

Chapter 1

Introduction to Toxicology

Histological Background (1)

- Identification and use of toxic substances have occurred throughout recorded history.
 - Records from as early as 1500 B.C. describe plant poisons such as hemlock, aconite, and opium, as well as toxic metals such as antimony (Sb), copper (Cu) and lead (Pb).
- A Greek physician, Dioscorides (circa A.D. 50-90), was the first to attempt the classification of poisons.
 - He divided the substances into three categories: plant poisons, animal poisons, and mineral poisons.
 - Master herbalist, father of pharmacy

Histological Background (2)

- As early as the 15th century it was recognized that individuals associated with certain occupations were being exposed to toxic substances.
 - Workers involved in occupations such as goldsmithing, mining, printing, and pottery-making were exposed to toxic substances such as mercury (Hg) and lead (Pb).
- Two major publications:
- “On the Miners’ Sickness and Other Diseases of Miners” (Paracelsus, 1567)
- “Discourse on the Diseases of Workers” (Ramazzini, 1700)

Histological Background (3)

- **The Swiss-German physician Paracelsus is often referred to as the father of toxicology. He developed many of the ideas that comprise the major toxicological principles used today.**
 - He believed that the toxic agent, which he referred to as the toxicin, was a single chemical found in a toxic substance. In order to understand the effects of “toxicin”, he believed that
 - It was necessary to use experimentation to identify and understand response to chemicals;
 - There is a difference between toxic and therapeutic properties of chemicals;
 - The dose of the chemical is important in making the distinction between therapeutic effects and harmful effects; and
 - It is possible to identify --- to some extent --- a degree of chemical specificity.
 - **"All things are poison and nothing is without poison; only the dose makes a thing not a poison." This is often condensed to: "The dose makes the poison".**

Histological Background (4)

- Ramazzini is referred to as the father of occupational medicine.
- Along with the many benefits brought by industrialization and chemical use came an increase in the number of occupational disease and illnesses being observed.
 - An increased rate of scrotal cancer among chimney sweeps was observed by Percival Pott in 1775.
 - the first documented evidence of polycyclic aromatic hydrocarbon (PAH) induced cancer.

Histological Background (5)

- **In the 1960s the long-term effects of pesticides were documented in Rachel Carson's book *Silent Spring*.**
- **Ether and chloroform were used as anesthetics. Their use during pregnancy resulted in numerous fetal deaths.**
- **Thalidomide was administered during the early stages of pregnancy for "morning sickness." This drug caused several thousand babies to be with serious birth defects, such as problems with arm and leg development.**
- **Sulfanilamide used to fight infection was dissolved in ethylene glycol. Since ethylene glycol affects the kidneys, many patients died from kidney dysfunction.**
 - **The harmful effects associated with the use of sulfanilamide led to the formation of the U.S. Food and Drug Administration (FDA) in 1938.**

Definition of Toxicology

- **Toxicology** is the study of the adverse effects of chemicals on living organisms. It is the study of symptoms, mechanisms, treatments and detection of poisoning, especially the poisoning of people.

Source of Chemical Information (1)

- Environmental Protection Agency (EPA)
 - The specific chemicals regulated by EPA and the associated standard are found in the Code of Federal Regulations (CFR).
- National Institute for Occupational Safety and Health (NIOSH)
 - NIOSH is a federal agency established by the Occupational Safety and Health Act of 1970. NIOSH is a part of the Centers for Disease Control and Prevention (CDC).
 - It has several functions, such as investigating potentially hazardous work conditions, evaluating chemical hazards in the workplace, and conducting research on chemicals.
 - Information derived from these efforts is used to help reduce disease, injury, and disability in the workplace.
 - The information is assembled into criteria documents, which OSHA utilizes to establish standards.

