Unit 2
Fundamentals of Biochemistry and Toxicological Chemistry

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Reference: "Fundamentals of Biochemistry and Toxicological Chemistry," Chapter 2 in ***Fundamentals of Environmental and Toxicological Chemistry***, 4th ed., Taylor & Francis/CRC Press, Boca Raton, FL, 2013.

Additional resources pertaining to environmental chemistry, sustainability, green chemistry, industrial ecology, and related areas may be obtained from the website below:

https://sites.google.com/site/manahan1937/

2.1 Life Chemical Processes

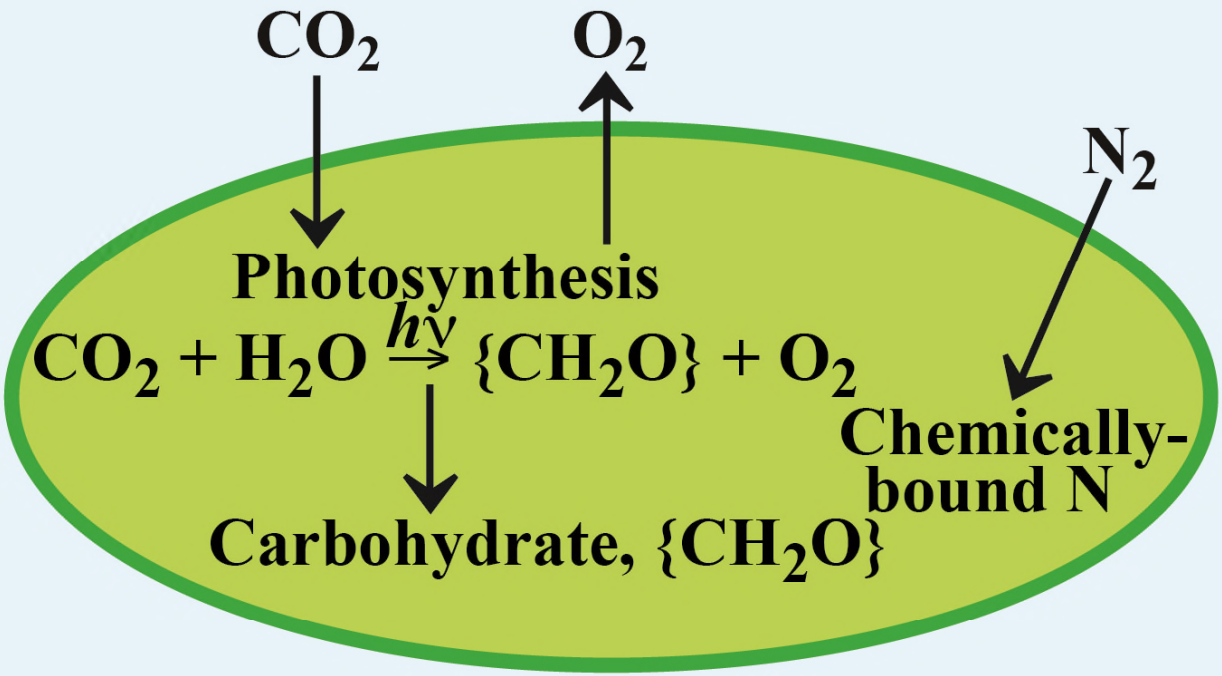
Biochemistry: Science of chemical processes that occur in living organisms

- **Green Biochemistry**: Processes under mild, safe conditions
- **Environmental biochemistry**: Biochemical processes in the environment

Toxicological chemistry: Biochemical processes of toxic substances

2.2 Biochemistry and the Cell

Figure 2.1 Life biochemical processes normally occur in cells, such as those of single-celled photosynthetic cyanobacteria:

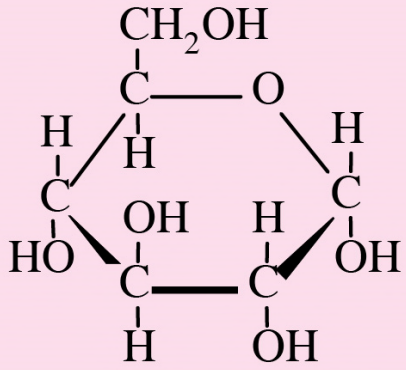


Prokaryotic Cells: Bacteria, no cell nucleus membrane

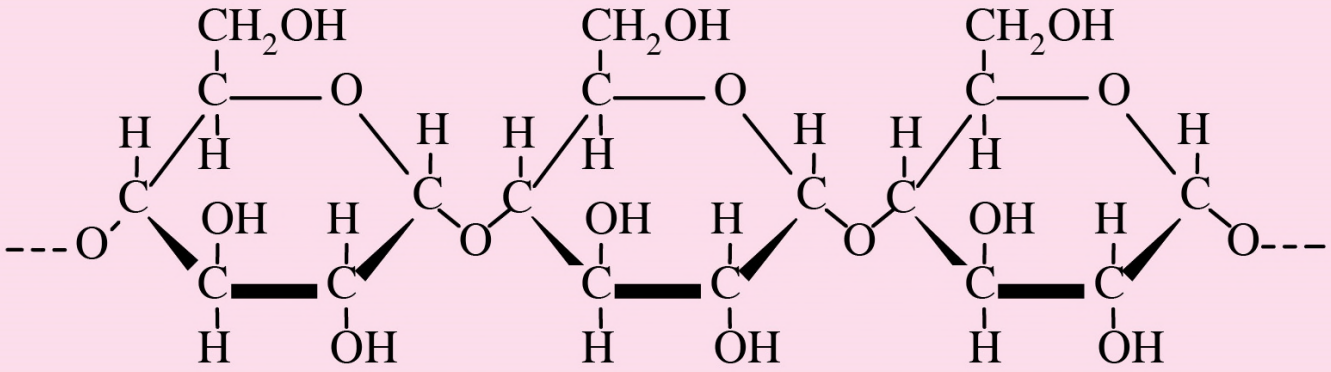
Eukaryotic Cells: Most organisms other than bacteria

