

# Toxicology

## Toxicology

*Toxicology* is the study of the adverse effects of chemical or physical agents on living organisms. Toxicological research examines the cellular, biochemical, and molecular mechanisms of action as well as functional effects such as neurobehavioral and immunological, and assesses the probability of their occurrence. Fundamental to this process is characterizing the relation of exposure (or dose) to the response.

*Risk assessment* is the quantitative estimate of the potential effects on human health and environmental significance of various types of chemical exposures (e.g., pesticide residues on food, contaminants in drinking water). The variety of potential adverse effects and the diversity of chemicals in the environment make toxicology a broad science, which often demands specialization in one area of toxicology. Our society's dependence on chemicals and the need to assess potential hazards have made toxicologists an increasingly important part of the decision-making processes.

The professional activities of toxicologists fall into three main categories:

1. Descriptive
2. Mechanistic, and
3. Regulatory

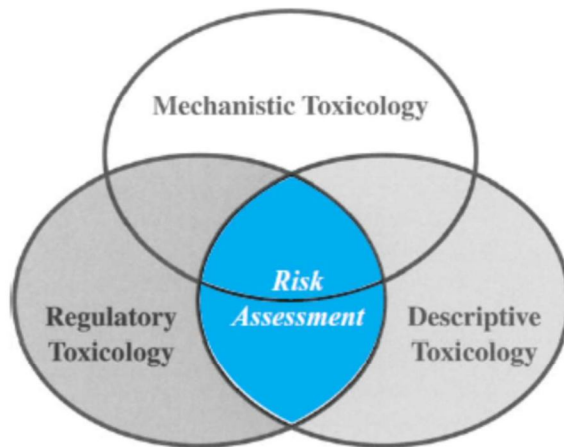
1. *Mechanistic toxicologist*: He/she is concerned with identifying and understanding the cellular, biochemical, and molecular mechanisms by which chemicals exert toxic effects on living organisms. The results of mechanistic studies are very important in many areas of applied toxicology. In risk assessment, mechanistic data may be very useful in demonstrating that an adverse outcome (e.g., cancer, birth defects) observed in laboratory animals is directly relevant to humans. For example, the relative toxic potential of

organophosphate insecticides in humans, rodents, and insects can be accurately predicted on the basis of an understanding of common mechanisms (inhibition of acetylcholinesterase) and differences in biotransformation for these insecticides among the different species.

2. *Descriptive toxicologist*: He/she is concerned directly with toxicity testing, which provides information for safety evaluation and regulatory requirements. The appropriate toxicity tests in cell culture systems or experimental animals are designed to yield information to evaluate risks posed to humans and the environment from exposure to specific chemicals. The concern may be limited to effects on humans, as in the case of drugs and food additives. Toxicologists in the chemical industry, however, must be concerned not only with the risk posed by a company's chemicals (insecticides, herbicides, solvents, etc.) to humans but also with potential effects on fish, birds, and plants, as well as other factors that might disturb the balance of the ecosystem. Descriptive toxicology is of course not divorced from mechanistic studies, as such studies provide important clues to a chemical's mechanism of action, and thus contribute to the development of mechanistic toxicology through hypothesis generation. Such studies are also a key component of risk assessments that are used by regulatory toxicologists. The recent advent of so-called "omics" technologies (genomics, transcriptomics, proteomics, metabolomics, etc.) form the basis of the emerging subdiscipline of toxicogenomics. The application of these new technologies to toxicity testing is in many ways "descriptive" in nature, yet affords great mechanistic insights into how chemicals produce their toxic effects.

3. *Regulatory toxicologist*: He/she has the responsibility for deciding, on the basis of data provided by descriptive and mechanistic toxicologists, whether a

drug or other chemical poses a sufficiently low risk to be marketed for a stated purpose or subsequent human or environmental exposure resulting from its use. The Food and Drug Administration (FDA) is responsible for allowing drugs, cosmetics, and food additives to be sold in the market according to the Federal Food, Drug and Cosmetic Act (FFDCA). The U.S. Environmental Protection Agency (EPA) is responsible for regulating most other chemicals according to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), the Resource Conservation and Recovery Act (RCRA), the Safe Drinking Water Act, and the Clean Air Act.



*Figure 2-1. Graphical representation of the interconnections between different areas of toxicology.*

## CLASSIFICATION OF TOXIC AGENTS

Toxic agents are classified in a variety of ways, depending on the interests and needs of the classifier. In this textbook, for example, toxic agents are discussed in terms of their target organs (liver, kidney, hematopoietic system, etc.), use (pesticide, solvent, food additive, etc.), source (animal and plant toxins), and effects (cancer, mutation, liver injury, etc.). The term *toxin*

generally refers to toxic substances that are produced by biological systems such as plants, animals, fungi, or bacteria. The term *toxicant* is used in speaking of toxic substances that are produced by or are a by-product of anthropogenic (human-made) activities. Thus, zeralanone, produced by a mold, is a toxin, whereas "dioxin" [2,3,7,8-tetrachlorodibenzo-pdioxin (TCDD)], produced during the production and/or combustion of certain chlorinated organic chemicals, is a toxicant. Some toxicants can be produced by both natural and anthropogenic activities.

For example, polyaromatic hydrocarbons are produced by the combustion of organic matter, which may occur both through natural processes (e.g., forest fires) and through anthropogenic activities (e.g., combustion of coal for energy production; cigarette smoking).

Arsenic, a toxic metalloid, may occur as a natural contaminant of groundwater or may contaminate groundwater secondary to industrial activities. Generally, such toxic substances are referred to as toxicants, rather than toxins, because, although they are naturally produced, they are not produced by biological systems.

Toxic agents may also be classified in terms of their physical state (gas, dust, liquid), their chemical stability or reactivity (explosive, flammable, oxidizer), general chemical structure (aromatic amine, halogenated hydrocarbon, etc.), or poisoning potential (extremely toxic, very toxic, slightly toxic, etc.). Classification of toxic agents on the basis of their biochemical mechanisms of action (e.g., alkylating agent, cholinesterase inhibitor, methemoglobin producer) is usually more informative than classification by general terms such as irritants and corrosives. But more general classifications such as air pollutants, occupation-related agents, and acute and chronic poisons can

provide a useful focus on a specific problem. It is evident from this discussion that no single classification is applicable to the entire spectrum of toxic agents and that combinations of classification systems or a classification based on other factors may be needed to provide the best rating system for a special purpose. Nevertheless, classification systems that take into consideration both the chemical and the biological properties of an agent and the exposure characteristics are most likely to be useful for regulatory or control purposes and for toxicology in general.