NATIONAL OPEN UNIVERSITY OF NIGERIA

SCHOOL OF SCIENCE AND TECHNOLOGY

COURSE CODE: EHS 405

COURSE TITLE: ENVIRONMENTAL TOXICOLOGY

COURSE GUIDE

EHS 405
ENVIRONMENTAL TOXICOLOGY

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INTRODUCTION

Environmental toxicology is a multidisciplinary field of science concerned with the study of the harmful effects of various chemicals in the surrounding on living organisms. A chemical is a substance obtained by a chemical process or that produces a chemical effect on a living system. It is a hybrid pharmacology and pathology aimed at quantifying the health-threatening effects of chemicals on biologic systems in order to detect, treat and possibly prevent any damage. It involves the study of the mechanisms of poisoning or intoxication.

These harmful chemical agents are found at everyplace for diverse purposes. Can you identify them in hospitals, pharmacies, laboratories, schools, markets, industries, farms, air, water, land, at homes, etc.? Environmental toxicology is a specialty that studies chemicals or materials found in man's surrounding which may have adverse chemical effect on him, directly or indirectly.

Environmental toxicology therefore investigates pollutants and their interaction with man. Consequently, it deals with the study of how the substance enters the body to determine its fate (toxicokinetics) and the action of the drug or response of the body to its presence (toxicodynamics).

Thus, Environmental toxicology is relevant to everybody, especially those involved in environmental health and chemical safety.

WHAT YOU WILL LEARN IN THIS COURSE

This is a three-credit unit's course. This course guide explains to you what you should be expecting from this course material. The study of Environmental toxicology equips you with the knowledge and skill to identify harmful or potential harmful materials in man's surroundings.

Environmental toxicology answers questions as what makes a chemical agent harmful or deadly; what measures can you take to prevent the toxicity or lethality of the poisonous material around you; how can a substance in your environment or in your food chain affect your health.

In this course, you will learn all the basic concepts, processes and applications in environmental toxicology. You will understand terms like toxicodynamics, toxicokinetics, toxicity, median dose and so on. You will appreciate the role of toxicology in chemical safety and environmental health.

COURSE AIM

The aim of this course is to provide a good understanding of the concepts of applications of environmental toxicology in ensuring chemical safety and environmental health.

COURSE OBJECTIVES

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

- define and explain the basic concepts of chemical pathology and environmental toxicology
- state the applications of chemical pathology and environmental toxicology
- explain how toxicants have effect on the body
- explain how the human body interacts with the toxicants exposed to it
- identify and classify environmental toxicants
- identify and classify environmental pollutants
- explain the health effects of pollutants
- explain the dose – response concept
- explain the basic concept of pharmaco-environmentology
- enumerate how to evaluate the toxicity of known and unknown substances found in the environment

WORKING THROUGH THIS COURSE

This course has been carefully put together bearing in mind that you might be new to the course. However, efforts have been made to ensure that adequate explanation and illustrations were made to enhance better understanding of the course. You are therefore, advised to spend quality time to study this course and ensure that you attend tutorial sessions where you can ask questions and compare your knowledge with that of your classmates.

COURSE MATERIALS

You will be provided with the following materials:

i. A course guide
ii. Study units

In addition, this course comes with a list of recommended text books which are not compulsory for you to buy or read, but are essential to give you more insight to various topics discussed.

STUDY UNITS

The study units in this course are as follows.

Module 1 Introduction to Chemical Pathology and Environmental Toxicology

Unit 1 Introduction to Chemical Pathology
Unit 2 Introduction to Environmental Toxicology
Unit 3 Practice of Chemical Pathology and Environmental Toxicology

Module 2 Basic Concepts in Toxicant- Body Interactions

Unit 1 Basic Concepts in Toxicodynamics
Unit 2 Basic Concepts in Toxicokinetics
Unit 3 Meaning and Classification of Environmental Toxicants
Unit 4 Toxicity of Environmental Toxicants

Module 3 Basic Toxicology of Environmental Toxicants

Unit 1 Toxicology of Pesticides
Unit 2 Other Organic Toxicants
Unit 3 Toxicology of Heavy Metals
Unit 4 Toxicology of Radioactive Materials
Unit 5 Toxicology of Food Additives and contaminants
Unit 6 Toxicology of Pharmaceuticals and Other Drugs in the Environment

Module 4 Basic Toxicology of Environmental Pollutants

Unit 1 Basic Concepts in Environmental Pollution
Unit 2 Air Pollutants: Concepts, Exposure Pathways, Effects and Pathophysiology
Unit 3 Water Pollutants: Concepts, Exposure Pathways, Effects and Pathophysiology
Unit 4 Land Pollutants: Concepts, Exposure Pathways, Effects and Pathophysiology

Module 5 Basic Toxicity Indices and Applications

Unit 1 Dose-Response Concepts
Unit 2 Concept of Lethal Dose (Concentration)
Unit 3 Probit Analysis
Unit 4 Application of Toxicology in Safety and Environmental Health

Module 1

This module is designed to introduce you to chemical pathology; environmental toxicology and their uses. In Unit 1, you will learn about the evolution, basic definition of concepts and specialised roles of pathology. In Unit 2, you will learn about the basic toxicological concepts/terms; trace the historical development of toxicology and identify specialties in this field. In Unit 3, you will learn about the applications of chemical pathology and environmental toxicology, their equipment and techniques. You will also learn the functions of chemical pathologists and environmental toxicologists.

Module 2

This module is designed to teach you the concept of concentration – response concept. In Unit 1, you will learn the concentration-response concept, the relationship between concentration and effect, and the general mechanisms of toxicants. In Unit 2, you will learn about how the living system interact or affect the drug before its effect. You will understand mechanisms of drug liberation, absorption, distribution, metabolism (biochemical transformation) and excretion any living organism, including man. Unit 3 focuses on how to identify and classify numerous environmental toxicants. Unit 4 explains the concept of toxicity. Toxicity is commonly associated with poisons or toxicants. You will also discuss the various factors that affect toxicity and the mechanisms of chemical interactions that influence toxicity.

Module 3

This module is designed for you to learn about the concepts and harmful effects of toxicants in the environment. Unit 1 deals with the toxicology of pesticides and the mechanism of their toxicity and pathophysiology. In Unit 2, you will learn the toxicology of organic toxicants other than pesticides or pharmaceuticals. In Unit 3, you will learn about heavy metals can produce toxicity when exposed to in sufficient quantities. The substances that produce harmful nuclear particles (radiations) in the environment are the focus of Unit 4. Unit 5 discusses some substances ingested with food and which may have adverse effect on the consumers. In Unit 6, we will discuss about therapeutic and illicit drugs released in the environment which may have harmful effects on man or his environment.

Module 4

This module is designed for you to learn about anthropogenic and natural waste products in the environment which may pose unwanted effects to man and his environment. In Unit 1, you will study the basic concepts and principles that will enable you to understand the study of numerous pollutants found in our environment. Unit 2 discusses the concept of air pollution, pathways and effects of pollutants found in the atmosphere. In Unit 3, you will understand the concept of water pollution and how the pollutants in water are dangerous to man and his environment. Unit 4 explains the concepts, pathways, effects and pathophysiology of harmful substances discharged on our lands/soil.

Module 5

This module will finally equip you for the practical application of your knowledge so far. In Unit 1, you will learn about the *dose* as the most important factor that affects the effect of toxicant. In Unit 2, you will study the concept of lethal dose or concentration as well as toxic dose or concentration which is very important to you as an enforcer of environmental regulations. Unit 3 enumerates how to statistically convert the crude dose-response curves obtained experimentally into a straight line slope to enable you draw reasonable extrapolations and conclusions. In Unit 4, you will be exposed how you can apply the entire knowledge of environmental toxicology to ensure chemical safety; identify and proffer suggestions to the challenges of the discipline in your locality.

TEXT BOOKS/REFERENCES

The following are list of textbooks, journals and website addresses that can be consulted for further reading:

"http://en.wikipedia.org/w/index.php?title=Heavy_metal_(chemistry)&oldid=501640966

Babu, B.V., & S. Karthik (2005). An overview of waste from the nuclear fuel cycle.*Energy Education Science and Technology*, 14, 93–102.

Beychok, Milton R. (1967). *Aqueous Wastes from Petroleum and Petrochemical Plants*. (1st ed.). John Wiley & Sons.

Casarett, L. J. & Doull, J. (Eds). (1975). *Toxicology: The basic science of poisons*. New York: Macmillan Publishing Co. Inc.

Finney, D. J. (1971). *Probit Analysis. (3rd ed.).* Cambridge, UK: Cambridge University Press,.

Foreman, H. (1958). Toxicology of Radioactive Materials. *Annual Review of Medicine Vol. 9*: 369-386.

Gilden, R. C, Huffling, K & Sattler, B (2010). "Pesticides and health risks". J Obstet *Gynecol Neonatal Nurs 39* (1): 103–10.

Goodman, L.S. & Gilman, A. (Eds). (1975). *The Pharmacological Basis of Therapeutics.* (5th ed.). New York: Macmillan Publishing Co. Inc.

Hodgson, E. (2010). "A Textbook of Modern Toxicology". John Wiley and Sons. p.10.

http/en. Wikipedia.com/pesticides. Retrieved on 2012-08-02.

http://en.wikipedia.org/w/index.php?title=Pesticide&oldid=482925552

http://www.clemson.edu/entox/

Iwuji, S. C. (2010). *Basics and Applications of General Pharmacology*. (2010). Owerri, Nigeria:Milestone Publishers.

Katzung, B. G. (2007). *Basic and Clinical Pharmacology*. (10th ed.). U.S.A.Appleton and Lange: Prentice-hall International Inc.

Klaassen, C. D. (2001). Principles of Toxicology and Treatment of Poisoning. In: *Goodman and Gillman's pharmacological Basis of Therapeutics.* (10th ed.). New York: Mc Graw-Hill Co. Inc.

Landis, W. G. & Yu, M. H. (n. d.). *Introduction to Environmental Toxicology*. (3rd ed.).

Robbins, S. (2010). *Robbins and Cotran Pathologic Basis of Disease.* (8th ed.). Philadelphia PA.

Spengler, J. D. & Sexton, K. A.(1983). "Indoor Air Pollution: A Public Health Perspective." *Science (New Series) 221(4605*). pp. 9–17.

ASSESSMENT

There are two components of assessment for this course. They are:

1. Tutor-Marked Assignment (TMA)
2. End of Course Examination

TUTOR-MARKED ASSIGNMENTS (TMAs)

The TMA is the continuous assessment component of your course. It accounts for 30% of the total score. The TMAs will be given to you by your facilitator and you will return it after you have done the assignment.

FINAL EXAMINATION AND GRADING

The end of course examination will be for about three hours and it has a value of 70% of the total course work. The examination will consist of questions which will reflect the type of self-testing, practice exercise and tutor-marked assignment problems you have previously encountered. All area of the course will be assessed.

COURSE MARKING SCHEME

ASSIGNMENT	**MARKS**
Assignments 1-4	Four assignments, best three marks of the four count 10% each of the 30% marks
End of course examination	70% of overall course marks
Total	**100% of course materials**

FACILITATORS/TUTORS AND TUTORIALS

You will be informed of the dates, times and location of the tutorials as well as the name and phone number of your facilitator in your group.

Your facilitator will mark and comment on your assignments. You are expected to submit your TMAs before the scheduled date (at least two working days required)

Contact your facilitator when you:

- do not understand any part of the study areas
- have difficulty with self tests
- have a question or problem with an assignment or with the grading of an assignment.

You should endeavour to attend the tutorials. This is the only chance to have face to face contact with the facilitator. To gain more benefit from course tutorials prepare a question list before attending them. You will learn a lot from participating actively in discussions.

SUMMARY

This course intends to provide you with the knowledge of environmental toxicology and its application in the control or minimisation of exposure to harmful substances or materials within human surroundings.

At the end of this course, you will be able to answer the following questions:

- Differentiate the following terms/concepts:
  a. Health and disease
  b. Prognosis and Diagnosis
  c. Anatomical pathology and Chemical Pathology
  d. Clinical signs and symptoms.
- Differentiate the following pairs:
  a. Ecotoxicology and environmental toxicology
  b. Clinical toxicology and forensic toxicology
  c. Clinical pathologist and toxicologist
  d. Regulatory toxicology and experimental toxicology
  e. Toxicodynamics and toxicokinetics.
- a. Explain the term ‘toxicity’.
  b. Differentiate drug side effect from drug toxicity.
  c. List five outcomes of exposure to environmental toxicants.
- a. What are pesticides?
  b. Classify pesticides based on their target organisms.
  c. What are heavy metals?
  d. Enumerate four health importance of heavy metal.
  e. List five heavy metals in Nigeria.
  f. What are chelators?
  g. What is radiation?
  h. How does radiation cause harm to man?
  i. List four possible effects of radiations.

j. Define environmental pollution
k. Define environmental pollutant
l. Give causes of pollution
m. Identify four pollutants in the environment
n. Give two units of measuring dose.
o. Define dose
p. Give three types of doses
q. Explain dose-response curve
r. What is probit analysis?
s. Explain the principle of probit analysis
t. Who can apply environmental toxicology?
u. Identify two applications of toxicology for environment health.
v. Outline four challenges facing environmental toxicology in Nigeria.

We wish you success in this course and hope that you will apply the knowledge gained to ensure chemical safety and promote environmental health. Best wishes!

MAIN COURSE

CONTENTS PAGE

MODULE 1 INTRODUCTION TO CHEMICAL PATHOLOGY AND ENVIRONMENTAL TOXICOLOGY

UNIT 1 INTRODUCTION TO CHEMICAL PATHOLOGY

CONTENTS

1.0 INTRODUCTION

So far, you have taken courses in Anatomy and Physiology; can you recall the physical and chemical characteristics of the normal human body? You are advised to revise the homeostatic mechanisms of an healthy individual. This knowledge is a prerequisite for the understanding of various changes that occur in a disease process.

Pathology provides a logical means of relating the knowledge of normal structure and functions to abnormal structure and function as seen in a diseased human body. To understand and diagnose diseases in the living patient or in the postpartum (dead) body, therefore, you need a sound knowledge of pathology.

Clinical chemistry (also known as chemical pathology and clinical biochemistry) is the area of pathology that is generally concerned with analysis of bodily fluids. It also studies the disease process that results from or to changes in the chemistry of the human body.
In this Unit, we will discuss the evolution, basic definition of concepts and specialised roles of pathology.

2.0 OBJECTIVES

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

- define basic concepts or terms used in chemical pathology
- mention the major historical landmarks of pathology
- state the various specialisations of chemical pathology in health care.

3.0 MAIN CONTENT

3.1 Basic Concepts and Definitions in Chemical Pathology

Chemical pathology addresses four components of disease: cause/aetiology, mechanisms of development (pathogenesis), structural alterations of cells (morphologic changes), and the consequences of changes (clinical manifestations) (Robbins, 2010).

At this point, it is pertinent to define the various concepts or terms used in chemical pathology so as to facilitate your understanding:

- **Chemical** is any substance obtained by a chemical process or producing a chemical effect on a living system.
- **Pathology** is a scientific study of the molecular, cellular, tissue, or organ system response to injurious agents or adverse influences.
- **Enzyme** is a substance produced by living cells which aids in speeding up the process of chemical reactions in the body.
- **Disease** is a state of critical departure from the normal with clinical manifestations of signs or symptoms. It is a state in which an individual exhibits an anatomical, physiological, and psychological or biochemical deviation from the normal.
- **Aetiology** is a study of the cause of a disease. An etiologic agent is the factor (bacterium, virus, etc.) responsible for lesions or a disease state.
- **Predisposing causes of diseases** are those factors which make an individual more susceptible to a disease (damp weather, poor ventilation, etc.).
- **Exciting causes of disease** are those factors which are directly responsible for a disease **(bacteria, viruses, hypoxia, chemical agents, etc**.).
- **Clinical sign** is any functional evidence of disease which can be determined objectively or by the observer (swelling, salivation, stunted growth, obese, paleness). It is observable by both the patient and others.

- **Clinical symptom** is any functional evidence of disease that can be determined subjectively or by the patient only (feeling, stomach ache, head ache, confusion, dizziness, etc.)
- **Prognosis** is a probably outcome of a disease in a living individual. It is the clinician's estimate of the severity and possible result of a disease.
- **Diagnosis** is the exact determination of the nature or kind of a disease expressed. Definitive diagnosis is made on the basis of the specific disease entity involved while a clinical diagnosis is made on the basis of clinical signs observed in the patient.
- P**athogenesis** refers to the progressive development (sequence of events) of a disease from the time it is initiated to its final stage in recovery or death.
- **Serum** is the part of the blood that is left after blood has been allowed to clot and the blood cells have been removed, it is often watery and yellow in colour.
- **Plasma** is also the supernatant (that part of the blood left above the sediment) after centrifuging uncoagulated whole blood.

