NATIONAL OPEN UNIVERSITY OF NIGERIA

ESM 231

Introductory Toxicology

Module 1

ESM 231 Introduction to Toxicology
Module 1

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Module 1

Unit 1 Background and Principles of Toxicology

1.0 Introduction

This unit will explain toxicology and its history. It will also introduce you to the main areas in the science of toxicology such as environmental, forensic and clinical toxicology.

2.0 Objectives

At the end of this unit, you should be able to:

- trace the history of toxicology
- define the term "toxicology"
- name major areas of toxicology.

3.0 Main Content

3.1 The History of Toxicology

The historical development of toxicology began with early cave dwellers who recognised poisonous plants and animals and used their extracts for hunting in warfare. By 1500 BC, written records indicated that hemlock, opium, arrow poisons, and certain metals were used to poison enemies or for state executions.

Paracelsus (Theophrastus Phillipus Auroleus Bombastus von Hohenheim 1493 – 1541) determined that specific chemicals were actually responsible for the toxicity of a plant or animal poison. He also developed the concept of dose. His studies revealed that small doses of substances might be harmless or beneficial whereas larger doses could be toxic. This is now known as the dose-response relationship, a major concept of toxicology.

Paracelsus is often quoted for his statement:

> *All things are poison and nothing is without poison; only the dose makes a thing a poison.*

This is often condensed to: "The dose makes the poison".

Mathieu Orfila (1787 – 1853) is considered to be the father of modern toxicology, having given the subject its formal treatment in 1813 in his *Toxicologie generate* (*Trait des poisons*). Orfila prepared a systematic correlation between the chemical and biological properties of poisons of the time. He demonstrated the effects of poisons on specific organs by analyzing autopsy materials for poisons and their associated tissue damage.

The 20th century was marked by advanced level of understanding of toxicology. DNA (the molecule of life) and various biochemicals that maintain body functions were discovered. Our level of knowledge of toxic effects on organs and cells is now being revealed at the molecular level. It is recognized that virtually all toxic effects are caused by changes in specific cellular molecules and biochemicals.

3.2 What is Toxicology?

The society of toxicology defines toxicology as "the discipline that integrates all scientific information to help preserve and protect health and the environment from the hazards presented by chemical and physical agents".

The hazard of a chemical or physical agent is its capacity to produce particular types of adverse effect. Hazards are usually determined using information collected from studies conducted in animals, and also from studies in which human populations have been exposed to chemicals.

Wikipedia defines toxicology as 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.

The traditional definition of toxicology is "the science of poisons". A more descriptive definition of toxicology is "the study of the adverse effects of chemicals or physical agents on living organisms." These adverse effects may occur in many forms; ranging from immediate death to subtle changes not realized until at various levels within the body, such as an organ, a type of cell or a specific biochemical.

Toxicology is an inter-disciplinary science that integrates the principles and methods of many fields (Figure1): chemistry, biology, pharmacology, molecular biology, psychology and medicine. For example, by combing the study of the physiological effects of certain structures and the molecular biological mechanisms that explain those effects, the toxicology can provide better understanding of the actions of a class of chemical substances, and finding of value for the chemist.

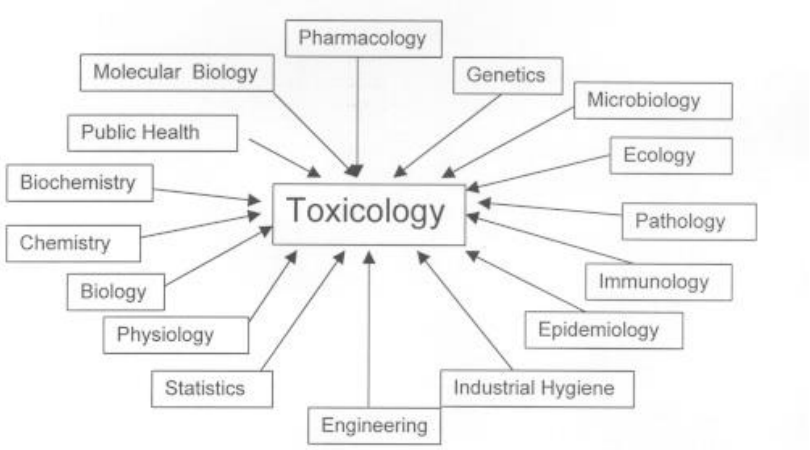


Fig. 1: Toxicology as an Inter-disciplinary Science

In the practice of toxicology, other disciplines are also frequently relied upon. Hydro ecologists, environmental engineers and air modellers are often employed in the determination of the route, concentration and migration of chemicals in water, soil and air, respectively.

Clinicians rely on signs and symptoms and conduct differential diagnoses, to determine if a certain disease process is present and to eliminate other non-environmental causes. The scientific pursuit of toxicology is typically divided between observational studies looking at what effects result from exposure to a particular substance and mechanistic studies, which attempt to understand and explain the basis for such effects. These two activities form the basis of toxicology as an experimental science; that is, that which takes place in the laboratory or occasionally in the field, as one usually thinks of science.

3.3 The Scope of Toxicology

The science of toxicology may be subdivided into the following major areas:

3.3.1 Environmental Toxicology

Environmental or ecological toxicology is concerned with the harmful effects of chemicals that are present in air, water, soil, food, or other environmental vectors of exposure to man, domestic animals, fish, wildlife, and other biota. The environmental toxicologist is concerned with the entire range of potential effects of chemicals on the quality of our environment, including the aesthetic aspects. He is concerned with the possible extinction of certain species of wildlife as a result of chemical pollution of their food or habitat.

3.3.2 Forensic Toxicology

Toxicologists with specialized knowledge of law work together with pathologists and medical examiners to establish the cause of death or illness for medico-legal purposes in incidents in which a crime is suspected to have occurred. Forensic toxicologists analyse the fluids and tissues of the body for the presence of poisonous substances and try to determine if they are present in sufficient amount to account for death or the symptoms experienced by the victim. In cases involving criminal prosecution, the toxicologist may be called upon to testify to his findings in a court of law.

3.3.3 Clinical Toxicology

The physician who specializes in the treatment of toxic reactions to therapeutic drugs as well as management of illness caused by poisons is a clinical toxicologist.

3.3.4 Safety Evaluation Toxicology

Safety evaluation toxicologists are constantly working to improve test procedures to decrease even further the chances that potentially hazardous chemicals would be released for use by the general population and thus into the environment.

4.0 Conclusion

This unit has examined the history of toxicology, what toxicology is and the areas of toxicology. Also, it has showed that toxicology integrates the principles and methods of many fields: chemistry, biology, pharmacology, molecular biology, psychology and medicine, and many others.

5.0 Summary

This unit has introduced you to the history, definition and scope of the subject matter, toxicology. It has stated that all things are poison and nothing is without poison; only the dose makes a thing a poison. It has also stated that the scientific foundation of toxicology was laid by Paracelsus and Mathieu Orfila. Unit Two will discuss the relationship between dose and poison.

6.0 Self-Assessment Exercise

1. Define toxicology.
2. Give a brief history of toxicology.
3. Mention at least three major areas of the science of toxicology.
4. Mention two scientists that were important in the development of toxicology.
5. Explain the term "toxicology" using your own words.

7.0 References/Further Reading

Bhatia, S.C. (2005). *Environmental Pollution and Control in Chemical Industries.* New Delhi: Khanna Publishers.

Asthana, D.K. & Asthana, M. (2003). *Environment*: *Problems and Solution*, Delhi: S. Chand and Company Ltd.

Wikipedia on - Line Dictionary

Edinburgh Centre for Toxicology (Edintox On line Toxicology Course http:// www.bio.hwac.uk /edintox / edintox.htm

NURS 735- Applied Toxicology http://www.sis.nlm.nih.gov/Tox/ToxTutor.html

http://www.uoguelph.ca/cntc/educat/guide/intro.shtml

Unit 2 Dose-Response Concept

1.0 Introduction

Unit 2 will explain to you the underlying principles of toxicology, the connection between dose, exposure and effect. In this unit you will come across terms such as toxicant, threshold, dose response, effective doses, no observed effect level (NOEL) and $LD_{50.}$

2.0 Objectives

At the end of this unit, you should be able to:

- explain the use of dose – response relationships to quantify toxicity
- demonstrate the use of concentration – response relationships to quantify toxicity
- show that the shape and slope of the dose-response curve is extremely important
- explain the meaning of LD_{50}, LC_{50}, NOEL and toxic dose.

3.0 Main Content

3.1 Doses-Response Concepts

The underlying principles of toxicology rely on an understanding of the relationships between exposure and effect. In order to comprehend how exposure-related effects can be explained, the concept of dose-response is important.

Toxicants have widely varying effects upon organisms. Quantitatively, these variations include minimum levels at which the onset of an effect is observed, the sensitivity of the organism to small increments of toxicant, and levels at which the ultimate effect (particularly death) occurs in most exposed organisms. Some essential substances, such as nutrient minerals, have optimum ranges above and below which detrimental effects are observed.

Factors such as those just outlined are taken into account by the dose-response relationship, which is one of the key concepts of toxicology. Dose is the amount usually per unit body mass of a toxicant to which an organism is exposed. Response is the effect upon an organism resulting from exposure to a toxicant.

The doses- response relationship is a fundamental concept in toxicology. It correlates exposures and the spectrum of induced effects. Generally, the higher the dose, the more severe the response. The dose response relationship is based on observed data from experimental animal, human, clinical or cell studies.

Knowledge of the dose-response relationship:

- establishes causality that the chemical has induced the observed effects
- establishes the lowest dose where an induced effect occurs the threshold effect

- determines the rate at which injury builds up the slope for the dose- response.

3.2 Dose-Response

The measurable end-point of toxicology may be pharmacological, biochemical or a pathological change which shows percentage or proportional change.

The dose-response relationship is graded between a dose at which no effect is measurable and one at which the maximal effect is demonstrated. The basic form of this relationship is presented in Figure 2.1.

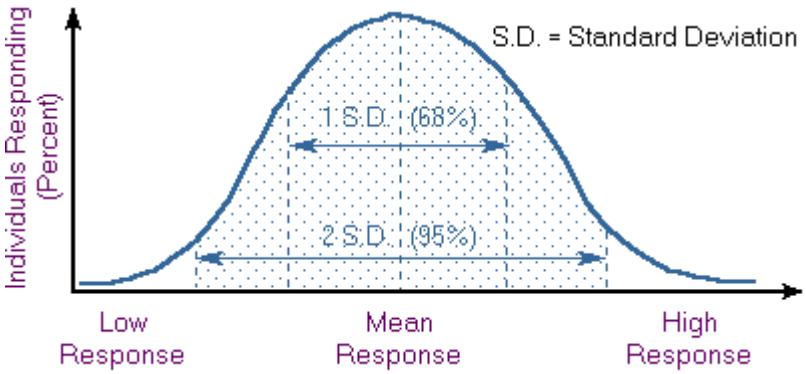


Fig. 2.1: The Dose-Response Curve

The dose-response relationship is, however predicated on certain assumptions that:

- the toxic response is a function of the concentration of the compound at the site of action
- the concentration at the site of action is related to the dose
- the response is causally related to the compound given.