Carbohydrates

Figure 2.2. Simple sugar glucose and starch polysaccharide



Glucose

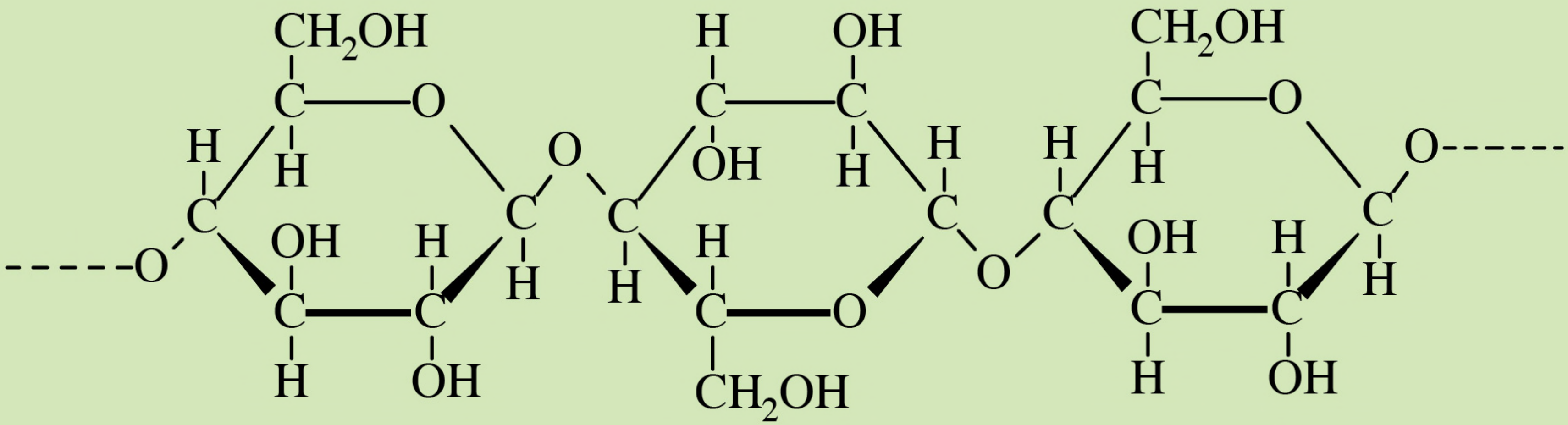


Three units of the starch macromolecule

Carbohydrates serve to

- Capture and store solar energy
- Capture and store carbon

Figure 2.3. Segment of a cellulose macromolecule



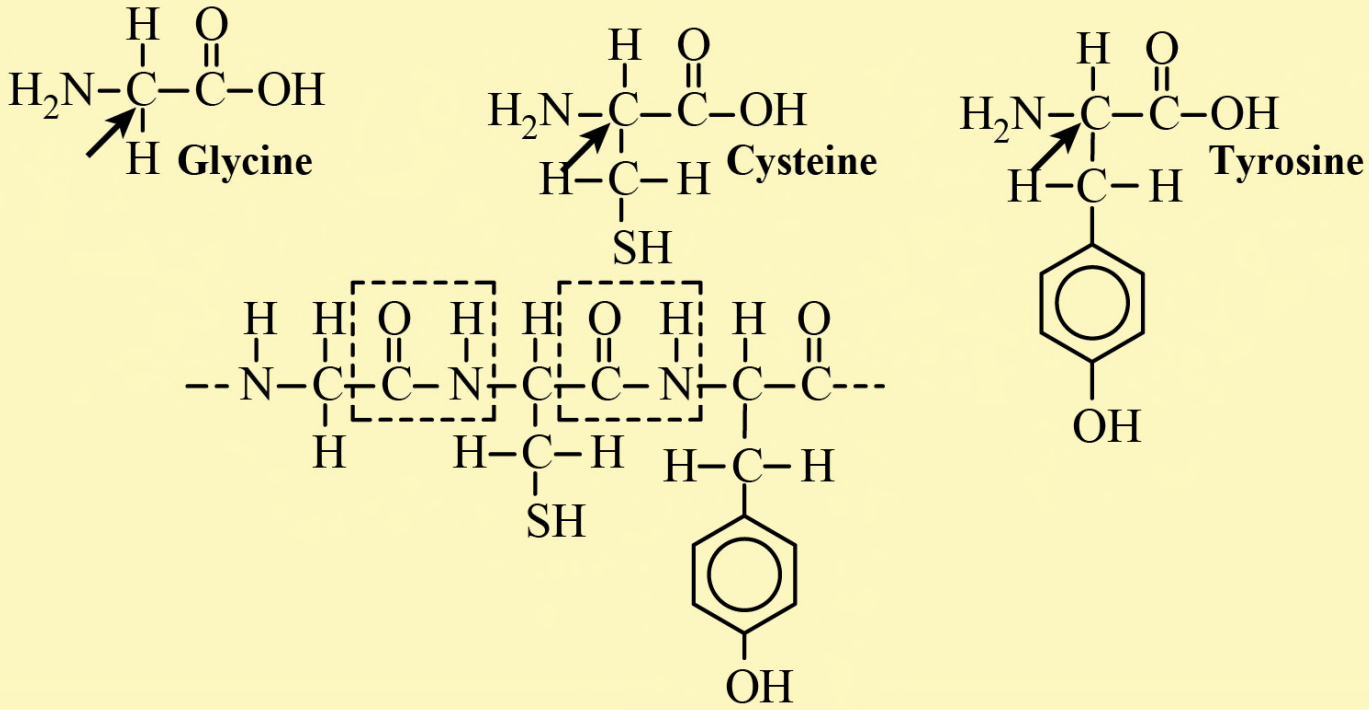
2.4 Proteins

Macromolecules of N, C, H, O and some S

From 20 naturally occurring amino acids

Proteins are macromolecules that are composed of nitrogen, carbon, hydrogen, and oxygen along with smaller quantities of sulfur. The small molecules of which proteins are made are composed of 20 naturally occurring amino acids.

Figure 2.4. Three amino acids and a tripeptide made from them. Amino acids differ in the groups substituted on the C atom designated by the arrow.



Protein Structure

Primary: Order of amino acids

Other structural levels: Folding and pairing of protein molecules

Importance of protein structures

Enzymes are proteins

Denaturation of proteins in which their structural features are altered

2.5 Lipids: Fats, Oils, and Hormones

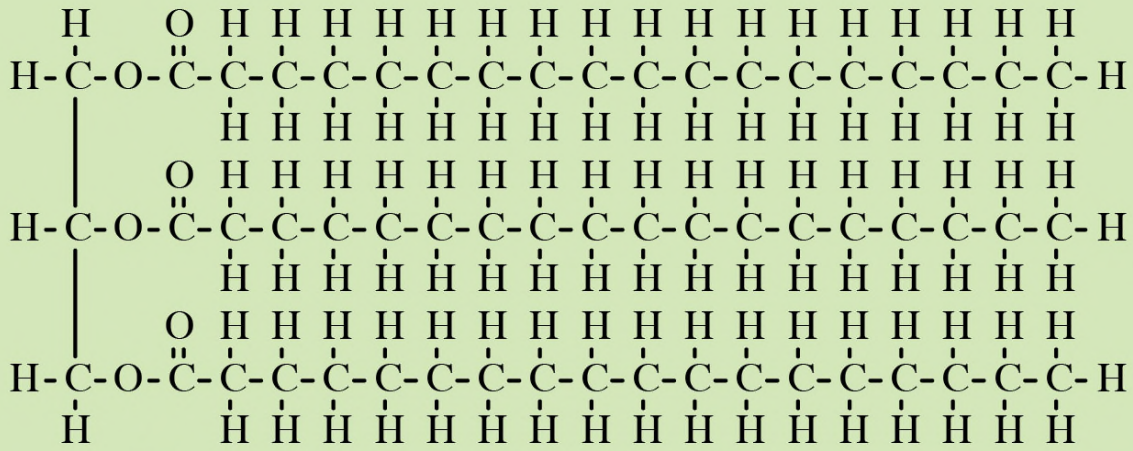
Lipids are repelled by water

- **Extracted into organic solvents**

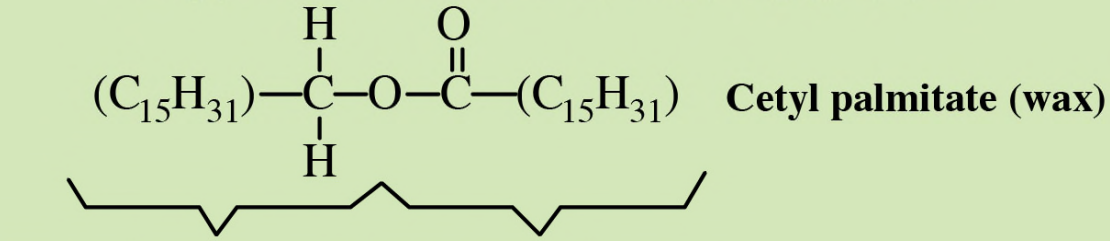
Figure 2.5

Examples of lipids

- **Hydrocarbon-like**



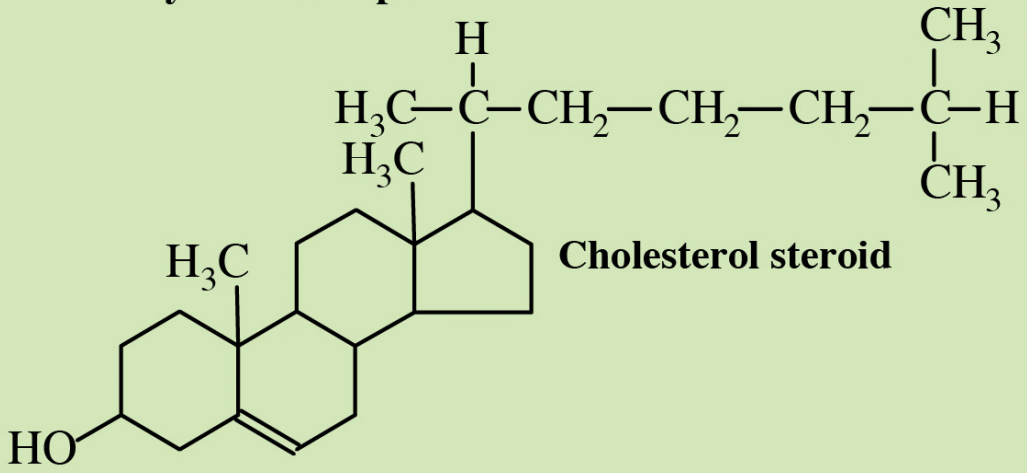
Triglyceride of stearic acid, $CH_3(CH_2)_{16}C(O)OH$



Cetyl palmitate (wax)

Part of ester from cetyl alcohol

Part of ester from palmitic acid



Cholesterol steroid

2.6 Nucleic Acids

Figure 2.6. Fundamental units of nucleic acids

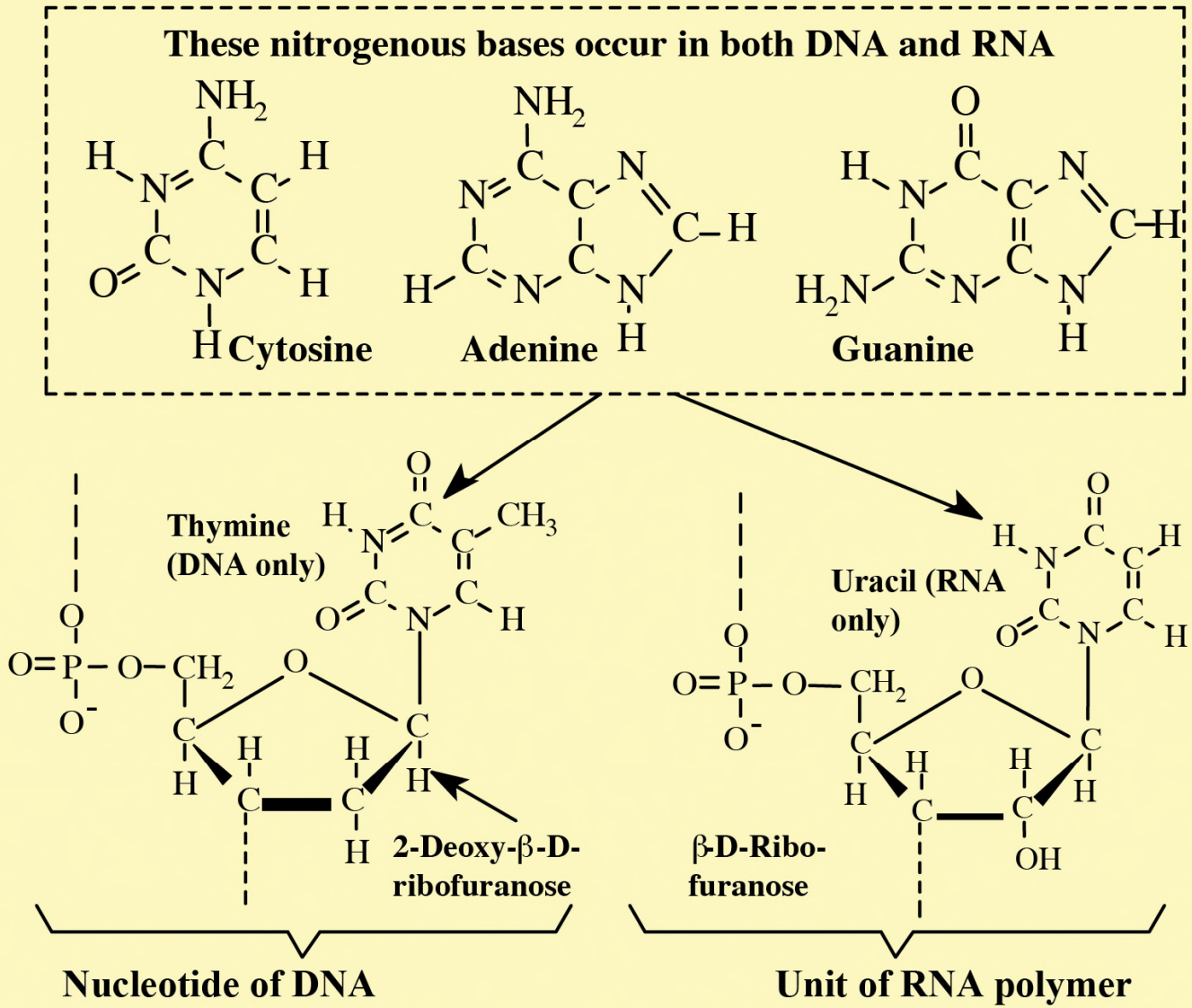
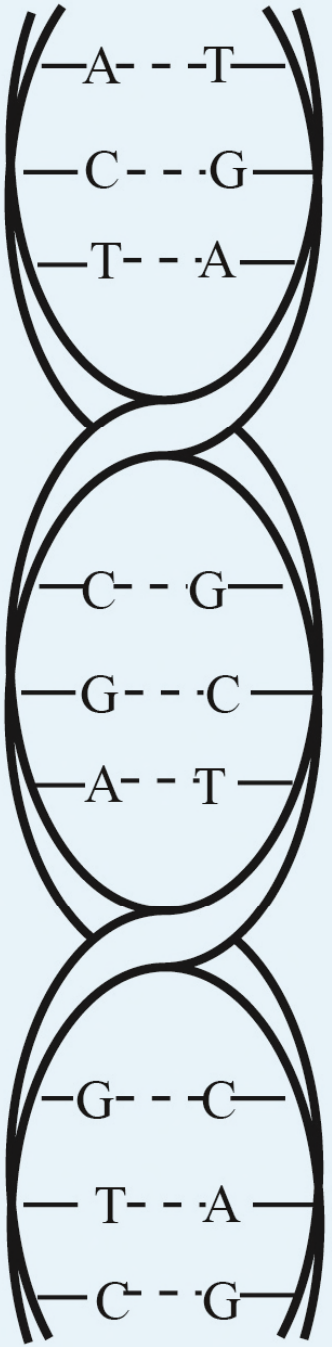


