Toxicology

Toxicology is the study of the adverse effects of chemical or physical agents on living organisms.

A *toxicologist*
is trained to examine and communicate the nature of those effects on human, animal, and environmental health.

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.

Risk assessment
is the quantitative estimate of the potential effects on human health and environmental significance of various types of chemical exposures (eg, pesticide residues in 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.

Different Areas of Toxicology

The professional activities of toxicologists fall into 3 main categories:

descriptive,

mechanistic,

and regulatory.

Although each has distinctive characteristics, each contributes to the other, and all are vitally important to chemical risk assessment.

A *mechanistic toxicologist*
is concerned with identifying and understanding the cellular, biochemical, and molecular mechanisms by which chemicals exert toxic effects on living organisms.

A clear understanding of mechanism of action led to the development of strict prescribing guidelines and patient monitoring

In risk assessment, mechanistic data may be very useful in demonstrating that an adverse outcome (eg, cancer, birth defects) observed in laboratory animals is directly relevant to humans. For example, the relative toxic potential of organophosphorus (OP) 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.

mechanistic data may be very useful in identifying adverse responses in experimental animals that may not be relevant to humans. For example, the propensity of the widely used artificial sweetener saccharin to cause bladder cancer in rats may not be relevant to humans at normal dietary intake rates.?

This is because mechanistic studies have demonstrated that bladder cancer is induced only under conditions where saccharin is at such a high concentration in the urine that it forms a crystalline precipitate.

Dose–response studies suggest that such high concentrations would not be achieved in the human bladder even after extensive dietary consumption.

Mechanistic data are also useful in the design and production of safer alternative chemicals and in rational therapy for chemical poisoning and treatment of disease.

For example, the drug thalidomide was originally marketed in Europe and Australia as a sedative agent for pregnant women. However, it was banned for clinical use in 1962 because of devastating birth defects that occurred if the drug was ingested during a critical period in pregnancy.

But mechanistic studies over the past several decades have demonstrated that this drug may have a unique molecular mechanism of action that interferes with the expression of certain genes responsible for blood vessel formation (angiogenesis).

With an understanding of this mechanism, thalidomide has been "rediscovered" as a valuable therapeutic agent that may be highly effective in the treatment of certain infectious diseases (eg, leprosy) and multiple myeloma.

This provides an interesting example of how a highly toxic drug with selectivity toward a specific population (pregnant women) can be used relatively safely with proper precautions. ?

A *descriptive toxicologist*

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. ?H.W

A *regulatory toxicologist*

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 (or, in the case of drugs, a favorable risk/benefit profile) 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

In addition to the above categories, there are other specialized areas of toxicology such as forensic, clinical, and environmental toxicology.

Forensic toxicology is a hybrid of analytic chemistry and fundamental toxicological principles. It is concerned primarily with the medicolegal aspects of the harmful effects of chemicals on humans and animals. The expertise of forensic toxicologists is invoked primarily to aid in establishing the cause of death and determining its circumstances in a post-mortem investigation.

Clinical toxicology designates an area of professional emphasis in the realm of medical science that is concerned with disease caused by or uniquely associated with toxic substances

Environmental toxicology focuses on the impacts of chemical pollutants in the environment on biological organisms.

General Characteristics of the Toxic Response

One could define a poison as any agent capable of producing a deleterious response in a biological system, seriously injuring function or producing death.

This is not, however, a useful working definition for the very simple reason that virtually every known chemical has the potential to produce injury or death if it is present in a sufficient amount.

Paracelsus (1493–1541), a Swiss/German/Austrian physician, scientist, and philosopher, phrased this well when he noted, "What is there that is not poison? All things are poison and nothing [is] without poison. Solely the dose determines that a thing is not a poison."

Among chemicals there is a wide spectrum of doses needed to produce deleterious effects, serious injury, or death.

This is demonstrated in the next Table, which shows the dosage of chemicals needed to produce death in 50% of treated animals (lethal dose 50 [LD50]).

Some chemicals produce death in microgram doses and are commonly thought of as being extremely poisonous.

Other chemicals may be relatively harmless after doses in excess of several grams.

It should be noted, however, that measures of acute lethality such as LD50 do not accurately reflect the full spectrum of toxicity, or hazard, associated with exposure to a chemical. For example, some chemicals with low acute toxicity may have carcinogenic, teratogenic, or neurobehavioral effects at doses that produce no evidence of acute toxicity. ?

Approximate Acute LD50s of Some Representative Chemical Agents	
AGENT	LD50 (mg/kg)*
Ethyl alcohol	10,000
Sodium chloride	4000
Ferrous sulfate	1500
Morphine sulfate	900
Phenobarbital sodium	150
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
d-Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

is the dosage (mg/kg body weight) causing death in 50% of

*LD exposed animals.

CLASSIFICATION OF TOXIC AGENTS

Toxic agents are classified in a variety of ways, depending on the interests and needs of the classifier.

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, zearalenone, produced by a mold, is a toxin, whereas "dioxin" is a toxicant.?

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, size, eg, nanotoxicology),

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).

their biochemical mechanisms of action (eg, alkylating agent, cholinesterase inhibitor, endocrine disruptor)

Classifications such as air pollutants, occupation-related agents, and acute and chronic poisons can provide a useful focus on a specific problem.