An examination of these assumptions indicates that there are various factors which may affect the relationship.

The majority of responses to a toxicant in a population are similar; however, a wide variance of responses may be encountered, some individuals are susceptible and others resistant. As presented in Figure 2.1, a graph of individual responses can be depicted as a bell-shaped standard distribution curve.

Dose- responses are commonly presented as mean + 1 S.D (Standard deviation), which incorporates 68% of the individuals. The variance may also be presented as two standard deviations, which incorporates 95% of the responses. A large standard deviation indicates great variability of response. For example, a response of 15 + 8 mg indicates considerably more variability than 15 + 2 mg.

The dose-response curve normally takes the form of a sigmoid curve; see Figure 2.2 below. It conforms to a smooth curve as close as possible to the individual data points. For most effects, small doses are not toxic. The point at which toxicity first appears is known as the threshold dose level. From that point, the curve increases with higher dose levels. In Figure 2.2, no toxicity occurs at 10.mg whereas at 35mg 100% of the individuals experience toxic effects.

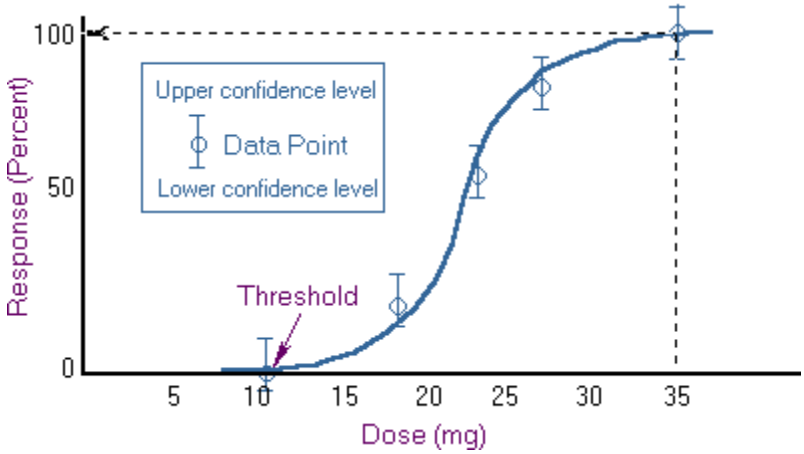


Fig. 2.2: Shape of Dose-Response Curve

A threshold for toxic effects occurs at the point where the body's ability to detoxify a xenobiotic or repair toxic injury has been exceeded. For most organs there is a reserve capacity so that loss of some organ function does not cause decreased performance. For example, the development of cirrhosis in the liver may not result in a clinical effect until over 50% of the liver has been replaced by fibrous tissue.

Knowledge of the shape and slope of the point dose-response curve is extremely important in predicting the toxicity of a substance at specific dose levels. Major differences among toxicants may exist not only in the point at which the threshold is reached but also in the percentage of population responding per unit change in dose (i.e., the slope). As illustrated in Figure 2.3, Toxicant A has a higher threshold but a steeper slope than Toxicant B.

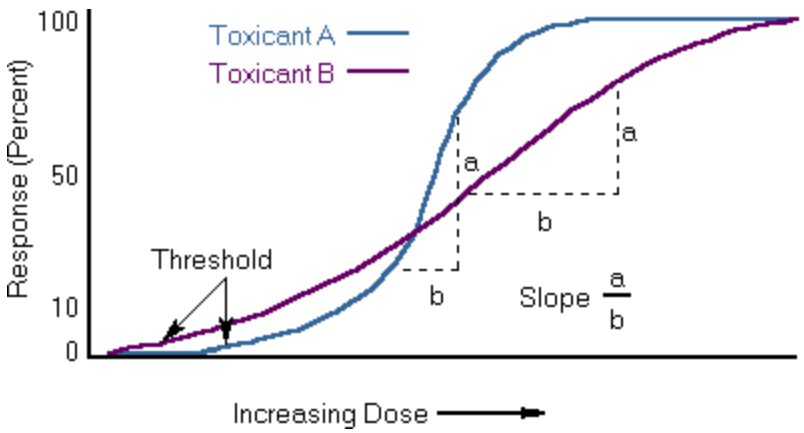


Fig. 2.3: Dose-Response Curve for Two-Toxicants

3.3 Dose Estimates of Toxic Effects (LD, EC, TD)

Dose-response curves are used to derive dose estimates of chemical substances. A common dose estimate for acute toxicity is the LD_{50} (Lethal Dose 50%). This is a statistically derived dose at which 50% of the individuals will be expected to die.

Other dose estimates also may be used: LD_O represents the dose at which no individuals are expected to die. This is just below the threshold for lethality. LD_{IO} refers to the dose at which 10% of the individuals will die.

For inhalation toxicity, air concentrations are used for exposure values. Thus, the LC_{50} (which stands for lethal concentration 50%) is utilized to denote the calculated concentration of a gas lethal to 50% of a group.

3.4 Effective Doses

Effective Doses (EDs) are used to indicate the effectiveness of a substance. Normally, effective dose refers to a beneficial effect (relief of pain). It might also stand for harmful effects (paralysis). Thus the specific end point must be indicated. The usual terms are;

ED_0	Effective for 0% of the population
ED_{10}	Effective for 10% of the population
ED_{50}	Effective for 50% of the population
ED_{90}	Effective for 90% of the population

3.5 Toxic Doses (TDs)

Toxic Doses (TDs) are utilized to indicate doses that cause adverse toxic effects. The usual dose estimates are listed below:

TD_0	Toxic to 0% of the population
TD_{10}	Toxic to 10% of the population
TD_{50}	Toxic to 50% of the population
TD_{90}	Toxic to 90% of the population

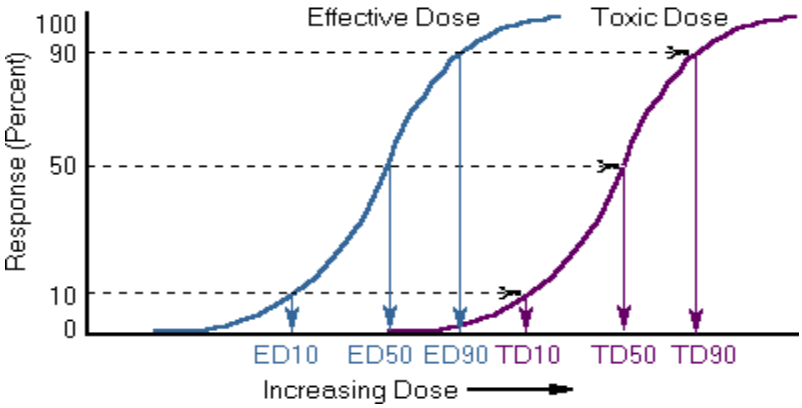


Fig. 2.4: The Dose-Response Curve Explanation for Effective and Toxic Doses

The knowledge of the effective and toxic dose levels aids the toxicologist and clinician in determining the relative safety of pharmaceuticals. As shown above, two dose-response curves are presented for the same drug: one for effectiveness and the other for toxicity. In this case, a dose that is 50-75% effective does not cause toxicity whereas a 90% effective dose may result in a small amount of toxicity.

3.6 No Observed Adverse Effect Level (NOAEL) and Low Observed Adverse Effect Level (LOAEL)

Two terms often encountered are No Observed Adverse Effect Level (NOAEL) and Low Observed Adverse Effect Level (LOAEL**)**. They are the *actual data points* from human clinical or experimental animal studies.

NOAEL	**Highest data point** at which there ***was not*** an observed toxic or adverse effect
LOAEL	**lowest data point** at which there ***was*** an observed toxic or adverse effect

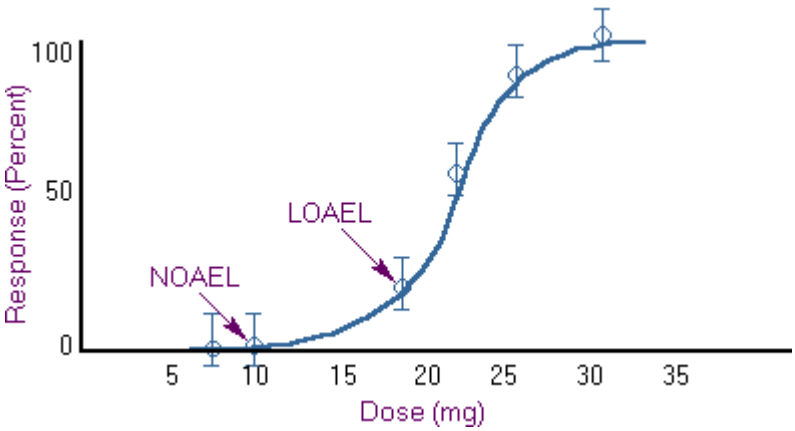


Fig. 2.5: Curve Dose-Response for NOEL

Sometimes the terms No Observed Effect Level (NOEL**)** and Lowest Observed Effect Level (LOEL) may also be found in the literature. NOELs and LOELs do not necessarily imply toxic or harmful effects and may be used to describe beneficial effects of chemicals as well.

The NOAEL, LOAEL, NOEL and LOEL have great importance in the conduct of risk assessments.

3.7 Hazard and Risk Assessment

Another important role of the dose-response relationship is its use in the extrapolation of toxic effects seen at high dose to lower dose in order to undertake hazard and risk assessment. For some types of toxic effect, there will be a threshold dose below which there is no detectable response. This is referred to as No Observed Effect Level (NOEL) (Figure 2. 6).

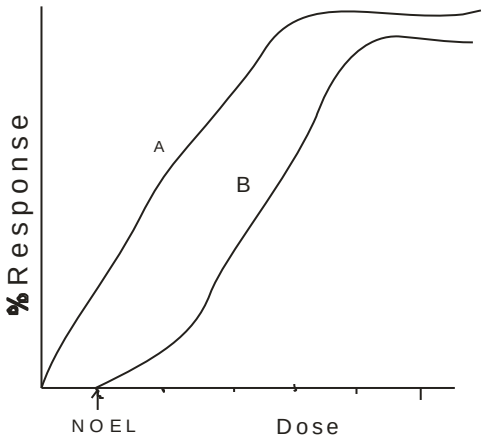


Fig. 2:6: The Curve Dose-Response for Two Compounds NOEL (from Timbrel, 2000)

In Figure 2.6, for compound A there is a response at all dose with no threshold; for compound B there is a dose or threshold below which there is a No Observed Effect (NOEL). The concept of a threshold dose is an important one in toxicology in terms of the extrapolation of toxic dose derived from animal experiments and the subsequent assessment of risk to man.

