Estimating the Toxicity of a Chemical (Chapters 14, 16)

SUPPLEMENT 17

Scientists Use Live Laboratory Animals to Estimate Toxicity

The most widely used method for determining toxicity is to expose a population of live laboratory animals to measured doses of a specific substance under controlled conditions. Laboratory-bred mice and rats are widely used because they are small, they can reproduce rapidly under controlled laboratory conditions, and as mammals, their systems function somewhat like human systems do.

Animal tests take 2–5 years, involve hundreds to thousands of test animals, and cost as much as $2 million per substance tested. Such tests can be painful to the test animals and can kill or harm them. The goal is to develop data on the responses of the test animals to various doses of a chemical, but estimating the effects of low doses is difficult.

Animal welfare groups want to limit or ban the use of test animals or ensure that they are treated in the most humane manner possible. More humane methods for carrying out toxicity tests are available, including computer simulations. Substances can also be tested on tissue cultures of cells and bacteria, chicken egg membranes, and individual animal cells.

These alternatives can greatly decrease the use of animals for testing toxicity. But some scientists point out that some animal testing is needed because the alternative methods cannot adequately mimic the complex biochemical interactions taking place in a live animal.

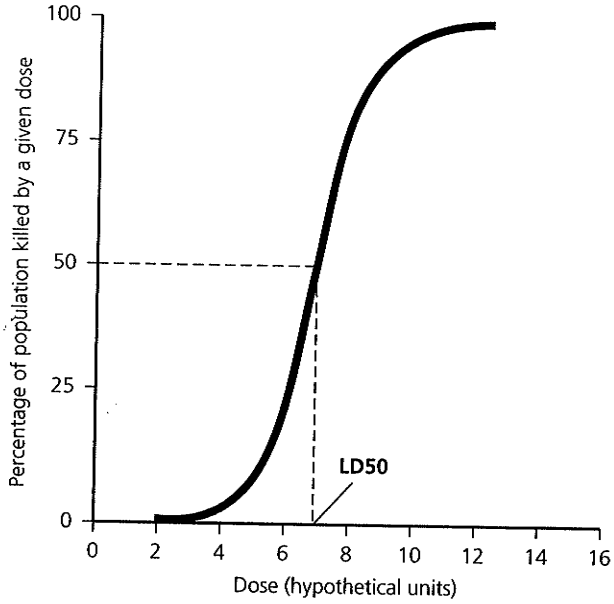

Figure 1 Hypothetical *dose-response curve* showing determination of the LD50, the dosage of a specific chemical that kills 50% of the animals in a test group. Toxicologists widely use this method to compare the toxicities of different chemicals.

One approach is to determine the lethal dose of a chemical needed to kill an animal. A chemical's *median lethal dose* (LD50) is the dose that kills 50% of the animals (usually rats and mice) in a test population within an 18-day period (Figure 1).

Chemicals vary widely in their toxicity (Table 1). Some poisons can cause serious harm

Table 1

Toxicity Ratings and Average Lethal Doses for Humans

Toxicity Rating	LD50 (milligrams per kilogram of body weight)*	Average Lethal Dose†	Examples
Supertoxic	Less than 0.01	Less than 1 drop	Nerve gases, botulism toxin, mushroom toxins, dioxin (TCDD)
Extremely toxic	Less than 5	Less than 7 drops	Potassium cyanide, heroin, atropine, parathion, nicotine
Very toxic	5–50	7 drops to 1 teaspoon	Mercury salts, morphine, codeine
Toxic	50–500	1 teaspoon to 1 ounce	Lead salts, DDT, sodium hydroxide, sodium fluoride, sulfuric acid, caffeine, carbon tetrachloride
Moderately toxic	500–5,000	1 ounce to 1 pint	Methyl (wood) alcohol, ether, phenobarbital, amphetamines (speed), kerosene, aspirin
Slightly toxic	5,000–15,000	1 pint to 1 quart	Ethyl alcohol, Lysol, soaps
Essentially nontoxic	15,000 or greater	More than 1 quart	Water, glycerin, table sugar

*Dosage that kills 50% of individuals exposed

†Amounts of substances in liquid form at room temperature that are lethal when given to a 70.4-kilogram (155-pound) human

death after a single acute exposure at very
v dosages. Others cause such harm only at
sages so huge that it is nearly impossible to
enough into the body to cause injury or
ath. Most chemicals fall between these two
remes. In 2004, the U.S. Environmental Pro-
tion Agency listed arsenic, lead, mercury,
yl chloride (used to make PVC plastics), and
lychlorinated biphenyls (PCBs) as the top five
ic substances, in order, in terms of human
d environmental health.

Scientists also use acute toxicity tests to de-
op a **dose-response curve,** which shows the
ponses of a group of test animals to various
sages of a toxic agent. In *controlled experiments,*
responses of a *test group* are compared with
responses of a *control group* of organisms not
posed to the chemical. Care is taken that or-
nisms in each group are as identical as possi-
in terms of age, health status, and genetic
keup, and that all are exposed to the same
vironmental conditions.

There are two general types of dose-response
rves (Figure 2). With the *nonthreshold dose-re-*
nse model (Figure 2, left), any dosage of a
ic chemical causes harm that increases with
dosage. With the *threshold dose-response model*
gure 2, right), a threshold dosage must be
ched before any detectable harmful effects
ur, presumably because the body can repair
damage caused by low dosages of some sub-
nces.