SPECTRUM OF UNDESIRED EFFECTS

The spectrum of undesired effects of chemicals is often broad.
Some effects are deleterious and others are not.
In therapeutics, for example, each drug produces a number of effects,
but usually only one effect is associated with the primary objective of the therapy; all the other effects are referred to as *undesirable* or *side effects* of that drug for that therapeutic indication.

However, some of these side effects may be desired for another therapeutic indication.

For example, the "first-generation" antihistamine diphenhydramine (Benadryl) is effective in reducing histamine responses associated with allergies, but it readily enters the brain and causes mild central nervous system (CNS) depression (drowsiness, delayed reaction time).

With the advent of selective histamine receptor antagonists that do not cross the blood–brain barrier and thus do not have this CNS-depressant side effect, diphenhydramine is used less commonly today as an antihistamine.

However, it is widely used as an "over-the-counter" sleep remedy, often in combination with analgesics (eg, Tylenol PM, Excedrin PM), taking advantage of the CNS-depressant effects.

Some side effects of drugs are never desirable and are always deleterious to the well-being of humans. These are referred to as the *adverse*, *deleterious*, or *toxic* effects of the drug.

Immediate versus Delayed Toxicity

Immediate toxic effects can be defined as those that occur or develop rapidly after a single administration of a substance, whereas

delayed toxic effects are those that occur after the lapse of some time.

Carcinogenic effects of chemicals usually have a long latency period, often 20 to 30 years after the initial exposure, before tumors are observed in humans.

Reversible versus Irreversible Toxic Effects

Some toxic effects of chemicals are reversible, and others are irreversible. If a chemical produces pathological injury to a tissue, the ability of that tissue to regenerate largely determines 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 CNS is largely irreversible because differentiated cells of the CNS cannot divide and be replaced. Carcinogenic and teratogenic effects of chemicals, once they occur, are usually considered irreversible toxic effects.

Local versus Systemic Toxicity

Another distinction between types of effects is made on the basis of the general site of action.

Local effects are those that occur at the site of first contact between the biological system and the toxicant. Such effects are produced by the ingestion of caustic substances or the inhalation of irritant materials.

For example, chlorine gas reacts with lung tissue at the site of contact, causing damage and swelling of the tissue, with possibly fatal consequences, even though very little of the chemical is absorbed into the bloodstream.

. Systemic effects

require absorption and distribution of a toxicant from its entry point to a distant site at which deleterious effects are produced. Most substances except highly reactive materials produce systemic effects. For some materials, both effects can be demonstrated.

For example, tetraethyl lead produces effects on skin at the site of absorption and then is transported systemically to produce its typical effects on the CNS and other organs. If the local effect is marked, there may also be indirect systemic effects.

Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs; instead, they usually elicit their major toxicity in only 1 or 2 organs.

These sites are referred to as the *target organs* of toxicity of a particular chemical.

Route and Site of Exposure

The major routes (pathways) by which toxic agents gain access to the body are through

the gastrointestinal tract (ingestion),

the lungs (inhalation), or

the skin (topical, percutaneous, or dermal).

Toxic agents generally produce the greatest effect and the most rapid response when given directly into the bloodstream (the intravenous route).

An approximate descending order of effectiveness for the other routes would be inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and dermal.

The "vehicle" (the material in which the chemical is dissolved) and other formulation factors can markedly alter absorption after ingestion, inhalation, or topical exposure.

In addition, the route of administration can influence the toxicity of agents. For example, an agent that acts on the CNS, but is efficiently detoxified in the liver, would be expected to be less toxic when given orally than when given via inhalation, because the oral route requires that nearly all of the dose pass through the liver before reaching the systemic circulation and then the CNS.?

Occupational exposure to toxic agents most frequently results from breathing contaminated air (inhalation) and/or direct and prolonged contact of the skin with the substance (dermal exposure),

whereas accidental and suicidal poisoning occurs most frequently by oral ingestion

Duration and Frequency of Exposure

Toxicologists usually divide the exposure of experimental animals to chemicals into 4 categories:

acute,
subacute,
subchronic, and
chronic.

Acute exposure is defined as exposure to a chemical for less than 24 hours,
and examples of exposure routes are intraperitoneal, intravenous, and subcutaneous injection; oral intubation; and dermal application.

Subacute exposure refers to repeated exposure to a chemical for 1 month or less,

subchronic for 1 to 3 months, and

chronic for more than 3 months,

although usually this refers to studies with at least 1 year of repeated dosing.

These 3 categories of repeated exposure can be by any route, but most often they occur by the oral route, with the chemical added directly to the diet.

In human exposure situations, the frequency and duration of exposure are usually not as clearly defined as in controlled animal studies, but many of the same terms are used to describe general exposure situations.

Thus, workplace or environmental exposures may be described as *acute* (occurring from a single incident or episode), *subchronic* (occurring repeatedly over several weeks or months), or *chronic* (occurring repeatedly for many months or years).

For many chemicals, the toxic effects that follow a single exposure are quite different from those produced by repeated exposure. For example, the primary acute toxic manifestation of benzene is CNS depression, but repeated exposures can result in bone marrow toxicity and an increased risk for leukemia.?

THANK YOU