The NOEL is used in setting exposure limits such as the Acceptable Daily Intake (ADI) for chemicals such as food additives or Threshold Limit Values (TLV) for industrial chemicals usually with a 100-fold or sometimes greater safety factor to take account of species differences in response and human variability in response:

$$\text{ADI} = \frac{\text{NOEL (mg/kg) day}}{100}$$

4.0 Conclusion

This unit has taught the dose - response relationship which is central to toxicology. From the dose – response curve, it is possible for you to determine the LD_{50}, ED_{50} and NOEL. Also, you should be able to mention at least two assumptions on the dose – response relationship and the importance of this concept in risk and hazard assessment.

5.0 Summary

This unit has introduced you to the main concept in toxicology, dose – response principles, and the assumptions on which the dose –response relationship is based. The next unit will discuss dose and the toxic relationship between dose and poison.

6.0 Self-Assessment Exercise

1. Illustrate what is meant by the terms NOEL and toxic dose.
2. On what assumption is the dose-response relationship predicated?

7.0 References/Further Reading

Timbrel J. (2000). *Principles of Biochemical Toxicology.* UK: Taylor & Francis.

NURS 735- *Applied Toxicology* http://aquaticpath.umd.edu/appliedtox/module1-dose.html

The Edinburgh Centre for Toxicology (Edintox On – line Toxicology course http:// www.bio.hwac.uk /edintox / dose.htm

Unit 3 Toxicity

1.0 Introduction

This unit will help you to acquire knowledge about what toxicity is, factors that affect toxicity, degrees of toxicity and the physical forms of toxic substances.

2.0 Objectives

At the end of the unit, you should be able to:

- explain what toxicity is
- list the types of toxicity
- in your own words explain chronic and acute exposure.

3.0 Main Content

3.1 What is Toxicity?

Toxicity is a measure of the degree to which something is toxic or poisonous. Toxicity is the ability of a chemical molecule or compound to produce injury once it reaches a susceptible site in the body. Hazard is the probability that injury may be caused by the circumstance of the exposure. Toxicity refers to the effect on a whole organism, such as a human or a bacterium or a plant or to a substructure, such as a cell (cytotoxicity) or an organ (organotoxicity such as the liver).

A central concept of toxicology is that effects are dose-dependent; even water generally not considered to be toxic can lead to water intoxication when taken in large enough doses, whereas for even a very toxic substance such as snake venom, there is a dose below which there is no detectable toxic effect.

3.2 Types of Toxicity

One subdivision of toxicity may be made on the basis of duration of exposure:

Acute exposures: This term refers to exposure 'of short duration'. As applied to materials which are inhaled or absorbed through the skin, it refers to a single exposure of a duration measured in seconds, minutes, or hours. As applied to materials which are ingested, it refers generally to a single quantity or dose.

Sub-acute exposure: This refers to exposures of intermediate duration, i.e., between acute and chronic durations up to about 90 days.

Chronic exposure: This term will be used in contrast to acute exposure and it is of long duration. As applied to materials which are inhaled or absorbed through the skin, it refers to prolonged or repeated exposures of a duration measured in days, months or years. As applied to materials which are ingested, it refers to repeated doses over a period of days,

months, or years. The term 'chronic' will not refer to severity of symptoms but will carry the implication of exposures or dose which would be relatively harmless unless extended or repeated over a long period of time (days, months or years).

It is important to differentiate between acute and chronic exposure and acute and chronic effects. Although the expression "chronic toxicity" is sometimes used to indicate the result of repeated exposure to a chemical or to ionizing radiation; it would be much clearer if 'chronic toxicity' were equated with chronic illness resulting from these agents without any commitment regarding the duration of exposure. The fact is that some compounds have a strong tendency to produce chronic illness even though the exposure may be acute (i.e., only a single dose). Such compounds include the heavy metals and most carcinogens. Of course, their tendency to produce chronic sickness is accentuated if they are absorbed in repeated dose.

At the opposite extreme are compounds such as CN^- with which it is virtually impossible to produce chronic illness-even though a single excessive dose may produce acute poisoning and rapid death. Most compounds lie somewhere between the two extremes.

The words 'acute' and 'chronic' applied to illness have nothing to do with severity but only with the duration and character of illness. The common cold, intoxication from social drinking, plague and parathion poisoning are all acute illnesses. The first two are mild, the last two potentially fatal; all are brief with little tissue reaction. Pulmonary tuberculosis and poisoning are almost always chronic diseases. They are characterized by a prolonged course and by pathological changes in tissues that reflect continuing injury and perhaps ineffectual repair.

Toxic effects may also be subdivided on the basis of site of action: This includes:

Local effect: This means that the action takes place at the point or area of contact. The site may be skin, mucous membranes of the eyes, noise, mouth, throat, or anywhere along the respiratory or gastrointestinal system. Absorption does not necessarily occur.

Systemic effect: This refers to a site of action other than the point of contact and presupposes that absorption has taken place. It is possible, however, for toxic agents to be absorbed through a channel (skin, lungs, or intestinal canal) and produce later manifestations on one of those channels which are not a result of the original direct contact. Thus, it is possible for some agents to produce harmful effects on a single organ or tissue as a result of both local and systemic actions.

The single most important factor in determining whether or not illness will occur as the result of exposure to a specific chemical compound is dosage. In unit 1 in the history of toxicology, we noted Paracelsus as stating the concept that "the dose makes the poison" or that "all things are poisons, for there is nothing without poisonous qualities, it is only the dose which makes a thing poison". At extremely low dose, a given substance may be non-toxic and even beneficial (a concept known as hormesis), while at intermediate dose, it may be toxic. At high dose, it may be lethal.

The dosage concept leads to the condition that no chemical safe and that is none is entirely harmful. Compounds vary tremendously in their toxicity. In comparing the toxicity of different compounds standardized notation are used for describing the toxic level. The commonly used notation is the median lethal doses or LD_{50}. The LD_{50} is a statistical

estimate of the dosage necessary to kill 50% of an infinite population of the test animals. The LD_{50} is usually expressed in terms of the weight of poison /unit of body weight (mg) of different species regardless of their size. The LD_{50} is a special case of a more general measure of effect, the median effective dosage (ED_{50}). The ED_{50} is the dosage necessary to produce any specified effect in 50% of the test animals. The effect can be anything that can be observed (i.e., degree of inhibition of an enzyme or the production of tumour. These measures of effect (ED_{50} or LD_{50}) for a particular compound have meaning only if experimental conditions are defined, including the species, age and sex of experimental animal, the number of dose and the route of administration.

Compounds may be classified into several levels of toxicity based on the dosage necessary to produce poisoning. Since the dosage to cause illness in man is seldom accurately known, this classification is usually based on a more easily obtainable measure of toxicity. The value which is generally used is the acute oral LD_{50} for the laboratory rat. It is important to note here that the acute oral LD_{50} value measures only the acute systemic effect of a compound. Serious delayed effects such as tumours, or local effects such as those on the eye or mucous membranes, have to be expressed in other ways. To know more about the meaning of these values, the following rule may follow:

The lower the LD50 value, the higher the toxicity.

- Compounds which are essentially non-toxic (acute oral LD_{80} to the laboratory rat greater than 5000mg/kg). These are materials which are unlikely to produce harm under any normal conditions of occupational use or exposure. Ingestions of quantities of the order of one pint or more would probably be required to produce significant illness in an adult.
- Compounds of slight toxicity (LD_{50} between 1000 and 5000 mg/kg). These compounds would be expected to cause illness following ingestion or absorption of quantities of the order of an ounce to a pint.
- Compounds of moderate toxicity (LD_{50} between 100 and 1000mg/kg). These compounds would be expected to cause illness following ingestion or absorption of quantities of the order of a teaspoonful to an ounce.
- Compounds of high toxicity ($LD_{50,}$ less than 100mg/kg). These compounds would be expected to cause illness following ingestion or absorption of quantities of the order of a few drops or even a taste for the more highly toxic materials (i.e. very low LD_{50} values):

Threshold Limit Values

Another procedure for expressing toxic levels for different compounds is the use of Threshold Limit Values (TLV), formerly known as Maximum Allowable Concentration (MAC).

TLV represents an arbitrarily set value on the basis of experimental and other available data while LD_{50} represents an experimentally derived value. The acute oral LD_{50} value is most useful if one is dealing with an ingestion case while TLV is useful for industrial and occupational exposure restrictions.

Closely related to TLVs are the so-called acceptable concentration standards promulgated by the American Standards Association (ASA). According to the ASA, these standards are designed to prevent

1. undesirable changes in body biochemistry
2. undesirable functional reactions that may have no discernible effects on heath; and
3. irritation or other adverse sevisory effects.

For gases and vapours, the TLV is usually expressed in parts per million (ppm); that is, parts of the gas or vapour per million parts of air. For fumes and mists and for some dusts, the TLV is usually given as milligrams per cubic meter (mg/m^3) or per $10m^3$ of air. For some dusts particularly those containing SiO_2, the TLV is usually expressed as millions of particles per cubic foot air (mppcf).

3.3 Classes of Toxic Substances

Toxic substances to which we are exposed in the environment may be in several different physical forms and may be classified as follows:

3.3.1 Gases

Gases are substances such as carbon monoxide in air that is normally in gaseous states under ambient conditions of temperature and pressure.

3.3.2 Vapours

Vapours are the gaseous form of substances which are normally in solid or liquid state and which can be changed to these states by increasing the pressure or by decreasing the temperature.

3.3.3 Dusts

Dusts are solid particles produced by grinding bulk solid, detonation of organic or inorganic materials such as rocks, ore, metal, coal, wood, grains, etc. Dusts do not tend to flocculate except under electrostatic forces; they do not diffuse in air, but settle under the influence of gravity.

Solid particles are generated from the condensation of vapours, often metals or metal oxides. Fumes flocculate and sometimes coalesce.

3.3.4 Mists

Mists are the suspended liquid droplets generated by condensation from the gaseous to the liquid state or the breaking up of liquid into a dispersed state such as splashing, foaming and atomizing.

4.0 Conclusion

This unit has taught toxicity and divisions of toxicity. It has shown that toxicity can be sub-divided on the basis of duration of exposure and site of action. It has also examined the physical forms of toxic agents in our environment.