3.2 History of Chemical Pathology

The history of chemical pathology can be traced back to antiquity when people began examining bodies. The oldest civilised people (Chinese, Indians, and Egyptians) were under the impression that disease occurred when demons or evil spirits were displeased with an individual. The medicine men were concerned with appeasing these evil spirits.

The Egyptians began to influence medicine around 4000 B.C. The Greek culture had a profound effect on the scientific approach to medicine. Greek physicians elucidated the principles of exact and careful clinical observations. The word pathology is from ancient Greek, *pathos*, "feeling, suffering"; and, *logia*, "the study of". However, they did not deal with the nature or the changes that occurred subsequent to disease.

Pathology began to develop as a subject during the 19th century through teachers and physicians that studied pathology. They referred to it as “pathological anatomy” or “morbid anatomy.” However, pathology as a field of medicine was not recognised until the late 19th and early 20th centuries. In the 19th century, physicians realised that disease-causing pathogens, germs, created themselves and that symptoms were not the vital characteristics of a disease. Pathology has its roots deeply implanted in medical history.

In order to determine the causes of diseases, medical experts used the most common and widely accepted assumptions or symptoms of their times. This is true for those in the past and today (King, 1991 and Machevsky, 2004).

By the late 1920s to early 1930s, pathology was deemed as a medical specialty (Rothstein, 1979). During the following years, the decision to split pathology in to sub-specialties arose. Today, anatomical, clinical, molecular, plant, forensic, oral, veterinary, dermatopathology, hematopathology, and pathology exist as medical specialties (Long, 1965).

The chemical pathology discipline originated in the late 19th century with the use of simple chemical tests for various components of blood and urine. Subsequent to this, other techniques were applied including the use and measurement of enzyme activities, spectrophotometry, electrophoresis and immunoassay.

SELF-ASSESSMENT EXERCISE

i. In six sentences, summarise the evolution of chemical pathology.
ii. List three techniques used in chemical pathology.

3.3 Specialisations of Chemical Pathology in Health Care

Chemical pathology is the study of chemical changes in the fluids and tissues of the body as the result of disease. This branch of pathology is merely a portion of clinical pathology. Chemical pathology is one of the two major divisions of pathology, the other being anatomical pathology. Often, pathologists practice both anatomical and clinical pathology, a combination sometimes known as general pathology.

Specialties of chemical pathology include:

1. General or routine chemistry.
2. Special chemistry - elaborate techniques such as electrophoresis.
3. Clinical endocrinology - the study of hormones, and diagnosis of endocrine disorders.
4. Therapeutic Drug Monitoring - measurement of therapeutic medications blood levels to optimise dosage.
5. Urinalysis - chemical analysis of urine for a wide array of diseases, along with other fluids such as CSF and effusions.
6. Faecal analysis - mostly for detection of gastrointestinal disorders.

4.0 CONCLUSION

In this unit, you have been introduced to the basics of chemical pathology, including definition of concepts/terms, historical development and specialisations of chemical pathology.

This unit should enable you to understand what chemical pathology is, in relation to other specialisations of pathology. It also made it easier for you to comprehend other literatures in chemical pathology. You now know when to refer disease cases to chemical pathologists.

In the next unit, you will be introduced to an aspect of pathology and pharmacology known as Environmental toxicology which is very important for you to ensure chemical safety.

5.0 SUMMARY

This unit contains an introduction to chemical pathology. It consists of three major subtopics:

- Definitions of basic concepts/terms, such as pathology, chemical pathology, anatomical pathology, disease, aetiology, pathogenesis, prognosis, enzyme, etc.
- Historical landmarks in the genesis of the concept and practice of chemical pathology. Chinese, Indians, Egyptians play notable roles in the development of modern pathology
- Specialties in the field of chemical pathology. These include:
  i. General or routine chemistry
  ii. Special chemistry - elaborate techniques such as electrophoresis.
  iii. Clinical endocrinology - the study of hormones, and diagnosis of endocrine disorders.
  iv. Therapeutic Drug Monitoring - measurement of therapeutic medications blood levels to optimise dosage.
  v. Urinalysis - chemical analysis of urine for a wide array of diseases, along with other fluids such as CSF and effusions.
  vi. Faecal analysis - mostly for detection of gastrointestinal disorders.

6.0 TUTOR-MARKED ASSIGNMENT

1. Define the following terms:
   a. chemical
   b. pathology
   c. chemical pathology
   d. pathogenesis.

2. Differentiate the following terms/ concepts:
   e. health and disease
   f. prognosis and diagnosis
   g. anatomical pathology and chemical pathology
   h. clinical signs and symptoms.
3. a. List two common samples and two common techniques used in chemical pathology.
   b. Enumerate four specialties in chemical pathology.

7.0 REFERENCES/FURTHER READING

Iwuji, S. C. (2010). *Basics and Applications of General Pharmacology*. Owerri, Nigeria: Milestone Publishers.

Lester (1991). *Transformations in American Medicine: From Benjamin Rush to William Osler*. Baltimore: Johns Hopkins

Long, E. (1965). *History of Pathology*. New York: Dover King.

Machevsky, A. (2004). Evidence-Based Medicine, Medical Decision Analysis, and Pathology. *Human Pathology*, 35 (10): 1179-88.

Robbins, S. (2010). *Robbins and Cotran Pathologic Basis of Disease.* (8th ed.). Philadelphia PA.

Rothstein, W. G. (1979). Pathology: The Evolution of a Specialty in American Medicine. *Medical Care 17* (10): 975.

Runnels, Monlux & Monlux. (n.d.). *Principles of Veterinary Pathology*. (7th ed.). pp. 6-21.

UNIT 2 INTRODUCTION TO ENVIRONMENTAL TOXICOLOGY

CONTENTS

1.0 INTRODUCTION

In Unit 1, you were introduced to chemical pathology as an aspect of pathology that studies the chemical changes in a diseased body. Chemicals are known to bring about changes in the living system.

Poisoning emergencies or deaths occur when people ingest certain mushrooms or are exposed to certain gases or smoke in their surroundings. Secondly, have you thought of what causes your reaction when you spray an aerosol insecticide in your room? These are the adverse effects of chemicals.

Environmental toxicology is a multidisciplinary field of science concerned with the study of the harmful effects of various chemicals in the surrounding on living organisms. In this unit, we will define the basic toxicological concepts / terms; trace the historical development of toxicology and identify specialties in this field.

2.0 OBJECTIVES

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

- define basic toxicological terms or concepts
- trace the historical development of environmental toxicology
- identify the divisions of toxicology.

3.0 MAIN CONTENT

3.1 Concept, Definitions and Abbreviations in Toxicology

3.1.1 Concept of Environmental Toxicology

As defined in Unit 1, a chemical is a substance obtained by a chemical process or substance that produces a chemical effect on a living system. The field of science that studies the nature and biological effects of chemicals (also referred to as drugs) is known as Pharmacology. These effects could be desirable/useful or undesirable/harmful.

While medical pharmacology tends to concentrate on useful (medicinal) chemicals, toxicology (another major branch of pharmacology) aims at quantifying the health-threatening effects of chemicals on biological systems in order to detect, treat and possibly prevent any damage. It involves the study of the mechanisms of poisoning or intoxication.

These harmful chemical agents are found at everyplace for diverse purposes. Can you identify them in hospitals, pharmacies, laboratories, schools, markets, industries, farms, air, water, land, at homes, etc.? Consequently, there are sub divisions of Pharmacology that study the various chemicals based on the place the chemicals are found or on the importance (or purpose) of the chemicals. These specialties in toxicology include clinical toxicology, forensic toxicology, industrial toxicology, ecotoxicology, environmental toxicology, toxinology and phytotoxicology.

Environmental toxicology is that aspect of pharmacology that studies toxicants (poisons) found within man's surroundings, including pollutants and their interactions with man.

3.1.2 Definitions in Environmental Toxicology

The following concepts or terms used in toxicology are defined to enable you comprehend literatures in toxicology; these include:

Acceptable Daily Intake (ADI): This is the daily intake of a quantity of chemical which during an entire lifetime appears to be without appreciable risk on the basis of all known facts at the time.

Acute exposure: this is a single exposure or multiple exposures occurring over one or two days.

Acute or immediate toxicity: this is the rapid appearance of toxic effects just after acute exposure.

Additive effect: This occurs when the biological effect of a mixture of poisons is the summation of the effects of the individual chemicals.

Adjuvant: This is a substance added to another substance to stabilise the active chemical or aid absorption.

Aerosol: This is composed of solid or liquid particles of microscopic size dispersed in a gaseous medium.

Agonist: is a drug that binds to a receptor and cause a physiologic response.

Antagonist: is a drug that binds to a receptor and blocks a response, or prevents other drugs from binding to the receptor.

Bioavailability: is the rate and extent of absorption of a drug (toxicant) from a concentration as estimated in its systemic circulation.

Biotransformation: is the chemical changes a substance undergo in the body, as may occur by the action of an enzyme on a substance.

Carcinogen: any agent that can initiate or promote the development of malignant or potentially malignant tumours, malignant neoplastic proliferation of cells or that possesses such material is called carcinogen.

Carcinogenicity: is the ability to cause or stimulate cancer.

Chemical asphyxiant: is a substance that has the ability the deprive tissue of oxygen or render the body incapable of utilising an adequate oxygen supply.

Chemical safety: is a practical certainty that injury will not result from use of a chemical under a specified condition of quantity and manner of use.

Chronic exposure: is multiple exposures continuing over a longer period of time (more than three months).

Chronic toxicity: is the manifestation of the toxic effects after a prolonged or chronic exposure to a toxicant.

Clearance: is the measure of the ability of the body to eliminate a drug.

Clinical toxicologist: carry out toxicity testing (as part of clinical trials) in clinics or hospital.

Drug is any substance that brings about a change in biologic function; mainly through its chemical actions (fewer drugs have physical effects).

Environment includes all the surroundings of an individual organism (as man), particularly the air, land, water and all plants and human beings or animals living therein and the interrelationships, which exist among these or any of them.

Environmental health: is the control of all the environmental influences on human health. It is a branch of Public Health concerned with controlling health risks (toxicants) associated with the physical environment.

Environmental toxicologist carries out toxicity testing in environmental conditions.

Hazardous chemical (Substance), any element, chemical compound, or mixture of elements or compounds, which is a physical hazard or a health hazard

***In vitro* testing:** a scientific laboratory study that involves the use of a part or sample of the animal or human body separated from the entire system.

***In vivo* testing:** a scientific investigation involving the use of whole animal or human body.

Local toxicity: is the toxic effect of the drug at site of first contact between the biologic system and the toxicant.

Low-level, long-term exposure: is a continuous exposure to small concentrations of chemicals over a long period of time.

Maximum Atmospheric Concentration or Maximum Allowance Concentration (MAC): is the concentration of a toxicant in air (or water) below which deleterious effects are insignificant for eight hours a day, five days a week over a working lifetime.

Maximum Permissible Level (MPL): is the limit of radiation or isotope exposure below which one is unlikely to see serious deleterious effect over a lifetime exposure.

Median Lethal Dose (LD50): is the dose of a toxicant at which 50% of the population of same specie dies within a specified time and under the specified conditions of the experiment.

Median Toxic Dose (TD50): is the dose of a toxicant which causes 50% toxic response point in a specified population and conditions.

Pharmacoenvironmentology: is the study of the interaction between drugs and the environment in terms of benefit and risk or it is the study of the effects of drugs on the environment in order to safeguard our environment. The study allows a comprehensive risk assessment of pharmaceuticals on our environment.

Poisons or toxicants: are drugs that produce harmful effects when given at a certain dose or circumstance.

Pollutant: this is a substance that occurs in the environment, at least in part as a result of human activity, and which has a deleterious effect on living organisms.

Risk is the expected frequency of the occurrence of an undesirable effect arising from exposure to a chemical or physical agent.

Route of exposure is the route of entry for chemicals into the body.

Safety officer: this is a personnel that instigates or enforces a code of practice in the conduct of safety for the work place.

Sub acute toxicity: this is lesser intense than acute effect and is produced after repeated exposure over a short period of time (within 1 month).

Sub chronic toxicity: this is produced after repeated exposure over a period of 1 -3 months.

Systemic toxicity: is the toxic effect that required the absorption and distribution of the toxicant to a part distant from site of entry where effects are produced.

Teratogenicity: is the ability to cause toxic effects to the unborn offspring.

Threshold Limit Value (TLV): is the maximum concentration of chemical the body can tolerate without having its toxic effect.

Threshold Limit Value –Short Term Exposure Limit (TLV-STEL): is the maximum concentration that should not be exceeded at any time during a 15-minute exposure period.

Threshold Limit Value-Ceiling (TLV-C): is the concentration of chemical that should not be exceeded even instantaneously.

Threshold Limits Value–Time -Weighed Average (TLV-TWA): is the concentration for a normal 8-hour workday or 40-hour workweek to which workers may be repeatedly exposed without adverse effect.

Toxicity: this is the capacity of a chemical agent to cause injury.

Toxicodynamics: these involve the study of the injurious effects of toxins or toxicants; toxic (overdoses) doses of therapeutic agents and their metabolites on the vital functions of cell or biosphere.

Toxicogenomics: this is a new field of chemical safety assessment of biological effects using technologies such as DNA microarrays or high powered NMR and protein expression analysis. It is meant to aid scientists in understanding the molecular and cellular effects of chemicals in biological systems

Toxicokinetics: is a division of toxicology that studies the absorption, distribution, excretion and biotransformation of poisons, toxic doses of therapeutic agents or the metabolites.

Toxicology, an aspect of pharmacology, is the scientific study of substances with harmful effects on the living systems, from individual cells to complex ecosystems.

Toxicovigilance: this is an aspect of pharmacovigilance which ensures that relevant information on all hazardous substances are provided to prevent the unwanted effects in the use of these substances and thereby contribute to public health and safety.

Toxins: these are poisons of biologic origin, that is, from plants or animals.

Untoward effect: this is a side effect that is harmful to the patient.

Xenobiotics: these are substances absorbed across the lungs, skin or ingested intentionally or accidentally.

3.1.3 Some Abbreviations used in Toxicology

Ad lib	taking a drug freely as desired or required.
Amp.	(Ampoule) means a vial or sealed small bulbous glass vessel that is used to hold drug or diluent for injection
b.d. or *bid*	two times daily
cc	cubic centimeter
d/7	administer the drug for **d** day(s)
g, Kg	gram, kilogram
I.D	(intra dermal) means injection into the skin, below epidermis
I.M.	(intramuscular) means injection of the drug into the muscle
I.V.	(intravenous) means injection of the drug into the veins.
Inj.	Injection
m/12	administer the drug for **m** month (s)
N.P.O.	not per oral
o.h.	every hour
P.O.	(per oral or mouth) means oral administration of drug
P.R.	(per rectal) means administration of drug through the rectum.
q.o.d	every other day
qds/qid	four times daily
S.C.	(Subcutaneous) means injection of drug into the
Stat	first or immediate dose
tds/*tid*	three times daily
w/52	administer the drug for **w** week (s)

3.2 Historical Development of Environmental Toxicology

The toxic effects of substances from certain animals and plants were known to the earliest men who used such knowledge for hunting, warfare or to eliminate undesirable members of the ancient society. Medical records in Egypt dated 1500 B.C. contained such information extending many centuries back. Some identified poisons were hemlock, aconite, opium, lead, copper and antimony. Hippocrates (400 B.C) recognized more poisons and wrote primitive principles of toxicology in the form of attempts to control absorption of the toxic substances in therapy and in overdose. The first professional treatment of poisons started with Theophrastus (350 B.C.), a student of Aristotle (400 B.C.).

Toxicology is from the Greek words – *toxicos* "poisonous" and *logos* "study". Pedanius Dioscorides (A.D. 50), a Greek physician in the court of the Roman emperor Nero, made the first attempt to classify plants according to their toxic and therapeutic effect (Hodgson, 2006). Ibn Wahshiya wrote the Book on Poisons in the 9th or 10th century (Levey, 1966).

Mathieu Orfila is considered to be the modern father of toxicology, having given the subject its first formal treatment in 1813 in his *Traité des poisons*, also called Toxicologie générale.

