

# Casarett & Doull's Toxicology: The basic science of poisons

*Klaassen CD, Amdur MO, Doull J; (3rd Ed, 1986) Macmillan Publishing*

## PRINCIPLES OF TOXICOLOGY Chapter - Selected quotation

### Risk & Safety - P 12

The question of what constitutes an acceptable risk is a matter of judgement. Such decisions are multifaceted and complex, and involve a balance of risk and benefit. High risks may be acceptable in the use of lifesaving drugs, but would be unacceptable for food additives. Some of the factors considered in determining an acceptable risk are (1) benefits gained from the use of the substance, (2) the adequacy of available alternative substances to meet the identified use, (3) the anticipated extent of public use, (4) employment considerations, (5) economic considerations, (6) effects on environmental quality, and (7) conservation of natural resources.

### Route & Site of Exposure - P 13

Toxic agents generally elicit the greatest effect and produce the most rapid response when given by the intravenous route. An approximate descending order of effectiveness for other routes would be: inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral and topical.

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In addition, the route of administration can influence the toxicity of agents. For example, an agent that is detoxified in the liver would be expected to be less toxic when given via the portal circulation (oral) than when given by the systemic circulation (inhalation).

### Duration & Frequency of Exposure - P 14

For many agents, the toxic effects following a single exposure are quite different from those produced by repeated exposure. For example, the primary acute toxic manifestation of benzene is central nervous system depression, but repeated exposures can result in leukemia. Acute exposure to agents that are rapidly absorbed is likely to produce immediate toxic effects, but acute exposure can also produce delayed toxicity that may or may not be similar to the toxic effects of chronic exposure. Conversely, chronic exposure to a toxic agent may produce some immediate (acute) effects after each administration, in addition to the long-term, low-level, or chronic effects of the agent. In characterizing the toxicity of a specific chemical agent, it is evident that information is needed not only for the single dose (acute) and long term (chronic) effects, but also for exposures of intermediate duration.

### Local versus Systemic Toxicity - p 16

The target organ of toxicity most frequently involved in systemic toxicity is the central nervous system. Even with many compounds having a prominent effect elsewhere, damage to the central nervous system, particularly the brain, can be demonstrated by the use of appropriate and sensitive methods. Next in order of frequency of involvement in systemic toxicity are the circulatory system, the blood and hematopoietic system, visceral organs such as liver, kidney and lung, and the skin. Muscle and bone are least often the target tissue for systemic effects. With substances having predominantly a local effect, the frequency with which tissues react depends largely on the portal of entry (skin, gastrointestinal tract, respiratory tract).

### Reversible versus Irreversible Toxic Effects - P 16

Some toxic effects of chemicals are reversible and others are irreversible. If a chemical injury causes pathologic injury to a tissue, the ability of the tissue to regenerate will largely determine whether the effect is reversible or irreversible. Thus, for a tissue such as liver, which has a high ability to regenerate, most injuries are reversible, whereas injury to the central nervous system is largely irreversible since differentiated cells of the central nervous system cannot divide and be replaced. Carcinogenic effects of chemicals are also irreversible toxic effects.

### Calculations - p19 - 21

In toxicology, the quantal dose-response is used extensively. Determination of the median lethal dose (LD50) is usually the first experiment performed with a new chemical. In practice, this is experimentally determined usually using mice or rats and using either the oral or intraperitoneal route of administration. At least ten animals are used per dose, and a range of doses is administered so that at least three and preferably more of the doses result in producing some deaths and some survivals, i.e., kill less than 100 percent and more than 0 percent.

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Determination of the LD50 has become a public issue because of increasing concern for the welfare and protection of laboratory animals. However the LD50 is essential for characterizing the toxic effects of chemicals and thus determining their hazard to humans. In determination of the LD50, more than a number is obtained.

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When animals are exposed to the air they are breathing or the water they (fish) are living in, the dose the animals received is usually not known. For these situations the lethal concentration 50 (LC50) is usually determined. ... When reporting the an LC50, it is imperative that the time of exposure be indicated.

The LD50 and LC50 are not constants. There are many factors that can influence these values. For example, the LD50 can depend on the species, strain, sex, age, etc., as well as environmental factors such as temperature, exposure to other chemicals such as insecticides, the number of animals in the cage and diet.