You should now be able to explain the following:

- Acute exposure
- Chronic exposure
- Threshold limit values (TLV)
- LD_{50}

5.0 Summary

This unit has introduced you to toxicity and its types and the physical forms of toxic substances. It has also shown that toxicity can be divided into acute exposure, chronic exposure, local effect and systemic effect. These toxic substances in our environment can exist in different physical forms such as gas, liquid and solid.

6.0 Self-Assessment Exercise

1. Using your own words, define the term Toxicity.
2. List the physical forms in which toxic substances can occur in our environment.

7.0 References/Further Reading

Manahan, S. E. (2000). *Environmental Chemistry. (*7th ed.). London: Lewis Publishers.

Bhatia, S.C. (2005). *Environmental Pollution and Control in Chemical Industries.* Delhi: Khanna Publishers.

Asthana, D.K.; Asthana, M. (2003). *Environment: Problems and Solutions*. New Delhi: S. Chand and Company Ltd.

Unit 4 Routes of Entry of Toxic Agents and Bio Transformation of Toxic Agents

1.0 Introduction

This unit will discuss the routes of entry of toxic agents, absorption of chemicals and biotransformation of these toxic substances in the human body. It will also discuss biotoxification, toxicodynamics, immunotoxicity and the factors that affect the degree of toxicity of toxic agents after their entry into the body.

2.0 Objectives

At the end of this unit, you should be able to:

- identify routes of passage of toxic substances into the human body
- mention the phases of biotransformation
- explain why fat soluble substances may cause special problems.

3.0 Main Content

3.1 Absorption of Chemicals

For a chemical to cause its effect, it must enter a cell; to enter a cell, it must pass through a biological membrane:

3.1.1 Membrane Structure

Biological membranes exist as a protein-lipid bilayer. The lipid portion is primarily phospholipid, which have ionic polar head groups oriented outward (the spheres), and non-polar lipid chains (tails) oriented inward. The globular structures represent integral membrane proteins, which may be transport, receptor or other types of proteins. Biological membranes are primarily a lipid sandwich. Non-polar, lipid soluble compounds are, therefore, absorbed most efficiently.

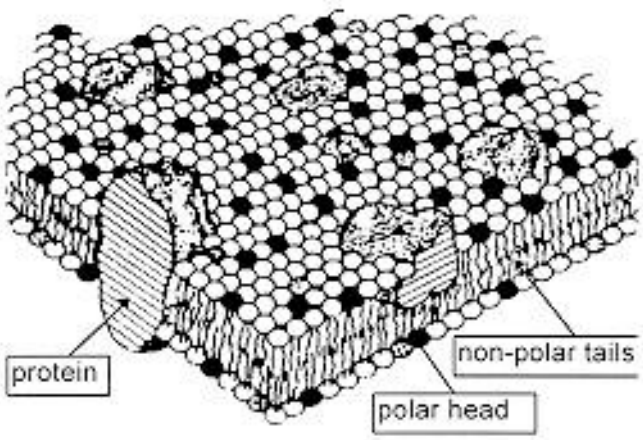


Fig. 4.1:

If we ignore the medical administration of drugs, there are several routes by which people can take in foreign chemicals (xenobiotics). The main routes are:

- through the skin or mucous membranes such as the conjunctiva
- through the lungs (inhalation)
- through the gastro-intestinal tract (ingestion).

Figure 4.1 shows what happens to xenobiotics absorbed by these routes.

The severity of the effects produced by any given dose, amount or concentration of a chemical or chemical formulation is related to the route of absorption, among other things .Usually absorption is most rapid from the lungs, less rapid from the gastro intestinal tract and least rapid through the skin. The lungs evolved for efficient exchange of gases and present little resistance to the uptake of chemicals in the vapour state.

Respirable particulates may lodge in the lungs if they are small enough (less than 7 micrometres in diameter) and/or of a shape or chemistry that prevents their removal by the normal bronchial ciliary action. Diseases which can result from inhalation of particulates include silicosis, asbestosis, berylliosis, etc.

Some respirable particulates may dissolve easily in the fluids of the respiratory tract: such particulates may affect the upper respiratory tract more than the bronchioles and alveoli.

The gastro-intestinal tract evolved to absorb nutrients in a selective manner; potentially toxic chemicals that are chemically similar to normal nutrients may be absorbed preferentially.

The skin evolved as a protective covering against a hostile environment and is relatively impermeable to many chemicals. However, many chemicals are readily absorbed through the skin; for example, phenols and organophosphate pesticides, and these can be lethal.

The capacity of the toxic agents to dissolve in lipids and fats appears to be an important factor in determining their permeability through the skin. For example, carbon tetrachloride can be absorbed through the skin in sufficient concentration to produce liver toxicity. Stratum cormeum, the outermost corny layer of the skin, plays an important role in

determining the permeability of this layer. Abrasions or chemical treatment of this layer raises the permeability of skin significantly.

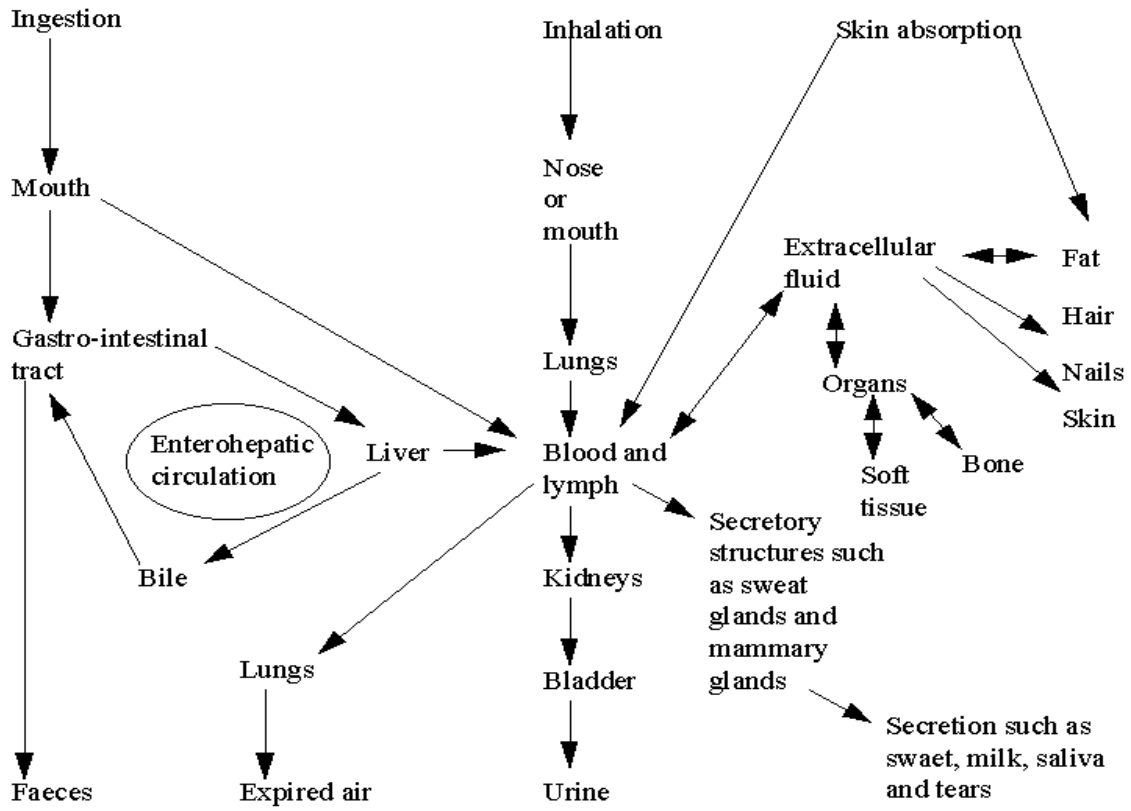


Fig. 4.2: Routes of Absorption, Distribution and Excretion of Potentially Toxic Substances (Curled from Edintox on – line Toxicology course)

Transport of drug through membranes occurs by one of two general processes:

- Passive diffusion
- Specialised transport

Passive diffusion: Most toxicants enter this way; through

- hydrophilic compounds: via aqueous channels in the membrane; and
- hydrophobic compounds: (most toxicants and drugs) via lipid portions of the membrane.

The rate and extent of absorption of hydrophobic chemicals depends on three factors:

- Lipid solubility
- Molecular size
- Degree of ionization

Lipid solubility: This is measured by octanol: water partition coefficient in a separatory funnel.

The lipid solubility of a compound is commonly measured by adding it to a mixture of water (polar, hydrophilic phase) and octanol (non-polar, hydrophobic phase) in a separatory funnel. The amount of compound in each phase is then measured. The relative amount of compound in either phase gives the partition coefficient (Pc) of the compound. The higher the Pc the more lipid soluble is the compound. A compound with a large Pc is generally able to efficiently enter a cell. Pc increases with increasing chain length.

Molecular size: Small particles absorbed more readily.

Degree of ionization: Many drugs and toxic chemicals exist in either ionized or non-ionized forms.

- Ionized forms: Susceptible to ionic interactions with membranes-absorption is hindered (less lipid soluble)
- Non-ionized forms: Lipid soluble; will diffuse.

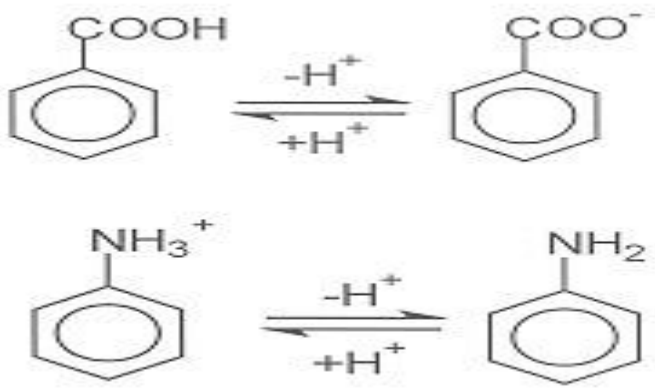
The degree of ionization is dependent upon:

- dissociation constant of the chemical (pK)
- pH of the environment, according to the Henderson-Hasselbalch equation:

For acids: $pKa - pH = \log \frac{[\text{nonioinized}]}{[\text{ionized}]}$ Acids such as R-COOH, etc.