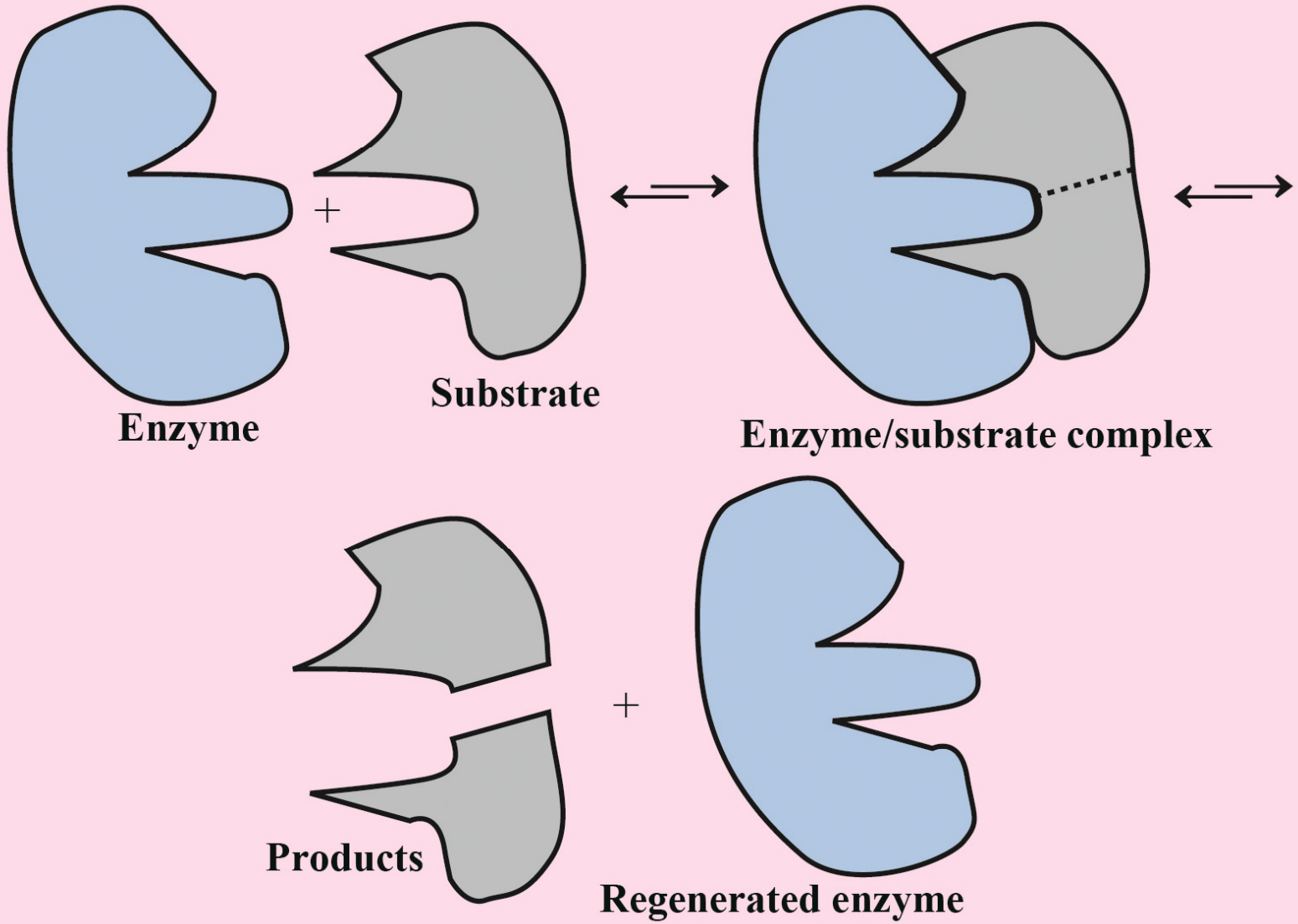
Figure 2.7

Representation of the double helix structure of DNA showing the allowed base pairs held together by hydrogen bonding between the phosphate/sugar polymer "backbones" of the two strands of DNA. The letters stand for adenine (A), cytosine (C), guanine (G), and thymine (T). The dashed lines, ---, represent hydrogen bonds.



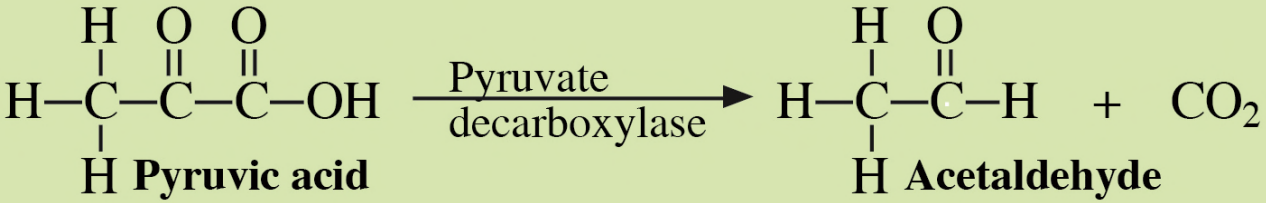
2.7 Enzymes

Figure 2.8. Representation of enzyme action



Enzymes perform many biochemical functions including the following:

- Energy utilization
- Biosynthesis
- Hydrolysis reactions
- Biodegradation
- Example of carbon chain shortening



Oxidoreductase reactions mediated by enzymes

- Cellular Respiration: $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O +$ energy

Effects of Toxic Substances on Enzymes

Toxic Substances may alter or destroy enzymes

- **Examples: Heavy metals, cyanide, organophosphates**
- **Heavy metals such as Pb^{2+}, Hg^{2+}, bind with –SH on enzyme active sites**
- **Sarin nerve gas that binds with acetylcholinesterase**

2.8 Biochemical Processes in Metabolism

Metabolism: Alteration, breakdown, and synthesis of biomolecules

- **Anabolism (synthesis)**
- **Catabolism (degradation)**

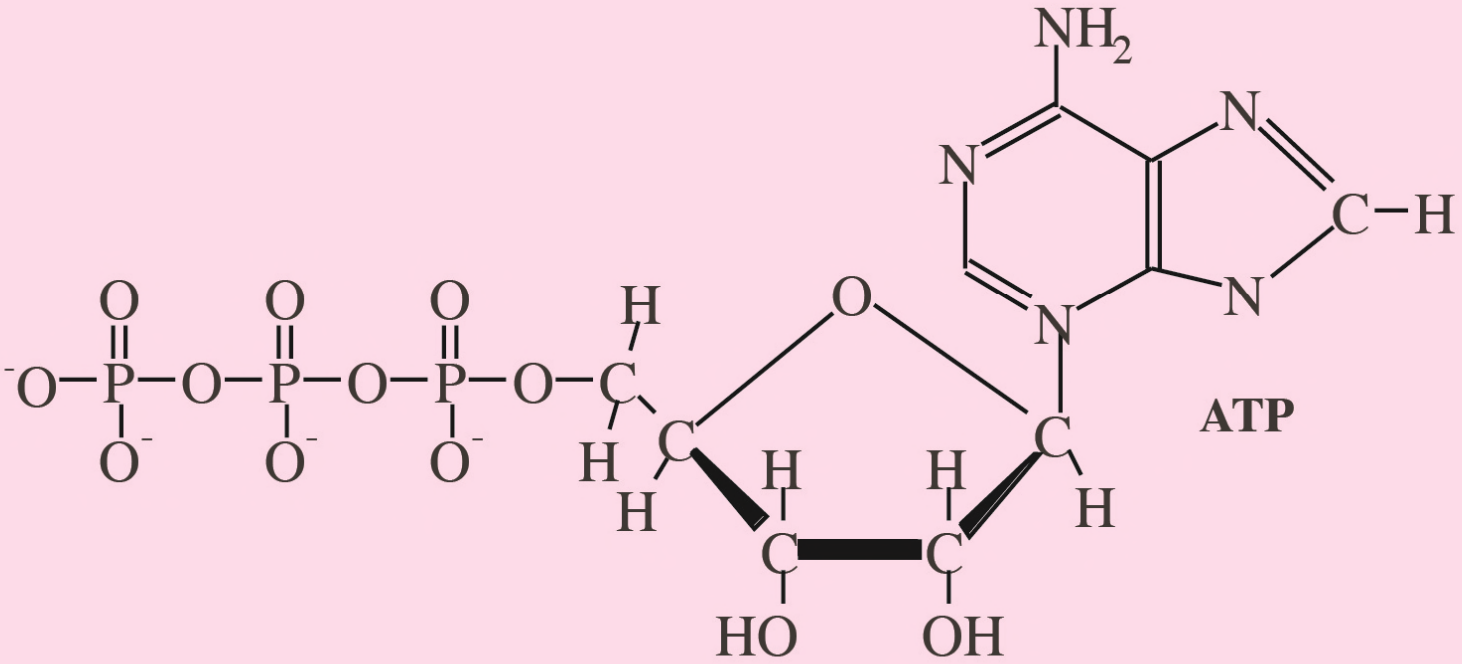
Importance of metabolism in green chemistry and sustainability

