methyl carbamates, blood must be tested rapidly and with minimal dilution. One method that uses a scintillation counter to measure the transformation of radioactive acetate into an organic solvent phase and thus gauge the level of activity of the cholinesterase in the sample is available for measuring inhibition due to carbamates. The method requires little manipulation of the sample and, therefore, will not lead to dilutional false-negative results due to reactivation.[7,8]

Urinary metabolites of certain *N*-methyl carbamates can be detected in urine. The EPA handbook on pesticide poisonings[9] identifies several unique metabolites of *N*-methyl carbamates, including α-napthol from carbaryl, isopropoxyphenol from propoxur, carbofuran phenol from carbofuran, and aldicarb sulfone and nitrile from aldicarb. The handbook also recognizes that tests for the presence of these metabolites are complicated and not generally available.



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Pyrethroids

Pyrethroids are a widely used group of insecticides with low levels of human toxic effects. Based on synthetic analogs of the natural insecticide pyrethrum, which is derived from chrysanthemums, pyrethroids are more environmentally stable, are less allergenic, and have higher and broader insect toxicity than pyrethrum. The chemicals interfere with sodium channel action and, much like organochlorines, cause overexcitation of excitable tissues and ultimately muscular paralysis. Symptoms reported by overexposed workers include tingling, burning, and numbness of extremities and mucous membranes. High-level exposure may induce prolonged-course muscular fasciculations, tremors, and seizures, but human intoxications are rare. Testing for pyrethroids involves measuring serum and urinary metabolites or parent compounds using GC, gas-liquid chromatography, or high-pressure liquid chromatography. The chemicals can be detected unchanged in urine but are excreted rapidly,[10] and presently the assay does not appear to be available for clinical use. Substantial organ damage does not seem to be a usual consequence of pyrethroid exposure, and, except in the rare cases of death, recovery has been reported to be complete.[11]

Organochlorines

Few organochlorines are still on the market in the United States. One of these, endosulfan, is related to the cyclodienes (dieldrin, endrin, and heptachlor, which are all now banned). Endosulfan appears to act by affecting the function of the γ-aminobutyric acid receptors, bringing about increased irritability in the central nervous system. This rapidly metabolized pesticide can cause seizures, and subsequent persistent cognitive dysfunction has been identified in humans after acute intoxication. Testing of blood samples for the parent compound involves GC with electron capture.[12]

Another important and as yet unbanned organochlorine is lindane. Used widely for control of ectoparasites,[13] the chemical also is sold abroad as an agricultural insecticide. Overexposure to lindane has been associated with nausea, vomiting, headache, ataxia, tremors, and tonic-clonic seizures. It has a half-life in the body of 2 to 3 days and can be measured in blood by using GC–electron capture techniques. Despite its brief half-life, it is detectable in the general human population at low levels, a fact that testifies to its broad distribution in the environment but also complicates testing in exposed subjects. Endosulfan and lindane can induce liver and kidney damage given sufficient exposure.

Fig 1. Pesticides are commonly applied with the use of a "crop duster" in both developed and developing countries.

Fungicides

Fungicides, which generally result in low levels of acute toxic effects in humans, include wood preservatives, as well as agents that closely resemble medicinal preparations designed to treat fungal infections in humans.

Pentachlorophenol

Pentachlorophenol, a common wood preservative, has been used as a herbicide, a fungicide, and an insecticide. The clinical effects of overexposure are hypermetabolism and hyperthermia due to the uncoupling of oxidative phosphorylation. Testing for the presence of pentachlorophenol can be done in blood and urine samples by using GC mass spectroscopy. The chemical has an excretion half-life of 12 days and is excreted principally through urine. The ubiquity of this chemical is such that 72% of a US population sample contained an average of 6.3 mg/mL in urine.

Thiocarbamates

Several other fungicides, including the dithiocarbamates, occasionally have been responsible for human intoxication. These chemicals, unlike the N-methyl carbamates, do not inhibit cholinesterase and generally are of low toxicity. They are metabolized to carbon disulfide in vivo, and this metabolite may be responsible for some of their toxicity. They have been associated with liver, renal, and peripheral neuropathic injury in

Fig 2. Orchards often use airblast sprayers to ensure consistent application of pesticides. Photo courtesy the Pacific Northwest Agricultural Safety and Health Center. Photographer Richard Fenske.

heavily overexposed workers.[14] Among their characteristics is an ability to interfere with thyroid function and alcohol metabolism. They have been shown also to interfere with radioactive iodine uptake in the thyroid, and prolonged exposure may lead to the development of goiter. Recently exposed subjects may experience a disulfiram-like reaction after the ingestion of alcohol.[9]

