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ABCs OF TOXICOLOGY: BASIC DEFINITIONS

The world of toxicology can be mind-boggling. Many of us have been in situations in which we've gathered together information about chemicals and their health effects, only to find that we don't know how to decipher it. Whether the information comes from journal articles, government documents, or newspapers, radio and TV, we can't figure out what it all means.

This article provides a brief introduction to basic toxicology terms. We hope this information will help you make sense of what you read and what you hear. It focuses on pesticides rather than all chemical and physical agents, and on humans as opposed to other living organisms.

What is Toxicology?

Toxicology is often defined as "the study of the nature and mechanism of toxic effects of substances on living organisms and other biologic systems."[1] In simpler words, "Toxicology is the study of the adverse effects of chemical and physical agents on living organisms."[2]

Frequency and Duration of Exposure

Frequency of exposure refers to the number of times a person is exposed and the time between exposures. Duration of exposure can be acute, subchronic, or chronic. Acute exposure is once or twice in a short period of time, such as a week or less. Chronic exposure is long-term or lifetime exposure and spans at least 10 percent of a lifetime. For humans, this is considered seven or more years. Subchronic exposure is somewhere in between acute and chronic, and it extends from more than a week to less than 7 years.[2,3]

Routes of Exposure

For humans, there are three primary routes of exposure: inhalation (by breathing); oral (by eating or drinking); and dermal (through the skin).[2,4]

Inhalation exposure can be acute, for example breathing a chemical during short-term use, or chronic, for example longer-term inhalation of chemicals in an indoor environment.[5]

Oral exposure can be direct (eating or drinking) or indirect such as from hand to mouth contact after touching a chemical. It can also be either acute or chronic.[5]

Dermal exposure is usually short-term from splashing or spilling the chemical during use or from contact with treated surfaces. It can result in damage to the skin or absorption through the skin into the body. Dermal exposure can also be chronic if it occurs repeatedly over a long period of time.[5]

A minor route of exposure is ocular (through the eye).[4] Ocular exposure is also usually short term and results from splashing or spilling the chemical during use or from rubbing the eye with contaminated hands after touching treated surfaces.[5]

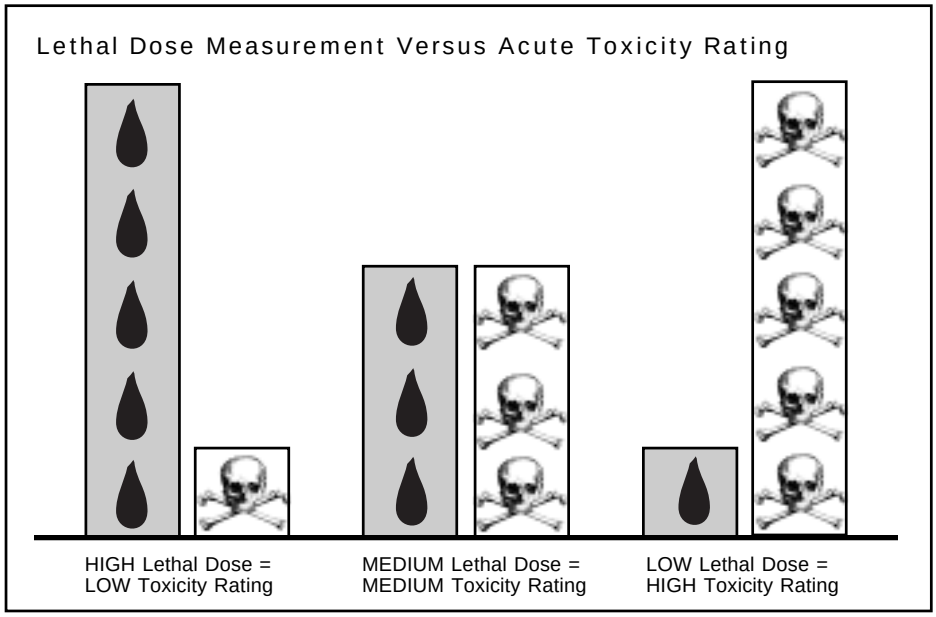
Health Effects

Commonly studied health effects from chemical exposure include the ability to cause cancer (carcinogenicity), effects on organs, reproductive effects, and developmental effects. Lung cancer, skin cancer, leukemia, breast cancer, and prostate cancer have all been associated with chemical exposure. Reproductive effects involve a decrease or loss of fertility. Developmental effects are those that lead to death of the fetus (fetotoxicity) or those that cause birth defects (teratogenicity). Organs often targeted by chemicals include the liver, kidneys, and nervous system.[6]