- **Toxicants may impair metabolism**
- **Metabolic processes make and modify renewable raw materials**
- **Photosynthesis provides raw materials**

Energy-Yielding and Processing Metabolic Processes

- Cellular respiration: $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + \text{energy}$
- Fermentation in the absence of O_2: $C_6H_{12}O_6 \rightarrow 2CO_2 + 2C_2H_5OH$
- Fermentation to produce methane: $2\{CH_2O\} \rightarrow CH_4 + CO_2$
- Photosynthesis: $6CO_2 + 6H_2O + h\nu \rightarrow C_6H_{12}O_6 + 6O_2$

Figure 2.9. Adenosine triphosphate in energy transfer



2.9 Toxic Substances and Toxicology

Toxicology is the science of poisons or toxicants, substances that damage or destroy living tissue or that cause biochemical processes to malfunction.

- **Xenobiotics are substances foreign to living systems**
- **Protoxicants are activated to toxic forms in the body**
- **Exposure to toxic substances (see next slide)**

Figure 2.10 Toxicants in the Body

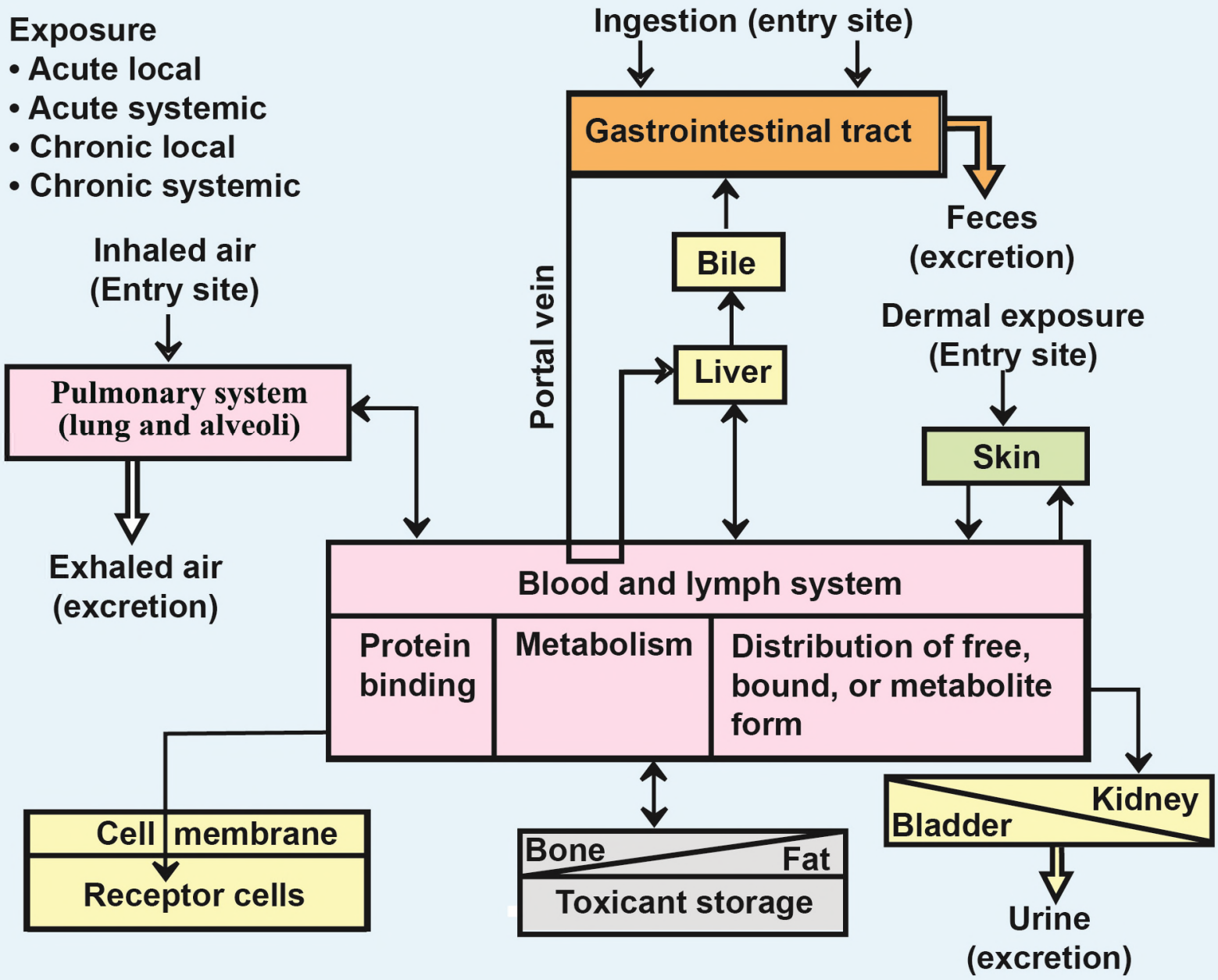


Figure 2.11. Dose-Response Plot

- LD_{50} values by which toxicities are commonly expressed can be derived from this kind of plot

