

APPENDIX E

Industrial Toxicology Overview

Chemical Toxicology

Toxicology is the study of the nature and action of poisons.

Toxicity is the ability of a chemical molecule or compound to produce injury once it reaches a susceptible site in or on the body.

Toxicity hazard is the probability that injury will occur considering the manner in which the substance is used.

Dose-Response Relationships

The potential toxicity (harmful action) inherent in a substance is manifest only when that substance comes in contact with a living biological system. A chemical normally thought of as "harmless" will evoke a toxic response if added to a biological system in sufficient amount. The toxic potency of a chemical is thus ultimately defined by the relationship that is produced in a biological system.

Routes of Entry into the Body

There are four main routes by which hazardous chemicals enter the body:

- Inhalation: Absorption through the respiratory tract. Most important in terms of severity.
- Skin absorption.
- Ingestion: Absorption through the digestive tract. Can occur through eating or smoking with contaminated hands or in contaminated work areas.
- Injection. Can occur by accidental needle stick or puncture of skin with a sharp object.

Most exposure standards, Threshold Limit Values (TLVs) and Permissible Exposure Limits (PELs), are based on the inhalation route of exposure. They are normally expressed in terms of either parts per million (ppm) or milligrams per cubic meter (mg/m^3) concentration in air.

If a significant route of exposure for a substance is through skin contact, the TLV or PEL will have a "skin" notation. Examples are pesticides, carbon disulfide, carbon tetrachloride, dioxane, mercury, thallium compounds, xylene, hydrogen cyanide.

Types of Effects

Acute poisoning is characterized by rapid absorption of the substance and the exposure is sudden and severe. Normally, a single large exposure is involved. Examples are carbon monoxide or cyanide poisoning.

Chronic poisoning is characterized by prolonged or repeated exposures of a duration measured in days, months or years. Symptoms may not be immediately apparent. Examples are lead or mercury poisoning, pesticide exposure.

Local refers to the site of action of an agent and means the action takes place at the point or area of contact. The site may be skin, mucous membranes, the respiratory tract, gastrointestinal system, eyes, etc. Absorption does not necessarily occur. Examples are strong acids or alkalis and war gases.

Systemic refers to a site of action other than the point of contact and presupposes absorption has taken place. For example, an inhaled material may act on the liver. Examples are arsenic affects the blood, nervous system, liver, kidneys and skin; benzene affects bone marrow.

Cumulative poisons are characterized by materials that tend to build up in the body as a result of numerous chronic exposures. The effects are not seen until a critical body burden is reached. Examples are heavy metals.

Substances in combination, meaning two or more hazardous materials present at the same time whose resulting effect is greater than the effect predicted based on the individual substances. This combined effect is called a **synergistic** or **potentiating** effect. An example is exposure to alcohol and chlorinated solvents.

Other Factors Affecting Toxicity

Rate of entry and route of exposure; that is, how fast the toxic dose is delivered and by what means.

Age can effect the capacity to repair tissue damaged.

Previous exposure can lead to tolerance, increased sensitivity, or make no difference.

State of health, medications, physical condition, and life style can affect the toxic response. Pre-existing disease can result in increased sensitivity.

Environmental factors, such as temperature and pressure.

Host factors, including genetic predisposition and the sex of the exposed individual.

Physical Classifications of Toxic Materials

Gas applies to a substance which is in the gaseous state at room temperature and pressure.

A **vapor** is the gaseous phase of a material which is ordinarily a solid or a liquid at room temperature and pressure.

When considering the toxicity of gases and vapors, the **solubility** of the substance is a key factor. Highly soluble materials like ammonia irritate the upper respiratory tract. On the other hand, relatively insoluble materials like nitrogen dioxide penetrate deep into the lung. Fat soluble materials, like pesticides, tend to have longer residence times in the body.

An **aerosol** is composed of solid or liquid particles of microscopic size dispersed in a gaseous medium. The toxic potential of an aerosol is only partially described by its concentration in milligrams per cubic meter (mg/m³). For a proper assessment of the toxic hazard, the size of the aerosol's particles is important. Particles above 1 micrometer tend to deposit in the upper respiratory tract. Below 1 micrometer particles enter the lung. Very small particles (< 0.2 um) are generally not deposited.

Physiological Classifications of Toxic Materials

Irritants are materials that cause inflammation of mucous membranes with which they come in contact. Inflammation of tissue results from concentrations far below those needed to cause corrosion. Examples include:

- ammonia
- nitrogen dioxide
- diethyl/dimethyl sulfate
- hydrogen chloride
- arsenic trichloride
- hydrogen fluoride

- halogens
- phosphorus chlorides
- ozone
- phosgene
- alkaline dusts and mists

Irritants can also cause changes in the mechanics of respiration and lung function.

Examples include:

- sulfur dioxide
- iodine
- formic acid
- formaldehyde
- acetic acid
- acrolein
- sulfuric acid

Long term exposure to irritants can result in increased mucous secretions and chronic bronchitis.

A **primary irritant** exerts no systemic toxic action either because the products formed on the tissue of the respiratory tract are non-toxic or because the irritant action is far in excess of any systemic toxic action. Example: hydrogen chloride.