For bases: $pKa - pH = \log \frac{[\text{ionized}]}{[\text{nonionized}]}$ Bases such as R-NH_2

Consider the ionization of two compounds:

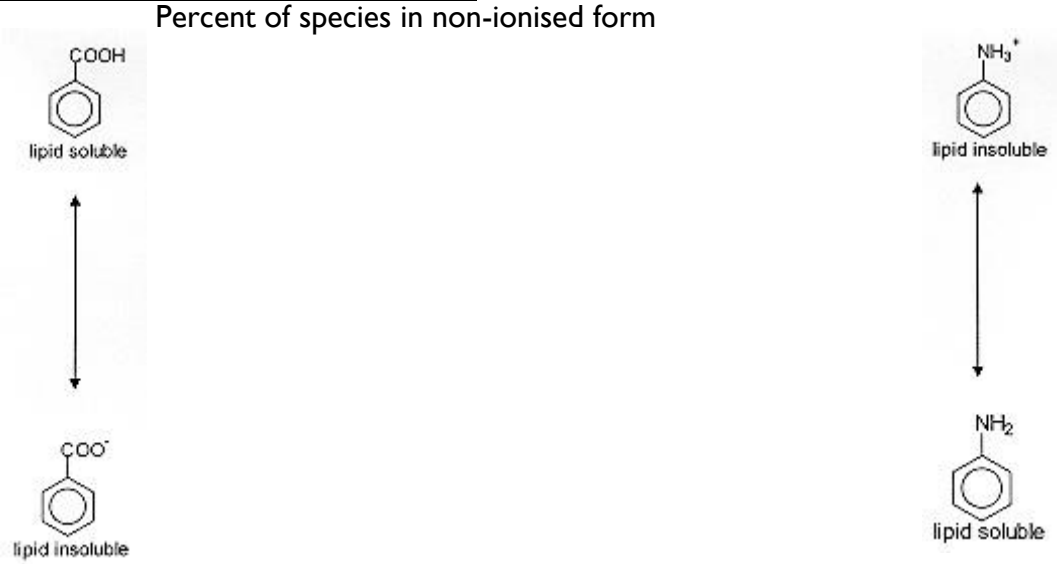


benzoic acid (weak acid:pKa=4)

aniline (weak base: pK=5)

pH	benzoate	aniline
1	99.9	0.01
2	99.0	0.10
3	90.0	1.00
4	50.0	10.0
5	10.0	50.0
6	1.00	90.00
7	0.10	99.0

Percent of species in non-ionised form



Toxicological consequences of interaction between pH and pK:

- weak acids concentrate in areas of higher pH
- weak bases concentrate in areas of lower pH

Specialized transport

1. Characteristics of active transport:

- absorption against concentration gradient
- saturable
- selective
- requires energy.

2. Carrier-mediated
3. Endocytosis: pinocytosis/phagocytosis:

- requires energy
- for small amounts of compounds: peptides, AG:AB complexes.

Absorption of chemicals by specific routes

1. Percutaneous route (skin is a good barrier)

transepidermal: (most here)
transfollicular: via sweat glands and follicles (Pb)
Absorption of chemicals through the skin is promoted by:

- high lipid solubility and non-ionisation
- sweaty, hot skin
- wrapping of skin
- abrasion, injury, rash
- presence of solvents

2. Pulmonary route: rapid since epithelium is 1-2 cells thick

- principal route of absorption for gases, vapours, aerosols

3. Gastrointestinal route

- epithelial linings are only one cell thick
- extremely large surface area in many areas (the stomach is not as good an absorptive surface and is continually emptying)
- due to tremendous pH ranges, diffusion of drug occurs where it is present in most lipid soluble form:

1. weak acids diffuse best at lower pH (stomach--pH 2)
2. weak bases diffuse best at higher pH (intestines--pH 6).

Some compounds are absorbed well, regardless of pH/pK characteristics:

4. paraquat (has two positive charges), 2-PAM
5. factors promoting absorption: ulceration, GI irritation, starvation.
   factors decreasing absorption: food in gut, vomiting

Effect of meal on plasma concentration of a chemical:

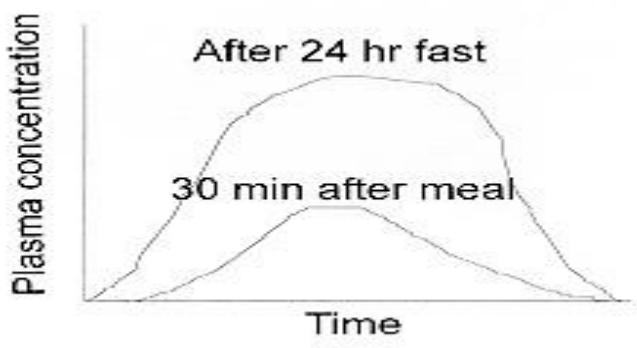


Fig. 4.3

For a lipid-soluble chemical, the route of absorption is an important determinant of the rate at which effects occur.

Route	Time until death (min)
pulmonary	15-30
eye	15-30
gastrointestinal	30-120
skin	1-4 hr

4. Distribution
Factors affecting distribution:

6. Binding to charged particles: The blood contains charged proteins to which chemicals will bind (such as albumin, globulins, and proteins) chemical bound chemical (crosses membranes) (does not cross membranes)
7. Fat storage: Depends on lipophilicity of compound.

5. Volume of distribution (Vd): That volume that would exist in the body if all parts of the body had the same drug concentration as the plasma.

Most of the body is composed of water. Pharmacologists divide the body water into three distinct compartments:

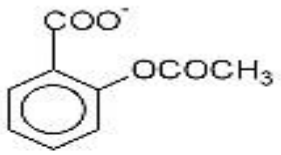
Type of water	% of total	Volume (L)
Plasma	4	3
Interstitial	13	9
Intracellular	41	28

If chemical has a low Pc, apparent Vd will be approximately 3L or Vd equal to that of plasma water.

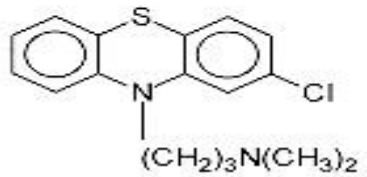
If drug has a high Pc (i.e., is very lipophilic), and therefore able to traverse membranes,

Vd will be greater than 3L.

Examples:



Acetylsalicyclic acid Vd = 0.15L



Chlorpromazine (thorazine) Vd = 21 L

3.2 Distribution and Metabolism of Chemicals

A biological system is constantly exposed to a variety of foreign man made chemical or and their absorption brings about interference in the system. A biological system is particularly defenceless against lipid soluble substances, which have free access across the plasma membrane entering the cell simply by dissolving and diffusing through the lipid layer. The biochemical reactions which alter and detoxify chemical agents are cumulatively known as biotransformation reactions.

Location of biotransformation reaction: Liver is by far the most important organ in which most of the biotransformation reactions are carried out. Most of the enzymes which catalysed biotransformation reactions have been shown to be present in the cells of the liver on endoplasmic reticulum which is a network of inter-connected structures made up of lipoproteins.

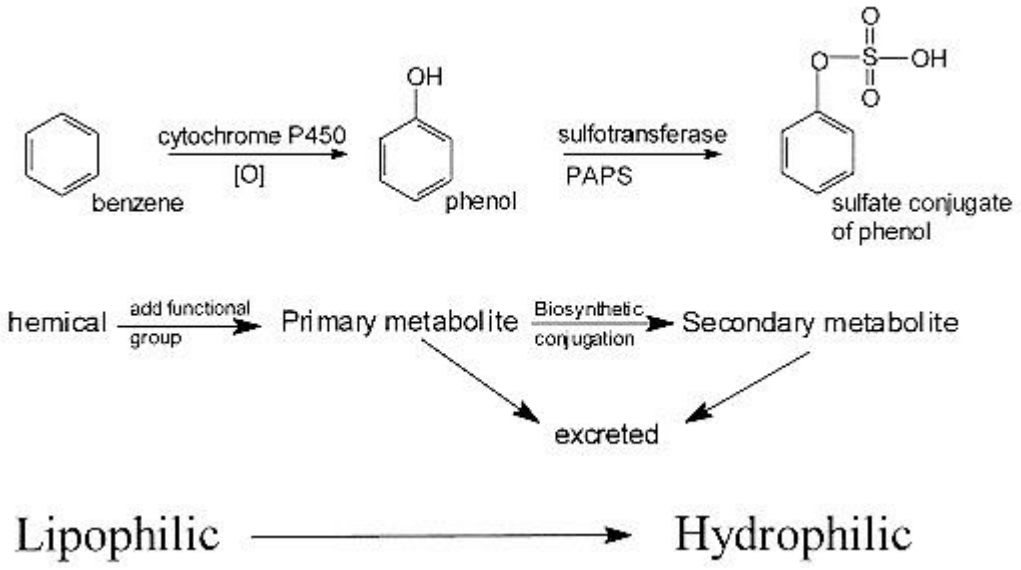
Toxic agents are metabolized in the liver cells by unique pathways which appear to exist mainly for the purpose and are capable of dealing with a tremendous variety of compounds.

The processes by which an organism metabolizes xenobiotic species are enzymes-catalysed phase I and phase II reactions.

3.2.1 Phase I Reactions

Lipophilic xenobiotic species in the body tend to undergo phase I reactions that make them more water-soluble and reactive by the attachment of polar functional groups, such as –OH, most phase I processes are "imicrosonal mixed function oxidase" reactions catalysed by the cytochrome p-450 enzymes system associated with the endoplasmic reticulum of the cell and occurring most abundantly in the liver.

In general, ingested chemicals are modified by the body to increase excretion and thereby limit their toxic action.



- inhaled benzene is metabolized by an initial (or "phase I") reaction to phenol
- relative to benzene, phenol is more hydrophilic and is easily excreted.
- phenol may be further metabolized (called a "phase II"reaction) by a sulfate molecule to further increase hydrophilicity and thereby its excretability

The majority of the phase I reactions are catalyzed by an enzyme called cytochrome P^{N}-450 (CYP)

- a hemoprotein (contains Fe atom in active site)
- present in most tissues, but highest in liver
- in the cell, resides in the smooth endoplasmic reticulum (SER**)** (microsomes)
- inserts a molecule of oxygen into substrate
- requires an electron source to reduce iron (III) (Fe+3) to iron (II) (Fe+2)
- product may either be excreted or further metabolized by subsequent phase II reactions.

For the majority of chemicals, this reaction produces stable, detoxified metabolites. Unfortunately, for some chemicals a more toxic metabolite is formed.