Source of Chemical Information (2)

- **Occupational Safety and Health Administration (OSHA)**
 - In 1970 the Occupational Safety and Health Act was passed. The Act is enforced by the Occupational Safety and Health Administration. OSHA's stated mission is to save lives, prevent injuries, and protect the health of America's workers.
 - Exposure to toxic substances in the workplace is one of the major areas of interest to OSHA. Like EPA, OSHA is involved in the accumulation and evaluation of toxic chemical information in order to establish acceptable exposure levels for chemicals found in the workplace.
 - OSHA regulations – which establish standards for a variety of hazardous and toxic chemicals – are found in 29 CFR 1910.

Source of Chemical Information (3)

- American Conference of Governmental Industrial Hygienists (ACGIH)
 - It is a professional organization that produces a listing of Threshold Limit Values (TLV) and Biological Exposure Indices (BEI) for several hundred chemicals, updating them every year.
 - The TLVs are used as guidelines for occupational exposure to hazardous chemical.

U.S. Government Agencies for Toxic Chemical Regulation

Agency	Legislation	Covers
FDA	Federal Food, Drug, and Cosmetic Act	Drugs; food additives; food contact substance; coloring (no carcinogens)
EPA	Federal Insecticide, Fungicide, and Rodenticide Act; Clean Air Act; Safe Drinking Water Act and 1996 Amendment; Food Qual. Protection Act 1996; Toxic Substances Control Act; Superfund Amendments and Reauthorization	Air and water pollutants; contaminated sites; environmental estrogens/endocrine disruptors; pesticides; toxic substances
OSHA	Occupational Safety and Health Act; Federal Hazardous Substance Act	Occupational exposure
CPSC	Consumer Product Safety Act	Consumer products
DOT	Hazardous Materials Transportation Act	Shipping hazardous materials

Role of the Toxicologist (1)

- Descriptive Toxicology
 - Descriptive toxicologists are involved in obtaining toxicological information from animal experimentation. These types of experiments are used to establish dose-response relationships and may involve either acute or chronic exposure to a toxic substance.
- Mechanistic Toxicology
 - Observations on how toxic substances cause their effects form another specialized of toxicology, mechanistic toxicology. The effects of exposure are dependent on a variety of factors such as the solubility of the substance in water or fatty tissues, the size of the molecule, and the specific tissue type and cellular components affected.

Role of the Toxicologist (2)

- Forensic Toxicology
 - Forensic toxicologists are often involved in providing toxicological information in support of legal activities.
- Environmental Toxicology
 - Environmental toxicologists are concerned with the interaction of toxic substances with all components of the ecosystem.
- Regulatory Toxicology
 - Regulatory toxicologists are involved in compiling and evaluating existing toxicological information to establish concentration-based standards of “safe” exposure.

Role of the Toxicologist (3)

- Food Toxicology
 - Food toxicologists are involved in delivering a safe and palatable supply of food to the consumer.
- Clinical Toxicology
 - Clinical toxicologists are concerned with diseases and illnesses associated with acute or chronic exposure to toxic chemicals.

Terminology

- Dose
 - The dose is the actual amount of a chemical that enters the body.
- Acute versus chronic exposure
 - Acute exposure
 - An acute exposure occurs over a very short period of time, usually 24 hours.
 - Chronic exposure
 - Chronic exposures occur over long periods of time such as weeks, months, or years.

Chemical Accident: Bhopal, India (1)

- **Occurred on December 3, 1984.**
- **Methyl isocyanate (MIC), used in the manufacture of carbaryl, was discharged from a Union Carbide facility into the surrounding community of Bhopal, India with a population of 800,000.**
- **Water leaked into a tank containing MIC. Mixing of MIC with water produced heat and caused an increase in tank pressure, eventually resulting in the MIC into air. The released gas was heavier than air and formed a deadly cloud close to the ground.**
- **The leak occurred as a result of human error and non-operational safety equipment.**
- **It was estimated that 2,500 deaths caused immediately and up to 300,000 were injured. An additional 8,000 have died since the initial exposure. 40,000 people still has respiratory problems three months after exposure.**

Chemical Accident: Bhopal, India (2)