Theophrastus Phillipus Auroleus Bombastus von Hohenheim (1493–1541) (also referred to as Paracelsus) is also considered "the father" of toxicology. He is credited with the classic toxicology maxim, which translates as, "All things are poison and nothing is without poison; only the dose makes a thing not a poison." This is often condensed to: "The dose makes the poison".

Rachel Carson is considered the mother of environmental toxicology, as she made it a distinct field within toxicology in 1962 with the publication of her book *Silent Spring*, which covered the effects of uncontrolled pesticide use.

SELF-ASSESSMENT EXERCISE

i. What was the contribution of Rachel Carson to mankind?
ii. Enumerate the uses of poison in the history of man.
iii. Explain the historic relationship that exists between dosage and poison.

3.3 Divisions of Environmental Toxicology

3.3.1 Divisions Based on the Objective of Study

There are five recognised divisions of study:

a. Descriptive Toxicology

This is the area of study where toxicity tests are performed **to obtain information** that can be used to evaluate the risk which exposure to a chemical poses to human beings and to the biological environment. Apart from clinical toxicology that describes human or veterinary poisoning, environmental toxicology goes beyond. An example is the toxic effect of a herbicide on the earthworms.

b. Mechanistic Toxicology

This is the area of toxicology that determines **how chemical agents exert harmful effects** on living organisms. Toxicologists try to unveil the mechanism of action (toxicodynamics) of drugs in the living systems. For instance, experimental study to compare the actions of an unknown drug with the actions of a pharmacologically known drug, e.g. acetylcholine. Inferences drawn from such experiment can determine how the unknown drug causes toxic effects and factors that may influence its toxicity.

c. Regulatory Toxicology

This is an area of toxicology that **judges whether or not a chemical agent has low enough risk** to justify making it available for its intended purpose. This is applied by drug regulatory agencies like NAFDAC and EPAs. Industrial toxicologists carry out regulatory studies in the corporation to ensure that products, including wastes meet standards set by relevant local or international control agencies.

d. Experimental Toxicology

This is a study carried out under controlled, monitored conditions meant **to reveal, understand and extrapolate** the toxicodynamics and toxicokinetics in normal natural circumstances or environments.

e. Theoretical Toxicology

This is a scientific study meant to **propose arguable statements (theories) on the toxicity** of chemicals and chemical safety. Presently, computer can be used to analyse data fed to it to predict toxicological implications. It usually proceeds experimental prove.

3.3.2 Divisions Based on the Scope of Study

We have the following:

Environmental toxicology: This is the study of poisons in man's surroundings, including pollutants and their interaction with living organisms.

Sub-divisions of environmental toxicology include atmospheric toxicology, hydro toxicology or marine toxicology, ecotoxicology, industrial toxicology, toxinology, phytotoxicology and forensic toxicology,

a. **Ecotoxicology:** This is the study of substances on earth and their adverse impact on the biosphere. Ecotoxicology is concerned with studying the harmful effects of toxicants at the population and ecosystem levels.

Ecotoxicology differs from environmental toxicology because its studies involve effects of toxicants on all levels of biological organisation from the molecular to whole communities and ecosystems, whereas environmental toxicology focuses upon effects at the level of the individual and within.

b. **Marine toxicology:** is the study of pollutants and other chemical products in large waters and their effects on the living organisms therein.

c. **Forensic toxicology:** This is the study of poisoning cases with legal involvement.

d. **Industrial toxicology:** This is a toxicological application in the industry to ensure chemical safety.

e. **Toxinology:** This is the study of organic poisons produced by animals and plants.

f. **Phytotoxicology:** This is the study of the adverse effects of phytochemicals (plant extracts).

4.0 CONCLUSION

So far, we have explained the concept of environmental toxicology with definitions and abbreviations. Environmental toxicology is evolved from toxicology and shared most terms and abbreviations used in toxicology. The specialisations of environmental toxicology were based on the objectives and scope of study. We distinguished terms like clinical toxicology and ecotoxicology from environmental. The numerous definitions in this unit will make it easier for the understanding of literatures in environment toxicology applied in chemical safety for professionals in environmental health.

5.0 SUMMARY

This unit introduced you to environmental toxicology, it explained the concepts and also defined numerous terms used in the field of toxicology. Such terms include toxicology, ecotoxicology, environmental toxicology, pollutant, poison, carcinogen, forensic toxicology.

The historical development of environmental toxicology was traced from the ancient times when some poisons were used lawfully for hunting. This unit also identified the various fields of specialisation in environmental toxicology, such as ecotoxicology, marine toxicology and atmospheric toxicology.

In the next unit, you will learn how chemical pathology and environmental toxicology are applied in healthcare. It is hopeful that you will comprehend it well.

6.0 TUTOR-MARKED ASSIGNMENT

1. Define the following terms:
   a. toxicology
   b. environmental toxicology
   c. carcinogenicity
   d. *In vivo* study
   e. bioavailability.

2. Differentiate the following pairs:
   f. ecotoxicology and environmental toxicology
   g. clinical toxicology and forensic toxicology
   h. clinical pathologist and toxicologist
   i. regulatory toxicology and experimental toxicology.

7.0 REFERENCES/FURTHER READING

"Existing Non-animal Alternatives". Source: AltTox.org. 8 September 2011. http://alttox.org/ttrc/existing-alternatives/.

Cockerham, L. G. & Shane, B. S. (n.d.). *Basic Environmental Toxicology*.

Crosby, D. G. (n. d.). *Environmental Toxicology and Chemistry*.

Hamadeh, H. K, Amin, R. P, Paules, R.S & Afshari, C. A. (2002). An Overview of Toxicogenomics. *Curr. Issues Mol. Biol*.,4: 45-56.

Hodgson, E. (2010). *A Textbook of Modern Toxicology*. John Wiley and Sons. p.10.

http://www.biology.sfu.ca/degree/graduate/met

http://www.clemson.edu/entox/

Hughes, W. (n. d.). *Essentials of Environmental Toxicology*.

Iwuji, S. C. (2010). *Basics and Applications of General Pharmacology.* Owerri, Nigeria: Milestone Publishers.

Landis, W. G. & Yu, M. H. *Introduction to Environmental Toxicology.* (3rd ed.).

Levey, M. (1966). *Medieval Arabic Toxicology: The Book on Poisons of ibn Wahshiya and its Relation to Early Native American and Greek Texts.*

Newman, M. C. & Clements, W. H. (n. d.). *Ecotoxicology: A Comprehensive Treatment.*

Ottoboni, M. Alice (1991). *The dose makes the poison : a plain-language guide to toxicology.* (2nd ed.). New York, N.Y: Van Nostrand Reinhold.

William, C. Krieger (2001). "Paracelsus Dose Response". *Handbook of Pesticide Toxicology.*/Academic Press Oct01

U.S. National Library of Medicine (n. d.). *Biography of Mathieu Joseph Bonaventure Orfila (1787–1853).*

Wennig, R. (2009). "Back to the roots of modern analytical toxicology: Jean Servais Stas and the Bocarmé murder case". *Drug Test Anal (England)* 1 (4): 153–155. DOI:10.1002/dta.32. PMID 20355192.

Williams, P. L., R. C. James, R. C. & Roberts, S. M. (n. d.). *Principles of Toxicology-Environmental and Industrial Applications.* (2nd ed.).

Wright, D. A. & Welbourn, P. Environmental Toxicology.

Zakrzewski, S. F. (n. d.). *Environmental Toxicology.*

UNIT 3 PRACTICE OF CHEMICAL PATHOLOGY AND ENVIRONMENTAL TOXICOLOGY

CONTENTS

1.0 INTRODUCTION

In Units 1 and 2, you were introduced to chemical pathology and environmental toxicology. There, you learnt the basic concept and definitions of terms in these disciplines.

In this unit, we will explain the applications of chemical pathology and environmental toxicology, their equipment and techniques. You will learn the functions of chemical pathologists and environmental toxicologists. Their practices are very important in healthcare.

2.0 OBJECTIVES

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

- define the functions of a chemical pathologist
- define the functions of a environmental toxicologist
- describe some basic techniques applied in the fields.

3.0 MAIN CONTENT

3.1 Functions of a Chemical Pathologist

Clinical pathology is a medical specialty that is concerned with the diagnosis of disease based on the laboratory analysis of bodily fluids such as blood and urine, and tissues using the tools of chemistry, microbiology, haematology and molecular pathology. Clinical pathologists work in close collaboration with medical technologists, hospital administrations, and referring physicians to ensure the accuracy and optimal utilisation of laboratory testing.

A chemical pathologist is primarily concerned with the analysis of bodily fluids such as blood and urine. Chemical pathologists screen these fluids using a myriad of techniques including the measurement of enzyme levels, immunoassay, electrophoresis, and spectrophotometry. However, today's laboratories are largely automated and as such utilise assays that are closely monitored in order to assure quality control. These laboratories are large enough to accept as many as 700 samples and it is the duty of the chemical pathologist to administer to these tests and render a diagnosis based upon the results.

All biochemical tests fall under the discipline of the chemical pathologist. These may be performed on all types of bodily fluids, but are usually done on blood, plasma or serum.

Chemical pathologists very often, administer to the health of patients with diabetes, high blood pressure, osteoporosis, high cholesterol and rare inherited metabolic diseases. Many chemical pathologists are also involved in research and in teaching medicine to other healthcare specialists.

Chemical pathologists also are instrumental in interpreting test results to patients and other physicians as well as managing laboratory staff. As a result of the high degree of automation in today's laboratories, many chemical pathologists have moved into information technology and informatics studies.

3.1.1 Sub-Specialities of Chemical Pathology and Tests Carried Out

- General or routine chemistry - commonly ordered blood chemistries (e.g., liver and kidney function tests).
- Special chemistry - elaborate techniques such as electrophoresis manual testing methods.

- Clinical endocrinology - the study of hormones, and diagnosis of endocrine disorders.
- Toxicology - the study of effects of drugs, especially on the body fluids.
- Therapeutic Drug Monitoring - measurement of therapeutic medications blood levels to optimise dosage.
- Urinalysis - chemical analysis of urine for a wide array of diseases, along with other fluids such as CSF and effusions
- Faecal analysis - mostly for detection of gastrointestinal disorders.

3.1.2 Common Clinical Chemistry Tests include:

Common clinical chemistry tests include:

1. Electrolytes (Sodium, Potassium. Chloride. Bicarbonate)
2. Renal (Kidney) Function Tests (Creatinine, Blood urea nitrogen)
3. Liver Function Tests (Total protein (serum) , Albumin, Globulins, A/G ratio (albumin-globulin), Protein electrophoresis,Urine protein, Bilirubin, Aspartate transaminase (AST), Alanine transaminase (ALT), Gamma-glutamyl transpeptidase (GGT), Alkaline phosphatase (ALP)
4. Cardiac Markers (Troponin, Myoglobin, CK-MB, B-type natriuretic peptide (BNP))
5. Minerals (Calcium, Magnesium, Phosphate, Potassium)
6. Blood Disorders (Iron, Transferrin, TIBC, Vitamin B12, Folic acid)
7. Miscellaneous (Glucose, C-reactive protein, Glycated haemoglobin (HbA1c), Uric acid, Arterial blood gases ($[H^+], P_{CO_2}, P_{O_2}$), Adrenocorticotropic hormone (ACTH), Toxicological screening and forensic toxicology (drugs and toxins), Neuron-specific enolase (NSE), faecal occult blood test (FOBT)).

3.2 Functions of Toxicologist

An environmental toxicologist is a scientist who uses a variety of disciplines, including molecular biology, biochemistry, environmental chemistry, geochemistry, social sciences, computer science, etc. to determine the fate, effects, and risks of toxicants on the environment, wildlife, and human health.

In order to research and assess the effects of chemicals, toxicologists perform carefully designed studies and experiments. These experiments help to identify the specific amount of a chemical that may cause harm

and potential risks of being near or using products that contain certain chemicals.

Research projects of environmental toxicologists may assess the effects of toxic pollutants on the environment. While the basic duties of toxicologists are to determine the effects of chemicals on organisms and their surroundings, specific job duties may vary based on industry and employment. For example, forensic toxicologists may look for toxic substances in a crime scene, whereas aquatic toxicologists may analyse the toxicity level of wastewater.

3.2.1 Specimens for Toxicological Examination

The tissue samples collected for toxicological examination are dictated by the toxic agent suspected. If poisoning of undetermined origin is suspected, adequate amounts of stomach contents, urine, blood, liver and kidney should be collected during the necropsy. Each specimen is placed in a separate clean container and frozen until analysed (you do not use a preservative such as formalin, etc.).

3.2.2 Chemical Injuries

The list of chemical that may produce cell/tissue injury defies compilation. Simple chemicals such as glucose or salt in hypertonic concentrations may cause cell injury by deranging the fluid and electrolyte homeostasis of cells; even oxygen in high concentrations is severely toxic. On the other hand, the levels of toxicity of certain substances are so high that they are known as poisons and trace amounts (arsenic, cyanide, mercury salts) may destroy a sufficient number of cells within minutes or hours to cause death. Under certain conditions, toxic materials may be formed within the body and subsequently cause cell damage. Severe burns, uraemia, and gangrene may be associated with endogenous poisons.

3.3 Some Equipment and Techniques in the Fields

3.3.1 Spectrophotometry

Fig. 1.1: Spectrophotometer

Spectrophotometry is the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength. Spectrophotometry involves the use of a spectrophotometer. A spectrophotometer is a photometer that can measure intensity as a function of the light source wavelength. Important features of spectrophotometers are spectral bandwidth and linear range of absorption or reflectance measurement.

A spectrophotometer is commonly used for the measurement of transmittance or reflectance of solutions, transparent or opaque solids, such as polished glass, or gases. The amount of light that passes through the solution is indicative of the concentration of certain chemicals that do not allow light to pass through.

It is used in forensic examination, as well in laboratories for the study of chemical substances. Ultimately, a spectrophotometer is able to determine, depending on the control or calibration, what substances are present in a target and exactly how much through calculations of observed wavelengths.

Design

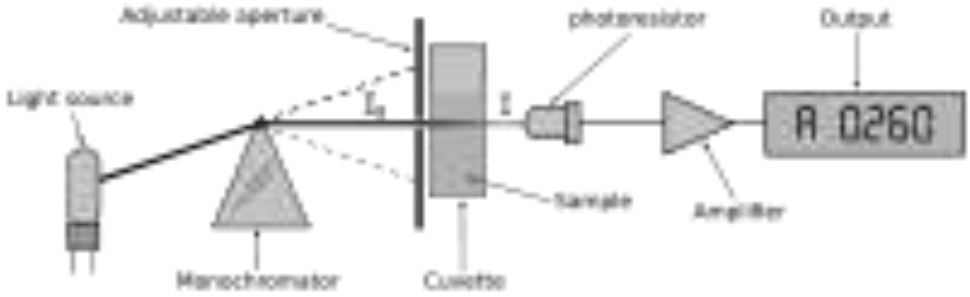


Fig. 1.2: Single Beam Spectrophotometer

In short, the sequence of events in a modern spectrophotometer is as follows:

1. The light source is imaged upon the sample
2. A fraction of the light is transmitted or reflected from the sample
3. The light from the sample is imaged upon the entrance slit of the monochromator
4. The monochromator separates the wavelengths of light and focuses each of them onto the photodetector sequentially.

3.3.2 Electrophoresis

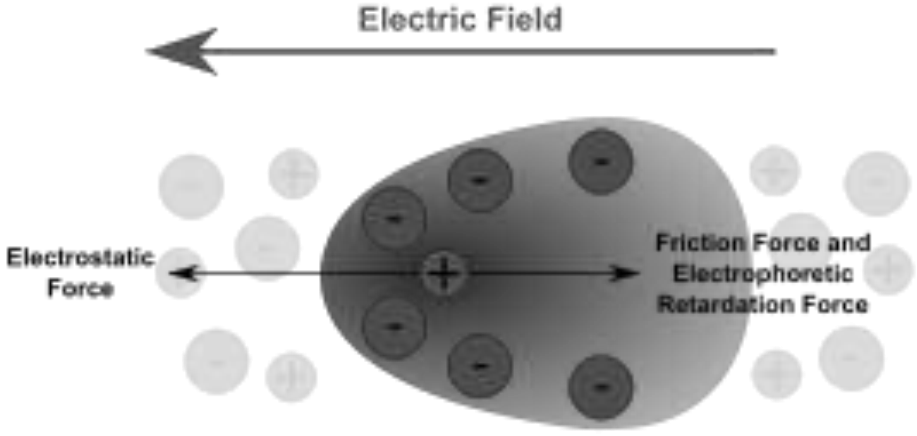


Fig. 1.3: Illustration of Electrophoresis

Electrophoresis is the motion of dispersed particles relative to a fluid under the influence of a spatially uniform electric field. This electrokinetic phenomenon was observed for the first time in 1807 by Reuss (Moscow State University),who noticed that the application of a constant electric field caused clay particles dispersed in water to

migrate. It is ultimately caused by the presence of a charged interface between the particle surface and the surrounding fluid.

