Toxicity of Pesticides [1]

O. Norman Nesheim, Frederick M. Fishel, and Mark Mossler[2]

This document describes how pesticides work on living things, so you can learn to reduce or eliminate human exposure.

Background

Pesticides are designed to control pests, but they can also be toxic (poisonous) to desirable plants and animals, including humans. Some pesticides are so highly toxic that very small quantities can kill a person, and almost any pesticide can make people ill if they are exposed to a sufficient amount. Because even fairly safe pesticides can irritate the skin, eyes, nose, or mouth, it is a good idea to understand how pesticides can be toxic so you can follow practices designed to reduce or eliminate your exposure and the exposure of others to them.

How Pesticides Enter the Body

Before a pesticide can harm you, it must be taken into the body. Pesticides can enter the body orally (through the mouth and digestive system); dermally (through the skin); or by inhalation (through the nose and respiratory system).

Oral Exposure

Oral exposure may occur because of an accident, but is more likely to occur as the result of carelessness, such as blowing out a plugged nozzle with your mouth, smoking or eating without washing your hands after using a pesticide, splashing concentrate while mixing, or eating fruit that has been recently sprayed with a pesticide containing residues above the tolerance set for the commodity by the Environmental Protection Agency. The seriousness of the exposure depends upon the oral toxicity of the material and the amount swallowed.

Dermal Exposure

Dermal (skin) exposure accounts for about 90% of the exposure pesticide users receive from nonfumigant pesticides. It may occur any time a pesticide is mixed, applied, or handled, and it often goes undetected. Both liquid pesticides and dry materials—dusts, wettable powders, and granules—can be absorbed through the skin.

The seriousness of dermal exposure depends upon:

- the dermal toxicity of the pesticide;
- rate of absorption through the skin;
- the size of the skin area contaminated;
- the length of time the material is in contact with the skin; and
- the amount of pesticide on the skin.

Absorption continues to take place on all of the affected skin area as long as the pesticide is in contact with the skin. The seriousness of the exposure is increased if the

1. This document is PI-13, one of a series of the Agronomy Department, UF/IFAS Extension. Original publication date July 1993. Revised July 2005 and February 2017. Visit the EDIS website at http://edis.ifas.ufl.edu.

2. O. Norman Nesheim, professor emeritus, Food Science and Human Nutrition Department; Frederick M. Fishel, professor, Agronomy Department, and director, Pesticide Information Office; and Mark Mossler, former Doctor of Plant Medicine, Agronomy Department; UF/IFAS Extension, Gainesville, FL 32611.

Use pesticides safely. Read and follow directions on the manufacturer's label.

The Institute of Food and Agricultural Sciences (IFAS) is an Equal Opportunity Institution authorized to provide research, educational information and other services only to individuals and institutions that function with non-discrimination with respect to race, creed, color, religion, age, disability, sex, sexual orientation, marital status, national origin, political opinions or affiliations. For more information on obtaining other UF/IFAS Extension publications, contact your county's UF/IFAS Extension office.

U.S. Department of Agriculture, UF/IFAS Extension Service, University of Florida, IFAS, Florida A & M University Cooperative Extension Program, and Boards of County Commissioners Cooperating. Nick T. Place, dean for UF/IFAS Extension.

contaminated area is large or if the material remains on the skin for a period of time.

Rates of absorption through the skin are different for different parts of the body. Usually, absorption through the forearm is the standard against which absorption rates in other areas of the body are tested. Absorption is over 11 times faster in the lower groin area than on the forearm (Table 1). Absorption through the skin in the genital area is rapid enough to approximate the effect of injecting the pesticide directly into the bloodstream.

Table 1. Parathion absorption rates through the skin on various bodily regions.

Body region	Percent relative absorption
Forearm	8.6
Palm of hands	11.8
Ball of foot	13.5
Abdomen	18.4
Scalp	32.1
Forehead	36.3
Ear canal	46.5
Genitalia	100

Inhalation Exposure

Inhalation exposure results from breathing pesticide vapors, dust, or spray particles. Like oral and dermal exposure, inhalation exposure is more serious with some pesticides than with others, particularly fumigant pesticides, which form gases.