## Selective toxicity - P24

Selective toxicity means that a chemical produces injury to one kind of living matter without harming some other form of life, even though the two may exist in intimate contact (Albert 1965, 1973). The living matter that is injured is termed the "uneconomic form", and the matter protected is called the "economic form". They may be related to one another as parasite and host, or they may be two tissues in one organism. This biologic diversity interferes with the ability of the toxicologist to predict the toxic effects in one species (humans) from experiments performed on another species (laboratory animals).

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Drugs and other chemical agents used for selective toxic purposes are selective for one of two reasons. Either (1) the chemical is equitoxic to both economic and uneconomic cells but is accumulated mainly in the uneconomic cells, or (2) it reacts fairly specifically with (a) a cytologic or (b) a biochemical feature that is absent from or does not play an important part in the economic form (Albert 1965, 1973). Selectivity due to differences in distribution is usually the result of differences in absorption, biotransformation, or excretion of the toxicant. The selective toxicity of an insecticide spray may be partly due to a larger surface area per unit weight causing the insect to absorb a proportionally larger dose than the mammal being sprayed.

## Descriptive Animal Toxicity Tests - p25-28

Two main principles underlie all descriptive animal toxicity testing. The first is that the effects produced by the compound in laboratory animals, when properly qualified, are applicable to humans. This premise applies to all of experimental biology and medicine. On the basis of dose per unit of body surface, toxic effects in humans are usually in the same range as those in experimental animals. On a body weight basis, humans are generally more vulnerable than experimental animals, probably by a factor of about ten.

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The second main principle is that exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible hazards in humans.

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To obtain statistically valid results from such small groups of [laboratory test] animals requires the use of relatively large doses so that the effect will occur frequently enough to be detected. For example, an incidence of a serious toxic effect such as cancer as low as 0.01 percent would represent 20,000 people in a population of 200 million and would be considered unacceptably high. To detect such a low incidence in experimental animals would require a minimum of about 30,000 animals. For this reason, there is no choice but to give large doses and then use toxicologic principles in extrapolating the results to estimate risk at low doses.

## Subchronic Exposure - P 26

Subchronic exposure can last for different periods of time, but 90 days is the most common test duration....

Observations on the animals include mortality, body-weight changes, diet consumption, pharmacologic and toxicologic signs, hematology and blood chemistry measurements. Hematology and blood chemistry measurements are usually done prior to, in the middle of, and at the termination of exposure. Hematology measurements usually include hemoglobin concentration, hematocrit, erythrocyte counts, total and differential leukocyte counts, platelet count, clotting time and prothrombin time. Clinical chemistry determinations commonly include glucose, potassium, calcium, urea nitrogen, SGPT, SGOT, lactic dehydrogenase, alkaline phosphatase, creatinine, bilirubin, triglycerides, cholesterol, albumin, globulin and total protein. Urinalysis is usually performed in the middle and at the termination of the testing period, and often includes determination of specific gravity or osmolarity, pH, glucose, ketones, bilirubin, and urobilinogen, as well as microscopic examination of the formed elements. At the end of the experiments the gross and microscopic condition of the organs and tissues (about 15 to 20) and the weight of various organs (about 12) are recorded and evaluated.

## Risk extrapolation - P 29 - 31

An acceptable risk depends on a number of factors, including benefits of the chemical to society. Some factors considered in establishing acceptable risk factors are given [in this table]

Beneficial aspects of the chemical		
Economic growth	Employment	Increased standard of living
Increased quality of life	Taxes generated	
Detrimental aspects of the chemical		
Decreased quality of life	Emotional difficulties	Health effects
Lawsuits	Loss of environmental resources	
Loss of work	Medical payments	

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The distribution [of risk extrapolation] are based on the assumption that every member of a population has a critical dosage below which the individual will not respond to the exposure in question.

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Mechanistic models are based on the presumed mechanism of carcinogenesis. ... This model is essentially equivalent to assuming that the dose-response curve is linear in the low-dose region.

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It is known that many chemicals are only carcinogenic after they have been biotransformed. ... This is referred to as non-linear pharmacokinetics. After the metabolite is formed, it is often destroyed by a second enzyme, such as epoxide hydrolase or glutathione transferase. These enzymes can also be saturated. The reactive metabolites that are not destroyed by these detoxication pathways often bind to DNA.