

TABLE 21-5. (continued)

Mammalian bone marrow chromosome aberration test
Mammalian erythrocyte micronucleus test
Rodent dominant lethal assay
Rodent heritable translocation assays
Bacterial DNA damage or repair tests
Unscheduled DNA synthesis in mammalian cells
Mitotic gene conversion in <i>Saccharomyces cerevisiae</i>
In vivo sister chromatid exchange assay
In vitro sister chromatid exchange assay
Group E: Neurotoxicity Test Guidelines
Acute & 28-day delayed neurotoxicity of OP substances
Neurotoxicity screening battery
Developmental neurotoxicity study
Schedule-controlled operant behavior
Peripheral nerve function
Neurophysiology: Sensory evoked potentials
Group F: Special Studies Test Guidelines
Companion animal safety
Metabolism and pharmacokinetics
Dermal penetration
Immunotoxicity

Source: Stevens & Breckenridge (2001)

ESTIMATION OF TOXICITY TO HUMANS

The dose, length of exposure and route of absorption are the other important variables beside toxicity. The amount of pesticide required to kill a human being can be correlated with the LD₅₀ of the material to rats in the laboratory. In Table 21-6, for example, the acute oral LD₅₀, expressed as mg/kg dose of the technical material, is extrapolated to estimate the amount needed to kill a 170-lb (77 kg) human. Dermal LD₅₀s are included for a better understanding of the relationship of expressed animal toxicity to human toxicity.

Generally speaking, oral ingestions are more toxic than respiratory inhalations, which are more toxic than dermal absorption. Additionally, physical and chemical differences between pesticides make them more likely or less likely to produce poisoning. For instance, parathion changes to the more toxic metabolite paraoxon under conditions of humidity and temperature. Parathion is more toxic than methyl parathion to field workers; yet there is not a great difference in their oral toxicities. Workers' exposure is usually dermal, which explains why many more illnesses are reported in workers exposed to parathion than those exposed to methyl parathion.

The Process of Risk Assessment

It was pointed out earlier in this chapter that toxicity is an inherent property of all substances and the actual hazard posed by a substance is a function of both toxicity and exposure. All chemical substances can produce adverse effects in some tissues of each species at some level of exposure.

TABLE 21-6.

World Health Organization classification for estimating the acute toxicity of pesticides.

	LD ₅₀ for the rat (mg/kg b.w.)				Probable lethal oral dose for humans
	Oral		Dermal		
	Solids	Liquids	Solids	Liquids	
Ia Extremely hazardous	≥5	≥20	≥10	≥40	A taste, a grain
Ib Highly hazardous	5-50	20-200	10-100	40-400	A pinch, 1 tsp
II Moderately hazardous	50-500	200-2000	100-1000	400-4000	1 teaspoon, 2 tbsp
III Slightly hazardous	≥501	≥2001	≥1001	≥4001	1 to 4 ounces
*Level at which an Acute Hazard is unlikely	≥2000	≥3000	—	—	1 pint to 1.5 pints

*Exposures at which product is unlikely to present acute hazard in normal use. (WHO does not show toxicity of fumigants in the above system).

Source: World Health Organization

Once data are available to characterize the toxicity and exposure of a product the process of risk assessment can begin. *Risk Assessment* has been defined as “the characterization of the potential adverse health effects of human exposures to environmental hazards” (National Research Council, 1983). The *role* of risk assessment is to determine if a pesticide is safe for users and the general population when handled and used as prescribed by its label. If not clearly safe, then the process also addresses the question as to whether changes can be made to meet the standards for safety.

The core risk assessment process comprises four steps:

- Hazard identification
- Dose-response assessment
- Exposure assessment
- Risk characterization

Hazard identification requires a clear understanding of the chemical’s toxic properties, particularly the adverse effects seen after conducting both short-(acute) and long-term (chronic) studies in laboratory animals. Well conducted multi-level feeding studies disclose if, and at what level, changes will occur in each organ of each test species and the nature of any change.

The *dose-response assessment* is the step that establishes the pattern of effects demonstrated by a pesticide when administered at different dose levels. In acute studies several dose levels are administered and lethality and other effects are monitored. In contrast, among the three or four feeding levels given in chronic studies the highest level(s) must cause clear adverse effects, but not death. Regulators require testing at this level in studies to evaluate carcinogenicity, referred to as the Maximum Tolerated Dose (MTD). Testing at the MTD is to validate that test animals have been physiologically stressed by the toxicant. The highest pesticide dose that

does not cause any observable harm or side effects to experimental animals is known as the No Observable Effect Level (NOEL). The NOEL is typically divided by a safety factor of 100 to 1000 to obtain what EPA calls the Reference Dose (RFD). The safety factor is designed to protect sensitive portions of the population and to correct for genetic or species differences due to the extrapolation to humans from animal studies. The RFD is the toxicity level normally used to estimate a level of exposure at or below which no adverse effect is expected to occur even if the agent is ingested daily over an entire lifetime.