Inhalation exposure can occur by breathing smoke from burning containers; breathing fumes from pesticides while applying them without protective equipment; and inhaling fumes while mixing and pouring pesticides. Some pesticides will have statements on their labels requiring the use of a specified respirator. Another means of inhalation exposure is smoking tobacco products containing pesticide residues.

Toxicity

Toxicity refers to the ability of a substance to produce adverse effects. These adverse effects may range from slight symptoms such as headaches to severe symptoms like coma, convulsions, or death. Poisons work by altering normal body functions. Most toxic effects are naturally reversible and do not cause permanent damage if prompt medical treatment is sought. Some poisons, however, cause irreversible (permanent) damage.

Toxicity is usually divided into two types, acute or chronic, based on the number of exposures to a poison and the time it takes for toxic symptoms to develop. Acute toxicity is due to short-term exposure and happens within a relatively short period of time, whereas chronic exposure is due to repeated or long-term exposure and happens over a longer period. (Table 2).

Table 2. Types of toxicity.

Type	Number of Exposures	Time for symptoms to develop
Acute	usually 1	immediate (minutes to hours)
Chronic	more than a few	one week to years

HOW TOXICITY IS MEASURED

All new pesticides are tested to establish the type of toxicity and the dose necessary to produce a measurable toxic reaction. In order to compare the results of toxicity tests done in different labs, there are strict testing procedures. Toxicity testing is extensive (involving many phases) and therefore expensive. Humans, obviously, cannot be used as test subjects, so toxicity testing is done with animals and plants. Since different species of animals respond differently to chemicals, a new chemical is generally tested in mice, rats, rabbits, and dogs. The results of these toxicity tests are used to predict the safety of the new chemical to humans.

Toxicity tests are based on two premises. The first premise is that information about toxicity in animals can be used to predict toxicity in humans. Years of experience have shown that toxicity data obtained from a number of animal species can be useful in predicting human toxicity, while data obtained from a single species may be inaccurate. The second premise is that by exposing animals to large doses of a chemical for short periods of time, we can predict human toxicity from exposure to small doses for long periods of time. Both premises have been questioned.

Chronic toxicity is tested using animal feeding studies. In these studies, the pesticide under investigation is incorporated into the daily diet and fed to animals from a very young to a very old age. These, as well as the reproductive effects studies, are designed to arrive at a No-Observable-Effect-Level (NOEL); that is, a level in the total diet that causes no adverse effect in treated animals when compared to untreated animals maintained under identical conditions. This NOEL is expressed on a mg/kg of body weight/day basis.

A Reference Dose (RfD), also known as Acceptable Daily Intake (ADI), is usually established at 1/100 of the NOEL, in order to add an additional margin of safety. The RfD (ADI) is the amount of chemical that can be consumed daily for a lifetime without ill effects.

ACUTE TOXICITY

The acute toxicity of a chemical refers to its ability to do systemic damage as a result of a one-time exposure to relatively large amounts of the chemical. A pesticide with a high acute toxicity may be deadly if even a very small amount is absorbed. The signal words on the label (Table 3) are based on the acute toxicity of the pesticide. Acute toxicity may be measured as acute oral (through the mouth), acute dermal (through the skin) and acute inhalation (through the lungs or respiratory system).

Acute Toxicity Measures

The commonly used term to describe acute toxicity is LD_{50}. LD means *lethal dose* (deadly amount) and the subscript 50 means that the dose was acutely lethal to 50% of the animals to whom the chemical was administered under controlled laboratory conditions. The test animals are given specific amounts of the chemical in either one oral dose or by a single injection, and are then observed for a specified time.