Mechanism and sequence of cytochrome P-450 catalysis:

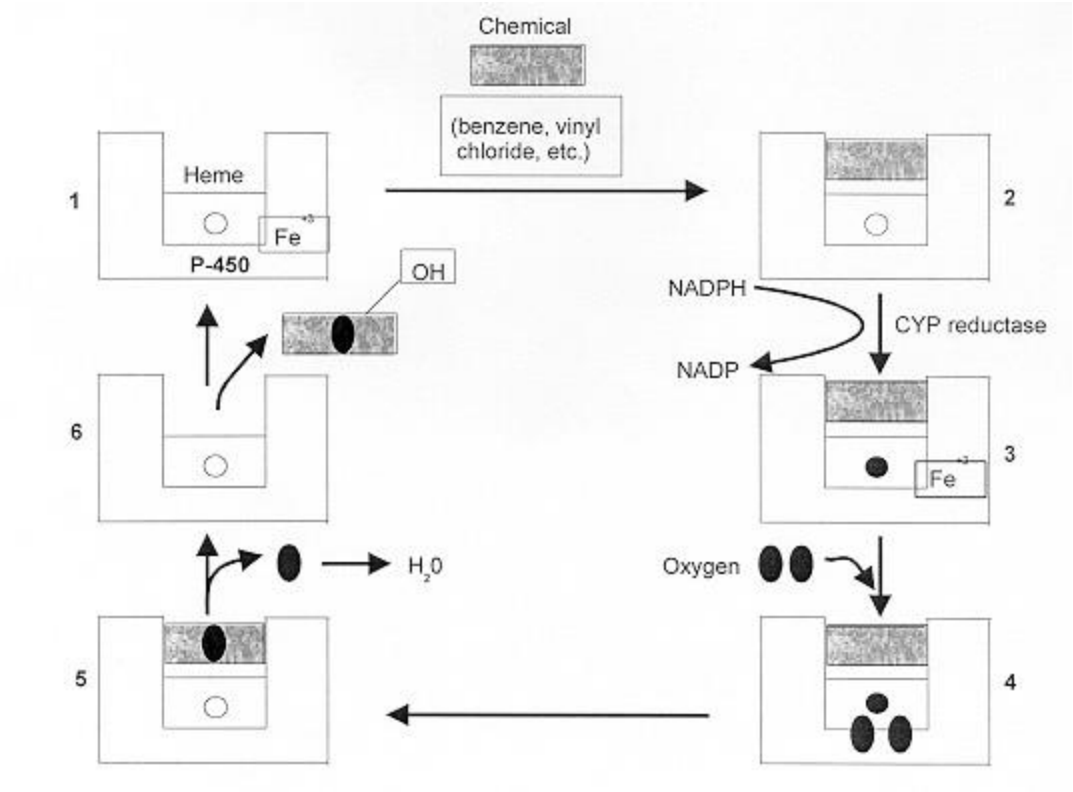
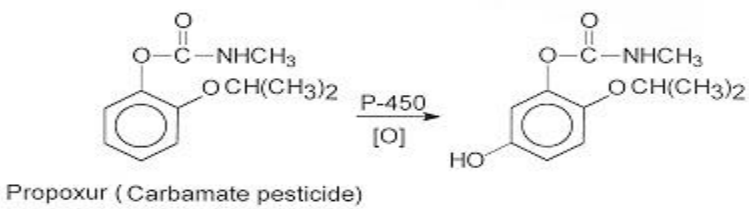


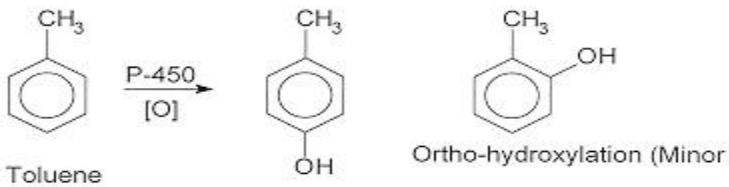
Fig.4.4: Phase I Biotransformation

P-450 mediated reactions**:**

Aliphatic and aromatic hydroxylations



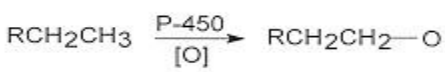
Propoxur (Carbamate pesticide)



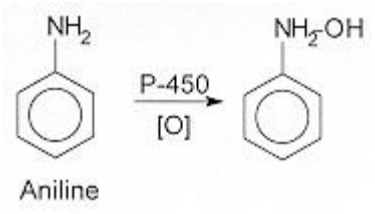
Toluene

Para-hydroxylation (Major)

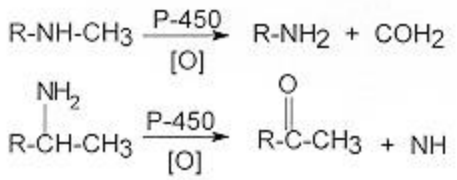
Ortho-hydroxylation (Minor

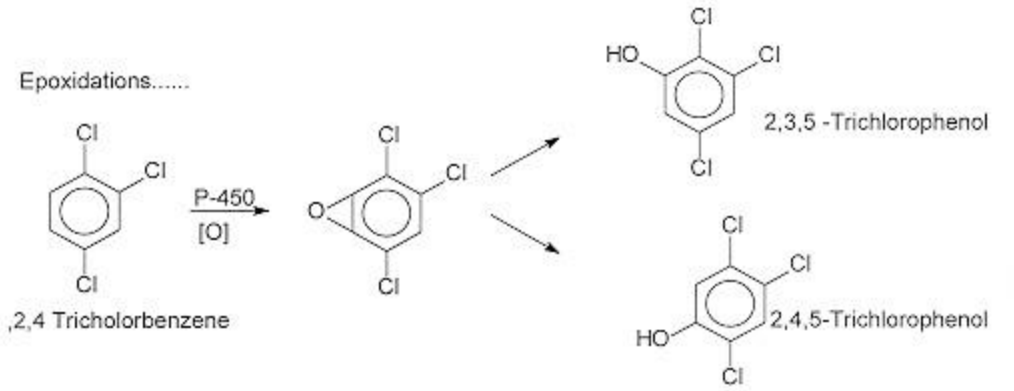


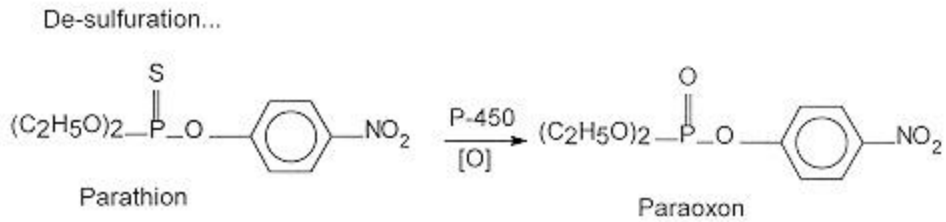
Nitrogen hydroxylation:



Dealkylations and deaminations



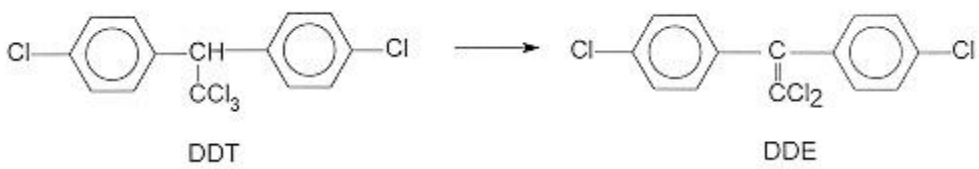




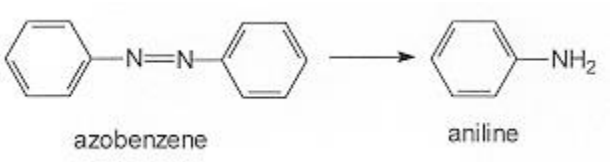
(paraoxon is more toxic than parathion)

Reductions: Occur in microsomes and other locations, by P-450s, oxidoreductases, and by intestinal microflora.

Reductive dehalogenation.



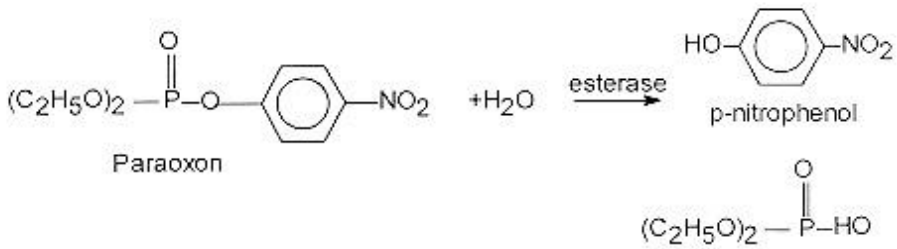
Azo reduction:



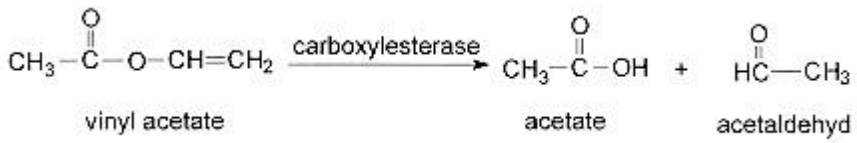
Nitro reduction:

3.2.1.1 Hydrolysis Reactions (add H_2O to ester Groups)

Phosphoric acid ester:

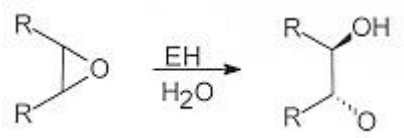


Carboxylic acid ester:

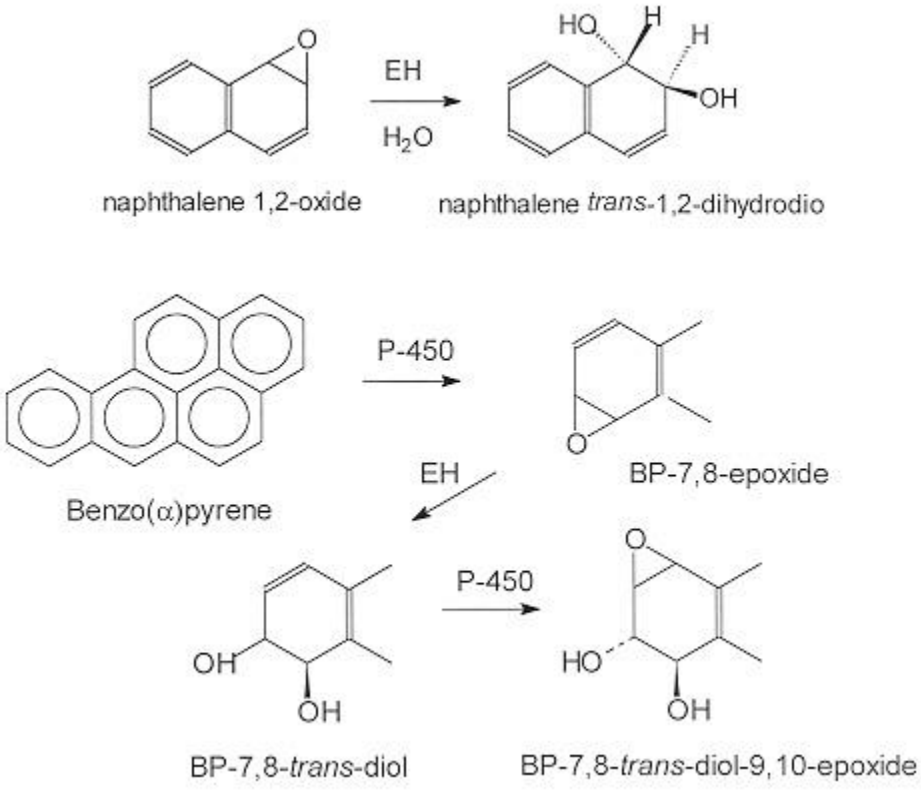


Epoxide Hydrolase:

- A hydrolytic enzyme in microsomes and soluble cellular fractions.
- Mainly in liver, but also in lung, kidney and intestines.
- Catalyses the transital addition of H_2O to epoxides to produce transitaldiols.