Establishing which of these models applies at
v dosages is extremely difficult and controver-
l. To be on the safe side, the nonthreshold
se-response model often is assumed. Fairly
gh dosages are used to reduce the number of
t animals needed, obtain results quickly, and
ver costs. Otherwise, tests would have to be
n on millions of laboratory animals for many
ars, and manufacturers could not afford to test
ost chemicals.

For the same reasons, scientists usually use
thematical models to extrapolate the results from high-dose exposures to low-dose exposures. Then they extrapolate the low-dose results from the test organisms to humans to estimate LD50 values for acute toxicity (Table 1).

Some scientists challenge the validity of extrapolating data from test animals to humans because human physiology and metabolism often differ from those of the test animals. Other scientists say that such tests and models work fairly well (especially for revealing cancer risks) when the correct experimental animal is chosen or when a chemical is toxic or harmful to several different test animal species.

RESEARCH FRONTIER

Computer modeling and other alternatives to animal testing

The problems with estimating toxicities using laboratory experiments get worse. In real life, each of us is exposed to a variety of chemicals, some of which can interact in ways that decrease or enhance their individual effects over the short and long term. Toxicologists already have great difficulty in estimating the toxicity of a single substance. But adding the problem of evaluating *mixtures of potentially toxic substances,* separating out which are the culprits, and determining how they can interact with one another is overwhelming from a scientific and economic standpoint. For example, just studying the interactions of three of the 500 most widely used industrial chemicals would take 20.7 million experiments—a physical and financial impossibility.

THINKING ABOUT
Animal Testing

Should laboratory-bred mice, rats, and other animals be used to determine toxicity and other effects of chemicals? Explain.

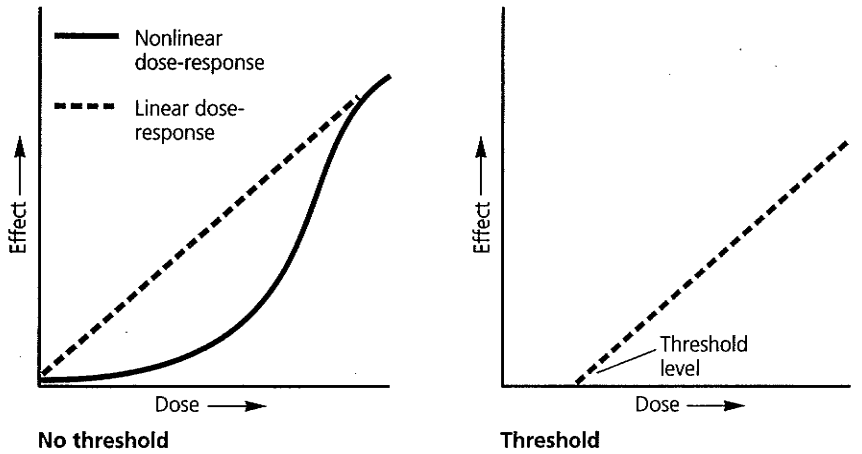

Figure 2 Two types of *dose-response curves.* The linear and nonlinear curves in the left graph apply if even the smallest dosage of a chemical has a harmful effect that increases with the dosage. The curve on the right applies if a harmful effect occurs only when the dosage exceeds a certain *threshold level.* Which model is better for a specific harmful agent is uncertain and controversial because of the difficulty in estimating the response to very low dosages. **Question:** Which model do you think should be used? Why?

There Are Other Ways to Estimate the Harmful Effects of Chemicals

Scientists use several other methods to get information about the harmful effects of chemicals on human health. For example, *case reports,* usually made by physicians, provide information about people suffering some adverse health effect or death after exposure to a chemical. Such information often involves accidental or deliberate poisonings, drug overdoses, homicides, or suicide attempts.

Most case reports are not reliable sources for estimating toxicity because the actual dosage and the exposed person's health status are often unknown. But such reports can provide clues about environmental hazards and suggest the need for laboratory investigations.

Toxicological studies of the effects of various chemicals on wildlife can provide clues about possible harmful effects of such chemicals on humans. Examples include the effects of hormonally active agents, HAAs, on alligators (pp. 332–333) and the effects of atrazine and other pesticides on amphibians (Case Study, p. 108).

Another source of information is *epidemiological studies,* which compare the health of people exposed to a particular chemical (the *experimental group*) with the health of a similar group of people not exposed to the agent (the *control group*). The goal is to determine whether the statistical association between exposure to a toxic chemical and a health problem is strong, moderate, weak, or undetectable.

Four factors can limit the usefulness of epidemiological studies. *First,* in many cases, too few people have been exposed to high enough levels of a toxic agent to detect statistically significant differences. *Second,* they usually take a long time. *Third,* conclusively linking an observed effect with exposure to a particular chemical is difficult because people are exposed to many different toxic agents throughout their lives and can vary in their sensitivity to such chemicals. *Fourth,* we cannot use epidemiological studies to evaluate hazards from new technologies or chemicals to which people have not yet been exposed.

Can a Little Bit of Arsenic Be Good for You?

There is a hypothesis that some toxic substances that can harm or kill us at high doses may have beneficial health effects at very low doses. This phenomenon is called *hormesis.* A possible explanation for this effect is that very small doses of some substances may stimulate cellular repair or other beneficial responses.

Edward Calabrese, a respected toxicologist at the University of Massachusetts, Amherst, has made a thorough examination of the literature on this subject. He has concluded that the idea has merit, and that more research is needed to test its validity and to discover the possible mechanisms involved.

Scientists are waiting for more evidence before accepting the hormesis hypothesis. Stay tuned for more developments about this fascinating idea.