The lower the LD_{50} value, the more acutely toxic the pesticide. Therefore, a pesticide with an oral LD_{50} of 500 mg/kg would be much less toxic than a pesticide with an LD_{50} of 5 mg/kg. LD_{50} values are expressed as milligrams per kilogram (mg/kg), which means milligrams of chemical per kilogram of body weight of the animal. *Milligram* (mg) and *kilogram* (kg) are metric units of weight. Milligrams per kilogram is the same measure as parts per million. To put these units into perspective, 1 ppm is analogous to 1 inch in 16 miles or 1 minute in 2 years.

For example, if the oral LD_{50} of the insecticide parathion is 4 mg/kg, a dose of 4 parts of parathion for every million parts of body weight would be lethal to at least half of the test animals.

LD_{50} values are generally expressed on the basis of active ingredient. If a commercial product is formulated to contain 50 percent active ingredient, it would take two parts of the material to make one part of the active ingredient. In some cases, other chemicals mixed with the active ingredient for formulating the pesticide product may cause the toxicity to differ from that of the active ingredient alone.

Acute inhalation toxicity is measured by LC_{50}. LC means *lethal concentration*. Concentration is used instead of dose because the amount of pesticide inhaled in the air is being measured. LC_{50} values are measured in milligrams per liter. Liters are metric units of volume similar to a quart. The lower the LC_{50} value, the more poisonous the pesticide.

CHRONIC TOXICITY

Chronic toxicity refers to harmful effects produced by long-term exposure to pesticides. Less is known about the chronic toxicity of pesticides than is known about their acute toxicity, not because it is of less importance, but because chronic toxicity is gradual rather than immediate and is revealed in much more complex and subtle ways. While situations resulting in acute exposure (a single large exposure) do occur, they are nearly always the result of an accident or careless handling. On the other hand, people may be routinely exposed to pesticides while mixing, loading, and applying pesticides or by working in fields after pesticides have been applied.

Chronic Toxicity Measures

There is no standard measure like the LD_{50} for chronic toxicity. How chronic toxicity of chemicals is studied depends upon the adverse effect being studied. Chronic adverse effects may include carcinogenic effects (cancers), teratogenic effects (birth defects), mutagenic effects (genetic mutations), hemotoxic effects (blood disorders), endocrine disruption (hormonal problems), and reproductive toxicity (infertility or sterility).

Carcinogenesis (Oncogenesis)

Carcinogenesis means the production of malignant tumors. Oncogenesis is a generic term meaning the production of tumors which may or may not be carcinogenic. The terms tumor, cancer, or neoplasm are all used to mean an uncontrolled progressive growth of cells. In medical terminology, a cancer is considered a malignant (potentially lethal) neoplasm. Carcinogenic or oncogenic substances are substances that can cause the production of tumors. Examples are asbestos and cigarette smoke.

Teratogenesis

Teratogenesis is the production of birth defects. A teratogen is anything that is capable of producing changes in the structure or function of an embryo or fetus exposed before birth. An example of a chemical teratogen is the drug thalidomide, which caused birth defects in children when their mothers used it during their pregnancies. Measles virus infection during pregnancy has teratogenic effects.

Mutagenesis

Mutagenesis is the production of changes in genetic structure. A mutagen is a substance that causes a genetic change. Many mutagenic substances are oncogenic, meaning they also produce tumors. Many oncogenic substances are also mutagens.

Reproductive Toxicity

Some chemicals have effects on the fertility or reproductive rates of animals. Males or females can be affected.

Label Identification of Acute and Chronic Toxicity

To alert pesticide users to the acute toxicity of a pesticide, a signal word may appear on the label. Four different categories are used (Table 3). Signal words are used to tell the user whether the chemical is highly toxic, moderately toxic, slightly toxic, or relatively non-toxic. These label warnings are based, for the most part, on the chemical's acute toxicity. For example, the acute oral and acute dermal toxicity of a pesticide may be in the slightly toxic category. But if the acute inhalation toxicity is in the highly toxic category, the pesticide label will have the signal words for a highly toxic pesticide. The degree of eye or skin irritation caused by the pesticide also influences the signal word.