- Deactivates many labile "ultimate carcinogens," but is also involved in the "activation" process of some carcinogens, such as benzo(a)pyrene.



3.2.2 Phase II Reactions

Phase II reactions are called conjugation reactions in which enzymes attach conjugating agent to xenobiotics, their phase I reaction products, and non-xenobiotic compounds: the conjugation product of such a reaction is usually less toxic than the original xenobiotic compound, less lipid soluble, more water-soluble, and more readily eliminated from the body. The major conjugating phase II reactions are gucurornde (UDP glucurony/transferase enzymes), sulphate (sulphotransferase enzyme), and acetyl (acetylation by acetylttransferase enzymes). The most abundant conjugation products are glucuronides. A glucuronic conjugate is illustrated in fig. where - X-R represents a xenobiotic species conjugated to glucuronride, and B is an organic moiety.

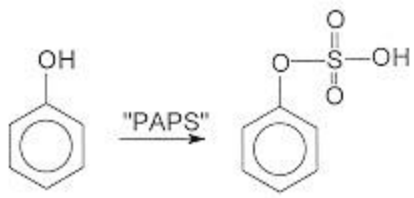
Chemicals modified by phase I reactions can be further metabolized by a variety of secondary, or “phase II” reactions.

Phase II reactions act to further increase hydrophilicity of the chemical, hastening its excretion.

Products of phase II reactions are generally detoxified.

Products of phase II reactions are called "conjugates”.

Chemicals may be conjugated to the following compounds:



I. Sulfate

Enzyme: Sulfotransferase

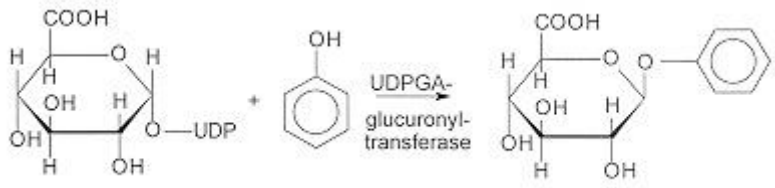
Coenzyme: Phoshoadenosine-5'-Phosphosulfate ("PAPS")

II. Glucuronic Acid

Enzyme: UDP-Glucuronyl Transferase

Coenzyme: Uridine diphosphoglucuronic acid (UDPGA)

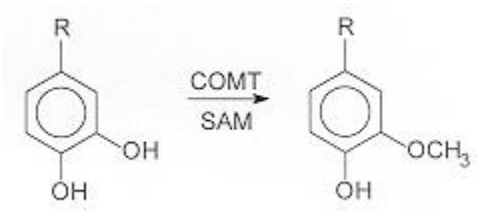
(During conjugation UDPGA is interconverted from ☐ to ☐ configuration)



III. Methyl Group

Enzyme: O-Methyltransferase

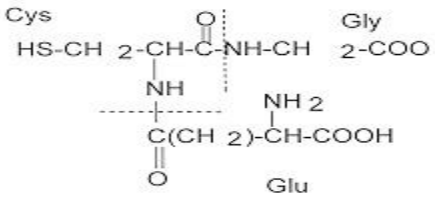
Coenzyme: S-Adenosyl Methionine ("SAM")



IV. Glutathione: important detoxifying pathway for electrophilic carbon atoms.

Enzyme: glutathione S-transferase (GST)

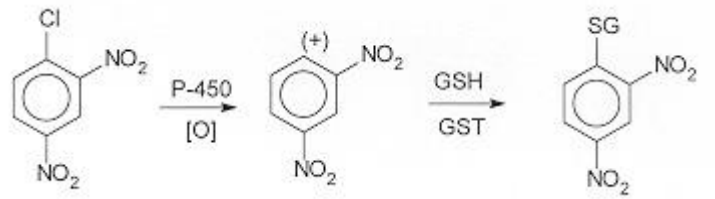
Coenzyme: glutathione (☐-glutamyl L-cysteinyl glycine; GSH) glutathione is a tripeptide with a backwards or ☐ peptide bond.



Inactivates compounds that are metabolised to an electrophilic (electron poor) atoms, which are highly reactive and toxic.

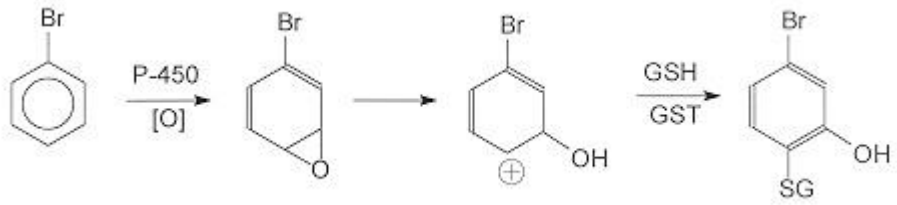
GSH conjugates are subsequently cleaved to cysteine derivatives in the kidney.

Dinitrochlorobenzene



"SG" is usually the cysteine derivative of GSH, thus, glutamate and glycine are by-products.

Bromobenzene



Once absorbed, chemicals from the lungs, skin and mouth may enter the general blood circulation directly and be rapidly spread round the body in an unmodified form.

Chemicals absorbed from the stomach or intestine enter the hepatic portal system and are taken to the liver where they may be modified by a series of reactions often referred to as biotransformation.

Biotransformation reactions in the liver have been referred as “detoxification” but this term is misleading because they can also increase the toxicity of a number of chemicals – “biotoxification”. Biotransformation reactions are subdivided into phase I and phase II reactions.

The phase I reactions are catalyzed by the cytochrome P-450 family of enzymes and other enzymes of the smooth endoplasmic reticulum.

Phase I reactions include oxidation, reduction, hydrolysis, dealkylation, deamination, dehalogenation, ring formation, and ring breakage.

Phase II reactions are conjugation reactions – co-valent linkage of the absorbed chemicals, or of the products of the phase I reactions, with compounds such as glutathione, glucuronic acid, or amino-acids. The conjugates produced are generally more water soluble than the chemicals from which they are derived and so are more easily excreted.

Chemicals which undergo phase I and phase II reactions are normally those which are fat soluble (lipophilic).

Fat soluble substances tend to accumulate in body tissue and milk if not converted to an excretable form. Excretion of conjugates mostly occurs in the bile. Some conjugates may be broken down to components by bacteria in the gut; the components may again be absorbed and go through phase II reactions: this process is called enterohepatic circulation.

Enterohepatic circulation slows excretion of the substances involved and must be allowed for in evaluating the likely effects of any potentially toxic substances.

Water soluble (hydrophilic) substances and dissociated polar substances go directly to the blood circulation, from which they may be lost in expired air from the lungs (if they vaporize readily), through the kidney in the urine following ultrafiltration and/or active secretion or in other secreted fluids such as tears, saliva, milk, sweat. etc.

Highly lipophilic and metabolically stable substances tend to accumulate in body fat; if this fat is mobilised under stress conditions, the substances may return to the blood and cause acute intoxication before undergoing phase I and phase II reactions in the liver and other organs. In the blood, fat soluble substances associate reversibly with blood cells, albumin, and lipoproteins.

3.3 Immunological Reactions

Free molecules can react with other body components, altering their properties and hence their biological functions; chemical alteration of body components may result in the immune system treating these components as foreign with harmful results.

Antibodies may be produced which bind to abnormally altered body components and trigger inflammation, tissue breakdown and other harmful effects.

3.4 Biotoxification

Polycyclic aromatic hydrocarbons are converted to arylating derivatives which can react with DNA and proteins to cause mutations, cancers, embryonic abnormalities (teratogenesis), immunological sensitization and cell death.

Aryl amines are converted to aryl hydroxylamines which can carry out arylation reactions and also convert haemoglobin to methaemoglobin, a derivative which can no longer carry oxygen.

Nitrate in the diet can be converted to nitrite by bacteria in the intestine and, in the presence of substances containing amino groups, converted further by the same bacteria to nitrosamines.

Nitrite can convert haemoglobin to methaemoglobin thus lowering the ability of the blood to carry oxygen.

This reaction has led to the death of babies given milk prepared from proprietary milk powder dissolved in water containing too much nitrate; death is caused by the tissues being deprived of oxygen ("blue baby" syndrome).

Nitrate contamination of drinking water may arise from excessive use of nitrate as fertiliser by farmers.

3.5 Toxicodynamics

Toxicodynamic phase covers the reactions which are the immediate cause of toxicity.

The alkylation and arylation of DNA to cause mutations (already referred to) is part of the toxicodynamic phase; one possible consequence of these reactions is tumour development and cancer as described later in unit 7. Molecules which can act as alkylating or arylating agents in their original state or following biotransformation may attack DNA causing changes in the molecular structure and thus causing mutations (mutagenesis).

If such mutations occur in gametes (eggs or sperm), they are heritable and may affect future generations. If mutations occur in other body cells, they are called somatic mutations and may cause benign or malignant tumour development.

A mutated cell does not necessarily form a tumour; if DNA repair mechanisms operate, as they often do, the damaged DNA may be removed and replaced and the cell will return to normal.

If DNA repair does not occur, the initiated cell may become the focus of a benign or malignant tumour. Alternatively, the cell with damaged DNA may be initiated and may function normally until exposed to another chemical called a promoter. A chemical causing such initiation is said to be an “initiator”.

Initiation may be defined as a stochastic process that involves one or more heritable alterations in DNA induced by diverse factors including mutagenic chemicals, ionising radiation and viruses.

A promoter is a substance which does not itself cause tumour development but which, by its action, permits a potentially carcinogenic mutation caused by an initiator to be expressed in local cell proliferation (promotion and progression) leading to tumour formation. One or more of these may become malignant and lead to cancer.