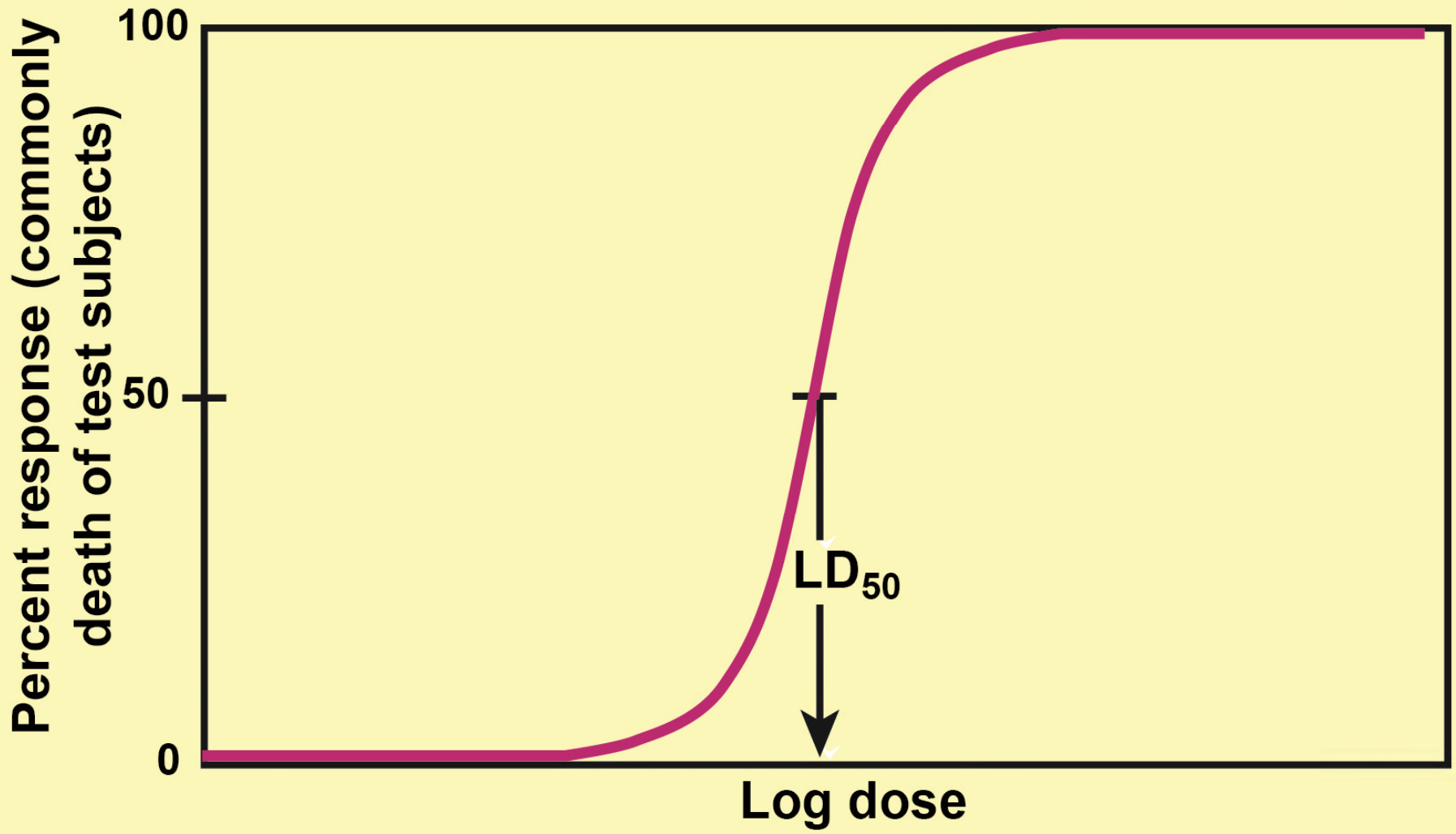
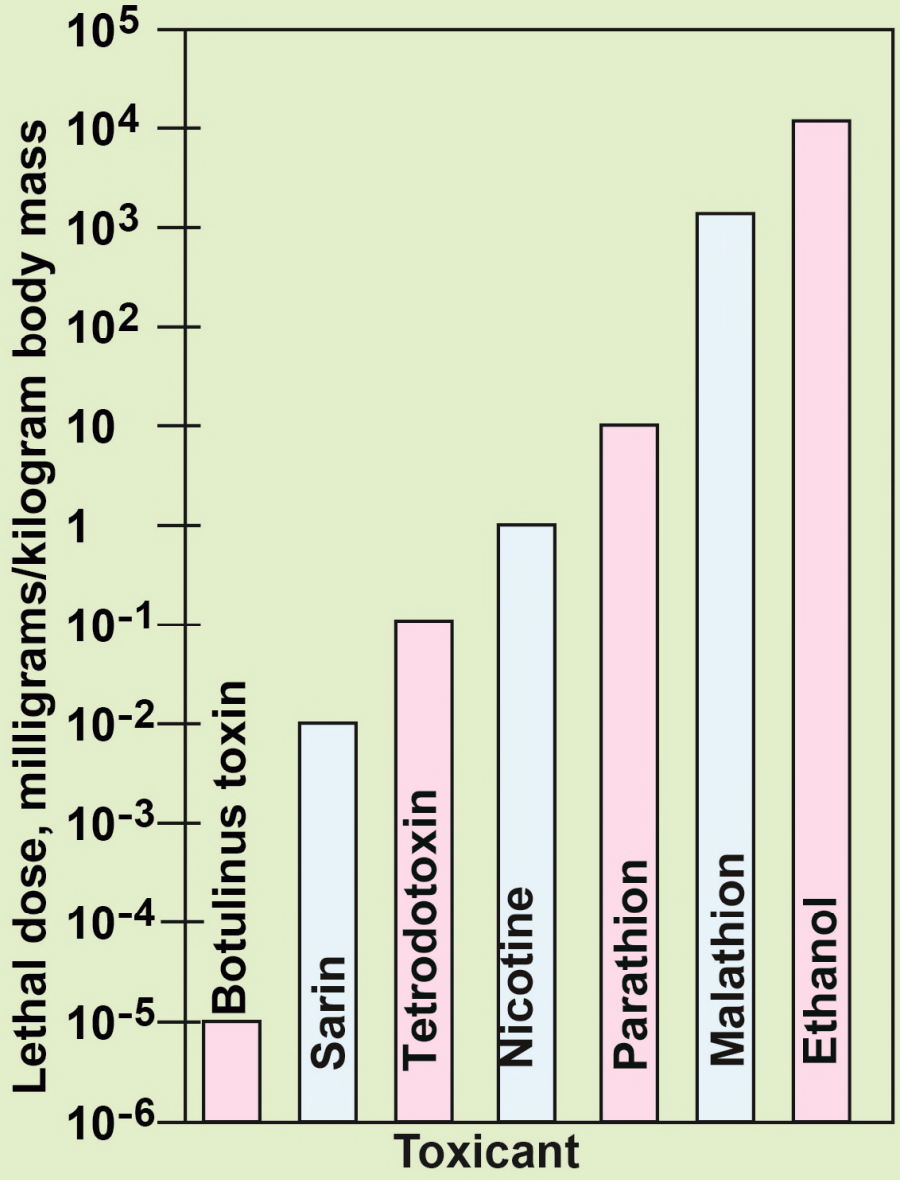
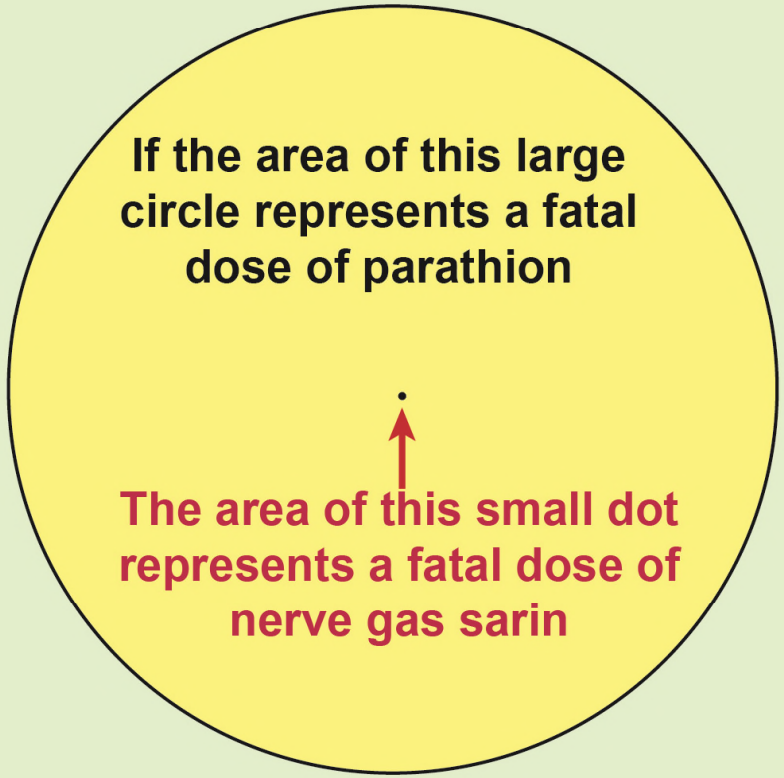


Figure 2.12. Relative Toxicities (LD_{50} values) of Some Toxicants





2.10 Toxicological Chemistry

Figure 2.13. Toxicological chemistry relates chemical properties to toxic effects

- **Sources and uses of toxic substances**
- **Chemical aspects of exposure, fates, and disposal**
- **Biochemical transformations of toxicants and protoxicants within living systems**
- **Quantitative structure-activity relationships (QSAR) that relate chemical nature of substances to their reactions and effects in organisms**

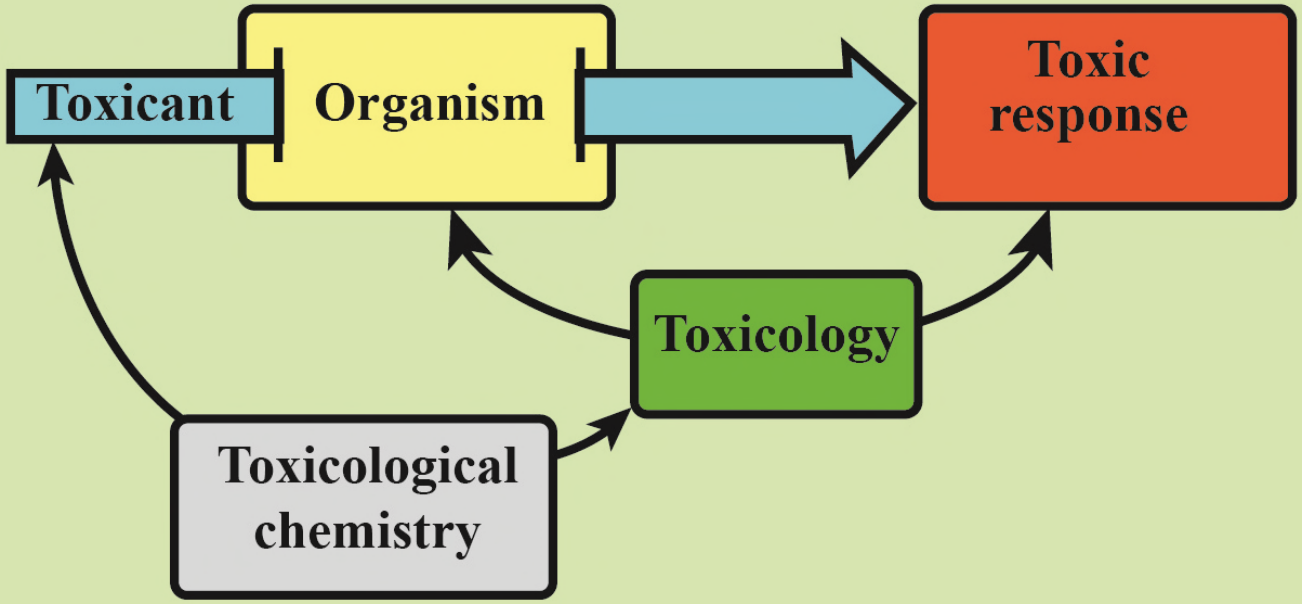
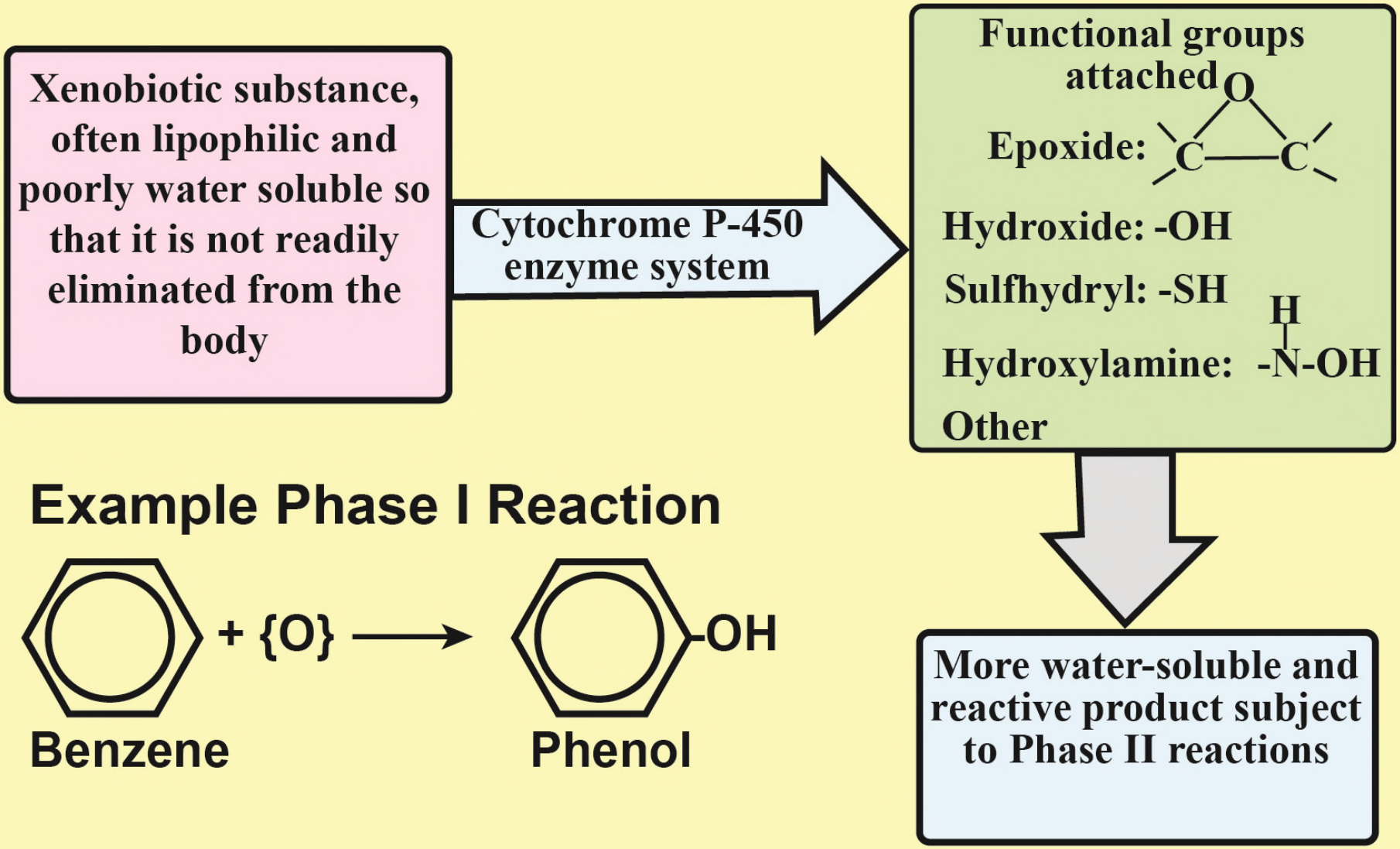