Electrophoresis of positively charged particles (cations) is called **cataphoresis**, while electrophoresis of negatively charged particles (anions) is called **anaphoresis**.

3.3.3 Immunoassay

An **immunoassay** is a specific type of biochemical test that measures the presence or concentration of a substance (referred to as the "analyte") in solutions that frequently contain a complex mixture of substances.

Analytes in biological liquids such as serum or urine are frequently assayed (i.e., measured) using immunoassay methods. In essence, the method depends upon the fact that the analyte in question is known to undergo a unique immune reaction with a second substance, which is used to determine the presence and amount of the analyte.

This type of reaction involves the binding of one type of molecule, the antigen, with a second type, the antibody. Immunoassays can be carried out using either the antigen or the antibody in order to test for the other member of the antigen/antibody pair. In other words, the analyte may be either the antigen or the antibody.

In most test systems, the substrate is allowed to react with the enzyme for 20 minutes, before the reaction is terminated. This ensures a high degree of accuracy and sensitivity.

Owing to their high sensitivity (ability to detect very small concentrations) and specificity (minimal to no cross-reactivity), immunoassays have been employed in the measurement of blood levels of vitamins, hormones, and porphyrins.

Immunoassay is used in sports anti-doping laboratories to test athletes' blood samples for prohibited recombinant human growth hormone (rhGH, rGH, hGH, GH).

SELF-ASSESSMENT EXERCISE

State the operational principles of:

i. Spectrophotometry
ii. Electrophoresis
iii. Immunoassays

4.0 CONCLUSION

In this unit, we explained the functions of chemical pathologists and environmental toxicologist, including the techniques they commonly used. You have learnt what these experts do and how they do them.

5.0 SUMMARY

This unit showed that chemical pathologists screen the body fluids using a myriad of techniques including the measurement of enzyme levels, immunoassay, electrophoresis, and spectrophotometry to diagnose disease.

Environmental toxicologists carry out studies to determine the fate, effects, and risks of toxicants on the environment, wildlife, and human health. Common techniques like immunoassay, electrophoresis and spectrophotometry were discussed.

In the next unit, you will learn the major aspects of toxicological studies: toxicodynamics and toxicokinetics.

6.0 TUTOR-MARKED ASSIGNMENT

1. a. State two functions of the chemical pathologists.
   b. List three body fluids used by the pathologist.
2. a. State two functions of the environmental toxicologists.
   b. List three samples collected by an environmental toxicologist.

7.0 REFERENCES/FURTHER READING

Allen, D., Cooksey, C., & Tsai, B. (2010). *Spectrophotometry*. Retrieved from http://www.nist.gov /pml/div685/ grp03/ spectrophotometry.cfm

Crosby, D. G. (n. d.). *Environmental Toxicology and Chemistry*.

Cockerham, L. G. & Shane, B. S. (n. d.). *Basic Environmental Toxicology*.

"Existing Non-animal Alternatives". Source: AltTox.org. 8 September 2011. http://alttox.org/ttrc/existing-alternatives/.

Hughes, W. (n. d.). *Essentials of Environmental Toxicology*.

Hodgson, E. (2010). "A Textbook of Modern Toxicology". John Wiley and Sons. p.10.

http://www.biology.sfu.ca/degree/graduate/met

http://www.clemson.edu/entox/

http://doctorfinders.com/chemical-pathologist.php

http://en.wikipedia.org/wiki/Spectrophotometry. download date on 20-07-12

http://en.wikipedia.org/wiki/Electrophoresis download date: 20-07-12.

http://en.wikipedia.org/wiki/Immunoassay download date: 20-07-12.

Iwuji, S. C. (2010). *Basics and Applications of General Pharmacology.* (2010). Owerri, Nigeria: Milestone Publishers.

Landis, W. G. & Yu, M. H. (n. d.). *Introduction to Environmental Toxicology.* (3rd ed.).

Levey, M. (1966). *Medieval Arabic Toxicology: The Book on Poisons of ibn Wahshiya and its Relation to Early Native American and Greek Texts.*

Newman, M. C. & Clements, W. H. (n. d.). *Ecotoxicology: A Comprehensive Treatment.*

Ottoboni, M. Alice (1991). *The dose makes the poison : a plain-language guide to toxicology*. (2nd ed.). New York, N.Y: Van Nostrand Reinhold.

William, C, Krieger (2001). *Paracelsus Dose Response. The Handbook of Pesticide Toxicology*. Academic Press.

U.S. National Library of Medicine (n. d.). *Biography of Mathieu Joseph Bonaventure Orfila (1787–1853).*

Williams, P. L., James, R. C. & Roberts, S. M. (n. d.). *Principles of Toxicology-Environmental and Industrial Applications*. (2nd ed.).

Wright, D. A. & Welbourn, P. (n. d.). *Environmental Toxicology*.

Wennig, R. (2009). "Back to the roots of modern analytical toxicology: Jean Servais Stas and the Bocarmé murder case". *Drug Test Anal (England) 1* (4): 153–155. DOI:10.1002/dta.32. PMID 20355192.

Zakrzewski, S. F. (n. d.). *Environmental Toxicology*.

MODULE 2 BASIC CONCEPTS IN TOXICANT- BODY INTERACTIONS

UNIT 1 BASIC CONCEPTS IN TOXICODYNAMICS

CONTENTS

1.0 INTRODUCTION

In Unit 3 of Module 1, you learnt about the functions of chemical pathology and environmental toxicology, including the various techniques applied. In this unit, you will learn the basic concepts in Toxicodynamics.

Having known what a toxicant is, think of what happens when you spread aerosol insecticide in your room. You will notice that the concentration of aerosol determines the magnitude of your reaction to the insecticide. Toxicodynamics involves the study of the dose (concentration)-effect relationship of toxicants; their mechanisms of action; factors that modify their effects and their toxic effects (diseases).

You need to understand how a toxicant brings about an effect in a living system. This unit will explain the concentration- response concept, the relationship between concentration and effect, and the general mechanisms of toxicants.

2.0 OBJECTIVES

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

- explain the concentration–response concept
- explain the concentration-effect relationships
- identify some factors that can influence the effects of toxicants
- explain the general mechanisms of action of toxicants
- state the phases of toxicological studies.

3.0 MAIN CONTENT

3.1 Basic Concentration-Response Concept

This is the basis for safety evaluation of substances as knowledge of toxicodynamics will assist you to predict toxicity and how to intercept it. The knowledge that a substance can be a poison at a particular dose and unharmful to the body at a lower dose makes this concept very important in toxicological studies to assess safety margin.

An increase in the concentration of a solution proportionally increases the effect on the living system. For instance, put 5mg, 10mg and 15mg of table salt into **3** tea cups and pour the same quantity of water into the cups and shake vigorously. Taste the content of the **3** cups at different times. This can give you an idea of what happens when the concentration of a pollutant is in your environment increases.

3.1.1 Factors that Influence the Concentration (Dose)-Effect

From the above illustration, you can relate the concentration of toxicants to their effects. However, these effects are not usually the same. The relationship between the concentration of a toxicant and its response can be influenced by the following factors:

i. type of toxicants
ii. specie
iii. age
iv. sex
v. individual genetic makeup
vi. drug interaction
vii. state of health and
viii. environmental factors.

Usually this relationship is expressed graphically as a dose-response curve.

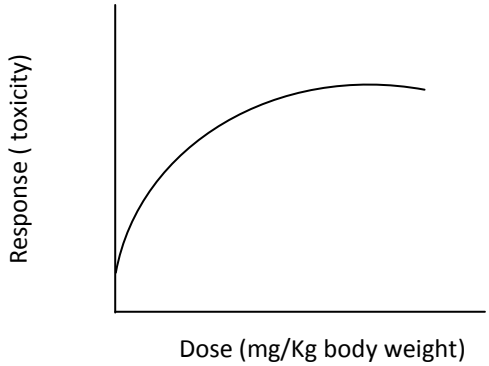


Fig. 2.1: Typical Dose-Response Curve

The *median toxic dose* that causes a particular unwanted effect is usually accepted as standard of measuring chemical safety. It is expressed as TD_{50}. The median toxic dose is the dose that causes 50% of the toxic effect or response in a population. However, to determine the median toxic effect in man, prior information about the chemical must have been gotten following toxicological screening with smaller animals and testing using other measures of toxicity.

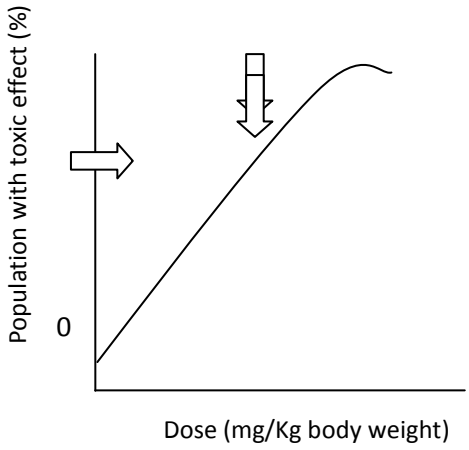


Fig. 2.2: Arrow Showing the Median Toxic Dose (TD_{50})

For a new substance, lethality studies ($LD_{50)}$ provide the starting index in toxicological/ safety studies. It gives a precise quanta death response to varying doses of the toxicant. Lethality studies provide information for the planning of the subsequent toxicological studies.

In each concentration (dose)-relationship (curve), you can determine the potency, slope and maximal efficacy of the effect of the toxicant.

a. Potency

This is the location of drug dose-effect curve along the dose axis. Potency is determined by the toxicokinetics of the drug and its inherent ability to bind with the receptors. A toxicant with lower potency will require larger dose to bring about its effect.

b. Slope or Gradient

Linear slope is useful in correlation of results. It is practically more useful when the slope is linear. It can be used in prediction of response to a certain dose of toxicant. It can also be used to identify the potency of unknown substance. For instance, if the slope of an unknown substance mimics that that of pilocarpine, you will conclude the substance is acetylcholine-like or cholinomimetic. Based on this further studies can be carried out in that direction.

c. Maximal efficacy

This is the maximum effect produced by a drug. The plateau in the dose-response curve represents it. The undesired or toxic effects of drugs are higher if the maximum efficacy is achieved with over dosage. Drugs can have the same potency but different maximal efficacy. Morphine and aspirin as potent pain-relievers can exemplify this. Morphine has higher maximum efficacy because increase in dose (even at overdose) correspondingly increases its pain relief, unlike aspirin.

3.2 General Mechanism of Action of Toxicants

This is an important aspect of toxicodynamics. Its study is meant to identify the primary action of the drug at the receptor sites or in the internal environment of the body. It explains the details of the chemical reaction between the drug and the cell or endogenous substances and the features of the full action-effects sequence.

The general mechanisms of action of toxicants include:

a. The toxicant may bind on their specific receptors inside or outside the cells e.g. atropine.
b. The toxicant may alter the physical properties of a targeted part of the body, e.g. osmotic substances.
c. The toxicant may chemically combine with other substances, e.g.
    (i) Isopropyl alcohol denatures the proteins on the surface of bacterial cells which in turn kills the bacteria by rupturing the cells.
    (ii) Antacids neutralise hydrochloric acid in stomach.

d. Drugs that act by altering a normal metabolic pathway, e.g. some anticancer and antiviral drugs are chemical analogs of normal metabolic substrates.

3.3 Toxicodynamic Studies

Toxicodynamic studies are required to ascertain the effects of toxicants on organisms. They are usually involve two phases:

a. Pre-mortal phase study is a careful, disciplined, detailed observation of the intact animal extending from the time of administration of the toxicant to the death of the animal.
b. Post-mortal phase study is the histology examination of major tissues and organs for abnormalities. The toxicity or lethality dose-responses are usually represented in dose-response curves.

4.0 CONCLUSION

At last, we were able to explain how drugs (toxicants) act on living systems. You learnt that the outcomes or effects of drugs generally depend on a number of factors. A very important determining factor discussed was the dose (amount) or concentration or the toxicant.

In the next unit, you will study how the body in turn acts on the drugs within it.

5.0 SUMMARY

In this unit, we explained the basic dose (concentration)-response concept which differentiated a poison from a therapeutic, as same drug can be a poison at higher dose and a therapeutic at lower dose.

We also discussed the concentration (dose)-effect relationships which were shown graphically by the dose–response curves. The curve may determine the potencies, slope and the efficacies of drugs.

This unit also highlighted the general mechanisms of drugs/toxicants which showed the various activities of the drugs/toxicants on the living systems to bring about the changes in their biologic functions.

Lastly, we discussed how to carry out toxicodynamic studies for various purposes. Effects of drugs/toxicants could be seen in living or dead bodies following exposure.

6.0 TUTOR-MARKED ASSIGNMENT

1. Explain the following terms:
   a. Toxicodynamics
   b. Potency
   c. Median toxic dose (TD_{50})
   d. Post mortal phase study
2. With an example, outline four general mechanisms of action of toxicants.

7.0 REFERENCES/FURTHER READING

Casarett, L. J. & Doull, J. (Eds). (1975). *Toxicology: The Basic Science of Poisons*. New York: Macmillan publishing Co. Inc.

Goodman, L. S. & Gilman, A. (Eds.). (1975). *The Pharmacological Basis of Therapeutics.* (5^{th} ed.). New York: Macmillan Publishing Co. Inc.

Iwuji, S. C. (2010). *Basics and Applications of General Pharmacology.* Owerri, Nigeria: Milestone Publishers Ltd.

Katzung, B.G. (2007). *Basic and Clinical Pharmacology*. (10^{th} ed.). Appleton and Lange U.S.A: Prentice-hall International Inc.

Klaassen, C. D. (2001). Principles of Toxicology and Treatment of Poisoning. In: *Goodman and Gillman's pharmacological Basis of Therapeutics.* (10^{th} ed.). New York: Mc Graw-Hill Co. Inc.

UNIT 2 BASIC CONCEPTS IN TOXICOKINETICS

CONTENTS

1.0 INTRODUCTION

In the previous unit, we discussed how drug affect the living system, in this unit, we are going to discuss how the living system interact or affect the drug before its effect.

Toxicokinetics deals with the mechanisms of liberation, absorption, distribution, metabolism (biochemical transformation) and excretion of toxicants in any living organism, including man.

These mechanisms are similar to the digestive processes you learnt in physiology. You can revise it now at this point.

2.0 OBJECTIVES

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

- explain the basic concept in toxicokinetics
- identify the processes involved in the mechanisms of toxicokinetics
- explain the processes that determine the fate of a poison in the body.

3.0 MAIN CONTENT

3.1 Basic Concept in Toxicokinetics

Toxicokinetics studies the fate of a poison in the body which determines its level of toxicity. The physical and chemical properties of a toxicant determine its kinetics in the body. For instance, lipid-soluble gaseous toxicants are easily absorbed and transported across the cell membranes than water-soluble solid toxicants. Consequently, the gaseous toxicants cause acute systemic toxicity than the solid toxicants.

The processes in toxicokinetics usually take place in compartments called cells. These processes are facilitated by the functional abilities of the cells.

3.2 Processes involved in Toxicokinetics

These processes determine the fate of toxicants in the body. They are as follow (LADME):

a. **Liberation** – this is how solid toxicants disintegrate or break down into smaller particles.
b. **Absorption**- this is how toxicants are absorbed in the internal environment of the body, through the skin, intestine and oral mucosa.
c. **Distribution**- this is how the toxicant is spread through the body.
d. **Metabolism**- this is the biotransformation of toxicant. It is a chemical process.
e. **Excretion**- this is how toxicants are eliminated, through the bile, urine, breathes, skin and nail.

3.2.1 Liberation of Toxicants

This is the process involved in the breakdown of solid toxicants whose active components are bound within complex matrices or structures. The process is similar to digestion of foods like rice and meat where it takes mechanical and chemical efforts to liberate the absorbable products like glucose and amino acids. In toxicokinetics, the liberated products are toxicants.

3.2.2 Absorption of Drugs or Toxicants

This is the process by which the toxicant is able to pass through the body membranes and enter the bloodstream. The main routes by which toxicants are absorbed from the environment are:

1. Skin and mucous membranes
2. Lungs
3. Gastrointestinal tract (oral, enteral, rectal).

The mode of exposure influences the rate of absorption of the toxicant. A toxicant given by intramuscular, subcutaneous or buccal routes must be able to absorb into blood circulation through the walls of capillaries.