- **Initially the Indian government sought \$3 billion in liabilities related to the release, but it eventually settled for \$470 million and agreed not to recognize any future civil claims.**
- **A report issued in December of 1996 stated that as many as 50,000 people continue to be affected by the events associated with the accident.**
- **Post-traumatic stress disorders were observed in the people.**

Lead (1)

- **Lead has a wide range of uses. Its main use is in the manufacture of storage batteries. Other uses include the production of chemicals, including paint, gasoline additives, various metal products (for example, sheet lead, solder and pipes), and ammunition.**
- **People may be exposed to lead and lead compounds from breathing air, drinking water, and eating soil or foods that contain lead.**
- **The activity is known as pica (an abnormal eating habit). Children who put toys or other items in their mouths may also swallow lead if lead-containing dust and dirt are on these items.**
- **The burning of gasoline has been the single largest source (90%) of lead in the atmosphere since the 1920s. Today less than 35% of the lead released to the air comes from gasoline because EPA reduced the amount of lead allowed in the gasoline.**
- **The major sources of lead released to water are lead plumbing and solder in houses, schools, and public buildings.**

Lead (2)

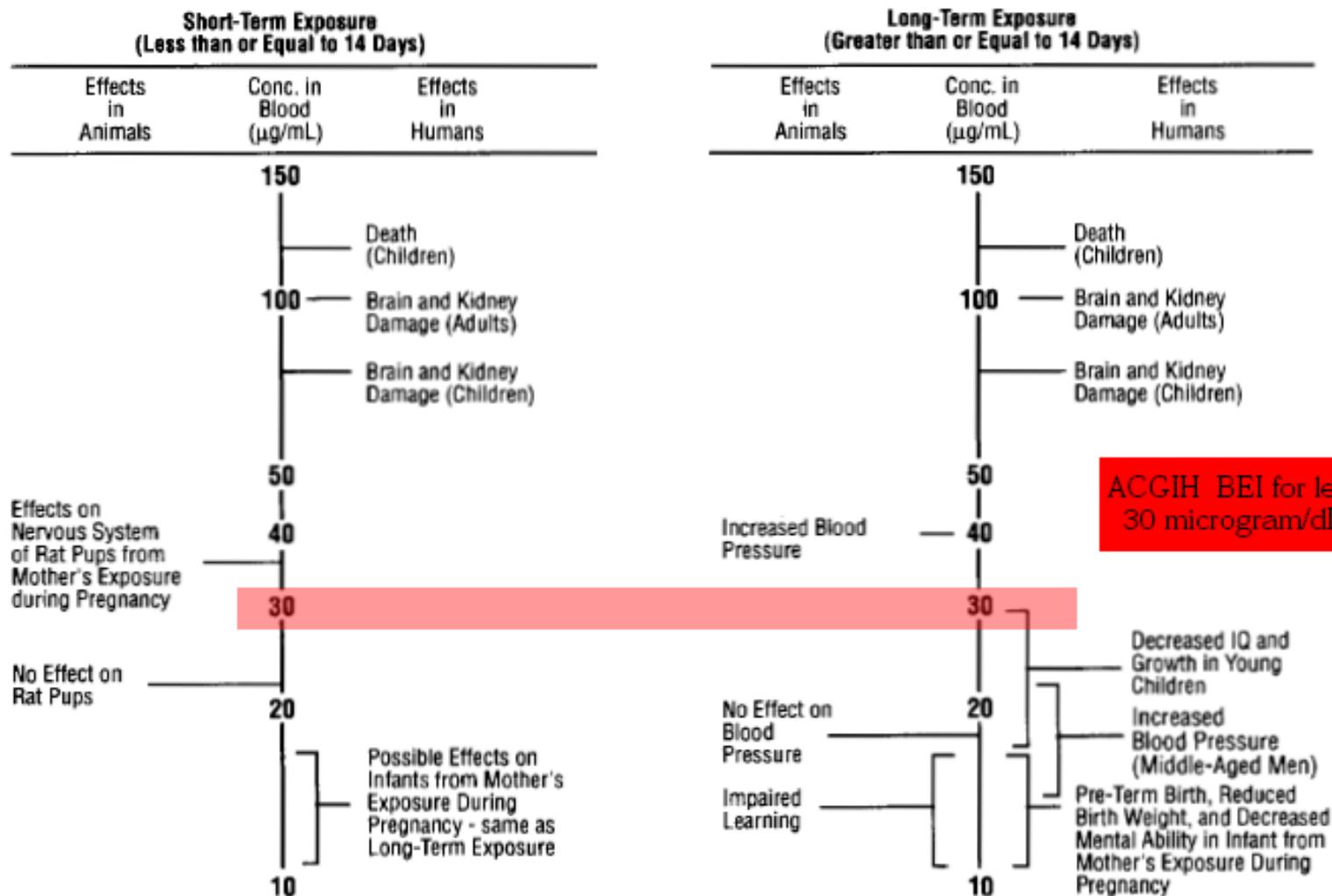
- **Food and beverages may contain lead if lead-containing dust deposits onto crops while they are growing and during food processing.**
- **Workers may be exposed to lead in a wide variety of occupations including smelting and refining industries. Steel welding and cutting operations, battery manufacturing plants, gasoline stations, and radiator repair shops.**
- **Lead can enter your body when you breathe air containing lead dust. Almost all of the lead in the lungs enters the blood and moves to other parts of the body.**
- **Almost all of the lead in the lungs enters the blood and moves to other parts of the body.**
- **When lead-containing substances are ingested much more of the lead enters the blood in children than it does in adults.**