Other important health effects include impairment of the immune system, genetic damage (mutagenicity), and inhibition of the body's ability to break down chemicals.[7]

Toxicity Measurements

The dose is the amount of exposure to a potentially toxic agent and is



A high lethal dose means low acute toxicity, and a low lethal dose means high acute toxicity.

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usually measured in milligrams per kilogram (mg/kg), or mg per liter (mg/l) where mg is the amount of chemical present, kg refers to the weight of the person or animal exposed and l is a liter of air.[5] The toxicity of chemicals is often measured using what is called an LD_{50} (lethal dose) or an LC_{50} (lethal concentration). The LD_{50} and the LC_{50} refer to the dose that produces death in half of the test animals[2] (usually rats and mice). A high LD_{50} or LC_{50} implies a lower toxicity because more of the chemical is required to result in death. A low LD_{50} or LC_{50} implies a higher toxicity; just a small amount of the chemical results in death of 50 percent of the population being tested.[2] Both the LD_{50} and LC_{50} measure acute effects, and therefore provide no information about a chemical's connection to chronic (long-term) health effects. Another problem with using LD_{50}s or LC_{50}s as a measure of toxicity is that when researchers calculate them they usually do so based on exposure to only one chemical, yet "in the real world we are not exposed to only one chemical at a time."[2]

The Environmental Protection Agency (EPA) requires that pesticide products be labeled with a signal word (danger, warning or caution). The signal words refer to toxicity categories established by the EPA. There are 4 categories, with I (danger) being the most toxic and III or IV (caution) being the least toxic. EPA assigns pesticide products' toxicity categories based on five acute toxicity tests.[8] Like the LD_{50} or LC_{50}, they do not provide information about many other effects which are associated with exposure to pesticide products. (See "Signal Words on Pesticide Labels Are Based on Limited Information," this page.)

Metabolism and Distribution

Metabolism refers to how the body breaks down a chemical, what the chemical turns into in the body, and how fast the chemical is processed. In people, the primary organ for breaking down chemicals is the liver.

Distribution describes where the chemical accumulates in the body. If a chemical is water-soluble it will be distributed throughout the body, as our bodies are largely made of water. If it is fat-soluble it may accumulate in body fat. Chemicals can also accumulate in bones or other organs.[2]

Variability and Susceptibility

How the body responds to exposure to chemical exposure depends a great deal on the individual. Certain populations of people are generally more sensitive, including the young and the old and those with compromised immune systems or livers. Males and females may respond differently to chemical exposures and are at risk for different health effects. Some people are more susceptible to chemical exposure and more likely to suffer health effects because of their genetic make-up.[2] People with previous chemical exposure may be more sensitive to exposure to the same chemical or other chemicals in the future.[5]