Factors that may reduce absorption include:

i. Shock
ii. Acidosis
iii. hypothermia and
iv. oedema.

Factors that may increase absorption include:

i. hyperthermia
ii. fever
iii. increased tissue vascularity (capillarity).

Muscles are more vascular than subcutaneous tissue; therefore it may have faster absorption. A toxicant given endotracheally must be absorbed through the capillaries in the lungs. This is a convenient route when intravenous access is delayed or unavailable.

In toxicological studies, specialised routes such as intra peritoneal and subcutaneous routes are commonly used. Toxicants can also be administered through parenteral routes. Most parenteral routes do not require absorption and they have bioavailability of one (100%).

The skin is not highly permeable and, therefore, it is a relatively good lipoid barrier separating man from his environment. However, chemicals like nerve gases, carbon tetrachloride and various insecticides can be absorbed through skin in sufficient quantities to produce systemic effects.

The most frequent cause of poisoning (carbon monoxide) and probably the most important occupational disease (silicosis) are due to airborne poisons absorbed through the lungs. Inhaled poisons may be in form of gases (e.g. sulphur dioxide), in volatile liquids (e.g. benzene) and aerosols (e.g. silica). Aerosols consist of solid particulate matter (e.g. smokes, dusts or pollens) and fine liquid droplets (e.g. fogs or sprays).

Many environmental toxicants enter the food chain and are absorbed from the gastrointestinal tract. Gastrointestinal tract is the most frequent

route of poisoning used by children and suicide victims. Absorption can take place along the length of the tract- from the mouth to the rectum.

3.2.3 Drug Transport and Distribution Processes

i. Transport of drugs across cell membrane

The toxicants apply various transport mechanisms to cross the cell membrane during absorption or excretion or to reach the target site(s).

There are two major types of transport systems:

a. Passive transport
b. Active Transport.

Passive Transport

Passive transport of toxicants does not utilise energy (adenosine triphosphate (ATP) of the cell. There are two common passive transports in the body:

a. Simple diffusion
b. Filtration.

Simple Diffusion is the movement of toxicants from the area of higher concentration to the area of lower concentration in the body depending on their lipid/water partition coefficient. For instance, lipid soluble ethyl alcohol readily passes the cell membranes by simple diffusion.

Filtration is the passage of relatively minute toxicants in a bulk flow across the porous cell membrane. Here, the cell membrane acts as filter and the toxicant is the filtrate. This is the type of transport seen in the kidney with porous capillary network (glomerulus).

Active Transport

This specialised transport system is responsible for the movement of most xenobiotics, including nutrients and toxicants.

It has the following features:

(i) The xenobiotic is moved against a concentration or electrochemical gradient.
(ii) The transport system can be saturated and exhibits a transport maximum.

(iii) The system has a characteristic of selectivity and specificity (chemical affinity).
(iv) Competitive inhibition can occur among substances transported by the same mechanism.
(v) Since the process involves expenditure of energy, metabolic inhibitors can block the transport.

Active transport system is important in the excretion of xenobiotics or their metabolites.

Other transport systems include:

a) Facilitated diffusion

This is an active carrier transport that has all the properties of active transport except that the substrate does not move against a concentration gradient. Typical example is the transport of glucose in the body.

b) Cellular transport processes

These include phagocytosis and pinocytosis. This transport system involves the flowing movement of the cell membrane around the molecules to be engulfed or transported. It is important in the removal of particulate matter or poisons in the alveoli or blood.

c) Distribution of drugs/poisons in the body

After absorption or intravenous injection, the toxicants enter the plasma fluid for distribution throughout the body. Distribution of toxicants depends on their ability to cross the cell membranes and on their affinity to various body components. Drugs or toxicants can be taken to their target sites in the body where they cause useful or toxic effects or to their storage sites from where they are gradually released back into the plasma.

The concentration of a toxicant that reaches its target site(s) and the effects depends on the volume of distribution of the exposed toxicant. If the toxicant evenly enters into all the body water compartments (plasma, interstitial and intracellular space), and also bind to various storage sites (like fat, liver, kidney, bone or plasma proteins), the concentration that reaches the target sites will be highly lowered. Consequently, the target effect is slower and prolonged as the toxicant is released from the storage depots.

d) Volume of Distribution (V_d)

This is the apparent volume into which a substance is distributed in the body. It is equivalent to dose of drug given per plasma concentration of the drug after distribution in the body. Drugs with large volumes of distribution such as antidepressants, phenothiazines and lidane are not easily removed from the body by blood purifying process like haemodialysis. Whereas drugs with relatively small volumes of distribution such as theophylline, salicylate, lipoid, phenobarbital, lithium and phenytoin are easily removed.

e) Physiological barriers to distribution of drugs/toxicants

These include:

1. Blood-Brain Barrier

Blood-Brain Barrier (BBB) is not an absolute barrier to the passage of toxic materials into the central nervous system, but rather represents a site that is less permeable than most other areas of the body. Many toxicants cannot pass from the plasma to the extra cellular space of the brain in appreciable quantities to cause toxic central nervous effects. Lipoid soluble poisons can easily cross through blood-brain barrier than the water-soluble toxicants. Also, the blood-brain barrier is not well developed in infants and chemicals like morphine or lead produces higher central nervous effects in the newborn than in adults.

2. Placental barrier

Apart from being the site of exchange of substances between the foetus and mother, the placenta acts as a protective barrier against passage of some noxious chemicals from mother to foetus. Most toxicants cross the placenta by simple diffusion.
The protective function of the placenta is based on the number of layers of cells; its biotransformation mechanism and the lipid/water partition coefficient of the toxicants.

3. Testicular barrier

This special membrane shields certain drugs from entering the seminiferous tubules in the testes.

3.2.4 Metabolism of Drugs

The living systems are exposed to a lot of natural or synthetic xenobiotics which are toxic at different doses or following

bioaccumulation of chemicals. Metabolism involves processes of biotransforming the foreign substances to become more active and toxic or passive and detoxified. Metabolism of toxicants also enhances their elimination by making them more water-soluble. It is therefore part of the defense mechanisms of the body for toxic substances.

There are four main enzymatic processes that bring about the transformation of xenobiotics:

1. Hydrolysis, i.e. addition of water molecule
2. Oxidation i.e. addition of oxygen
3. Reduction i.e. removal of oxygen
4. Conjugation i.e. a variety of chemical reactions like alkylation, esterification and acylation which involves the combination of the toxicant with a highly polar or ionic group giving rise to soluble products that are quickly eliminated.

Numerous Biotransformation processes happen in the liver. Microsomal enzymes found in the endoplasmic reticular of hepatocytes (*hepato* – liver, *cytes*-cells) perform most of the metabolising. (Some enzymes are also found in the lungs, kidney and GI tract in smaller quantities).

First-Pass Effect

All drugs absorbed in the GI tract must pass through the liver, as the blood supply from the gastrointestinal (GI) tract passes through the liver via the portal vein. This can partially or completely inactivate the drug, a phenomenon known as the **first-pass effect**.

The first-pass effect is the term used for the hepatic metabolism of a pharmacological agent when it is absorbed from the gut and delivered to the liver via the portal circulation. The greater the first-pass effect, the less the agent will reach the systemic circulation when the agent is administered orally.

This is why some drugs cannot be given orally but are given parenteral. Drugs that can be given both orally and intravenously during studies will require a higher dose when given orally.

3.2.5 Excretion of Toxicants

This is the process of eliminating foreign toxic substances from the body. The following are the routes of excretion of toxicants: urinary system, liver and biliary system, lung, gastrointestinal tract, cerebrospinal fluid, breast milk, sweat, saliva, tears, hair and nail.

Drugs are eventually cleared, or eliminated from the body, either in their original form, or as metabolites. Drug clearance is primarily achieved through one or more of the following body systems:

a) **Kidneys/Renal System:** Urinary excretion is a major route for elimination of drugs from the body. Changes, such as the reduction of nephrons, the functioning unit of the kidney, associated with aging, can significantly alter drug clearance capacity in the geriatric client. The result of a decline in concentrating ability and decreased excretory function can result in prolonged increased serum levels of certain drugs. Processes, not necessarily associated with aging, such as renal failure, markedly alter clearance, and create a whole new patient management dynamic.
b) **Liver/Hepatic System**: One of the factors contributing to the effectiveness of hepatic clearance is blood supply and blood flow. Decreased liver mass and blood flow, as typically seen in the geriatric population, will alter clearance times. Hepatic disease processes will also negatively impact clearance. Some compounds are excreted in the bile.
c) **Gastrointestinal Tract**: Some metabolites are excreted in the faeces.
d) **Pulmonary System**: Some excretion occurs via gas exchange at the alveolar level.

However, Kidney is the most important organ for the excretion of toxicants. Toxicants or their metabolites are removed during the formation of urine. They are either secreted or filtered into the urinary tubules as low threshold substances. When the rate of absorption of toxicants is higher than the rate of excretion, the toxic compounds accumulates to a toxic level in the body.

3.2.6 Clearance of Drugs

This is a measure of the volume of plasma that is cleared of drug per unit time. Total clearance is the sum of clearances carried out by all the routes or organs of excretion in the body. If 95% of a drug is cleared by liver metabolism, it will be a wasteful effort to increase the urinary output in order to clear this drug. Therefore, detoxification strategy depends on the major organ(s) of elimination of the toxicants involved.

3.3 Kinetics of Plasma Toxicant Following Intravenous Administration

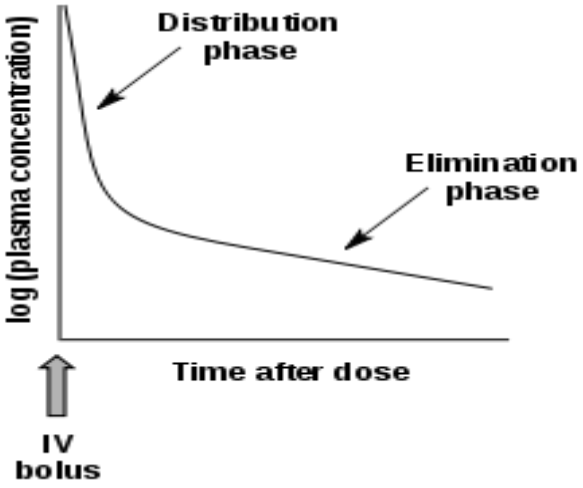


Fig. 2.3: Plasma Drug Concentration vs. Time after an Intravenous (IV) Dose

Drugs injected intravenously are removed from the plasma through two primary mechanisms:

(1) Distribution to body tissues
(2) metabolism + excretion of the drugs.

The resulting decrease of the drug's plasma concentration follows a biphasic pattern (Figure 2.3).

Alpha phase: An initial phase of rapid decrease in plasma concentration. The decrease is primarily attributed to drug distribution from the central compartment (circulation) into the peripheral compartments (body tissues). This phase ends when pseudo-equilibrium of drug concentration is established between the central and peripheral compartments.

Beta phase: A phase of gradual decrease in plasma concentration after the alpha phase. The decrease is primarily attributed to drug metabolism and excretion (Gill et al., 1999).

3.4 Toxicokinetics of Drug-Response Curve

The kinetics of increased dosage of toxicant may differ from the kinetics of lower doses. For instance, if the capacity of the liver to metabolise a toxicant is exceeded, the excess drug will be delivered to systemic circulation. With a dramatic increase in the concentration of the toxicant

in the blood, tissue-binding capacity may be exceeded, resulting in an increased fraction of free drug and greater toxicity.

At lower dosage, most drugs are eliminated at a rate proportional to the plasma concentration (first-order kinetics), that is, the rate of excretion increases with increasing plasma concentration (Figure 2.4).

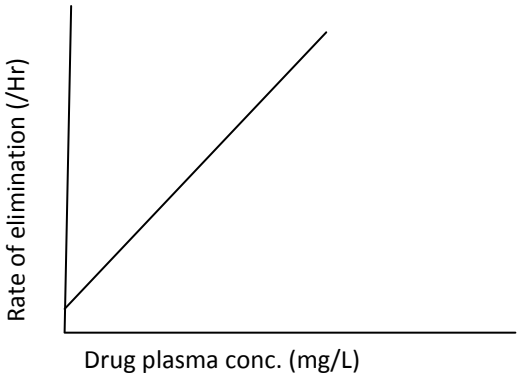


Fig. 2.4: First-Order Kinetics for Lower Dosage

Similarly, at lower concentration exposure, the drug plasma concentration declines at its peak; the rate of elimination becomes faster than the increase in plasma concentration.

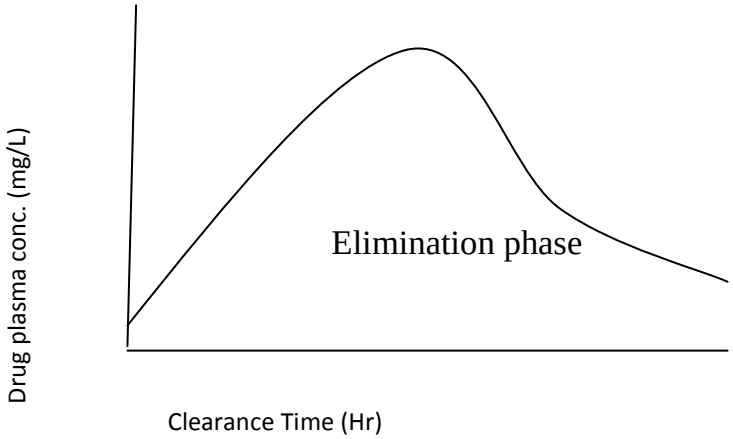


Fig. 2.5: First-Order Kinetics for Normal Dosage

The plasma concentration of the drug will reach near-zero following clearance.

The rate of drug elimination increases initially with the plasma concentration until the peak level when elimination rate is constant (zero-order).

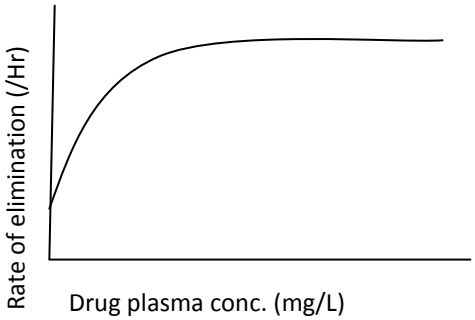


Fig. 2.6: Zero –Order Kinetics for Toxic or Over Dosage

The clearance time is much longer in drug overdose

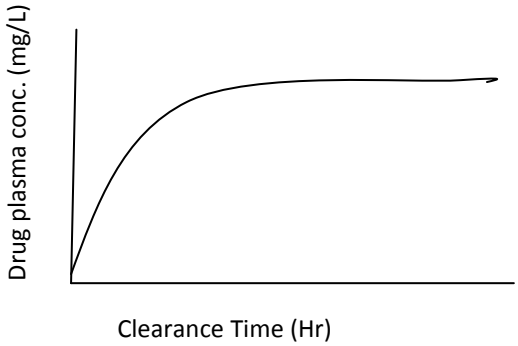


Fig. 2.7: Zero –Order Kinetics for Toxic or Over Dosage

The plasma concentration is peak and normal metabolism is saturated, the rate of elimination may become fixed (Zero-order Kinetics). Zero-order kinetics may markedly prolong the apparent serum half-life and increase the toxicological effect.

4.0 CONCLUSION

In this unit, we have discussed an important aspect of body - toxicant interaction known as toxicokinetics. This aspect dealt with how the body determines the fate of the toxicant as it enters the body internal environment by absorption or injection.

The main processes involved in toxicokinetics play important role in releasing the active constituent of the solid toxicant; enhance the absorption, distribution, biotransformation and excretion of toxicant. This process ultimately determines the response of the body to toxicant.

5.0 SUMMARY

This unit explained the basic concepts in toxicokinetics and processes involved.

These processes determine the fate of toxicants in the body. They are as follow (LADME):

- **Liberation** – this is how solid toxicants disintegrate or break down into smaller particles.
- **Absorption**- this is how toxicants are absorbed in the internal environment of the body, through the skin, intestine and oral mucosa.
  Some factors that may reduce or increase absorption were outlined. These include shock, temperature, diarrhoea.
- **Distribution**- this is how the toxicant is spread through the body.
  There are two major types of transport systems: passive and active transport.

  There are two common passive transports in the body: simple diffusion and filtration.

  Other Transport Systems include: Facilitated diffusion and cellular transport processes.

  This unit also defined volume of distribution (V_d) and explained the physiological barriers to distribution of drugs/toxicants. These include: blood-brain barrier (BBB); Placental barrier and testicular barrier.