Lead (3)

- **Much less lead enters the body through the skin than through the lungs or gastrointestinal tract.**
- **Regardless of how lead enters your body, most of it is stored in bone. Lead that is not stored in the body is removed in the urine and feces.**
- **Children's bodies absorb lead more easily and are more sensitive to its effects. For infants or young children, lead exposure has been shown to decrease intelligence (IQ) scores, to slow growth, and to cause hearing problems.**
- **Exposure to high levels of lead may cause the brain and kidneys of adults and children to be badly damaged. Also, high levels of lead may affect the sperm or damage other parts of the male reproductive system.**

Lead (4)

--- Levels of Exposure Resulting in Harmful health Effects



Lead (5)

- **The Centers for Disease Control (CDC) recommends that screening (testing) for lead poisoning be included in health care programs for children under 72 months of age, and especially for those under 36 months of age.**
- **If many children in a community have blood lead levels $\geq 10 \mu\text{g/dL}$, lead poisoning prevention activities throughout the community should begin.**
- **EPA regulations limit lead in drinking water to 0.015 mg/L and does not allow the amount of lead that a person breathes over 3 months to be more than $1.5 \mu\text{g/m}^3$. EPA also limits the amount of lead in lead gasoline to 0.1 g/gal , and in unleaded gasoline to 0.05 g/gal .**
- **NIOSH recommends that workers not be exposed to levels of more than $100 \mu\text{g/m}^3$ for up to 10 hours.**

Events at Love Canal

- **During late 1970s and early 1980s**
- **From 1942 to 1952, 21,000 tons of various types of chemicals wastes were disposed of at the Love Canal landfill.**
- **The site was covered and subsequently sold to the city of Niagara Falls for one dollar.**
- **It was not until the late 1970s – after years of complaints from local residents – increased numbers of illnesses, and visible signs of chemicals appearing in yards and homes, that the magnitude of the problem was discovered.**
- **As a result, residents were moved from the Love Canal area, and cleanup and removal of the buried chemicals was initiated.**

Minamata Disease: Mercury Poisoning (1)