For chronic toxicity there is no comparable set of signal words like those used for acute toxicity. Instead, a statement identifying the specific chronic toxicity problem is sometimes used on the label. Such a statement might read "This product contains (name of chemical), which has been determined to cause tumors or birth defects in laboratory animals." Chronic toxicity warning statements may be accompanied by label directions to wear certain kinds of protective clothing when handling or working with the pesticide to minimize or eliminate exposure to the pesticide.

It is important to read the label to look for signal words identifying the product's acute toxicity and for statements identifying any chronic toxicity problem. A pesticide may be low in acute toxicity (signal word caution), but it may have a label statement identifying potential chronic toxicity.

Safety Factors

Extensive residue trials are conducted on crops to determine levels of the pesticide that remain in or on growing crops after treatment with the pesticide. These trials lead to the establishment of a tolerance for residues of the chemical on food commodities. A tolerance is the maximum allowable amount of the pesticide permitted in or on a specific food commodity at harvest. The directions for use found on the product label are written to assure that residues in food commodities are below the tolerance. The tolerance is set low enough to assure that even if someone ate only food items with residues of a given pesticide at the tolerance limit, there would still be a safety factor of at least 100 when compared to a level causing no observable effects in laboratory animals. This is, of course, a worst-case situation, since all crops on which the pesticide is registered for use would not be treated with the chemical, and in most cases residue levels would be well below the tolerance because pre-harvest intervals are almost invariably longer than the minimum period stated on the label. Further reduction of residues may occur in storage or from washing, trimming, and processing.

Dose-response

Dose-response is the measure of the amount of a given substance an organism must absorb to produce an effect. The extensive amount of data developed about a given pesticide is often used against it because this key piece of information is ignored. For example, some acute toxicity studies, which are designed to include dosage levels high enough to produce deaths, are cited as proof of the chemical's dangers. Chronic effects seen at very high doses in lifetime feeding studies are misinterpreted and considered as proof that no exposure to the chemical should be allowed.

Major improvements in analytical chemistry permit detection of the presence of chemicals at extremely low levels of parts per billion (ppb) and even sometimes parts per trillion (ppt). A certain chemical may have been found in a food or beverage, and the amount found is expressed in parts per million or parts per billion. Often, no information is provided to assist consumers in comprehending the meaning of these numbers. Frequently, this information neglects the issue of dose-response, the key principle of toxicology, which, simply stated, is "the dose makes the poison." The concentration of a chemical in any substance is meaningless unless it is related to the toxicity of the chemical and the potential for exposure and absorption. Chemicals of low toxicity such as table salt or ethyl alcohol can be fatal if consumed in large amounts. Conversely a highly toxic material may pose no hazard when exposure is minimal.

Monitoring for Residues

Monitoring foods for pesticide residues is carried out by the Food and Drug Administration (FDA) and the United States Department of Agriculture (USDA). Crops found to contain residues over the official tolerance (maximum legal level) established by the EPA must be destroyed. The threat of crop destruction with resultant financial loss is a strong incentive for farmers to observe use instructions on pesticide labels and thus assures that residues will be below established tolerances. Crops grown for export are often checked for residues by foreign residue laboratories

to assure that local tolerance limits are not exceeded. Lastly, market-basket surveys (analyses of food items from grocery stores) have confirmed the low exposure of the general public to pesticides in foods.

Hazard

Hazard is a function of the toxicity of a pesticide and the potential for exposure to it. We do not have control of the toxicity of a pesticide because toxicity is a given characteristic of a particular pesticide; however, we can have control over our exposure to pesticides. We achieve control over exposure by following several safety practices including the use of protective clothing and equipment (PPE).

All pesticides are hazardous if misused, no matter what their toxicity. All pesticides can be handled safely by using safety practices that minimize or eliminate exposure to them.