- **Metabolism**- this is the biotransformation of toxicant. It is a chemical process.

There are four main enzymatic processes that bring about the biotransformation of xenobiotics:

a. Hydrolysis, i.e. addition of water molecule
b. Oxidation i.e. addition of oxygen
c. Reduction i.e. removal of oxygen
d. Conjugation i.e. a variety of chemical reactions like alkylation, esterification and acylation which involves the combination of the toxicant with a highly polar or ionic group giving rise to soluble products that are quickly eliminated.
   Portal circulation also ensures first-pass effect on ingested toxicants.

- **Excretion**- this is how toxicants are eliminated, through the bile, urine, breathes, skin and nail. The following systems are involved in excretion:

    a. Kidneys / Renal System: excreted during urine formation.
    b. Liver / Hepatic System: toxicant may undergo hepatic breakdown.
    c. Gastrointestinal Tract: Some metabolites are excreted in the faeces.
    d. Pulmonary System: Some excretion occurs via gas exchange at the alveolar level.

The concept of clearance of drugs was also discussed with various drug-response curves.

In the next unit, we will discuss the possible outcome of exposure to toxicant- toxicity.

6.0 TUTOR-MARKED ASSIGNMENT

1. Define toxicokinetics.
2. Explain the processes of toxicokinetics
3. Outline the barriers to drug distribution in the body.
4. State four mechanisms of drug biotransformation.

7.0 REFERENCES/FURTHER READING

Casarett, L. J. & Doull, J. (Eds). (1975). *Toxicology: The Basic Science of Poisons.* New York: Macmillan publishing Co. Inc.

Gill S. C., Moon-Mcdermott, L., Hunt, T. L., Deresinski, S., Blaschke T. & Sandhaus, R. A. (1999). "Phase I Pharmacokinetics of Liposomal Amikacin (MiKasome) in Human Subjects: Dose Dependence and Urinary Clearance". *Abstr Intersci Conf Antimicrob Agents Chemother Intersci Conf Antimicrob Agents Chemother* 39: 33 (abstract no. 1195).

http://gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102244695.html.

Goodman, L. S. & Gilman, A. (Eds). (1975). *The Pharmacological Basis of Therapeutics.* (5^{th} ed.). New York: Macmillan Publishing Co. Inc.

Iwuji, S. C. (2010). *Basics and Applications of General Pharmacology*. Owerri, Nigeria: Milestone Publishers Ltd.

Katzung, B. G. (2007). *Basic and Clinical Pharmacology*. (10th ed.) Appleton and Lange, U.S.A.: Prentice-hall International Inc.

Klaassen, C. D. (2001). Principles of Toxicology and treatment of poisoning. In: *Goodman and Gillman's pharmacological Basis of Therapeutics.* (10th ed.) New York: Mc Graw-Hill Co. Inc.

Leslie, Z. Benet (1984). Pharmacokinetics: Basic Principles and Its Use as a Tool in Drug Metabolism. p.199 in: *Drug Metabolism and Drug Toxicity*, J. R. Mitchell & M. G. Horning (Eds). New York: Raven Press.

Weiner, D. & Johan, G. (2000). "PK24 - Non-linear kinetics - flow II". Pharmacokinetic/pharmacodynamic data analysis: concepts and applications. *Apotekarsocieteten.* pp. 527–36.

UNIT 3 MEANING AND CLASSIFICATION OF ENVIRONMENTAL TOXICANTS

CONTENTS

1.0 INTRODUCTION

In Unit 2, we discussed the common outcome of exposure to environmental toxicant and factors that influence them. All organisms, such as plants, animals and human beings, as well as the physical surroundings with whom we interact, form a part of our environment. All these constituents of the environment are dependent upon each other. Thus, they maintain a balance in nature. Man carries out a lot of activities that disrupt this balance by introducing toxicants into the environment. It is therefore the responsibility of man to take necessary steps to control the environmental imbalances.

In this Unit, you will learn how to identify and classify these numerous environmental toxicants.

2.0 OBJECTIVES

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

- explain the meaning of toxicant
- classify toxicants based on different criteria.

3.0 MAIN CONTENT

3.1 What are Toxicants?

It is not easy to say that any substance is not a toxicant or poison. This is because a substance as simple and common as water can be a toxicant depending on dose and route of exposure, among other factors.

Situations where useful substances become toxicants include: breathing too much pure oxygen, drinking excessive amounts of water or eating too much salt can cause poisoning or death.

An environmental toxicant or poison can therefore be defined as any substance that is present in a state, dose or concentration which is capable of causing harm or injury on exposure through a particular route and circumstances.

It is the duty of environmental health personnel to identify toxicants in the environment and minimise the risk of poisoning or intoxication.

3.2 Classifications of Toxicants

There are different ways of classifying substances based on:

(a) source of the poison
(b) usage forms of the chemical products
(c) public health importance
(d) target sites.

3.2.1 Classification of Poisons Based on their Sources

This is the commonest way in practice. Poisons can be broadly classified as natural or artificial.

1. Natural poisons include animal, plant and mineral poisons.
    a. Animal poisons include venoms and toxins found in some animals like Snake, Spiders and Marine animals
    b. Plant poisons include chemical extracts from higher plants e.g. Curare, nicotine, atropine, cardiac glycosides and physostigmine. Plant poisons obtained from lower plants include ergot alkaloids, botulinus and mycotoxins.
    c. Mineral poisons can be metallic or non-metallic and organic or inorganic.
        i. Metallic poisons from natural sources include calcium, mercury, lead, copper, zinc and uranium.

ii. Non-metallic poisons in the natural sources include air pollutants, solvents and vapours. These include phosphorus, carbon compounds, organic acid and salts. These poisons are exposed to humans while using natural substances or in a natural environment

2. Artificial or synthetic sources

These are the commonest sources of poisons. The three major synthetic sources of poisons in U. S. are:

a. Cosmetics
b. Cleaning agents
c. Therapeutics.

3. Other sources include:

a. Agricultural sources
Like poisoned fish or meat, food crops with residual poisons, fertilizers, and pesticides.

b. Industrial sources
Such as: pesticides, fertilizers, fuels lubricants; laboratory chemicals, Solvent ink, crude oil, coal, cigarettes, effluents, solid and gaseous wastes.

c. Domestic sources
These poisons include food condiments and preservatives, pipe-borne water, cooking gas or smoke from oil lamp, stove, electricity generator, firewood, cooking pots, incinerators, storage tanks, air conditioners, refrigerators, wastes and expired products.

Classification based on the source of the poison is commonly used. Cosmetics and cleaning agents are most frequently responsible for human poisoning than therapeutic drugs in United States of America. Though such toxicological comparisons are not yet known in Nigeria, the continued indiscriminate use of uncertified chemical products and the constant use of smoky electricity generators and oil lamps are of great risk to public health. Deaths had been reported following such domestic poisoning.

3.2.2 Classification of Poisons Based on Usage Form of the Finished Products

These include:

a. Food and packaging additives
b. Medicines
c. Household and cleaning product
d. Occupational toxicants.

3.2.3 Classification Based on the Public Health Importance of the Toxicants

This depends on the source or health implications of the toxicants during their exposure or use. Toxicants can be classified as:

a. Plant or animal poisons
b. Corrosives
c. Carcinogens or mutagens
d. Pesticides including insecticides, herbicides, rodenticide, fungicides and fumigants.
e. Household materials
f. Airborne poisons
g. Ionising poisons
h. Solvents
i. Environmental pollutants e.g. heavy metals, organophosphates

Example of classification based on public health importance:

a. Heavy Metals

Metals differ from other toxic substances in that they are neither created nor destroyed by humans. Their use by humans plays an important role in determining their potential for health effects. Their effect on health could occur through at least two mechanisms: first, by increasing the presence of heavy metals in air, water, soil, and food, and second, by changing the structure of the chemical. For example, chromium III can be converted to or from chromium VI, the more toxic form of the metal.

b. Solvents and Vapours

Nearly everyone is exposed to solvents. Occupational exposures can range from the use of “white-out” by administrative personnel, to the use of chemicals by technicians in a nail salon. When a solvent evaporates, the vapours may also pose a threat to the exposed population.

b. Radiation and Radioactive Materials

Radiation is the release and propagation of energy in space or through a material medium in the form of waves, the transfer of heat or light by waves of energy, or the stream of particles from a nuclear reactor.

c. Dioxin/Furans

Dioxin, (or TCDD) was originally discovered as a contaminant in the herbicide. Dioxin is also a by-product of chlorine processing in paper producing industries.

d. Pesticides

The EPA defines pesticide as any substance or mixture of substances intended to prevent, destroy, repel, or mitigate any pest. Pesticides may also be described as any physical, chemical, or biological agent that will kill an undesirable plant or animal pest.

e. Plant Toxins

Different portions of a plant may contain different concentrations of chemicals. Some chemicals made by plants can be lethal. For example, taxon, used in chemotherapy to kill cancer cells, is produced by a species of the yew plant.

f. Animal Toxins

These toxins can result from venomous or poisonous animal releases. Venomous animals are usually defined as those that are capable of producing a poison in a highly developed gland or group of cells, and can deliver that toxin through biting or stinging. Poisonous animals are generally regarded as those whose tissues, either in part or in their whole, are toxic.

All of these substances may also be further classified based on their:

i. effect on target organs (liver, kidney, hematopoietic system)
ii. use (pesticide, solvent, food additive)
iii. source of the agent (animal and plant toxins)
iv. effects (cancer mutation, liver injury)
v. physical state (gas, dust, liquid)
vi. labelling requirements (explosive, flammable, oxidizer)
vi. chemistry (aromatic amine, halogenated hydrocarbon)
viii. poisoning potential (extremely toxic, very toxic, slightly toxic).

Note: A chemical may be poisonous at a given dose and through a particular route.

3.2.4 Classification Based on the Target Sites of the Toxicant

This is related to the organ with high significant toxic effect.

Examples include:

- **Hepatotoxicity** - when the poison has an unwanted effect on the liver.
- **Nephrotoxicity** - when the poison has an unwanted effect on the kidney.
- **Neurotoxicity** - when the drug adversely affects the nervous system.
- **Pneumotoxicity** - when the poison has an unwanted effect on the lung.
- **Dermatoxicity** - when the poison has an unwanted effect on the skin.

Site of toxicity depends on the manner of exposure and the mechanism of action of the poison e.g. most inhaled poisons cause pneumotoxicity due to the effect on the lungs.

3.2.5 Classification Based on the Original Nature of Toxicants

There are generally three types of toxic entities; chemical, biological, and physical.

a) Chemical toxicants include inorganic substances such as lead, mercury, asbestos, hydrofluoric acid, and chlorine gas, organic compounds such as methyl alcohol, most medications, and poisons from living things.

b) Biological toxicants include bacteria and viruses that can induce disease in living organisms. Biological toxicity can be difficult to measure because the "threshold dose" may be a single organism. Theoretically one virus, bacterium or worm can reproduce to cause a serious infection. However, in a host with an intact immune system the inherent toxicity of the organism is balanced by the host's ability to fight back; the effective toxicity is then a combination of both parts of the relationship. A similar situation is also present with other types of toxic agents.

c) Physical toxicants are substances that, due to their physical nature, interfere with biological processes. Examples include coal dust and asbestos fibers, both of which can ultimately be fatal if inhaled.

3.2.6 Global Classification of Toxicants

For substances to be regulated and handled appropriately, they must be properly classified and labelled. Classification is determined by approved testing measures or calculations and have determined cut off levels set by governments and scientists. While currently many countries have different regulations regarding the types of tests, amounts of tests and cut off levels, the implementation of Global Harmonisation was beginning to unifying these countries as early as 2008.

These are considered in three areas:

1. Physical Hazards (explosions and pyrotechnics),
2. Health Hazards and
3. Environmental Hazards.

1. Physical Hazards

a. Explosions

An explosion is a rapid increase in volume and release of energy in an extreme manner, usually with the generation of high temperatures and the release of gases. Supersonic explosions created by high explosives are known as detonations, and travel via supersonic shock waves. Subsonic explosions are created by low explosives through a slower burning process known as deflagration.

Examples:

i. Most natural explosions arise from volcanic processes of various sorts. Explosive volcanic eruptions occur when magma rising from below has much dissolved gas in it; the reduction of pressure as the magma rises causes the gas to bubble out of solution, resulting in a rapid increase in volume.
ii. Animal bodies can also be explosive, as some animals hold a large amount of flammable material such as animal fat. This, in rare cases, results in naturally exploding animals.
iii. Among the largest known explosions in the universe are supernovae, which result when a star explodes from the sudden starting or stopping of nuclear fusion, and gamma ray bursts, whose nature is still in some dispute. Solar flares are an example of explosion common on the Sun, and presumably on most other stars as well. The energy source for solar flare activity comes from the tangling of magnetic field lines resulting from the rotation of the Sun's conductive plasma. Another type of large

astronomical explosion occurs when a very large meteoroid or an asteroid impacts the surface of another object, such as a planet.

iv. The most common artificial explosives are chemical explosives, usually involving a rapid and violent oxidation reaction that produces large amounts of hot gas.

v. Accidental explosions may occur in fuel tanks, rocket engines, etc.

vi. A high current electrical fault can create an *electrical explosion* by forming a high energy electrical arc which rapidly vapourises metal and insulation material.

vii. Strictly a physical process, as opposed to chemical or nuclear, e.g., the bursting of a sealed or partially sealed container under internal pressure is often referred to as a 'mechanical explosion'. Examples include an overheated boiler or a simple tin can of beans tossed into a fire.

viii. Boiling liquid expanding vapour explosions are one type of mechanical explosion that can occur when a vessel containing a pressurised liquid is ruptured, causing a rapid increase in volume as the liquid evaporates.

ix. In addition to stellar (star) nuclear explosions, a man-made nuclear weapon is a type of explosive weapon that derives its destructive force from nuclear fission or from a combination of fission and fusion.

b. Pyrotechnics

Pyrotechnics is the science of using materials capable of undergoing self-contained and self-sustained exothermic chemical reactions for the production of heat, light, gas, smoke and/or sound. Pyrotechnics include not only the manufacture of fireworks but items such as safety matches, oxygen candles, explosive bolts and fasteners, components of the automotive airbag and gas pressure blasting in mining, quarrying and demolition.

Categories of pyrotechnics

Modern pyrotechnics are, in general, divided into categories based upon the type of effect produced or manufacturing method. The most common categories are:

i. Airburst - Hanging charges designed to burst into spheres of sparks.

ii. Binary kits - Powders divided into oxidiser and fuel intended to be mixed before use.

iii. Comets (meteor) - Rising shots resembling shooting stars.

iv. Preloaded Comet

v. Preloaded mine - Tubes containing a lift charge intended to project stars, sparks confetti or streamers.
vi. Preloaded smoke pot - Cartridges designed to release a mushroom cloud of smoke.
vii. Preloaded report (concussion tube) - Tubes designed to create a loud report.
viii. Falls - Devices intended to drop like falling stars.
ix. Fireballs/mortar hits - Containers creating mushroom clouds of flame.
x. Flame projector - Columns shooting pillars of flame.
xi. Flare (Torch) - Short, high intensity flames or various colours.
xii. Flash cotton (Sparkle string) - Cotton string impregnated with nitrocellulose.
xiii. Flashpaper - Sheets of nitrocellulose resembling tissue paper.
xiv. Flash pot - A container for creating a bright flash and smoke.
xv. Flash tray (split mine) - A long tube creating a wide, bright flash.
xvi. Gerb (including fountain, whistle, and waterfall) - A fountain of sparks.
xvii. Lance - A small brightly colored fountaĉin that produces few sparks.
xviii. Line rockets - Whistling gerbs traveling across wires.
xix. Multi-tube article (multi-shot plate, multiple shot repeater boards and bombardo boards; designed to function in sequence) - Multiple effects chained together.
xx. Pre-mixed powder - Powders intended to create various effects. (Concussions, flashes, etc.)
xxi. Squib - A small, pre-matched device typically used to replicate bullet hits.
xxii. Strobe - A device intended to create bright repetitive flashes.
xxiii. Wheel (Saxon) - Tubes that create a spinning wheel of sparks.

Pyrotechnics are dangerous and must be handled and used properly. Recently, several high profile incidents involving pyrotechnics have re-enforced the need to respect these explosives at all times.