- **A “strange disease” appeared in the mid-1950s in and around a small Japanese village called Minamata. In general, victims demonstrated symptoms consistent with nervous system degeneration.**
- **It was not until 1959 that a correlation was made between the occurrence of the “strange disease” and the presence of mercury in the diet of individuals who demonstrated these symptoms.**
- **The factory manufactured plastics, drugs, and perfumes using the chemical acetaldehyde. Acetaldehyde is produced using mercury. From 1932 to 1968, 27 tons of mercury compounds were dumped into Minamata Bay. In the bay, bacteria converted the mercury to methylmercury, which was subsequently concentrated in the fish and shellfish of Minamata bay.**

Food Additives: Safe or Harmful (1)

- **Artificial sweeteners such as saccharin, cyclamates, and more recently, aspartame, were developed and manufactured to replace sugar. Saccharin and aspartame are used in commercial foods and the diet drink industry. Cyclamates are not currently approved for use.**
- **1990s further efforts to produce “health food” additives resulted in the use of olestra as a substitute for fat in various products. The FDA approved its use in products such as potato, corn and tortilla chips, and crackers.**

Food Additives: Safe or Harmful (2)

- **Saccharin**

- It is about 300 times sweeter than sugar with fewer calories. Saccharin contains only 1 to 8 calories per teaspoon. Controversy exists concerning the carcinogenic properties of saccharin. In 1977 reports indicated that saccharin caused cancer in the urinary bladder. Other studies have suggested that it may cause cancer of the stomach and intestine.
- The FDA has concluded that saccharin is considered “safe” for use.

- **Cyclamate**

- In the 1980s studies indicated that the combination of saccharin and cyclamates caused cancer in lab rats. As a result cyclamate use in combination with saccharin was banned.

Food Additives: Safe or Harmful (3)

- **Aspartame**

- **It is one of the more recent additions to the list of artificial sweeteners. It is 180-200 times as sweet as sugar and contains only 4 calories per gram.**
- **There are several issues associated with the use of this product. Once ingested, aspartame is broken down in the digestive tract, releasing phenylalanine, which is absorbed into the bloodstream.**
- **One in 20,000 newborn babies have difficulty metabolizing phenylalanine. As a result, elevated blood levels of phenylalanine may occur, which may be toxic and cause mental retardation.**
- **More recent reports have suggested that there may be an association between an increase in the occurrence of brain tumors and the use of aspartame.**

Food Additives: Safe or Harmful (4)

- **Olestra**

- It was first developed for the purpose of increasing fat intake in premature babies.
- The olestra molecule is not broken down by enzyme or bacteria present in the digestive tract. Therefore, the molecule remains too large to be absorbed, and it passes out of the digestive tract.
- It binds with other vital nutrients, such as fat soluble vitamins A, D, E and K and removed them from the body. Adverse effects at this time have been limited to the gastrointestinal tract, with diarrhea being the primary symptom.

It Only Takes a Little --- Botulism (1)

- Loretta Boberg, a 62-year old woman, opened a jar of home-canned carrots. She dipped in a finger to taste the juice. Not liking the taste, she served home-canned beans to her guests instead. Within two days Mrs. Boberg became dizzy and had suffered a stroke because of her slurred speech and muscle weakness.
- The doctor did ask her if she had eaten any spoiled food lately. She was too weak to speak, but she wrote “carrots” on a piece of paper.
- The road to recovery for this lady was very slow. Six months later, she remained in the hospital on a respirator, still being fed intravenously. Hospital officials estimated that her bill was running about \$200,000.
- Botulism
 - The toxin moved through the respiratory system, paralyzing her muscles.

It Only Takes a Little --- Botulism (2)

- Because native spores of *Clostridium botulinum*, the bacteria that cause the potentially fatal botulism, are extremely difficult to destroy at boiling water temperatures, acid foods should be processed at the much higher temperatures achieved with pressure canners.
- Prevention
 - Botulism can be prevented by killing the spores by cooking at 121 °C (250 °F) for 3 minutes or providing conditions that prevent the spores from growing. Additional precautions for infants include not feeding them [honey](#).

