Principles of Toxicology Lec 1

INTRODUCTION TO 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.

Different Areas of Toxicology:

A mechanistic toxicologist 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 (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.

Similarly, 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.

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.

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.

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. Although toxicologists concerned with the effects of environmental pollutants on human health fi t into this defi nition, it is most commonly associated with studies on the impacts of chemicals on nonhuman organisms such as fi sh, birds, terrestrial animals, and plants. Ecotoxicology is a specialized area within environmental toxicology that focuses more specifically on the impacts of toxic substances on population dynamics in an ecosystem. The transport, fate, and interactions of chemicals in the environment constitute a critical component of both environmental toxicology and ecotoxicology.

Bioaccumulation: The increasing concentration of a substance in the environment as the result of environmental persistence and physical properties (eg, lipid solubility) that leads to accumulation in biologic tissues.

Endocrine disruptors: Chemicals in the environment that have estrogen-like or antiandrogen activity or disrupt thyroid function. There is concern that exposure to

endocrine disruptors may increase reproductive cancers, impair fertility, and have teratogenic effects.

Occupational toxicology : The area of toxicology that deals with the toxic effects of chemicals found in the workplace; regulated by the Occupational Safety and Health Administration (OSHA) in the United States.

Threshold limit value: The amount of exposure to a given agent that is deemed safe for a stated time period. It is higher for shorter periods than for longer periods.

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.

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 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).

Allergic Reactions

Chemical allergy is an immunologically mediated adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one. The term hypersensitivity is most often used to describe this allergic state, but

allergic reaction and sensitization reaction are also used to describe this situation when preexposure of the chemical is required to produce the toxic effect.

Idiosyncratic Reactions

Chemical idiosyncrasy refers to a genetically determined abnormal reactivity to a chemical . The response observed is usually qualitatively similar to that observed in all individuals but may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of the chemical.

AIR POLLUTANTS

A. Classification and Prototypes

The major air pollutants in industrialized countries include carbon monoxide (which accounts for about 50% of the total amount of air pollutants), sulfur oxides (18%), hydrocarbons (12%), particulate matter (eg, smoke particles, 10%), and nitrogen oxides (6%). Air pollution appears to be a contributing factor in bronchitis, obstructive pulmonary disease, and lung cancer.

B. Carbon Monoxide

Carbon monoxide (CO) is an odorless, colorless gas that competes avidly with oxygen for hemoglobin. The affinity of CO for hemoglobin is more than 200-fold greater than that of oxygen. per million (ppm); in heavy traffic, the concentration of CO may exceed 100 ppm.

1. Effects—CO causes tissue hypoxia. Headache occurs first, followed by confusion, decreased visual acuity, tachycardia, syncope, coma, seizures, and death. Collapse and syncope occur when approximately 40% of hemoglobin has been converted to carboxyhemoglobin. Prolonged hypoxia can result in irreversible damage to the brain and the myocardium.

2. Treatment—Removal of the source of CO and 100% oxygen are the main features of treatment. Hyperbaric oxygen accelerates the clearance of carbon monoxide.

C. Sulfur Dioxide

Sulfur dioxide (SO_2) is a colorless, irritating gas formed from the combustion of fossil fuels.

1. Effects—SO_2 forms sulfurous acid on contact with moist mucous membranes; this acid is responsible for most of the pathologic effects. Conjunctival and bronchial irritation (especially in individuals with asthma) are the primary signs of exposure. Presence of 5‑10 ppm in the air is enough to cause severe bronchospasm. Heavy exposure may lead to delayed pulmonary edema. Chronic low-level exposure may aggravate cardiopulmonary disease.

2. Treatment—Removal from exposure to SO_2 and relief of irritation and inflammation constitute the major treatment.

D. Nitrogen Oxides

Nitrogen dioxide (NO_2), a brownish irritant gas, is the principal member of this group. It is formed in fires and in silage on farms.

1. Effects—NO_2 causes deep lung irritation and pulmonary edema. Farm workers exposed to high concentrations of the gas within enclosed silos may die rapidly of acute pulmonary edema. Irritation of the eyes, nose, and throat is common.

2. Treatment—No specific treatment is available. Measures to reduce inflammation and pulmonary edema are important.

E. Ozone

Ozone (O_3) is a bluish irritant gas produced in air and water purification devices and in electrical fields.

1. Effects—Exposure to 0.01‑0.1 ppm may cause irritation and dryness of the mucous membranes. Pulmonary function may be impaired at higher concentrations. Chronic exposure leads to bronchitis, bronchiolitis, pulmonary fibrosis, and emphysema.

2. Treatment—No specific treatment is available. Measures that reduce inflammation and pulmonary edema are emphasized.