Pyrotechnics are dangerous substances that must always be treated with the utmost respect and with the proper training. Due to the hazardous nature of these materials, precautions must always be taken to ensure the safety of all individuals in the vicinity of pyrotechnics. Despite all precautions, accidents and errors occur from time to time, which may result in property damage, injury and in severe cases loss of life. These incidents may be the result of poorly manufactured product, unexpected or unforeseen events, or in many cases, the result of operator error. *Retrieved from "http://en.wikipedia.org/w/index.php?title=Pyrotechnics&oldid=507706642"*

2. Health hazards

The types of toxicities where substances may cause lethality to the entire body, lethality to specific organs, major/minor damage, or cause cancer. These are globally accepted definitions of what toxicity is. Anything falling outside of the definition cannot be classified as that type of toxicant.

Acute toxicity

Acute toxicity looks at lethal effects following oral, dermal or inhalation exposure. It is split into five categories of severity where Category 1 requires the least amount of exposure to be lethal and Category 5 requires the most exposure to be lethal. The table below shows the upper limits for each category

Table 2.1: The Upper Limits for each Category of Acute Toxicity

Method of administration	**Category 1**	**Category 2**	**Category 3**	**Category 4**	**Category 5**
Oral: LD_{50} measured in mg/kg of bodyweight	5	50	300	2 000	5 000
Dermal: LD_{50} measured in mg/kg of bodyweight	50	200	1 000	2 000	5 000
Gas Inhalation: LC_{50} measured in ppmV	100	500	2 500	20 000	Undefined
Vapour Inhalation: LC_{50} measured in mg/L	0.5	2.0	10	20	Undefined
Dust and Mist Inhalation: LC_{50} measured in mg/L	0.05	0.5	1.0	5.0	Undefined

Note: The undefined values are expected to be roughly equivalent to the category 5 values for oral and dermal administration.

Other methods of exposure and severity

Skin corrosion and irritation are determined through skin patches test analysis. This examines the severity of the damage done; when it is incurred and how long it remains; whether it is reversible and how many test subjects were affected.

Skin corrosion from a substance must penetrate through the epidermis into the dermis within four hours of application and must not reverse the damage within 14 days. **Skin irritation** shows damage less severe than corrosion if: the damage occurs within 72 hours of application; or for three consecutive days after application within a 14 day period; or causes inflammation which lasts for 14 days in two test subjects. **Mild skin irritation** minor damage (less severe than irritation) within 72 hours of application or for three consecutive days after application.

Serious **eye damage** involves tissue damage or degradation of vision which does not fully reverse in 21 days. Eye irritation involves changes to the eye which do fully reverse within 21 days.

Other categories of toxicity

- Respiratory sensitisers cause breathing hypersensitivity when the substance is inhaled.
- A substance which is a skin sensitiser causes an allergic response from a dermal application.
- Carcinogens induce cancer, or increase the likelihood of cancer occurring.
- Reproductively toxic substances cause adverse effects in either sexual function or fertility to either a parent or the offspring.
- Specific-target organ toxins damage only specific organs.
- Aspiration hazards are solids or liquids which can cause damage through inhalation.

3. Environmental hazards

Environmental hazards tend to focus on degradability, bioaccumulation and aquatic toxicity.

Mapping environmental hazards

There are many environmental health mapping tools. TOXMAP is a Geographic Information System (GIS) from the Division of Specialized Information Services of the United States National Library of Medicine (NLM) that uses maps of the United States to help users visually explore data from the United States Environmental Protection Agency's (EPA) Toxics Release Inventory and Superfund programs. TOXMAP is

a resource funded by the US Federal Government. TOXMAP's chemical and environmental health information is taken from NLM's Toxicology Data Network (TOXNET) and PubMed, and from other authoritative sources.

Aquatic toxicity

Aquatic toxicity testing submerges key indicator species of fish or crustacean to certain concentrations of a substance in their environment to determine the lethality level. Fish are exposed for 96 hours while crustacean are exposed for 48 hours. While GHS does not define toxicity past 100 mg/l, the EPA currently lists aquatic toxicity as "practically non-toxic" in concentrations greater than 100 ppm.

Exposure	**Category 1**	**Category 2**	**Category 3**
Acute	≤ 1.0 mg/L	≤ 10 mg/L	≤ 00 mg/L
Chronic	≤ 1.0 mg/L	≤ 10 mg/L	≤ 00 mg/L

Note: A category 4 is established for chronic exposure, but simply contains any toxic substance which is mostly insoluble, or has no data for acute toxicity.

There are generally two types of toxic entities: chemical and physical:

a) Chemical toxicants include inorganic substances such as lead, mercury, asbestos, hydrofluoric acid, and chlorine gas, organic compounds such as methyl alcohol, most medications, and poisons (toxins) from living things.
b) Physical toxicants are substances that, due to their physical nature, interfere with biological processes. Examples include coal dust and asbestos fibers, both of which can ultimately be fatal if inhaled.

4.0 CONCLUSION

There exist thousands of chemical agents in the surroundings exposed to man. At certain doses and time these chemicals are injurious to man or his environment and constitute health and environmental hazards.

The definition or identification and classification of these chemicals are paramount in ensuring appropriate environmental health and management. There are several bases of classification discussed but the one based on the type of hazard is global now.

5.0 SUMMARY

In this unit, we identified what toxicants are. We differentiated toxicants from other useful substances in the environment.

Different bases of classifying toxicants included:

A. Classification of poisons based on their sources.

1. Natural Poisons include animal, Plant and Mineral Poisons.
2. Artificial or Synthetic Sources
   - i. Cosmetics
   - ii. Cleaning agents
   - iii. Therapeutics.
3. Other sources include:
   - i. Agricultural sources
   - ii. Industrial Sources
   - iii. Domestic Sources.

B. Classification of poisons based on usage form of the finished products include:

- i. Food and packaging additives
- ii. Medicines
- iii. Household and cleaning product
- iv. Occupational toxicants.

C. Classification based on the public health importance of the toxicants

- i. Plant or animal poisons
- ii. Corrosives
- iii. Carcinogens or mutagens
- iv. Pesticides including insecticides, herbicides, rodenticide, fungicides and fumigants.
- v. Household materials
- vi. Airborne poisons
- vii. Ionising poisons
- viii. Solvents
- ix. Environmental pollutants e.g. heavy metals, organophosphates.

D. Classification based on the affinity or target sites

This is related to the organ with high significant toxic effect.
Examples include: hepatotoxicity, nephrotoxicity
There are generally two types of toxic entities: chemical and physical.

Global classifications of toxicants are in three areas:

i. Physical hazards (explosions and pyrotechnics),
ii. Health hazards and
iii. Environmental hazards.

6.0 TUTOR-MARKED ASSIGNMENT

1. What are toxicants?
2. Differentiate toxicants from therapeutics.
3. Classify the toxicants based on their sources and Global classification.

7.0 REFERENCES/FURTHER READING

"Toxicity Endpoints & Tests". AltTox.org. Retrieved 25 February 2012. http://alttox.org/ttrc/toxicity-tests/.

United Nations Economic Commission for Europe Globally Harmonized System of Classification and Labelling of Chemicals.

EPA implementation of Global Harmonization.

Globally Harmonized System of Classification and Labelling of Chemicals – Part 2, *Physical Hazards.*

Globally Harmonized System of Classification and Labelling of Chemicals – Part 3, *Health Hazards.*

Globally Harmonized System of Classification and Labelling of Chemicals – Part 4, *Environmental Hazards.*

www.Feedburner.com/toxicology 6/1 feb 22, 2009.

"http://en.wikipedia.org/w/index.php?title=Pyrotechnics&oldid=507706642".

"http://en.wikipedia.org/w/index.php?title=Explosion&oldid=507946141".

UNIT 4 TOXICITY OF ENVIRONMENTAL TOXICANTS

CONTENTS

3.0 INTRODUCTION

In Units 1 and 2 of this Module, we discussed the drug-body interactions that may ultimately result in toxicity. In this unit, we will explain the concept of toxicity. Toxicity is commonly associated with poisons or toxicants. We need to understand the relative meaning of toxicity. We will also discuss the various factors that affect toxicity and the mechanisms of chemical interactions that influence toxicity.
This unit is very interesting as the knowledge acquired will help you to make critical decisions in chemical safety and poisoning managements.

4.0 OBJECTIVES

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

- explain the term ‘toxicity’
- outline possible outcomes of exposure to environmental substances
- enumerate factors that can modify the known effects of a toxicant on an individual
- explain the mechanisms of substance interactions.

5.0 MAIN CONTENT

3.1 Meaning of Toxicity

Chemical substances (drugs) are of health importance because of their wanted (therapeutic) and/or unwanted (toxic) effects on living systems. Every drug at a particular dose has either of these effects. For instance, paracetamol is therapeutic at an adult dose of 1g but toxic at a higher dose of about 5g. Consequently, dosage (concentration) determines the toxicity of any chemical substance. In Pharmacoenvironmentology, it is factual that accumulation of therapeutic drugs, e.g. anti-cancer drugs in the environment can cause adverse effects on the organisms or food chain.

Toxicity is a measure of adverse, harmful or unwanted effect of a substance on any living system (be it at individual, cell, tissue, organ, system, organism or community level). Toxicity may result from therapeutic overdose, idiosyncratic or allergic reaction or toxic exposure. The toxic effect could be acute or chronic; local or systemic and reversible or irreversible. It is, however, different from drug side effect which is a known predictable adverse effect of a substance that occurs following normal exposure.

3.1.1 Outcomes of Exposure to Environmental Toxicants

Toxicity (unwanted) outcomes of environmental exposures to substances depend on drug-body interactions. A drug- body interaction may result in one or more of these outcomes:

i. **Allergic** outcome – immune response to chemicals e.g. hypersensitivity reaction.
ii. **Genetic** effect like mutation
iii. **Idiosyncratic** effect- unusual response to chemicals by a few individuals in a population.
iv. **Cumulative** effect outcome - response to chemicals stored over time in the body.
v. **Dependence** outcome - psychic or physical response to chemicals of abuse.
vi. **Antagonistic** effect - response to chemical antagonist in the body.
vii. **Summation** outcome - additional response to 2 or more chemical effects in the body.
viii. **Synergistic** effect - greater than additional response to 2 or more chemical effects in the body
ix. **Potentiating** effect - increased response due to exposure of active chemicals with a passive chemical.

x. **Interference** or infra additive outcome - lower response than the response of combined chemicals.
xi. **Tolerance** outcome - decreased responsiveness to a chemicals following previous administration.
xii. **Tachyphylactic** outcome - rapid onset of tolerance following chemical exposure.
xiii. **Cross-tolerance** outcome - acquired tolerance due to previous exposure to a different chemical.

3.2 Factors that may modify the Outcome (s) of Exposures to Environmental Toxicants

These are factors that may alter the effect of an environmental toxicant on individuals or circumstances. These include:

a. When exposure allowance or concentration of a toxicant is altered exceedingly.
b. When route or mode of exposure of a toxicant is altered.
c. When the rate and extent of absorption is altered for a particular exposed concentration or dose. This can vary in individuals or in different health conditions and it determines the bioavailability of the toxicant.
d. When there is different body size and composition. For instance, the larger the body (muscle) masses the lower the drug effect or response. Obese or fatty individual has smaller volume of distribution and may have toxicity faster than a lean individual of same weight or age.
e. When a drug distribution in the body vary. A drug widely distributed in all the body fluids has an effect lesser than when the distribution is restricted to a compartment.
f. Ability to bind to plasma proteins and tissues. The ability of a drug to bind to plasma proteins and tissues reduces the free active drug molecules that bind to the target receptors and consequently causes reduced effect.
g. When the rate of elimination or clearance of a toxicant from an individual is altered, for instance, when a drug is slowly eliminated from a body, the plasma concentration increases which in turn increases toxicity.
h. Physiological changes e.g. that accompany pregnancy or environmental impacts (such as temperature change) may alter the effect of a toxicant on an individual. For instance, if pregnancy increases the volume of distribution of a drug, it may reduce toxicity.
i. Pathological factors, for instance, renal dysfunction may reduce the elimination of a drug and increase the concentration of toxicant at the target site.

j. Genetic factors, for instance, when an individual may has higher DNA-transcription for enzymatic catabolism of a toxicant to inactive product. This individual will suffer less toxicity.
k. Interaction with other drugs alters the normal effect of a toxicant. Drug interactions may cause additive, synergistic or antagonistic effect which is different from normal toxicity effect.
l. Development of tolerance. This occurs when prior use of a drug may develop a mechanism of reducing the responsiveness of the body to that drug. For instance, an alcoholic may have higher enzymes that can metabolise similar drugs thereby reducing the drug's effects.
m. Drug-receptor interaction may be altered by factors such as drug isomers, pH, physical states, etc.
n. Functional state of an individual, such states include age, pregnancy, sleep, anxiety or stress can alter toxicity. For instance, an infant can suffer toxicity of a substance greater than an adult.
o. Placebo effects. In this case, the real toxic effect of the drug is significantly influenced by pseudo response by the individual. The person feels worse and this is wrongly attributed to the drug.

3.3 Mechanisms of Toxicants Interactions in the Body

These are to explain how the outcome of an environmental exposure to a toxicant can alter due to concurrent presence of other drug (s).

The mechanisms of drugs interaction are classified as:

1. Toxicokinetics mechanisms
2. Toxicodynamic mechanisms
3. Combined toxicity.

3.3.1 Toxicokinetics Mechanisms

These are interactions that may occur at the stages of toxicant liberation, absorption, distribution, metabolism or excretion in the presence of another drug in the body. One of the drugs may cause a change in the body system that either increases or decreases the kinetics of the other drug(s).

Examples:

a. Antacids may adsorb toxicants in GIT and decrease their absorption into the blood. Such interacting drugs are Iron, Digoxin
b. Alcohol may induce an enzymatic action on another drug e.g. increase the hepatotoxicity of acetaminophen.
c. Probenecid may decrease renal excretion of penicillin by inhibiting its secretion, thereby causing penicillin toxicity.

3.3.2 Toxicodynamic Mechanisms

Drugs with similar toxicological effects exposed concurrently may cause additive or synergistic effects while drugs with opposing or competitive effects give antagonistic or reduced effects.

Examples:

a) Barbiturates given to alcoholic may cause additive CNS depression toxicity.
b) Mono amine oxidase inhibitors given to one on insulin may increase its hypoglycaemic toxicity.

3.3.3 Combined Organ Toxicity

The use of two or more drugs with the same organ toxicity may increase the damage of the organ(s).

Example:
Salicylates cause additive toxic effect on the gastric mucosa when given with corticosteroids.

6.0 CONCLUSION

Interestingly, we have discussed the main outcome of exposure to toxicants and factors that influence them. You were also taught the mechanisms of interactions of the toxicants.

With these you are prepared to study those substances in the environment that are injurious to man. In the next unit, we will identify and classify toxicants.

7.0 SUMMARY

In this unit, we explained the meaning of toxicity of a substance. The outcomes of Exposure to Environmental Toxicants, such as the following:

a. Allergic outcome
b. Genetic outcome
c. Idiosyncrasy outcome
d. Cumulative effect
e. Dependence outcome
f. Interaction outcome
g. Antagonism outcome
h. Summation outcome
i. Synergistic effect
j. Potentiating outcome
k. Interference or infra additive outcome
l. Tolerance outcome
m. Tachyphylactic outcome
n. Cross-tolerance.

Factors that may modify the outcome(s) of exposures to environmental toxicants include:

a. Exposure allowance or concentration
b. Route or mode of exposure
c. Rate and extent of absorption
d. Bioavailability
e. Body size and composition
f. Drug distribution
g. Ability to bind to plasma proteins and tissues;
h. Rate of elimination or clearance
i. Physiological changes
j. Pathological factors
k. Genetic factors
l. Drug interaction
m. Development of tolerance
n. Drug-receptor interaction
o. Functional state of an individual
p. Placebo effects.

Mechanisms of toxicants interactions in the body are:

a. Toxicokinetics mechanisms,
b. Toxicodynamic mechanisms, and
c. Combined toxicity.

8.0 TUTOR-MARKED ASSIGNMENT

1. a. Explain the term 'toxicity'.
2. Differentiate drug side effect from drug toxicity.
3. a. List five (5) outcomes of exposure to environmental toxicants
4. Explain four of these.
5. a. List ten (10) factors that may modify the outcome(s) of Exposures to Environmental.
6. Explain five of these.
7. a. Outline three mechanisms of substance interaction.
   b. Explain two with an example each.

9.0 REFERENCES/FURTHER READING

Casarett, L. J. & Doull, J. (Eds). (1975). *Toxicology: The basic science of poisons*. New York: Macmillan publishing Co. Inc.

Goodman, L. S. & Gilman, A. (Eds). (1975). *The Pharmacological Basis of Therapeutics.* (5th ed.). New York: Macmillan Publishing Co. Inc.

