

# DOSE-RESPONSE RELATIONSHIPS IN TOXICOLOGY

"The right dose differentiates a poison and a remedy." Paracelsus

## **INTRODUCTION**

The science of toxicology is based on the principle that there is a relationship between a toxic reaction (the response) and the amount of poison received (the dose). An important assumption in this relationship is that there is almost always a dose below which no response occurs or can be measured. A second assumption is that once a maximum response is reached any further increases in the dose will not result in any increased effect.

One particular instance in which this dose-response relationship does not hold true, is in regard to true allergic reactions. Allergic reactions are special kinds of changes in the immune system; they are not really toxic responses. The difference between allergies and toxic reactions is that a toxic effect is directly the result of the toxic chemical acting on cells. Allergic responses are the result of a chemical stimulating the body to release natural chemicals which are in turn directly responsible for the effects seen. Thus, in an allergic reaction, the chemical acts merely as a trigger, not as the bullet.

For all other types of toxicity, knowing the dose-response relationship is a necessary part of understanding the cause and effect relationship between chemical exposure and illness. As Paracelsus once wrote, "The right dose differentiates a poison from a remedy." Keep in mind that the toxicity of a chemical is an inherent quality of the chemical and cannot be changed without changing the chemical to another form. The toxic effects on an organism are related to the amount of exposure.

## **MEASURES OF EXPOSURE**

Exposure to poisons can be intentional or unintentional. The effects of exposure to poisons vary with the amount of exposure, which is another way of saying "the dose." Usually when we think of dose, we think in terms of taking one vitamin capsule a day or two aspirin every four hours, or something like that. Contamination of food or water with chemicals can also provide doses of chemicals each time we eat or drink. Some commonly used measures for expressing levels of contaminants are listed in table 1. These measures tell us how much of the chemical is in food, water or air. The amount we eat, drink, or breathe determines the actual dose we receive.

Concentrations of chemicals in the environment are most commonly expressed as ppm and ppb. Government tolerance limits for various poisons usually use these abbreviations. Remember that these are extremely small quantities. For example, if you put one teaspoon of salt in two gallons of water the resulting salt concentration would be approximately 1,000 ppm and it would not even taste salty!

**Table 1.** Measurements for Expressing Levels of Contaminants in Food and Water.

Dose	Abbrev	Metric. equivalent	Abbrev	Approx. amt. in water
parts per million	ppm	milligrams per kilogram	mg/kg	1 teaspoon per 1,000 gallons
parts per billion	ppb	micrograms per kilogram	ug/kg	1 teaspoon per 1,000,000 gallons

### **DOSE-EFFECT RELATIONSHIPS**

The dose of a poison is going to determine the degree of effect it produces. The following example illustrates this principle. Suppose ten goldfish are in a ten-gallon tank and we add one ounce of 100-proof whiskey to the water every five minutes until all the fish get drunk and swim upside down. Probably none would swim upside down after the first two or three shots. After four or five, a very sensitive fish might. After six or eight shots another one or two might. With a dose of ten shots, five of the ten fish might be swimming upside down. After fifteen shots, there might be only one fish swimming properly and it too would turn over after seventeen or eighteen shots.

The effect measured in this example is swimming upside down. Individual sensitivity to alcohol varies, as does individual sensitivity to other poisons. There is a dose level at which none of the fish swim upside down (no observed effect). There is also a dose level at which all of the fish swim upside down. The dose level at which 50 percent of the fish have turned over is known as the ED50, which means effective dose for 50 percent of the fish tested. The ED50 of any poison varies depending on the effect measured. In general, the less severe the effect measured, the lower the ED50 for that particular effect. Obviously poisons are not tested in humans in such a fashion. Instead, animals are used to predict the toxicity that may occur in humans.

One of the more commonly used measures of toxicity is the LD50. The LD50 (the lethal dose for 50 percent of the animals tested) of a poison is usually expressed in milligrams of chemical per kilogram of body weight (mg/kg). A chemical with a small LD50 (like 5 mg/kg) is very highly toxic. A chemical with a large LD50 (1,000 to 5,000 mg/kg) is practically non-toxic. The LD50 says nothing about non-lethal toxic effects though. A chemical may have a large LD50, but may produce illness at very small exposure levels. It is incorrect to say that chemicals with small LD50s are more dangerous than chemicals with large LD50s, they are simply more toxic. The danger, or risk of adverse effect of chemicals, is mostly determined by how they are used, not by the inherent toxicity of the chemical itself.