Figure 2.14. Illustration of Phase I Reactions

- May convert protoxicants to toxic forms
- May detoxify toxicants



Phase II Reactions

- **Enzymatically attach an endogenous conjugating agent to a toxicant which in many cases is a Phase I reaction product**

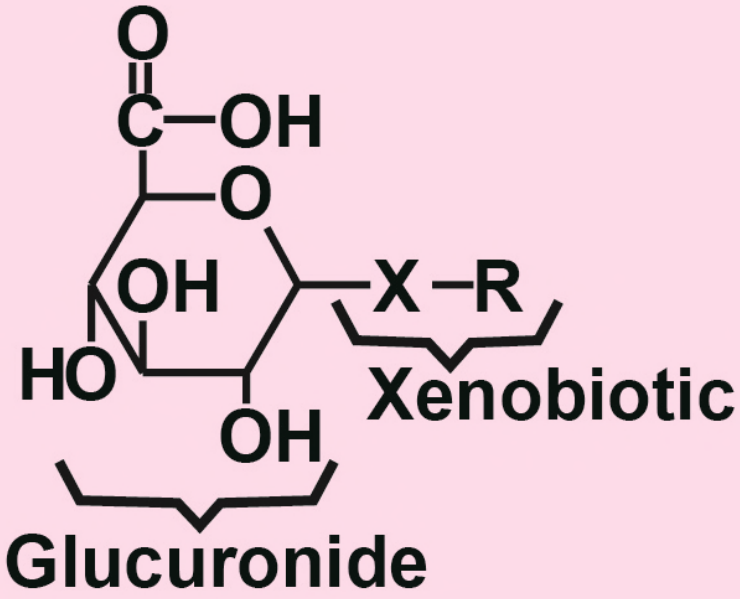
The product of a Phase II reaction

- **Is usually less toxic than the parent compound (in some cases more so)**
- **Usually less lipid-soluble, more water-soluble**

Endogenous conjugating agents include

- **Glucuronide (most common)**
- **Glutathione**
- **Sulfate**
- **Acetyl**

Figure 2.15. Glucuronide Phase II reaction product conjugate of a xenobiotic, HXR. In the case of phenol, HOC_6H_5, X represents O and R represents the benzene ring, C_6H_5.

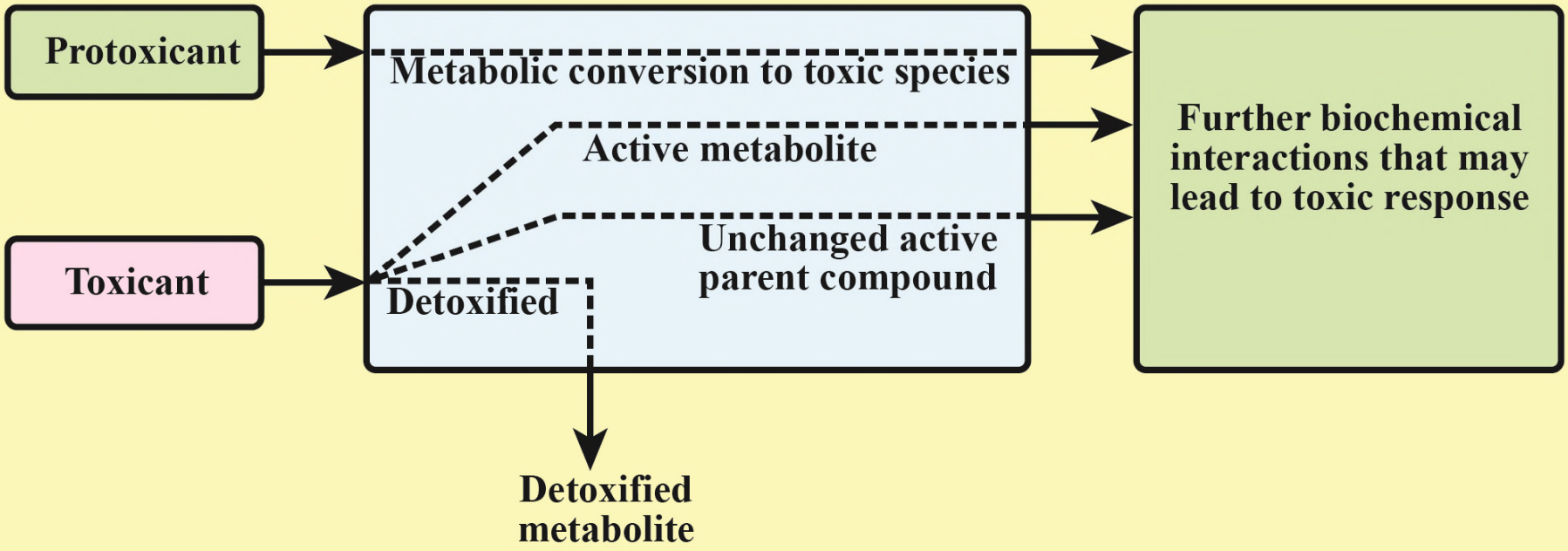


2.11 Kinetic Phase of Xenobiotic Metabolism

The kinetic phase refers to processes that occur prior to any biochemical interactions that directly cause a toxic response in which a toxicant may

- **Remain unchanged**
- **Be detoxified and excreted without doing harm**
- **Be converted to another toxicologically active form**

Figure 2.16. Illustration of the Kinetic Phase



2.12 Dynamic Phase of Toxicant Action

1. Primary reaction binding to a target organ or tissue

   Example: $HbO_2 + CO \leftrightarrow HbCO + O_2$

2. Biochemical response

   Example: Deprivation of tissue of O_2

3. Observable effect

   Example: Lowered consciousness, coma, death

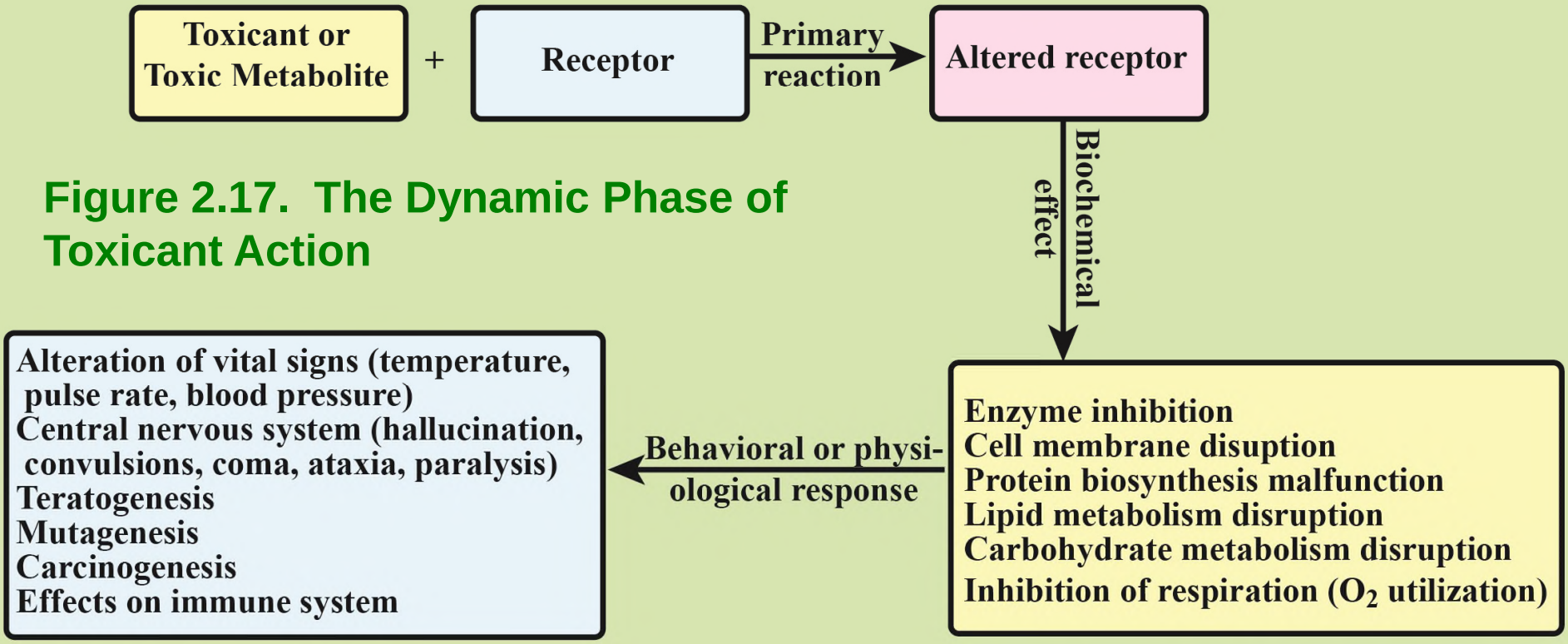


Figure 2.17. The Dynamic Phase of Toxicant Action

Table 2.1. Examples of Target Systems, Toxicants, and Effects of Toxic Substances