Exposure assessment includes an estimate of people's potential exposure to a chemical at work, at home, or in their diets and covers periods from acute to lifetime exposures. Levels of exposure are determined by measuring pesticide residues in food, water, ambient air and occupational exposure to applicators and workers. The results of animal metabolism, absorption and elimination studies also are helpful in establishing human exposure levels to pesticides.

Risk characterization is the process of bringing the *hazard identification* and *exposure assessment* results together and determining if probable actual exposures will be safe to individuals who are likely to come into contact with the pesticide in normal use. In the U.S., the EPA will calculate a series of safety factors for potentially exposed populations (e.g.- applicators, users, various segments of the general public including children) and will express the result as a safety factor. For example, if a level determined to be safe to a human is 0.1 mg/kg of body weight and the analysis used to characterize the risk shows the actual exposure as 0.0002 mg/kg then a safety factor of 400 would result.

The process is quite different if the product being evaluated has demonstrated evidence of being a rodent carcinogen. In this case, though complex, the process can be summarized by stating that when assessing risk to humans of potentially carcinogenic products very conservative mathematic models are applied and safety factors are calculated. Because of the inherent uncertainty the safety factors that are calculated always err on the side of human safety.

An additional step, *risk management*, comes into play when results of risk characterization do not demonstrate adequate safety margins for the product as it is intended for use. In this step alternatives for changing the scope or manner of use and/or protective measures during product use are considered. Risk management relies partly on science, but also considers social, economic and legal parameters before a policy decision is made. A product may not be sanctioned for any use unless sufficient changes to ensure safety are identified and put in place.

Cumulative risk assessment: The Food Quality Protection Act of 1996 mandated that EPA also consider a new and challenging type of risk assessment that previously had not been undertaken. The charge to EPA was to consider the *cumulative risks* posed by any and all members of a class of pesticides that act by a "common mode of action". Although a daunting task, EPA with help from many parties developed tentative methodology for such analysis and first used it in 2001. The preliminary assessment considers potential exposures to 31 organophosphate insecticides through food, drinking water and residential uses. Residential

uses include pesticide applications in and around homes, schools, public buildings, golf courses, parks, public health-related uses and other areas where people may come in contact with pesticide residues.

The new methodologies evaluate potential exposures for different age groups and take into account the variability in potential exposure at different locations across the country and at different times of the year. EPA relied on a large variety of data sources, such as monitoring data that measure pesticide residues found in food, in order to obtain the most realistic estimates of actual exposure to the population from organophosphate pesticides (National Research Council 1983).

Since the early 1980's, risk assessment has been an important and increasingly used tool in the hands of governmental regulators and others wanting to make reliable estimates of risk, not only for pesticides but to other chemicals and non-chemical risks. The effort has seen continual improvement and broader application to other chemicals or non-chemical hazards to humans and the environment. The benefits of the risk assessment approach have become clear and we expect to see many future improvements to this important tool.