The LD50s of different poisons may be easily compared; however, it is always necessary to know which species was used for the tests and how the poison was administered (the route of exposure), since the LD50 of a poison may vary considerably based on the species of animal and the way exposure occurs. Some poisons may be extremely toxic if swallowed (oral exposure) and not very toxic at all if splashed on the skin (dermal exposure). If the oral LD50 of a poison were 10 mg/kg, 50 percent of the animals who swallowed 10 mg/kg would be expected to die and 50 percent to live. The LD50 is determined mathematically, and in actual tests using the LD50, it would be unusual to get an exact 50% response. One test might produce 30% mortality and

another might produce 70% mortality. Averaged out over many tests, the numbers would approach 50%, if the original LD50 determination was valid.

The potency of a poison is a measure of its strength compared to other poisons. The more potent the poison, the less it takes to kill; the less potent the poison, the more it takes to kill. The potencies of poisons are often compared using signal words or categories as shown in the example in table 2.

The designation toxic dose (TD) is used to indicate the dose (exposure) that will produce signs of toxicity in a certain percentage of animals. The TD50 is the toxic dose for 50 percent of the animals tested. The larger the TD the more poison it takes to produce signs of toxicity. The toxic dose does not give any information about the lethal dose because toxic effects (for example, nausea and vomiting) may not be directly related to the way that the chemical causes death. The toxicity of a chemical is an inherent property of the chemical itself. It is also true that chemicals can cause different types of toxic effects, at different dose levels, depending on the animal species tested. For this reason, when using the toxic dose designation it is useful to precisely define the type of toxicity measured, the animal species tested, and the dose and route of administration.

**Table 2.** Toxicity Rating Scale and Labeling Requirements for Pesticides.

Category	Signal word required on label	LD50 oral mg/kg(ppm)	LD50 dermal mg/kg(ppm)	Probable oral lethal dose
I highly toxic	DANGER-POISON (skull and crossbones)	less than 50	less than 200	a few drops to a teaspoon
II moderately toxic	WARNING	51 to 500	200 to 2,000	over 1 teaspoon to 1 ounce
III slightly toxic	CAUTION	over 500	over 2,000	over 1 ounce
IV practically non-toxic	none required			

Toxicity assessment is quite complex, many factors can affect the results of toxicity tests. Some of these factors include variables like temperature, food, light, and stressful environmental conditions. Other factors related to the animal itself include age, sex, health, and hormonal status.

The NOEL (no observable effect level) is the highest dose or exposure level of a poison that produces no noticeable toxic effect on animals. From our previous fish example, we know that there is a dose below which no effect is seen. In toxicology, residue tolerance levels of poisons that are permitted in food or in drinking water, for instance, are usually set from 100 to 1,000 times less than the NOEL to provide a wide margin of safety for humans.

The TLV (threshold limit value) for a chemical is the airborne concentration of the chemical (expressed in ppm) that produces no adverse effects in workers exposed for

eight hours per day five days per week. The TLV is usually set to prevent minor toxic effects like skin or eye irritation.

Very often people compare poisons based on their LD50's and base decisions about the safety of a chemical based on this number. This is an over-simplified approach to comparing chemicals because the LD50 is simply one point on the dose-response curve that reflects the potential of the compound to cause death. What is more important in assessing chemical safety is the threshold dose, and the slope of the dose-response curve, which shows how fast the response increases as the dose increases. Figure 1 shows examples of dose-response curves for two different chemicals which have the same LD50. Which of these chemicals is more toxic? Answer this question for doses below the LD50 and it is chemical A which is more toxic, at the LD50 they are the same, and above the LD50, chemical B is more toxic. While the LD50 can provide some useful information, it is of limited value in risk assessment because the LD50 only reflects information about the lethal effects of the chemical. It is quite possible that a chemical will produce a very undesirable toxic effect (such as reproductive toxicity or birth defects) at doses which cause no deaths at all.

A true assessment of chemical toxicity involves comparisons of numerous dose-response curves covering many different types of toxic effects. The determination of which pesticides will be Restricted Use Pesticides involves this approach. Some Restricted Use Pesticides have very large LD50s (low acute oral toxicity), however, they may be very strong skin or eye irritants and thus require special handling.

The knowledge gained from dose-response studies in animals is used to set standards for human exposure and the amount of chemical residue that is allowed in the environment. As mentioned previously, numerous dose-response relationships must be determined, in many different species. Without this information, it is impossible to accurately predict the health risks associated with chemical exposure. With adequate information, we can make informed decisions about chemical exposure and work to minimize the risk to human health and the environment.

**DISCLAIMER:** The information in this brief does not in any way replace or supersede the information on the pesticide product label/ing or other regulatory requirements. Please refer to the pesticide product label/ing.

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