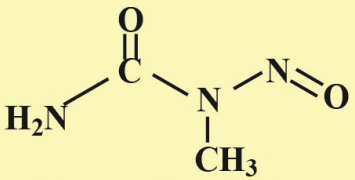
System affected	Toxicant	Effect
Respiratory system	Cigarette smoke, asbestos	Emphysema, cancer
Skin	Coal tar constituents	Skin cancer
Liver	Vinyl chloride	Haemangiosarcoma (cancer)
Blood	Aniline, nitrobenzene	Methemoglobinemia
Immune system	Allergens, such as beryllium	Hypersensitivity
Endocrine system	Bisphenol-A (plasticizer)	Disruption of system function
Nervous system	Organophosphates (Sarin)	Acetylcholinesterase inhibition
Kidney	Ethylene glycol	Calcium oxalate deposits in tubules
Bladder	Aromatic amines from coal tar	Bladder cancer

2.13 Mutagenesis and Carcinogenesis

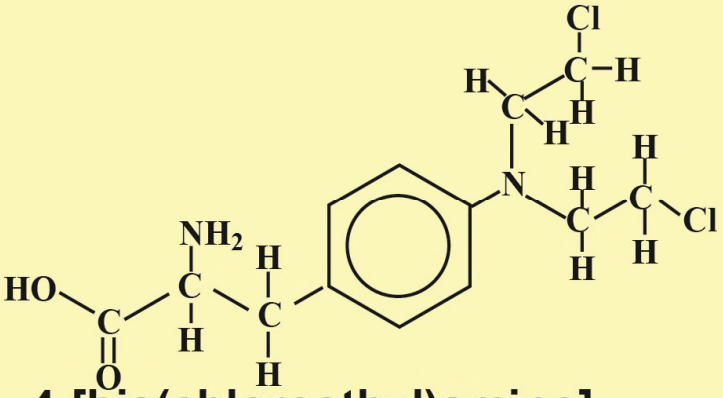
Mutagens are chemical species that alter DNA to produce traits that can be inherited

- **Exchange, addition, or deletion of any of the bases in DNA**
- **Replacement of $-NH_2$ group by -OH**
- **Alkylation by attachment of $-CH_3$ group**

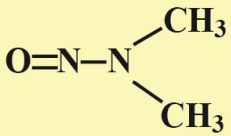
Figure 2.18. Examples of alkylating agents capable of causing mutations



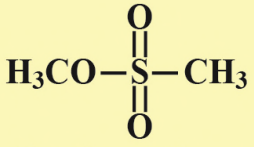
N-methyl-N-nitrourea



4-[bis(chloroethyl)amino]-phenylalanine (Melphalan)



Dimethylnitrosamine



Methylmethanesulfonate

Carcinogenesis

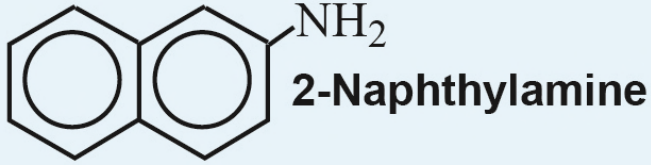
Uncontrolled replication and growth of body cells

Cancers caused by external influences are of concern

- **Radiation**
- **Chemical exposure**

Chemical carcinogenesis

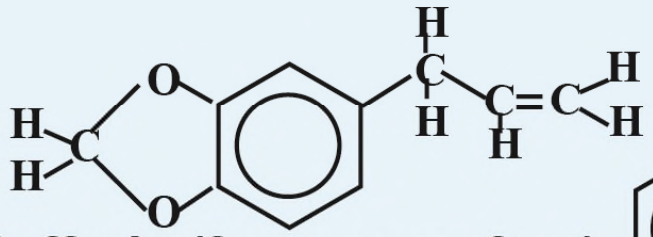
- **Around 1900 reports of bladder cancer in German dye workers**



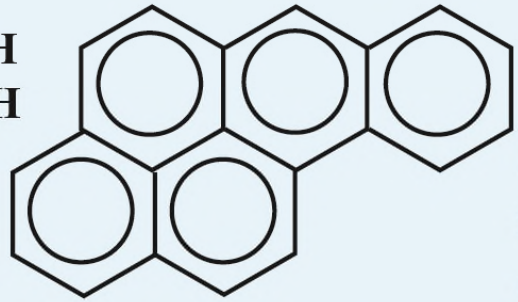
2-Naphthylamine

- **Procarcinogens biochemically activated to ultimate carcinogens**

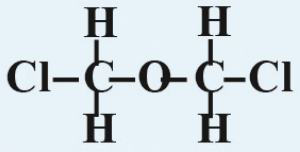
Figure 2.19. Examples of carcinogens



Saffrole (from sassafras) a natural product that requires bioactivation

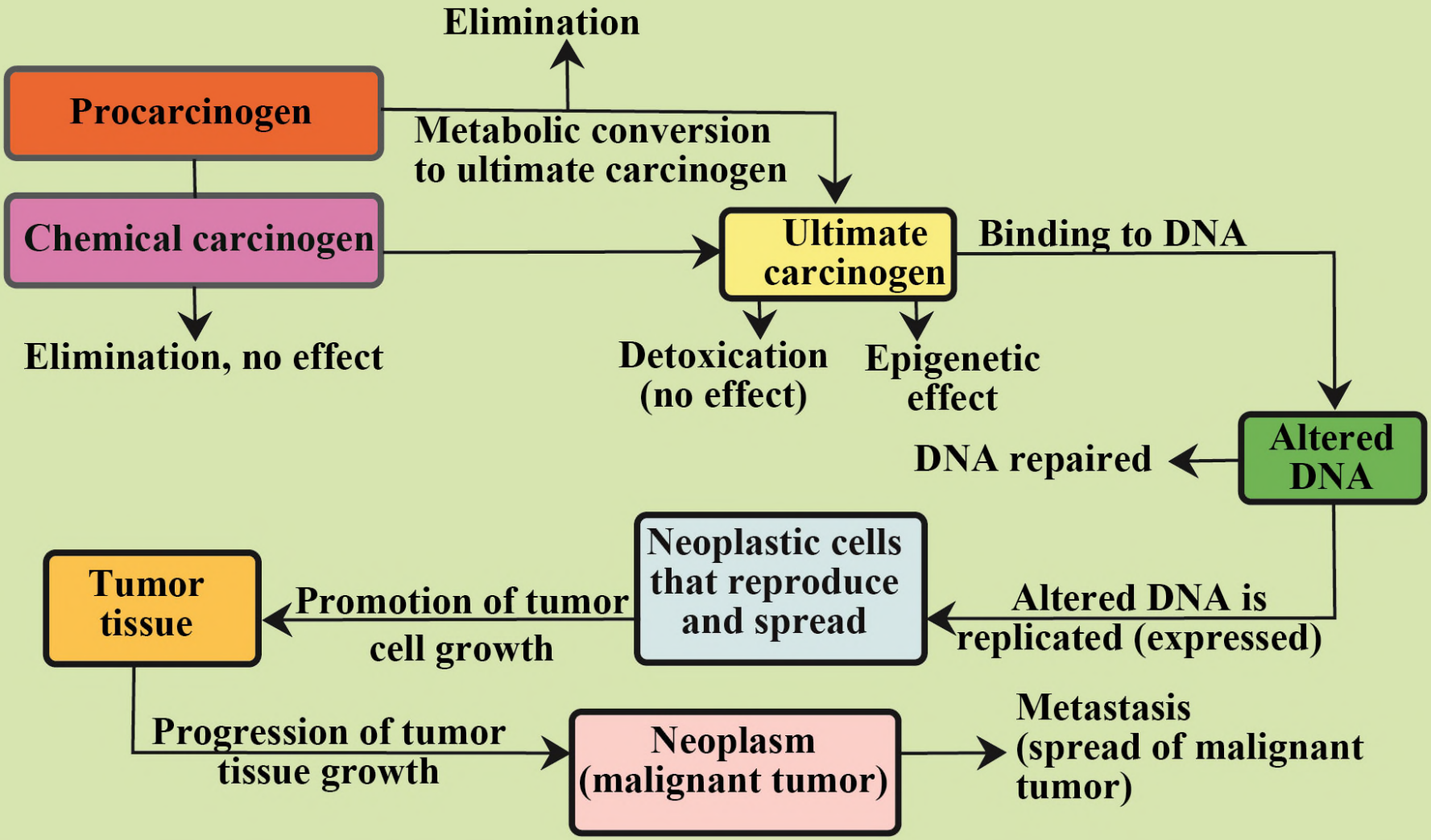


Benzo(a)pyrene, a synthetic chemical that requires bioactivation



Bis(chloromethyl)ether, a synthetic compound that does not require bioactivation

Figure 2.20. Process of Cancer Development Resulting from Exposure to Chemical Carcinogens