Maneb and zineb can be identified in urine by using GC or high-pressure liquid chromatography.[10] The results of exposure to metal ion with which mancozeb is complexed (manganese) have raised questions about its association with Parkinson disease. There is a known association between manganese and a parkinsonian-like syndrome in manganese miners, and researchers have found a similar syndrome among overexposed workers in agriculture.[15] Manganese can be measured in body fluids by atomic absorption, but, because it is a normal constituent of bodily fluids, the presence of added amounts of the metal may be difficult to determine.[16]

Nitrophenolics and Nitrocresolics

These fungicides, like pentachlorophenol, cause toxic effects in humans principally by increasing the metabolic rate. They uncouple oxidative phosphorylation, which leads to futile metabolic energy production. Heavy exposure can result in severe hyperthermia and seizures. They have the unique characteristic of staining skin, hair, and fingernails yellow and, if absorbed in sufficient quantity, can cause yellowing of the sclera and urine as well. They can be detected in serum and urine spectrophotometrically or by gas-liquid chromatography. Treatment of the hypermetabolic patient should not await laboratory results; therapy should be instituted based on clinical evaluation, although laboratory confirmation should be sought.

Herbicides

Most herbicides present little risk of acute toxic effects to humans. But several have been identified as causing significant human illness. Paraquat is one of the most toxic herbicides on the market. The median lethal dose for humans is estimated to be 35 mg/kg. A postemergent-contact pesticide (ie, sprayed on grown or growing weeds), paraquat is used worldwide and still available in the United States. The pesticide is acutely corrosive to normal skin and mucous membranes. Dermal penetration through intact skin is not high, and most acute episodes of toxic effects result from ingestion. Ingestion leads to multiple organ failure, including pulmonary, liver, and renal failure. Usually, the gastrointestinal tract also is damaged severely by contact with the pesticide. Serum and urine samples can be tested for the presence of the paraquat. One semiquantitative test for the chemical involves adding 1% sodium dithionite in 1N sodium hydroxide to the urine. Blue indicates the presence of paraquat in excess of 0.5 mg/L. Negative and positive controls should be run to ensure that the dithionite has not been oxidized in storage. Gas chromatography, spectrophotometry, liquid chromatography, and radioimmunoassays can be used on blood and urine samples to achieve accurate quantification. The half-life of the chemical is brief, so samples must be obtained promptly. Diquat, a herbicide in the same family as paraquat, also can be identified in urine samples, but its presence is indicated by green when the dithionite test is performed.[9]

Fumigants

Fumigants comprise a broad group of chemicals used for fumigating food, structures, vehicles, and soil. Included in the group are halogenated and nonhalogenated volatile organics, such as dichloropropene; inorganic gases, such as phosgene; carbon disulfide; and sulfur dioxide. Several fumigants are used principally in agriculture. Two important fumigants include the nematocide dichloropropene and the grain storage fumigant phosphene (derived from aluminum phosphide).

Overexposure to dichloropropene may occur through skin contact with the liquid preparation or through inhalation of the volatilized gas.

Fig 3. Homes circle active orchards in Wenatchee, Washington. Urban development encroaching on farmland may create exposure opportunities to agrochemicals.

Dichloropropene is irritating to skin and mucous membranes, and overexposure has resulted in cardiac, respiratory, and central nervous system symptoms, including loss of consciousness. Elevation of liver enzyme levels was found in subjects overexposed to the chemical because of a spill, and a study 2 years later revealed some of the subjects were experiencing persistent cardiac, neurological, and headache symptoms. Death due to an oral ingestion resulted in gastrointestinal, pulmonary, liver, and renal damage. A method for detecting the primary metabolite in urine has been devised; it involves measuring the *N*-acetyl-L-cysteine derivative metabolite in urine.

Aluminum phosphide, when exposed to water, produces phosphine gas. Aluminum phosphide tablets often are placed in sealed spaces (such as a warehouse or silo) with the product to be fumigated and allowed to combine with ambient moisture to produce the toxic gas. Phosphine denatures oxyhemoglobin and other proteins. Exposure may manifest as nausea, abdominal pain, chest tightness, excitement, restlessness, agitation, and chills. More severe exposure may result in diarrhea, cyanosis, shortness of breath, and pulmonary edema (along with respiratory failure), and hypotension. Toxic effects in the kidney may result in proteinuria or glucosuria and, if very severe, renal failure, while toxic effects in the liver result in the elevation of transaminases and bilirubin. No specific methods were found to identify the compound in body fluids. It has been noted, however, that persons who have ingested or inhaled phosphine are said to emit an odor of decaying fish.