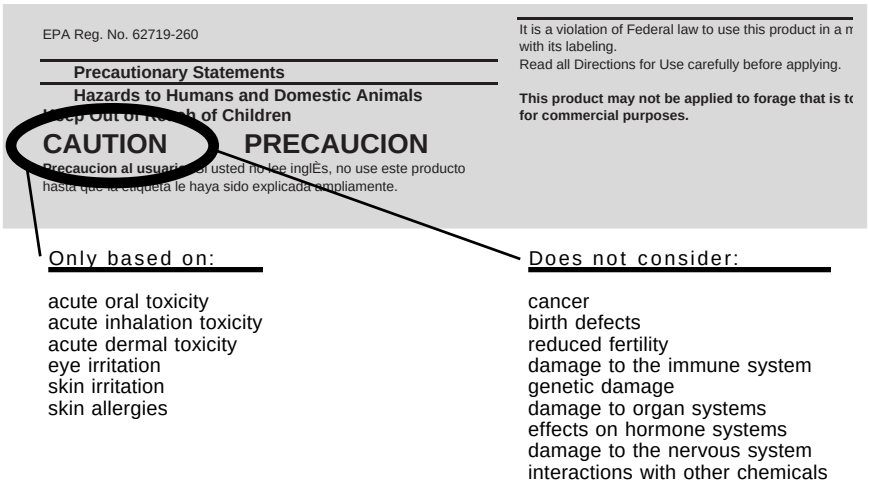
Summary

The adverse effects of a chemical depend on its toxicity, how people are exposed to the chemical, and each person's individual susceptibility. Exposure to chemical agents can lead to a wide range of health effects which may be expressed immediately or take years to develop. The toxicity ratings on pesticide labels are limited in that they refer only to acute toxicity.

Scientific journals, government documents, and the media all provide information about specific health effects associated with exposure to pesticides. A basic understanding of toxicology terms will help you understand these materials and use them to help reduce pesticide use in your community. Need more details? NCAP can help. Call or e-mail us!

—Megan Kemple

Signal Words (Danger, Warning, Caution) on Pesticide Labels Are Based on Limited Information



The signal word on a pesticide label is based only on acute toxicity tests.

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ABCs OF TOXICOLOGY, PART 2: DOSE AND RESPONSE

It might seem unlikely that a 16th century physician and alchemist who made his reputation by publicly burning classical medical books could be at the foundation of our pesticide regulatory system, but many pesticide activists have heard his writing repeatedly quoted by those who seek to minimize pesticide hazards.

This article will explain what connects this scholar from 500 years ago to current pesticide use, and how pesticide activists can best respond to the arguments from pesticide proponents based on his ideas.

Paracelsus

Paracelsus was born in Switzerland in 1493. Among his many accomplishments, he wrote the best clinical description of syphilis (of his day); understood that miners' silicosis was caused by breathing in minerals and was not a punishment for sins; and refused to accept the value of the pills and salves used as medicine at that time.[1] He also wrote, "All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison."[2] Now called the dose-response relationship, that concept has become the principle "on which the science of toxicology is based."[3]

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Caroline Cox is JPR's editor.

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What Is a Dose-Response Relationship?

A dose-response relationship "defines the potency of a chemical."[4] In other words, it describes how a chemical's effects (on people, laboratory animals, wildlife, etc.) change as exposure to the chemical increases. Although Paracelsus did not specify any quantitative details in his often-quoted sentences, the dose-response curve that is used in standard pesticide risk assessments (except for some cancer-causing pesticides)[5] has two important features. (See Figure 1.) First, it has a threshold. Below this threshold dose, no response can be measured.[5] Second, the response increases with increasing dose until it reaches maximum effects and then doesn't increase any more.[3]

How Does Pesticide Regulation Depend on Dose-Response Relationships?

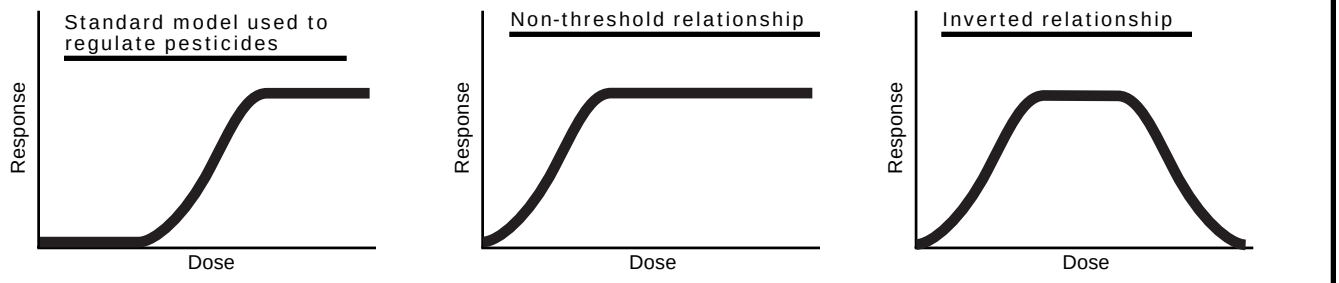
Pesticide regulation today assumes that almost all pesticides fit the relationship described above. In particular, the U.S. Environmental Protection Agency (EPA) and the other agencies and institutions that conduct pesticide risk assessments in general assume that they can identify a threshold dose or exposure. Exposures below this threshold are "safe," and do not cause problems. The setting of acceptable contamination levels on food (tolerances) as well as decisions about registering particular uses of a pesticide are made using this threshold concept.[6,7]

What's Changed Since Paracelsus?