Cancer may also result from exposure to substances which poison the immune system preventing it from removing potentially cancerous cells before tumours develop. Once tumours develop, some may prove to be cancerous (malignant) and spread throughout the body but many will be localized (benign) and may be safely left or removed by surgery.

Malignant tumours are characterized by their ability to invade adjacent tissues and to metastasize (cells break off from the original tumour and move in the lymphatics or blood stream to another part of the body which they invade and where secondary growths are formed).

3.6 Immunotoxicity

Many toxic effects are mediated through the immune system, a complex system with many components. Depression of the system will lower resistance to infectious disease and facilitate development of cancer.

Enhancement of the system can also lead to disease processes of which the most common are haemolytic anaemia, myasthenia gravis, glomerulonephritis, systemic lupus erythematosus, contact dermatitis, and even infertility.

However, it should be noted that immunomodulatory agents can stimulate some components of the immune system and, at the same time, depress others.

If a chemical or derivative (such as a modified body component) functions as an antigen, hypersensitivity to the chemical will result and, in the case of a body component, the ability of the immune system to distinguish between self and non-self-molecules may be compromised and result in immunological damage to essential cells and tissues.

Consequences may include asthma, conjunctivitis, haemolytic anaemia, glomerulonephritis, systemic lupus erythematosus, contact dermatitis, and even infertility.

4.0 Conclusion

You have read about the routes of entry of toxic substances into the human body and the transformation these toxic substances undergo in the body. Also you have been introduced to the biotransformation of potentially toxic substances in the human body and the fact that biotransformation of toxic substances is in two phases: phase I reactions and phase II reactions.

We have discussed the main routes of distribution of potentially toxic substances in the body. We have also identified the routes of excretion and the reasons why fat-soluble substances may not be excreted effectively and may remain in the body with long-term consequences.

The distinction between toxicokinetics and toxicodynamics has been explained and you should know the current ideas on some aspects of the toxicodynamics of mutagenesis and carcinogenesis.

You should be able to mention the enzyme system that is involved in biotransformation processes and the site of the transformation of these toxic substances in the human body.

5.0 Summary

This unit has introduced you to the routes of distribution of potentially toxic substances in the body and the related possibilities biotransformation. The major routes of entry are through the skin, through the lung, or through the gastro-intestinal tract. The biotransformation reactions are in phases.

6.0 Self-Assessment Exercise

1. What are the routes of human exposure to potentially toxic chemicals?
2. What are the phase I reactions?
3. What is the importance of body fat in relation to potentially toxic substances?
4. How can chemical reactions with body components lead to adverse immunological reactions?

7.0 References/Further Reading

The Edinburgh Centre for Toxicology (Edintox On–line Toxicology Course http:// www.bio.hwac.uk /edintox / human.htm

Manahan, S. E (2000). *Environmental Chemistry* (7th ed). London: Lewis Publishers.

Timbrel, J. (2000). *Principles of Biochemical Toxicology.* UK: Taylor, & Francis.

Unit 5 Toxic Inorganic Elements and Metals

1.0 Introduction

This unit discusses the relationship between to some of the major pollutants and hazardous substances. The unit deals with toxicological aspects of inorganic elements and heavy metals. It also discusses the toxicity of some commonly used elemental forms. The unit will help you to acquire basic knowledge about the toxicity and the hazards of toxic heavy metals and inorganic elements such as beryllium, lead, mercury, cadmium, arsenic, ozone, white phosphorus and chlorine

2.0 Objectives

At the end of this unit, you should be able to:

- mention and identify the inorganic toxic elements
- name the toxic heavy metal elements
- specify the health hazards of inorganic and metal toxicants.

3.0 Main Content

3.1 Toxic Elements

3.1.1 Ozone

Ozone has several toxic effects; gas inhalation of its at 1ppm by volume causes severe irritation and headache. Ozone irritates the eyes, upper respiratory system, and lungs. Inhalation of ozone can also cause chromosomal damage.

Ozone generates free radicals in tissues; these radicals can cause lipid peroxidation, oxidation of sulfhydry (-SH) groups and other destructive oxidation processes.

3.1.2 White Phosphorus

Elemental white phosphorus enters the body by inhalation, by skin contact, or orally. Phosphorus is a systemic poison; that is, one that is transported through the body to sites remote from its entry site. It causes anaemia, gastrointestinal system dysfunction, bone brittleness, and eye damage. White phosphorus also causes phossy jaw, a condition in which the jawbone deteriorates and becomes fractured.

3.1.3 Elemental Halogen

Elemental fluorine (F_2) is a pale yellow, highly reactive gas that is a strong oxidant. It is a toxic irritant and attacks the skin, eye tissue, and the mucous membranes of the nose and respiratory tract. Chlorine (Cl_2) gas reacts with water to produce a strongly oxidizing solution. This reaction is responsible for some of the damage caused to the moist tissue lining the respiratory tract when the tissue is exposed to chlorine.

Bromine (Br_2) is a volatile, dark red liquid that is toxic when inhaled or ingested. Bromine is also strongly irritating to the mucous tissue of the respiratory tract and eyes and may cause pulmonary edema. Elemental solid iodine (I_2) is irritating to the lungs.

3.2 Heavy Metals

Heavy metals are toxic and their toxicity varies with chemical form. Metallic toxicants in the cell membrane attack the proteins (enzymes) in the body; the sites of attack are the sulphur atoms, the free amino (-N1t_2) and carboxyl (-COOH) groups of the enzymes.

These interactions with proteins and enzymes in cell membranes interfere with the working order of the body system. The combined result of this interaction leads to a variety of health problems ranging from cancer to heart diseases.

3.2.1 Sources of Metallic Toxicants

Toxic metals arise from industries and business. Table 1 below gives a summary of the sources of metallic toxicants.

Table 1: Metallic Toxicants from Industries and Business (Ademoroti, 1996)

Waste generators	**Waste types**
1. Chemical manufacturing 2. Clearing agents and cosmetic manufacturing 3. Metal Manufacturing 4. Leather products manufacturing 5. Furniture and wood manufacturing & refinishing 6. Printing industry 7. Vehicle maintenance shops	1. Strong acids and bases. Spent solvents. Reactive wasters. 2. Heavy metal dusts. Ignitable wasters. Flammable solvents. Strong acids and bases. 3. Pint wastes containing heavy metals. Strong acids and bases. Cyanide wastes sludge containing heavy metals. 4. Waste toluene and benzene 5. Ignitable wastes. Spent solvents. 6. Heavy metal solutions. Waste inks. Spent solvents. Spent electroplating wastes. Inks sludge containing solvents. Strong acids and bases 7. Heavy metal paint wastes. Ignitable wastes. Used lead acid batteries. Spent solvents.

3.2.2 Beryllium

Beryllium (not truly a heavy metal, atomic mass 9.01) is one of the most hazardous toxic elements. The most serious effects of beryllium is berylliosis, a condition manifested by lung fibrosis and phenumonitis. Beryllium is a hyposensitizing agent and exposure to it causes skin granulomas and ulcerated skin.

3.2.3 Mercury

Mercury can exist in three forms: elemental, inorganic and organic forms, and all are toxic. Elemental mercury may be absorbed by biological system as a vapour; it readily passes across the blood-brain barrier into the central nervous system and also to the foetus. .All the forms of mercury will cross the placenta and gain access to the foetus, although elemental mercury and organic mercury show greater uptake.

Organic mercury, such as methyl mercury, is extremely toxic, mainly affecting the central nervous system. In Japan It caused a disease known as Minamata. Mercury in sediments is readily methylated and bioaccumulated by fish for years and it is transmitted to man by food chain. This resulted from industrial effluent containing inorganic mercury contaminating the water of Minamata Bay in Japan. The microorganisms in the sediments at the bottom of the bay biotransformed the inorganic mercury ions into methyl and dimethyl mercury. This form of mercury is lipid soluble and was able to enter the food chain and so become concentrated in fish as a result of their eating small organisms which had absorbed the methyl mercury.

An outbreak of Minamata has occurred in other places like Iraq, Ghana, Niigata in Japan, Pakistan, Canada, among others.

3.2.4 Lead

Lead has been known to be a poisonous compound for centuries, and exposure to it may be through the metal, lead salts and organic lead. Lead causes damage to a variety of organs and also causes significant biochemical effects. The bones, kidneys, testes, gastro-intestinal tract and the nervous system are all damaged by lead. Lead interferes with the synthesis of haem (the iron porphyrin component of haemoglobin) resulting in anaemia. Lead and most of the heavy metals have neurotoxic effects either on the peripheral nervous system (PNS) or on the central nervous system (CNS).

3.2.5 Cadmium

Cadmium is a metal which is widely used in industries in alloys, in plating, in batteries and in the pigments used in inks, paints, plastic, rubber and enamel. Cadmium has many toxic effects, primarily causing kidney and testicular damages. It adversely affects several important enzymes. It can also cause painful osteomalacia (bone disease) and kidney damage. Cadmium causes multi-organ toxicity; some of the toxic effects are due to it being a divalent metal similar to zinc and its ability to bind to subphyla groups.

3.2.6 Arsenic

Arsenic is a metalloid which forms a number of toxic compounds. The toxic till oxide, AS_20_3 is absorbed through the lungs and intestines. Arsenic can affect the blood system and interfere with the porphyrin biosynthesis and affect blood cells. It causes spontaneous abortion and loss of hearing. Arsenic affects the skin causing skin cancer and has also been implicated in lung cancer.

4.0 Conclusion

This unit treats toxic elements, sources of heavy metal toxicants and their health hazards. You should by now be able to mention the toxic effects of ozone, white phosphorus, halogens, beryllium, cadmium, mercury, arsenic and lead.

5.0 Summary

This unit has focused on the effects of inorganic toxic elements and heavy metals. Cadmium, mercury, lead, beryllium and arsenic have many toxic effects especially on the kidney, lung, liver, central nervous system and the brain. The toxic effects of mercury and lead depend on their forms.

6.0 Self-Assessment Exercise

1. List three elements that are invariably toxic in their elemental forms.
2. Mention four metals that are toxic to human being.
3. Discuss how metallic toxicants attack body enzymes to cause illness in man.
4. What do you understand by the term Minamata disease?

7.0 References/Further Reading

Manahan, S. E. (2000). *Environmental Chemistry* (7th ed). London: Lewis Publishers.

Timbrel, J. (2000). *Principles of Biochemical Toxicology.* UK: Taylor & Francis.

Ademoroti. C. M. A. (1996). *Environmental Chemistry and Toxicology*, Benin: Foludex Press Ltd.