Fertilizers

Exposure to fertilizers that include ammonia compounds can occur occupationally or paraoccupationally, but the diagnosis is rarely problematic. Potentially the broadest population exposure occurs through ingestion of contaminated well water. Nitrates in water are converted to nitrites by gut flora, and the absorbed nitrites oxidize ferrous to ferric iron in the blood. The ferric ion state of hemoglobin iron is known as methemoglobin.[17] In high concentrations, methemoglobin may cause substantial tissue hypoxia. The normal levels of methemoglobin are less than 1%. Infants are particularly susceptible to methemoglobinemia because of their immature enzymatic systems, higher levels of the easily oxidized fetal hemoglobin, and lower intestinal pH, which facilitates the conversion of nitrates to nitrites.[17] Pregnant females and other persons with high oxygen needs or limited ventilatory capacity may also be at risk for the effects of above-normal levels of methemoglobin.[18] Laboratories are occasionally asked to determine the level of methemoglobin in blood. A chocolate brown color of the blood despite a high oxygen reading is an early hint that the level is high. Another quick method for confirming an above-normal level is to compare a drop of "suspected" blood with a drop of normal blood on filter paper. After drying, the suspected blood will be dark brown or gray if substantial methemoglobin is present.[17]

Toxic Effects and Tests for Detection of Selected Chemicals

Chemicals	Clinical Toxic Effects	Primary Detection Method	Other Options
Fertilizers			
Nitrates	Cyanosis	Methemoglobin	
Fumigants			
Dichloropropene	Chemical burns and neurologic, gastrointestinal, pulmonary, liver, and renal effects	*N*-acetylcysteine derivatives in urine	
Aluminum phosphide	Mucosal destruction, agitation, chills, pulmonary edema hypotension, and kidney and liver effects	No specific test found	Liver function tests and urinalysis for tissue effects
Fungicides			
Pentachlorophenol	Hypermetabolism	Urinary or blood levels by GLC	Fat sampling by GLC
Dithiocarbamates	Hypothyroidism, goiter, antabuse reaction	Urinary levels by GC, HPLC	Manganese levels (for maneb)
Nitrophenolics	Hypermetabolism, yellow staining of nails and skin	Urine or serum spectrophotometry	Urine or serum levels by GLC
Herbicides			
Paraquat or diquat	Chemical burns, pulmonary, renal, liver damage	Urine or serum levels by GC, spectrophotometry, LC	Urine or serum radioimmunoassay, qualitative with sodium dithionite
Insecticides			
Organophosphates	MD SLUDGE	Cholinesterase	Urinary alkylphosphates
Carbamates	MD SLUDGE	Cholinesterase (specialized low-dilution method)	Various urinary metabolites
Pyrethroids	Tingling, irritability, tremor, seizures	Urinary or serum levels by GC, GLC, HPLC	
Organochlorines	Seizures, liver, kidney damage	Plasma levels by GC-EC	Fat sampling by GC-EC

MD SLUDGE indicates miosis, diaphoreses, salivation, lacrimation, urination, diarrhea, gastroenteric cramping, and emesis; GC, gas chromatography; GLC, gas-liquid chromatography; HPLC, high-pressure liquid chromatography; EC, electron capture; LC, liquid chromatography.

The Clinical and Legal Role of Laboratories

Cases of acute illness resulting from agrochemical overexposure occasionally are faced by clinicians, but more common is the situation in which a patient who is not acutely ill has reason to think that overexposure might have occurred. Indeed, the exact nature of the exposure might not be clear, as agrochemicals are frequently applied in mixtures, and mild overexposure manifests with nonspecific symptoms. Furthermore, the clinician may be acquainted only casually with laboratory testing options and ask the laboratory to confirm or deny that an overexposure took place. Chemicals, their toxic effects, and tests to identify the chemicals are summarized in the Table.

Of course, the laboratory will probably not be able to provide confirmatory information with sufficient promptness to assist the clinician at the time of initial patient contact. Nevertheless, its confirmation that overexposure has occurred will at the least provide rock-solid grounds for warning the patient to avoid reexposure. Avoidance may involve disposal of a chemical presently being used by the patient, delay of the use of the chemical until complete recovery, or, in a workers' compensation case, loss of work time and the

filing of a workers' compensation claim. If litigation occurs, the clinician may be asked to confirm exposure, and the laboratory also may become involved in the legal process.

Conclusion

Many clinical laboratories are not equipped to perform the assays necessary to confirm overexposure to the agrochemicals described in this article. Any laboratory, however, can provide an essential service by promoting the knowledge of its employees about such overexposure and by acting as a resource for clinicians in need of advice. A laboratory's ability to communicate who can and will do testing on body fluids and how samples should be collected and transported will be viewed as a valuable asset by clinicians who are confronted only rarely by cases of agrochemical overexposure.

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