Modern toxicology has shown that the standard pesticide dose-response relationship doesn't represent the complexities of interactions with toxic chemicals. Pesticide regulation hasn't kept up with these changes, but they're important! Recent significant advances include the following concepts:

Allergies: The shape of a dose-response relationship for allergic re-

Figure 1
Dose-Response Relationships



Sources: Ref. # 3, 4, and 13.

sponses can be completely different from the standard curve.[3] People who are allergic to a particular substance can have a significant reaction to even a tiny exposure. Allergies to pesticides have not been well studied, but a survey in California indicates that they seem to be surprisingly common. California's Department of Health Services found that almost 16 percent of Californians reported that they were "allergic or unusually sensitive to everyday chemicals."[8]

Special susceptibility of children: The standard pesticide dose-response curve fails to recognize "the exquisite sensitivity"[9] of fetuses, babies, and children. Their organ systems are developing and their exposure to chemicals, for their size, can be higher than adults.[8] For example, a new study from the Children's Cancer Group links children's brain cancers with exposure to pesticides before birth or during childhood.[10] This is a "response" that would be entirely missing from the standard dose-response relationship based on testing of adult laboratory animals. In 1996, Congress authorized EPA to use "an additional tenfold margin of safety"[11] to protect children, but otherwise left intact the use of the standard dose-response relationship.

Individual ability to detoxify pesticides: Every person is different, but the use of standard dose-response relationships omits these individual differences. For example, a study of workers at a Bayer AG facility who handled insecticides found that in certain individuals detoxification occurred slowly. These individuals more often showed signs of pesticide poisoning than individuals whose bodies were able to quickly remove the pesticide. For some of the pesticides studied, about half of the workers studied had slow detoxification abilities.[12]

Response relationships without a threshold: Not all dose-response relationships have thresholds.[4] This means that there is not a dose that is too low to exert adverse effects.[13] For example, a U.S. Food and Drug Administration study of hormone disruption in turtles found that every dose tested of the hormone estradiol changed the sex ratio. The lowest dose

USDA/ Doug Wilson

> "By insisting that only an old and simplistic dose-response relationship can be relevant to pesticides, pesticide proponents are hiding from modern toxicology."

was minuscule, 400 trillionths of a gram per egg. The scientists who conducted the study concluded that similar nonthreshold dose-response relationships will be "frequently encountered."[13] Another example is the insecticide chlorpyrifos; scientists from Duke University have found developmental effects at low doses that cause "no overt signs of toxicity."[14]

Inverted dose-response relationships: In the standard pesticide dose-response relationship, responses increase as dose increases. However, some chemicals have an inverted relationship and higher doses of the chemical "actually inhibit some responses that are stimulated by much lower doses."[15] Examples come from recent studies of bisphenol A, used in plastics and as an inert ingredient in pesticides. At "environmentally relevant"[16,17] concentrations, bisphenol A changed the developmental rate of mouse embryos[16] and altered the structure of breast tissue in adolescent mice in a way that is associated with breast cancer.[17] In both cases, researchers found that low doses had a greater effect than the higher doses.

Summing Up

Pesticide regulation needs to be based on good science, making continuous use of current research and the increased understanding that comes with it. By insisting that only an old and simplistic dose-response relationship can be relevant to pesticides, pesticide proponents are hiding from modern toxicology. Five hundred years ago, Paracelsus was actually searching for newer and better ways to understand how chemicals interact with the human body, not accepting obsolete ideas. Pesticide regulation today needs to follow his example.— *Caroline Cox*

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