2.14 Developmental Effects and Teratogenesis

Teratogens are substances that cause birth defects

Fetuses are vulnerable

- **Ineffective detoxification**
- **Developing organs are vulnerable**

2.15 Toxic Effects on the Immune System

Immune system

1. Defense against infectious agents

2. Destruction and neutralization of cancer cells

3. Resistance to xenobiotic substances

Immunosuppression

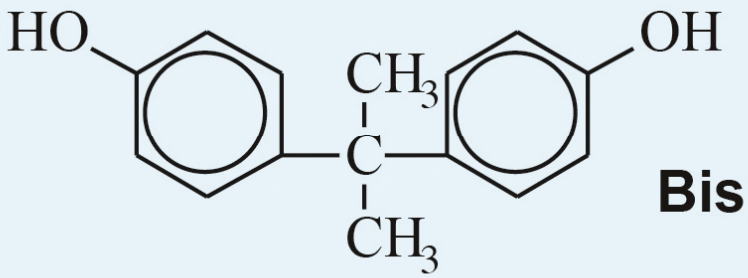
Hypersensitivity

2.16 Damage to the Endocrine System

Regulation of metabolism and reproduction

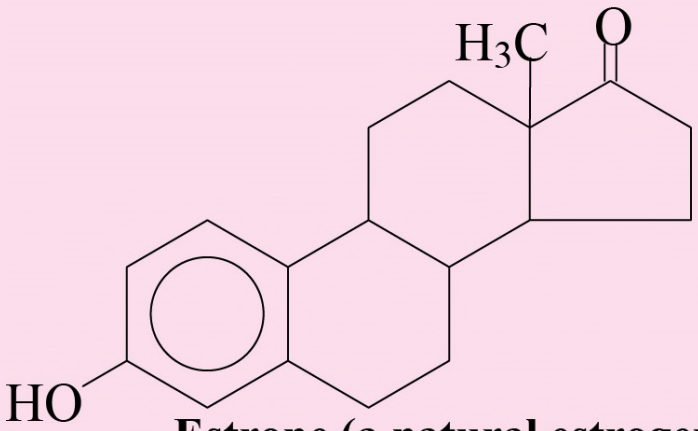
Hormonally active agents

- **Especially estrogens that act like female sex hormone**
- **Xenoestrogens from non-natural sources such as bisphenol-A**

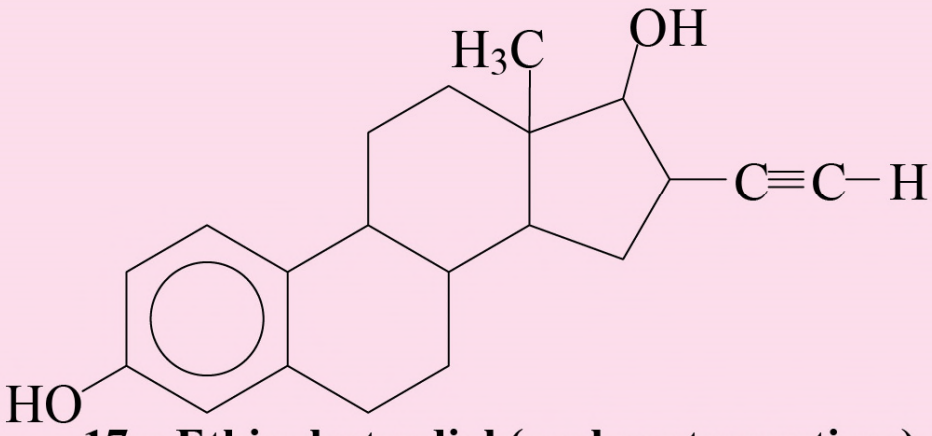


Bisphenol-A

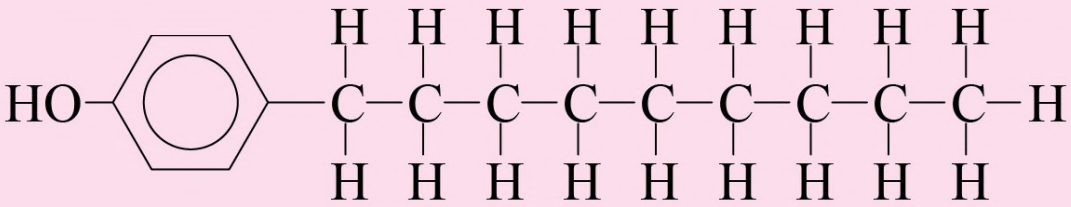
Figure 2.21. Examples of estrogenic agents found in water



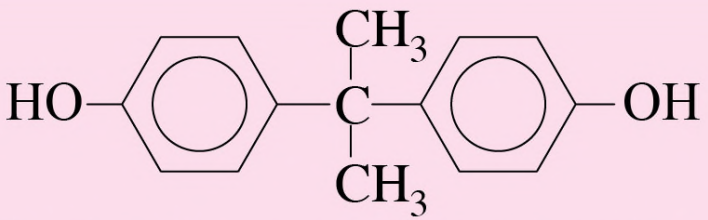
Estrone (a natural estrogen)



17α-Ethinylestradiol (oral contraceptives)



***p*-Nonylphenol (from surfactants)**



Bisphenol A (epoxy and polycarbonate resins)

2.17 Health Hazards of Toxic Substances

Establish relationship between disease and toxic agent

- **Presence of toxic agent or metabolite in the body**
- **Epidemiological studies**

Health risk assessment

2.18 Quantitative Structure-Activity Relationships (QSAR)

Chemical properties suggestive of toxic effects

1. **Corrosivity**
2. **Reactivity**
3. **Heavy metals**
4. **Binding species**
5. **Lipid-soluble compounds**
6. **Immunotoxicants**

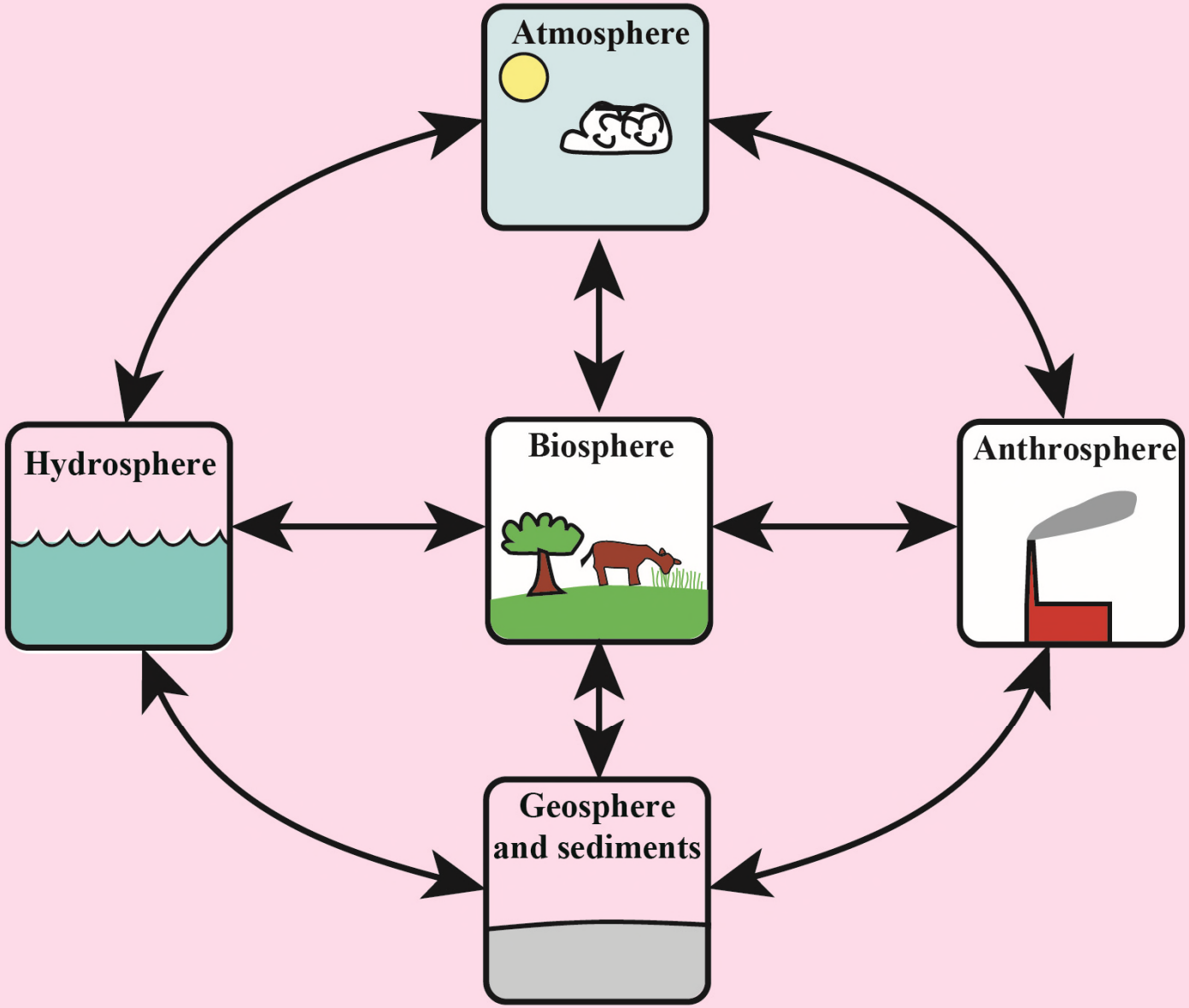
2.19 Toxicological Chemistry and Eco-toxicology

Eco-toxicology is a combination of toxicology and ecology that considers the effects of toxic substances upon ecosystems

Biomarkers of exposure

- **Presence of a toxic substance such as a heavy metal**
- **Presence of a metabolite of a toxic substance such as styrene 7,8-oxide from styrene exposure**
- **Observation of a biological effect such as feminization of aquatic organisms from exposure to endocrine disruptors**

Figure 2.22. Transfers of substances among the various environmental spheres, especially those involving the biosphere, are very important in determining their ecotoxicological effects.



2.20 Toxic Agents that May be Used in Terrorist Attacks

Examples

- **Cyanide**
- **Nerve gases**
- **Various toxic agents such as sulfur mustard, ricin, rodenticides**

Chemical forensics to trace sources of toxic substances