Federal laws regulating pesticides have placed the burden of proving safety of pesticide usage on the manufacturer. Hazard evaluation studies are generally done by scientific laboratories maintained by the manufacturer or through outside contract laboratories. Few products are subjected to the extensive and vigorous testing pesticides undergo before they are marketed. In fact, many promising pesticide products are *not* marketed because they do not pass the extensive toxicology testing. Older pesticide products that were registered before the current toxicology testing standards were established are being re-evaluated to ensure they meet current standards. Precautions and other safety information found on the product's label are based on information from these tests. By reading and following the directions on the label, users can minimize or eliminate hazards due to use of the pesticide to themselves and others.

Common Pesticide Poisonings

The pesticides most often implicated in poisonings, injuries, and illnesses, according to 2010 data from the American Association of Poison Control Center's Toxic Exposure Surveillance System, are listed in Table 4.

Cases listed as organophosphates (and the other categories as well) may also include other insecticides such as carbamates and organochlorine in a single product. Asymptomatic cases are included in Table 4 only.

This list canot be considered representative of all symptomatic poisonings because it only shows cases reported to Poison Control Centers. However, it does give a sense of the relative frequency and risk of poisoning from various agents or classes of agents. The relative frequency of cases generally reflects how widely a product is used in the environment. For example, a number of disinfectants occur in the top ten partly because they are far more commonly found in the home and work environment than other pesticides. Denominator information on the population at risk (numbers exposed) would be needed to better understand the relative risk of different pesticides. However, the main purpose is to give physicians a sense of what types of cases they are most likely to see in their practice.

Additional Information

Some of the preceding material was adapted from Pesticide Toxicities, Leaflet 21062, Division of Agricultural Sciences, University of California and the *Dose Makes the Poison* by Alice Ottoboni, Ph.D., Vincente Books.

Fishel, F. M. 2005. *Evaluation of pesticides for carcinogenic potential*. PI-37. Gainesville: University of Florida Institute of Food and Agricultural Sciences. http://edis.ifas.ufl.edu/PI074. Visited February 2017

National Pesticide Information Center (1-800-858-7378 or http://npic.orst.edu/). Visited February 2017

Poison Information Center Network (1-800-222-1222 or http://www.fpicn.org). Visited February 2017

Table 3. Acute toxicity measures and warnings.

		Categories of Acute Toxicity			
		LD_{50}	LC_{50}		
Categories	**Signal Word**	**Oral mg/kg**	**Dermal mg/kg**	**Inhale mg/l**	**Oral Lethal Dose**[1]
I Highly Toxic	DANGER, POISON (skull and crossbones)	0 to 50	0 to 200	0 to 0.2	a few drops to a teaspoonful
II Moderately Toxic	WARNING	50 to 500	200 to 2,000	0.2 to 2.0	over a teaspoonful to one ounce
III Slightly Toxic	CAUTION	500 to 5,000	2,000 to 20,000	2.0 to 20	over one ounce to one pint
IV Relatively Non-toxic	CAUTION (or no signal word)	5,000+	20,000 +	20 +	over one pint to one pound

[1] Probable for a 150 lb.-person.

Table 4. Selected pesticide single exposures reported to the National Poison Data System (2015) http://www.aapcc.org/datasystem/.

Pesticide or pesticide class	Child <5 years	6–12 years	13–19 years	≥20 years	Unknown age	Total
Pyrethroid insecticides	5,260	1,034	905	12,115	2,614	21,928
Anticoagulant rodenticides	6,071	156	80	641	177	7,125
Borates/boric acid	5,850	151	54	524	147	6,726
Pyrethrin insecticides	1,778	422	213	2,601	614	5,628
Unknown insecticides	1,059	195	178	2,174	690	4,296
Insect repellents with DEET	2,063	526	184	903	258	3,934
Glyphosate	729	122	81	1,792	393	3,117
Organophosphate insecticides	594	107	71	1,130	284	2,186
Chlorophenoxy herbicides	388	69	36	829	184	1,506
Fungicides	148	23	33	390	110	704
Fumigants	53	30	16	300	61	460
Total all pesticides and disinfectants	**34,163**	**3,837**	**2,410**	**30,641**	**7,517**	**78,568**