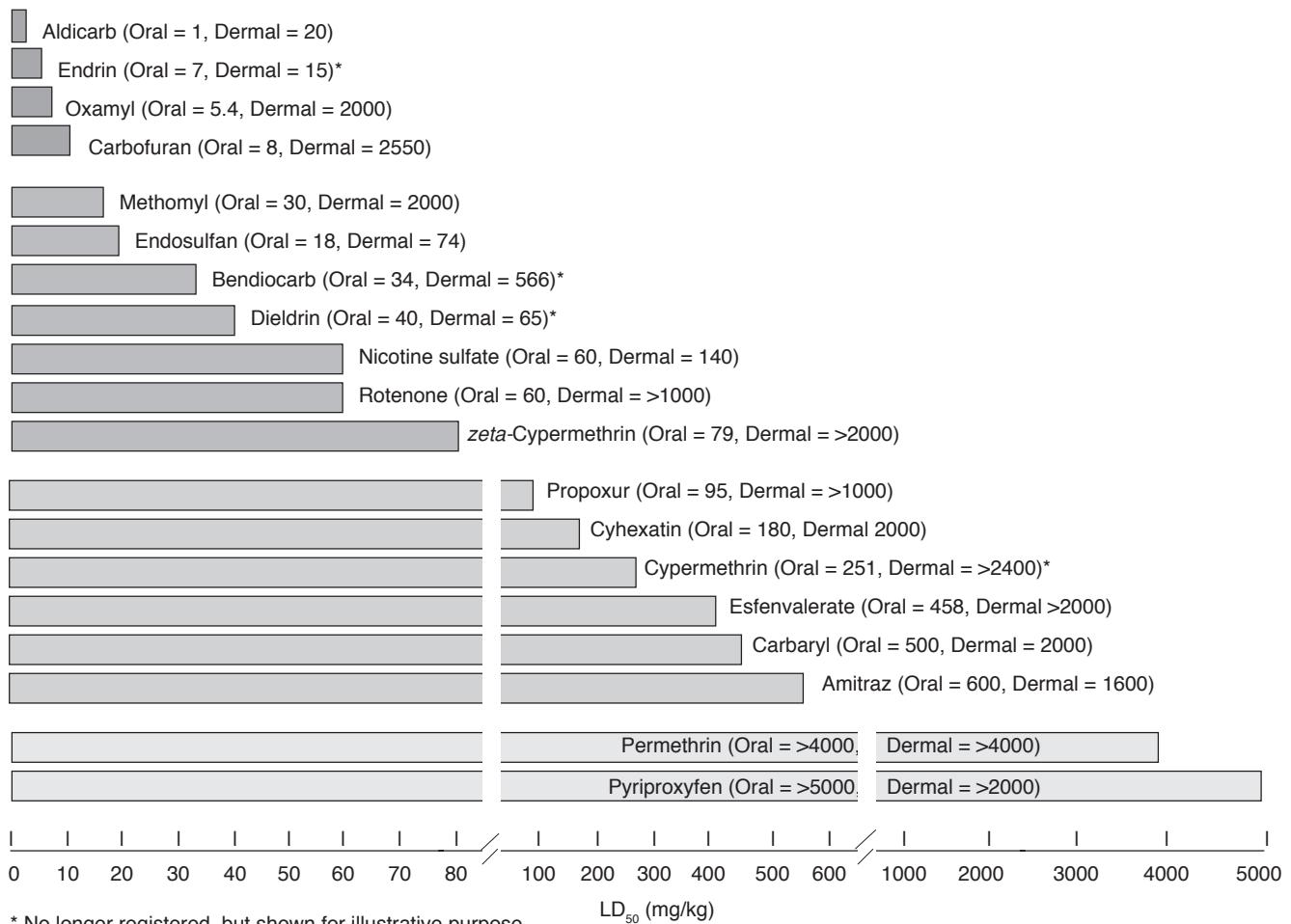


FIGURE 21-1

Acute Oral LD₅₀s for rats and Dermal LD₅₀s for rabbits for some organochlorine, carbamate, botanical, pyrethroid and formamidine insecticides.

TOXICITY AND LABELING

All pesticide labels must contain “signal words” in bold print, to attract the attention of the buyer/user: *Danger—Poison*; *Warning*; and *Caution*. These are significant words, since they represent a category of toxicity, and thus give an indication of the potential hazard (Table 21-7).

Category I. The signal words *Danger—Poison* and the skull and crossbones symbol are required on the labels for all *highly toxic* compounds. These pesticides all fall within the acute oral LD₅₀ range of 0 to 50 mg/kg.

Category II. The word *Warning* is required on the labels for all *moderately toxic* compounds. They all fall within the acute oral LD₅₀ range of 50 to 500 mg/kg.

Category III. The word *Caution* is required on labels for *slightly toxic* pesticides that fall within the LD₅₀ range of 500 to 5000 mg/kg.

Category IV. The word *Caution* is required on labels for compounds having acute LD₅₀s greater than 5000 mg/kg. However, unqualified claims for safety are not acceptable on any label, and all labels must bear the statement, “Keep Out of Reach of Children.”

TABLE 21-7

EPA labeling toxicity categories by hazard indicator.

<i>Toxicity categories</i>				
<i>Hazard indicators</i>	<i>I (Danger—Poison)</i>	<i>II (Warning)</i>	<i>III (Caution)</i>	<i>IV (Caution)</i>
Oral LD ₅₀	Up to and including 50 mg/kg	From 50 to 500 mg/kg	From 500 to 5000 mg/kg	Greater than 5000 mg/kg
Inhalation LD ₅₀	Up to and including 0.2 mg/liter	From 0.2 to 2 mg/liter	From 2 to 20 mg/liter	Greater than 20 mg/liter
Dermal LD ₅₀	Up to and including 200 mg/kg	From 200 to 2000 mg/kg	From 2000 to 20,000 mg/kg	Greater than 20,000 mg/kg
Eye effects	Corrosive; corneal opacity not reversible within 7 days	Corneal opacity reversible within 7 days; irritation persisting for 7 days	No corneal opacity; irritation reversible within 7 days	No irritation
Skin effects	Corrosive	Severe irritation at 72 hours	Moderate irritation at 72 hours	Mild or slight irritation at 72 hours

Source: “EPA Pesticide Programs, Registration and Classification Procedures, Part II.”
Federal Register 40: 28279.

Table 21-8 shows the relative acute toxic hazards to applicators of many of the commonly used pesticides. Examples of insecticides, herbicides, and fungicides in the three label toxicity classifications are shown.

With regard to the classifications of pesticides, their general toxicity in decreasing order is, insecticides > defoliants > desiccants > herbicides > fungicides. Within the most toxic class, the insecticides, the categories fall in the following general order of their dermal hazards to humans: