CHAPTER 5
TOXICITY AND TOXINS
Objectives

A student reading this chapter will be able to:

1. Discuss and define the concepts of toxic triangle, poison, hazardous material, and hazardous waste.
2. List and explain the various methods of absorption including diffusion, facilitated diffusion, active transport, and special processes.
Objectives

3. Explain the processes of endocytosis including phagocytosis, pinocytosis, and receptor-mediated endocytosis.

4. Describe and discuss the major mechanisms by which toxic materials produce their adverse effects including: (1) inactivation of enzymes, (2) direct effect on cells and tissues, and (3) production of intermediate compounds or secondary action.
Objectives

– 5. Describe and provide an overview of the immune system, the cellular and humoral immune system, and allergic mechanisms.
– 6. Discuss and describe the adverse health effects associated with endocrine disruptors, PCBs, dioxin, lead, mercury, asbestos, and organic solvents.
Introduction

– In the United States, there are currently more than 70,000 synthetic chemicals currently in commercial use, and for most of them, their toxicity is not widely known or understood.
Introduction

Since 1,000 - 2,000 new chemicals are introduced each year into our society, there is significant opportunity for untested materials to enter our environment and expose humans, wildlife, and plants to toxic effects.
Introduction

- A potentially toxic substance produces its adverse effect by interacting with humans (or organisms) and the environment in a relationship referred to as the toxic triangle (Fig. 5-1).
Fig. 5-1

Environment

HAZARD

Toxic Agent

Person or organism
TOXICITY AND TOXINS

Introduction

- A poison or toxic substance does not constitute a hazard unless contact is made with the organism in a form and quantity that can cause harm.
A hazardous substance is defined in the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) as any chemical regulated under the following acts:

- Clean Air Act (CAA)
- Toxic Substances Control Act (TSCA)
- Clean Water Act (CWA)
Toxic Substance

- Toxic substances are those that:
  - (1) can produce reversible or irreversible bodily injury;
  - (2) have the capacity to cause tumors, neoplastic effects, or cancer;
  - (3) can cause reproductive errors including mutations and teratogenic effects;
Toxic Substance

- Toxic substances are those that:
  - (4) produce irritation or sensitization of mucous membranes;
  - (5) cause a reduction in motivation, mental alertness, or capability;
  - (6) alter behavior; or cause death of the organism.
EXPOSURE AND ENTRY

ROUTES

• Exposure
  – In order for a toxic substance to produce its harmful effects on the human body, a person must first be exposed to the chemical.
Absorption

- The passage of substances across the membranes through some body surfaces into body fluids and tissues by any of a variety of processes that may include diffusion, facilitated diffusion, active transport, or special processes.
• Diffusion
  - A passive process that occurs when molecules move from areas of high concentration to one of low concentration.
• Facilitated Diffusion
  – Some molecules such as amino acids and sugars require specialized carrier proteins to be transported across a membranes.
  – No high energy phosphate bonds such as ATP are required in this process.
• Active Transport
  – In this process, ATP is required in conjunction with special carrier proteins to move molecules through a membrane against a concentration gradient (i.e., low concentration to high).
• Endocytosis
  – Particles and large molecules that might otherwise be restricted from crossing a plasma membrane can be brought in or removed by this process.
Three Major Types of Endocytosis

- Phagocytosis
- Pinocytosis
- Receptor-mediated endocytosis
  - Ligands
There are several ways in which toxic substances can enter the body:

- lungs by inhalation,
- through the skin,
- mucous membranes or eyes by absorption, or
- gastrointestinal tract by ingestion.
The Respiratory System

- The respiratory system is composed of the nose, pharynx, larynx, trachea, bronchi, and lungs (Fig 5-2).
The Respiratory System

- External Respiration
  - The act of breathing or ventilation brings air into and out of the lungs.

- Internal Respiration
  - The exchange of gases between blood and individual cells.
The Respiratory System

• Bronchoconstriction narrows the lumen and restricts the flow of air, other gases, and particles from reaching more delicate tissues deeper in the lung (Fig. 5-3).
Fig. 5-3
The Skin

- The skin is the body’s largest organs consisting of many interconnected tissues covering an area of nearly 3,000 in.² in the average adult.
The Skin

- The skin helps to:
  - (1) regulate body temperature through sweat glands;
  - (2) provide a physical barrier to dehydration, microbial invasion, and some chemical insults;
The Skin

- The skin helps to:
  - (3) excrete salts, water, and organic compounds;
  - (4) serve as a sensory organ for touch, temperature, pressure, and pain; and
  - (5) provide some important components of immunity.
The Skin

- The skin has two layers (Fig. 5-4):
  - Epidermis
  - Dermis
The Skin

- Materials may pass through the skin by:
  - Absorption through hair follicles or sweat glands
  - Breaks in the skin
  - Injections
  - Insect bites
  - High pressure steam or liquid
The Gastrointestinal Tract

- The gastrointestinal tract is a major route of absorption for many toxic agents including mercury, lead, and cadmium which appear in food and water.
The Gastrointestinal Tract

- The components of the GI tract include the:
  - Mouth
  - Pharynx
  - Esophagus
  - Stomach
  - Small and large intestine
  - Anus (Fig. 5-5)
The Gastrointestinal Tract

- Nutrients as well as toxic agents can penetrate through the epithelial cells of the villus, enter the blood and lymph vessels, and be carried to various parts of the body (Fig. 5-6).
Fig. 5-6
Mechanisms of Action

• The harmful effects of environmental toxins are dominated by three principal mechanisms which include:
  – (1) the toxins influence on enzymes;
  – (2) direct chemical combination of the toxin with a cell constituent and;
  – (3) secondary action as a result of the toxins presence in the system.
Effects of Toxic Agents on Enzymes

- Holoenzyme
  - Apoenzyme
  - Cofactor
Effects of Toxic Agents on Enzymes

– Enzymes act on substrates to add or remove molecules of water, oxygen or hydrogen, or amino- or other functional groups.
– Enzymes may also rearrange atoms within a molecule, or join molecules (Fig. 5-7).
Effects of Toxic Agents on Enzymes

- Many toxic substances have the ability to:
  - (1) interfere with or block the active sites of the enzyme;
  - (2) inactivate or remove the co-factor;
Effects of Toxic Agents on Enzymes

• Many toxic substances have the ability to:
  – (3) compete with the co-factor for a site on the enzyme; or
  – (4) altering enzyme structure directly thereby changing the specific three-dimensional nature of the active site (Fig. 5-8).
**Fig. 5-8**

- **Blocking the active site of the holoenzyme**
- **Inactivate or remove cofactor**
- **Compete with cofactor for the site on the enzyme**
- **Altering active site of enzyme**
The Direct Action of Pollutants on Cell Components

- Strong acids, bases, and phenols can directly etch tissue
- Nitrous and sulfuric acids, and ozone can oxidize cellular material
- Carbon monoxide can react directly with hemoglobin and prevent the attachment of oxygen
Pollutants that Cause Secondary Actions

- Otherwise harmless substances may cause the formation of chemicals in the body that are harmful or potentially lethal.
- Fluoroacetate (rodenticide 1080) may be converted in the body to fluorocitric acid which is often lethal in small quantities.
- Allergens may produce discomforting or even fatal reactions by causing the immune system to release intermediary products such as histamines.
Immunity and Allergies

- Immunity is based on the premise that certain immune cells in the body can recognize microbes, tissues and other substances that are “non-self” or foreign, and so destroy, encapsulate, or remove them.
Immunity and Allergies

• Two separate but cooperating components of the immune system are known as:
  – Humoral (antibody-mediated) immunity
  – Cellular (cell-mediated) immunity.
  • The responses of cellular and humoral immunity are quite different (Fig. 5-9).
This reaction developed within 72 hours of subcutaneous injection of PPD to which the rabbit had been previously exposed. The reaction is characterized by influx of macrophages and lymphocytes producing a raised, hard area.

Cellular immune response to purified protein derivative (PPD) from *Mycobacterium tuberculosis*.

This reaction developed within minutes of subcutaneous injection of BSA to which the rabbit had been previously exposed. The reaction is characterized by subcutaneous bleeding.

Humoral immune response to bovine serum albumin (BSA).
Immunity and Allergy

- Each component of the immune system is formed in the embryonic stages from lymphocytic stem cells that appear in bone marrow (Fig. 5-10).
Lymphocytic stem cells in bone marrow of embryo

Thymus

T-cell

T and B cells populate lymph nodes, spleen, gastrointestinal tract, bone marrow

Fetal liver, spleen, gut-associated tissue, or bone marrow

B-cell
Immunity and Allergy

• The Initial Immune Response
  – The immune system responds to agents, cells, or substances that are foreign or non-self, are collectively called antigens.
The Initial Immune Response

- Hapten
- Macrophage
- Human Leukocyte Associated antigens (HLA)
Cellular Immunity

- T cells respond to a particular antigen then enlarge, divide, and give rise to clones of several subpopulations of T cells (Fig. 5-11a,b).
Adapted from Tortora and Anagnostakos\textsuperscript{11} and Tortora.\textsuperscript{12}
Adapted from Tortora and Anagnostakos\textsuperscript{11} and Tortora.\textsuperscript{12}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{sensitized_tcell_diagram}
\caption{Sensitized T-cell}
\end{figure}

- **Cytotoxic (killer) T-cell**: Attacks antigen directly and releases substances to attract and activate macrophages.
- **Helper T-cells**: Also known as CD\textsubscript{4} cells.
- **Memory T-cells**: Recognizes and responds rapidly to re-invading antigen.
- **Suppressor T-cells**: Aids the immune system in maintaining balance.
- **Amplifier T-cells**: Enhances the immune response.
- **Delayed hypersensitivity T-cells**: Secretes lymphokines contributing to delayed hypersensitivity reaction.

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Humoral Immunity

- B Cells
  - Produce liquid proteins (humoral) known as antibodies and secrete them into the bloodstream where they can travel to the affected site and carry out their destructive action (Fig. 5-12).
Adapted from Tortora and Anagnostakos\textsuperscript{11} and Tortora.\textsuperscript{12}
Adapted from Tortora and Anagnostakos and Tortora.12

Fig. 5-12b

B-cell enlarges and proliferates

Plasma cells

Memory B-cells Recognize and respond rapidly to re-introduction of antigen

Antibodies to specific antigens produced by cloned plasma cells
The Antibody Molecule

- Antibodies (also called immunoglobulins) are proteins (Fig. 5-13).
The Antibody Molecule

• The five major classes of antibodies known as:
  – Immunoglobulins
  – IgG
  – IgA
  – IgM
  – IgD
  – IgE.
The Antibody Molecule

- The variable regions of the antibody are created in a specific three-dimensional form that is pre-configured in the B cell clone to only one antigenic group (Fig. 5-14).
Antibody Activities

- The binding of an antibody with its specific antigen can activate the complement system.
- The complement system enhances phagocytosis, inflammation, and cell lysis (Fig. 5-15).
Fig. 5-15

Antibodies combine with their specific antigens to form complexes that inactivate or destroy the antigen in several possible ways.

- Agglutination of cells
- Precipitation of soluble antigens
- Neutralizing viruses and toxins
- Activating complement

Agglutination, precipitation, and neutralization stimulate phagocytosis

Phagocytosis

Cell lysis

Inflammation

Activation of complement stimulates inflammation, vasodilation, and phagocytosis, and causes cell lysis

Adapted from Tortora and Anagnostakos and Tortora.
Hypersensitivity

- An exaggerated immune response to the presence of an antigen is termed hypersensitivity or allergy.
Hypersensitivity

• There are four major types of hypersensitivity reactions:
  – Cytotoxic,
  – Cell-mediated,
  – Immune complex
  – Anaphylactic (Fig. 5-16)
Fig. 5-16

Antigen bridging two adjacent IgE antibody molecules

IgE antibodies

Mast cell or basophil

Granules

Histamine and leukotrienes
Factors Governing Toxicity

The outcome of exposure to a toxin depends on a number of factors that may include:

- The Properties of the Chemical
- Concentration
  - Effective Dose
  - Bioaccumulation
  - Biotransformation
Factors Governing Toxicity

- The outcome of exposure to a toxin depends on a number of factors that may include:
  - Interactions
    - Synergistic
    - Antagonistic
  - Age
  - Exercise and Physical Stress
  - Health Status
SOME SPECIFIC EXAMPLES OF TOXIC AGENTS

- Endocrine Disrupters and Reproductive Health
- Hormone Function
  - Hormones are critical in the regulation of many life processes, including sexual development, metabolic functions, development of the brain, human growth, and stress response.
Hormone Function

• Androgens
  – Regulate the development and maintenance of male sexual characteristics

• Estrogens
  – Stimulate the development of female sexual characteristics
Adverse Effects of Endocrine Disruption

• (1) reduced sperm counts;
• (2) precocious puberty;
• (3) increase in non-Hodgkin lymphoma;
• (4) marked increase in males having undescended testicles, and
• (5) testicular cancer.
What are Endocrine Disruptors?

- Examples of Endocrine Disruptors
  - Pesticides such as DDT
  - Plasticizers such as phthalates and alkylphenols
  - PCBs, Dioxin
  - A variety of naturally occurring plant compounds or phytoestrogens
Endocrine Disruptors–How Do They Work?

– There are at least four different mechanisms by which endocrine disruptors can exert their adverse effects (Fig. 5-17).
Fig. 5-17a

1. ED may not exactly fit receptor on cell and so block hormone and its activities.

2. ED may replace native hormone on a carrier protein so that it is unavailable to target cells.

ED disruptor (ED)

Native hormone

Endocrine disruptor (ED)

Response triggered

Cell receptor

Carrier protein

ED may exactly fit receptor on cell and so mimic hormone and trigger reaction.

Native hormone
3. ED may alter hormone production, either increasing or decreasing baseline production.

4. ED may influence the number of hormone receptors on the cell.
Reducing Exposure

- Endocrine Disruptors find their way into the food supply through:
  - (1) ingestion of contaminated grains and grasses by livestock which then store the lipophilic chemicals in their fatty tissues;
  - (2) contamination of fruits and vegetables by spraying with pesticides; and
  - (3) leaching from plastic wrappers, plastic liners of cans, and polystyrene containers.
Reducing Exposure

- Exposure to endocrine disruptors may be reduced by:
  - 1. Reducing or limiting ingestion of dairy products and meat high in fat where organochlorines tend to accumulate.
  - 2. Avoiding synthetic pesticides by purchasing foods low in pesticide residues and switching to herbal or scent-based repellents.
Reducing Exposure

- 3. Keeping children from vinyl toys or teething rings
- 4. Using detergents, and shampoos that do not contain alkylphenols such as nonoxynol and octoxynol.
Dioxin

- Dioxin is an unwanted by-product from heating mixtures of chlorine and organic compounds in industrial processes (Fig. 5-18).
• Dioxin
- Dioxin slowly breaks down in the environment when it is exposed to the ultraviolet rays of the sun, otherwise, dioxin is a stable compound.
Dioxin

- Dioxin does not attach to the estrogen receptor; rather, it attaches to a receptor called the Ah-receptor, whose function is unknown.
• Anti-estrogenic Effects
  – Dioxin indirectly breaks down the body’s normal estrogen, and decreases the number of estrogen receptors available for naturally occurring estrogen.
Dioxin Contaminations

- Vietnam
- Seveso Italy
- Times Beach Missouri
Dioxin

• EPA Draft of Dioxin Reassessment Document in 1994
  – Dioxin poses increased risk for cancers, adverse reproductive and developmental effects, neurological damage from in utero exposure, endocrine disruption, and reproductive and development effects.
Polychlorinated biphenyls (PCBs)

- PCBs are chemically inert, nonflammable fluid with high plasticizing ability, and a high dielectric constant (Fig. 5-19).
PCB
In the United States from 1929 to 1977, PCBs were used in transformers, capacitors, hydraulic and heat transfer fluids, and solvents in adhesives and sealants.
PCBs

- More than 94 percent of fish collected in the U.S. show PCB residues at an average concentration of 0.53ppm.
• Japan, 1968
  – Yusho (rice oil) Disease
  – 1300 Japanese developed symptoms, which included chloracne, eye discharge, and swelling in the joints.
PCBs

- Taiwan, 1979
  - Yu-cheng Disease
  - Children at birth were observed to have abnormalities in teeth, nails and pigmentation, low birth weights, lower IQs were observed in the children as they aged.
In North America lead has been used in agriculture in the form of lead arsenate for pesticidal use, as solder in pipes, as a solder in food containers, and as an anti-knock compound in gasoline.
- In the 1970s, both federal regulatory and legislative efforts were begun to reduce lead hazards, including the limitation of lead in paint and gasoline (Fig. 5-20).
Fig. 5-20

Adapted from Schwartz et al.\textsuperscript{56}

Total lead used per 6 month period (thousands of tons)

Average blood lead levels (mg/dl)

120
110
100
90
80
70
60
50
40

Year

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The most significant sources of exposure to inorganic lead include food, water, soil and lead-based paint.

Lead may enter the body through ingestion and inhalation, while organic lead may also be absorbed through the skin.
Lead

- Lead affects the formation of blood in two distinct mechanisms:
  - (1) by slowing the normal maturation of red blood cells in the bone marrow, decreasing the number of red blood cells and possibly causing anemia; and
  - (2) lead inhibits the synthesis of hemoglobin.
Lead

- Over the past 10 years, there has been more and more evidence that lead may have serious health effects at lower exposure levels which were previously not thought to be harmful (Fig. 5-21).
Fig. 5-21

Blood lead level (μg/dl)

- CDC: 60
- CDC: 30
- CDC: 25
- WHO: 20
- EPA: 15

Year that level of recommended or regulatory maximum lead level established

- 1960 and before
- 1975
- 1986
- 1986
- 1986

10 to 15 μg/dl is the recommended maximum level.

Adapted from U.S. Congress.53
Effects of Lead

• Lead may:
  – Impair fertility in both men and women
  – Lower sperm counts
  – Cause spontaneous abortions and stillbirths
• Young children are at a greater risk for elevated lead levels due to:
  – (1) their increased oral activity;
  – (2) increased ability to absorb lead;
  – (3) higher retention of absorbed lead and;
  – (4) the incompletely developed nervous system.
A study in the Boston Suburbs documented the negative effects of lead on classroom behaviors (Fig. 5-22).
Adapted from Needleman and Rabinowitz.61

**Fig. 5-22**

![Graph showing the percentage of teachers reporting different behaviors among children. The graph compares children with dentine lead concentration above 27.0 ppm (red bars) to those with dentine lead concentration below 5.1 ppm (teal bars). The behaviors include distractable, not persistent, dependent, hyperactive, impulsive, frustrated, daydreamer, unable to follow simple directions, unable to follow sequences, and low overall functioning.](image-url)
Organic Solvents

- Organic solvents are a group of simple organic liquids, which have the capacity to change from liquids to gases in the presence of air.
Organic Solvents

- Organic solvents are components of many products including paints, varnishes, paint removers, adhesives, glues, degreasing and cleaning agents, pharmaceuticals, plastics and pesticides.
Organic Solvents

- Solvents enter the body by ingestion from contaminated drinking water supplies, but may enter the body via skin absorption and inhalation in the shower.
Organic Solvents

- There is disturbing evidence that organic solvents, most notably the glycol ethers, cause spontaneous abortions, birth defects and childhood cancers.
Asbestos

Asbestos is a collective term for a group of six fibrous silicate materials:

- Asmolite
- Chrysotile
- Tremolite
- Actinolite
- Anthophyllite
- Crocidolite
Asbestos

- Asbestos has been used in various products and processes, including building materials, brake linings, textiles and insulation, as well as floor tiles, cement and potholders (Fig. 5-23).
Asbestos enters our water through:

- Airborne settling
- Leaching from asbestos-cement pipes
- Dumping of effluent from mining operations
Exposure to asbestos is primarily achieved through the inhalation of these tiny fibers that are suspended in the air, often getting trapped deep within the lungs.
• Crocidolite is more likely to produce disease than other forms of asbestos.
  – Asbestosis
  – Lung Cancer
  – Mesothelioma
Asbestos

- The EPA estimated that 15 million students and 1.4 million teachers and other employees are in buildings that contain asbestos.

- Asbestos School Hazard Abatement Act (ASHAA) in 1984 to provide financial assistance to schools having significant asbestos problems.
Mercury

- Three Forms
  - Elemental mercury vapor
  - Inorganic mercury compounds
  - Organic (usually methyl) mercury (most toxic)
Mercury

- Mercury is used in the production of chlorine, for use in thermometers, batteries and fluorescent light bulbs.
Organic Mercury

- Minamata Bay Japan
- Numbness of tongue, lips, and fingers
- Developmental Toxin
**Elemetal Mercury**

- Found in dental amalgam fillings, thermometers and batteries
- Hazardous only when inhaled
Inorganic Mercury

- Vaporizes at room temperature
- Exposure due to inhalation or absorption
- Damage to kidneys and liver, tremors, interferes with coordination