A **secondary irritant's** effect on mucous membranes is over-shadowed by a systemic effect resulting from absorption. Examples include hydrogen sulfide and aromatic hydrocarbons.

Exposure to a secondary irritant can result in pulmonary edema, hemorrhage, and tissue necrosis.

Corrosives are chemicals which may cause visible destruction of or irreversible alterations in living tissue by chemical action at the site of contact. Examples include sulfuric acid, potassium hydroxide, chromic acid, and sodium hydroxide

Asphyxiants have the ability to deprive tissue of oxygen.

Simple asphyxiants are inert gases that displace oxygen. Examples include, nitrogen, nitrous oxide, carbon dioxide, hydrogen, and helium.

Chemical asphyxiants have as their specific toxic action rendering the body incapable of utilizing an adequate oxygen supply. They are toxic at very low concentrations (few ppm). Examples include carbon monoxide and hydrogen cyanide.

Primary anesthetics have a depressant effect upon the central nervous system, particularly the brain. Examples include halogenated hydrocarbons, ether, and alcohols.

Hepatotoxic agents cause damage to the liver. Examples include carbon tetrachloride, nitrosamines, and tetrachloroethane.

Nephrotoxic agents damage the kidneys. Examples include halogenated hydrocarbons and uranium compounds.

Neurotoxic agents damage the nervous system. The nervous system is especially sensitive to organometallic compounds and certain sulfide compounds. Examples include:

- trialkyl tin compounds
- insecticides
- thallium
- methyl mercury
- tetraethyl lead
- manganese
- organic phosphorus
- carbon disulfide

Some toxic agents act on the blood or hematopoietic system. The blood cells can be directly affected or bone marrow can be damaged. Examples include:

- nitrites
- benzene
- nitrobenzene
- toluidine
- aniline

There are toxic agents that produce damage of the pulmonary tissue (lungs) but not by immediate irritant action. Fibrotic changes can be caused by free crystalline silica and asbestos. Other dusts can cause a restrictive disease called pneumoconiosis. Examples include coal dust, cotton dust and wood dusts.

A **carcinogen** commonly describes any agent or mixture which contains an agent that can initiate or speed the development of malignant or potentially malignant tumors or malignant neoplastic proliferation of cells. Known human carcinogens include:

- asbestos
- alpha-naphthylamine
- 3,3'-dichlorobenzidine
- vinyl chloride
- ethylene oxide
- N-nitrosodimethylamine
- inorganic arsenic
- 1,2-dibromo-3-chloropropane (DBCP)
- coal tar pitch volatiles
- 4-nitrobiphenyl
- methyl chloromethyl ether
- bis-chloromethyl ether

A **mutagen** affects the chromosome chains of exposed cells. The effect is hereditary and becomes part of the genetic pool passed on to future generations.

A **teratogen** (embryotoxic or fetotoxic agent) is an agent which interferes with normal embryonic development without damage to the mother or lethal effect on the fetus. Effects are not hereditary. Examples include lead and dibromodichloropropane.

A **sensitizer** causes a substantial proportion of exposed people to develop an allergic reaction in normal tissue after repeated exposure to the chemical. The reaction may be as mild as a rash (contact dermatitis) or as serious as anaphylactic shock. Examples include:

- epoxides
- amines
- poison ivy
- toluene diisocyanate
- chromium compounds
- chlorinated hydrocarbons
- formaldehyde
- nickel compounds

Target Organ Effects

The following is a target organ categorization of effects which may occur, including examples of signs and symptoms and chemicals which have been found to cause such effects.

• **Hepatotoxics cause liver damage**

Signs and symptoms: jaundice, liver enlargement
 Example chemicals: carbon tetrachloride, nitrosamines, chloroform, toluene, perchloroethylene, cresol, dimethylsulfate

• **Nephrotoxics produce kidney damage**

Signs and symptoms: edema, proteinuria
 Example chemicals: halogenated hydrocarbons, uranium, chloroform, mercury, dimethyl sulfate

• **Neurotoxins affect the nervous system**

Signs and symptoms: narcosis, behavioral changes, decreased muscle coordination
 Example chemicals: mercury, carbon disulfide, benzene, carbon tetrachloride, lead, mercury, nitrobenzene

• **Hematopoietic agents decrease blood functions**

Signs and symptoms: cyanosis, loss of consciousness.
 Example chemicals: carbon monoxide, cyanides, nitrobenzene, aniline, arsenic, benzene, toluene

• **Pulmonary agents irritate or damage the lungs**

Signs and symptoms: cough, tightness in chest, shortness of breath.
 Example chemicals: silica, asbestos, nitrogen dioxide, ozone, hydrogen sulfide, chromium, nickel, alcohol.

• **Reproductive toxins affect the reproductive system. (mutations and teratogenesis)**

Signs and symptoms: birth defects, sterility.
 Example chemicals: lead, dibromodichloropropane.

• **Skin hazards affect the dermal layer of the body**

Signs and symptoms: defatting of skin, rashes, irritation.
 Example chemicals: ketones, chlorinated compounds, alcohols, nickel, phenol, trichloroethylene.

• **Eye hazards affect the eye or vision**

Signs and symptoms: conjunctivitis, corneal damage.
 Example chemicals: organic solvents, acids, cresol, quinone, hydroquinone, benzyl chloride, butyl alcohol, bases.