Iwuji, S. C. (2010). *Basics and Applications of General Pharmacology*. Owerri, Nigeria: Milestone Publishers Ltd.

Katzung, B.G. (2007). *Basic and Clinical Pharmacology*. (10th ed.). Appleton and Lange, U.S.A: Prentice-hall International Inc.

Klaassen, C. D. (2001). Principles of Toxicology and Treatment of Poisoning. In: *Goodman and Gillman's pharmacological Basis of Therapeutics.* (10th ed.). New York. Mc Graw-Hill Co. Inc.

MODULE 3 BASIC TOXICOLOGY OF ENVIRONMENTAL TOXICANTS

UNIT 1 TOXICOLOGY OF PESTICIDES

CONTENTS

10.0 INTRODUCTION

In Module 2, we introduced and classified environmental toxicants. One of the commonest groups with great public health significance is pesticides. These are substances used to control pests. Pests include insects, plant pathogens, weeds, molluscs, birds, mammals, fish, nematodes (roundworms), and microbes that destroy property, spread disease or are vectors for disease or cause nuisance.

Pesticides are substances or mixture of substances intended for preventing, destroying, repelling or mitigating any pest. Environmental Toxicology aims at quantifying the health-threatening effects of pesticides in the environment on biologic systems in order to detect, treat and possibly prevent any damage.

Agricultural exposure is the most common cause of organophosphates and carbamate poisoning. The World Health Organization (WHO) classifies these poisonings as Class I (extremely toxic) to Class III (slightly hazardous). The WHO advocates banning or strong restrictions on the use of Class I pesticides and a reduction in the use of pesticides to a minimal number of compounds that are less hazardous than others.
Organophosphate and organocarbamate pesticides are the two widely used classes of non-persistent insecticides. They are non-persistent because they break down readily into harmless and water-soluble products, once released into the environment. Because they do not last, they must be highly potent and they are powerful neurotoxins.

Since the main goal of this course is to ensure chemical safety to humans, animals and other forms of life, in this the concept of toxicity. Toxicity is commonly associated with poisons or toxicants. We need to understand the relative meaning of toxicity.

We will also discuss the various factors that affect toxicity of pesticides and the mechanisms of chemical interactions that influence toxicity.

11.0 OBJECTIVES

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

- define pesticides
- outline the uses of pesticides
- classify pesticides with examples
- explain the basic toxicology of pesticides
- identify other non pesticide, non-pharmaceutical organic toxicants
- state the toxicological implication of these toxicants.

12.0 MAIN CONTENT

12.1 What are Pesticides?

A pesticide is defined as any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the

production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thinning fruit or preventing the premature fall of fruit. Also used as substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport (FAO, 2002).

A pesticide may be a chemical, biological agent (such as a virus or bacterium), antimicrobial, disinfectant or device used against any pest. Pests include insects, plant pathogens, weeds, molluscs, birds, mammals, fish, nematodes (roundworms), and microbes that destroy property, spread disease or are vectors for disease or cause nuisance.

3.2 History of Pesticides and the Epidemiology of its Toxicity

Since before 2000 BC, humans have utilised pesticides to protect their crops. The first known pesticide was elemental sulphur dusting used in ancient Sumer about 4,500 years ago in ancient Mesopotamia. The Rig Veda, which is about 4,000 years old, mentions the use of poisonous plants for pest control. By the 15th century, toxic chemicals such as arsenic, mercury and lead were being applied to crops to kill pests. In the 17th century, nicotine sulphate was extracted from tobacco leaves for use as an insecticide. The 19th century saw the introduction of two more natural pesticides, pyrethrum, which is derived from chrysanthemums, and rotenone, which is derived from the roots of tropical vegetables. Until the 1950s, arsenic-based pesticides were dominant. Paul Müller discovered that DDT was a very effective insecticide. Organochlorines such as DDT were dominant, but they were replaced in the U.S. by organophosphates and carbamates by 1975. Since then, pyrethrin compounds have become the dominant insecticide. Herbicides became common in the 1960s, led by "triazine and other nitrogen-based compounds, carboxylic acids such as 2,4-dichlorophenoxyacetic acid, and glyphosphate".

The first legislation providing federal authority for regulating pesticides was enacted in 1910; however, decades later during the 1940s manufacturers began to produce large amounts of synthetic pesticides and their use became widespread. Some sources consider the 1940s and 1950s to have been the start of the "pesticide era." Although the U.S. Environmental Protection Agency was established in 1970 and amendments to the pesticide law in 1972, pesticide use has increased 50-fold since 1950 and 2.3 million tonnes (2.5 million short tons) of

industrial pesticides are now used each year. Seventy-five per cent of all pesticides in the world are used in developed countries, but use in developing countries is increasing. In 2001, the EPA stopped reporting yearly pesticide use statistics. A study of USA pesticide use trends through 1997 was published in 2003 by the National Science Foundation's Center for Integrated Pest Management.

The first organochlorine pesticide to be applied on a large scale was *para-dichlorodiphenyl trichloro ethane*,(DDT). It was introduced during World War II to control malaria and typhus. DDT is chemically stable, has low volatility, evaporates only slowly and has low solubility in water. It is because of these favourable characteristics, DDT was considered as an ideal insecticide.

One of the main drawbacks of DDT is that it is stable and persists in the environment and it accumulates in the food chain. The bioaccumulation of DDT can be explained as follows: if the plankton present in sea/river water contains DDT to the extent of 0.04 ppm, the clauses that consume plankton concentrate it ten times. (i.e. they contain about 0.4 ppm DDT) . From the clause to fish, which feed on the clause, it is increased to around 2 ppm and from fish to eating birds it is further concentrated to 3 to 75 ppm. It is well known that many birds which have consumes high levels of DDT are threatened with extinction, which was a serious threat to biodiversity.

In addition, DDT began to lose its effectiveness because of insect resistance. Because of these reason newer insecticides were developed to replace DDT such an attempt led to the discovery of other organochlorine molecules quite different from DDT which were also insect neurotoxins. Several of these were the products of an addition reaction between perchlorocyclopentadiene and an olefine molecule to give a cyclodiene pesticide. Rachel Carson wrote the best-selling book Silent Spring about biological magnification.

The agricultural use of DDT is now banned under the Stockholm Convention on Persistent Organic Pollutants, but it is still used in some developing nations to prevent malaria and other tropical diseases by spraying on interior walls to kill or repel mosquitoes.

Table 3.1: Chronology of Pesticide Development

Period	Example	Source	Characteristics
1800-1920s	Early organics, nitro-phenols, chlorophenols, creosote, naphthalene, petroleum oils	Organic chemistry, by-products of coal gas production, etc.	Often lack specificity and were toxic to user or non-target organisms
1945-1955	Chlorinated organics, DDT, HCCH, chlorinated cyclodienes	Organic synthesis	Persistent, good selectivity, good agricultural properties, good public health performance, resistance, harmful ecological effects
1945-1970	Cholinesterase inhibitors, organophosphorus compounds, carbamates	Organic synthesis, good use of structure-activity relationships	Lower persistence, some user toxicity, some environmental problems
1970-1985	Synthetic pyrethroids, avermectins, juvenile hormone mimics, biological pesticides	Refinement of structure activity relationships, new target systems	Some lack of selectivity, resistance, costs and variable persistence
1985-	Genetically engineered organisms	Transfer of genes for biological pesticides to other organisms and into beneficial plants and animals. Genetic alteration of plants to resist non-target effects of pesticides	Possible problems with mutations and escapes, disruption of microbiological ecology, monopoly on products

Source**:** (Stephenson and Solomon, 1993) Retrieved from "http://en.wikipedia.org/w/index.php?title=Water_pollution&oldid=505453536"

3.3 Classification of Pesticides

Gilden, Huffling and Sattler (2010) categorised pesticides into four main substituent chemicals: herbicides; fungicides; insecticides and bactericides or into herbicides, insecticides, fungicides, rodenticides, pediculicides, and biocides.

However, pesticides can be classified by target organism, chemical structure, origin and biological mechanism.

3.3.1 Classification Based on Target Organism

Table 3.2: Classification of Pesticides Based on Target Organism

Type of Pesticide	Target Pest Group
Algicides or Algaecides	Algae
Avicides	Birds
Bactericides	Bacteria
Fungicides	Fungi and Oomycetes
Insecticides	Insects
Miticides or Acaricides	Mites
Molluscicides	Snails
Nematicides	Nematodes
Rodenticides	Rodents
Virucides	Viruses

Subclasses of pesticides include: herbicides, insecticides, fungicides, rodenticides, pediculicides, and biocides (Gilden et al., 2010).
Prominent families of herbicides include phenoxy and benzoic acid herbicides (e.g. 2,4-D), triazines (e.g. atrazine), ureas (e.g. diuron), and Chloroacetanilides (e.g. alachlor). Phenoxy compounds tend to selectively kill broadleaved weeds rather than grasses. Many commonly used pesticides are not included in these families, including glyphosate.

3.3.2 Classification Based on Chemical Structure

Many pesticides can be grouped into chemical families. Prominent insecticide families include organochlorines, organophosphates, and carbamates.
Organochlorine hydrocarbons (e.g. DDT) could be separated into dichlorodiphenylethanes, cyclodiene compounds, and other related compounds.

Organophosphates are the basis of many pesticides. Thiocarbamate and dithiocarbamates are subclasses of carbamates.

3.3.3 Classification Based on Origin

Pesticides can also be classed as inorganic, synthetic, or biologicals (biopesticides), although the distinction can sometimes be blurred.

Biopesticides include microbial pesticides and biochemical pesticides. Plant-derived pesticides, or "botanicals", have been developing quickly. These include the pyrethroids, rotenoids, nicotinoids, and a fourth group that includes strychnine and scilliroside (Kamrin, 1997).

3.3.4 Classification Based on the Biological Mechanism or Application Method

Most pesticides work by poisoning pests. A systemic pesticide moves inside a plant following absorption by the plant. With insecticides and most fungicides, this movement is usually upward (through the xylem) and outward. Increased efficiency may be a result. Systemic insecticides, which poison pollen and nectar in the flowers, may kill bees and other needed pollinators.

In 2009, the development of a new class of fungicides called paldoxins was announced. These work by taking advantage of natural defense chemicals released by plants called phytoalexins, which fungi then detoxify using enzymes. The paldoxins inhibit the fungi's detoxification enzymes. They are believed to be safer and greener (EurekAlert, 2009).
The organochlorines operate by disrupting the sodium/potassium balance of the nerve fiber, forcing the nerve to transmit continuously. Organophosphate and carbamates largely replaced organochlorines. Both operate through inhibiting the enzyme acetylcholinesterase, allowing acetylcholine to transfer nerve impulses indefinitely and causing a variety of symptoms such as weakness or paralysis.

The phenoxy and benzoic acid herbicides function similar to plant growth hormones, and grow cells without normal cell division, crushing the plants nutrient transport system. Triazines interfere with photsynthesis.

3.4 Public Health Importance of Pesticides

Although there are benefits to the use of pesticides, some also have drawbacks, such as potential toxicity to humans and other animals.

There are two levels of benefits for pesticide use, primary and secondary. Primary benefits are direct gains from the use of pesticides and secondary benefits are effects that are more long-term.

Primary benefits

1. Controlling pests and plant disease vectors
   - improved crop/livestock yields
   - improved crop/livestock quality
   - invasive species controlled.

2. Controlling human/livestock disease vectors and nuisance organisms:
   - human lives saved and suffering reduced
   - animal lives saved and suffering reduced
   - diseases contained geographically.

3. Prevention of control organisms that harm other human activities and structures:
   - drivers view unobstructed
   - tree/brush/leaf hazards prevented
   - wooden structures protected.

Secondary benefits

1. Community benefits:
   - farm and agribusiness revenues
   - nutrition and health improved
   - food safety and security.

2. National benefits:
   - workforce productivity increased
   - increased export revenues
   - national agriculture economy.

3. Global benefits:
   - assured safe and diverse food supply
   - less greenhouse gas
   - reduced civil unrest.

On the other hand, according to the Stockholm Convention on Persistent Organic Pollutants, 9 of the 12 most dangerous and persistent organic chemicals are pesticides. The toxicities of organochlorides vary greatly, but they have been phased out because of their persistence and potential to bioaccumulate. Organophosphates are quite toxic to vertebrates, and have in some cases been replaced by less toxic carbamates.

3.5 Toxicokinetics of Pesticides

Pesticides can be absorbed when contacted, ingested or inhaled. The organophosphate chemicals are absorbed by the skin, conjunctiva, gastrointestinal and respiratory tracts. They undergo biotransformation in human body.

Although most patients rapidly become symptomatic, the onset and severity of symptoms depend on the specific compound, amount, route of exposure, and rate of metabolic degradation.

Most pesticides are highly lipid soluble compounds and are well absorbed from intact skin, oral mucous membranes, conjunctiva and the gastrointestinal and respiratory tracts. They are rapidly redistributed to all body tissues. The highest concentrations are found in the liver and kidney. This high lipid solubility means that they easily cross the blood/brain barrier and therefore produce potent effects on the CNS. Metabolism occurs principally by oxidation in the liver with conjugation and esterase hydrolysis producing a half-life of minutes - hours. The oxidative metabolites of malathion and parathion (malaoxon and paraoxon) are active forms and are subsequently hydrolysed into inactive metabolites. Elimination of organophosphorus compounds and its metabolites occur mainly via urine, bile and faeces.

3.6 Toxicodynamics of Pesticides

Many pesticides, e.g. organophosphates, are potent nerve agents, functioning by inhibiting the action of acetyl cholinesterase (AChE) in nerve cells. Early poisoning cases present predominantly with parasympathetic over-activity, and a characteristic garlic smell. The end result may be a multi-system manifestation involving the gastrointestinal, respiratory, cardiovascular and nervous systems, as well as involvement of skeletal muscle, other organs and metabolic effects such as hypo- or hyperglycaemia. Most fatalities occur within 24 hours and those who recover usually do so within 10 days.

3.6.1 Mechanism of Action of Pesticides

The organophosphates and carbamates presumably work by inhibiting the enzyme *acetyl cholinesterase* which hydrolyses the neurotransmitter *acetylcholine*.

The primary mechanism of action of organophosphate pesticides is inhibition of carboxyl ester hydrolases, particularly acetylcholinesterase (AChE). AChE is an enzyme that degrades the neurotransmitter acetylcholine (ACh) into choline and acetic acid. ACh is found in the

central and peripheral nervous system, neuromuscular junctions, and red blood cells (RBCs).

Organophosphates inactivate AChE by phosphorylating the serine hydroxyl group located at the active site of AChE. The phosphorylation occurs by loss of an organophosphate leaving group and establishment of a covalent bond with AChE.

Cleavage of the carbon-enzyme bond from ACh is complete in a few microseconds. However, the breaking of the phosphorus-enzyme bond requires a period varying from 60 minutes to several weeks, depending on the organophosphorus compound involved.

Once AChE has been inactivated, ACh accumulates throughout the nervous system, resulting in overstimulation of muscarinic and nicotinic receptors, and subsequently disrupts the transmission of nerve impulses in both the peripheral and central nervous system. Clinical effects are manifested via activation of the autonomic and central nervous systems and at nicotinic receptors on skeletal muscle.

In insects, the levels of active enzyme decreases. The acetylcholine is no longer decomposed rapidly enough and the nerve starts firing in an uncontrollable manner, with the result the insect is quickly killed.

The organophosphate insecticides are superior to many organochlorine insecticides because they readily undergo biodegradation and do not bioaccumulate.

3.6.2 Organochlorine Pesticides

Like many other insecticides, organochlorine pesticides attack the central nervous system. Because of its hydrophobicity, DDT is able to readily penetrate the waxy outer coating of insects and quickly paralyses the insect. But its toxicity to animals, including humans, is low, because animals absorb much less of chemical in their tissues.

13.0 CONCLUSION

Pesticides are purposeful environmental contaminants introduced in order to improve environmental quality for man and his domesticated animal and plants. Unfortunately, pesticides are chemical hazards of concern to public health. There are different classes of pesticides. Based on target organisms, we have herbicides, fungicides, insecticides and bactericides. Chemically, prominent insecticide families include organochlorides, organophosphates, and carbamates. Pesticides can be

absorbed when contacted, ingested or inhaled. Toxicology of pesticides explains the fate of pesticides and their effects of human.

14.0 SUMMARY

In this unit, the following were discussed:

- The meaning of pesticides: chemicals used in controlling pests
- History of pesticides: different types of pesticides have been used over the history of man.
- Classification of pesticides
    a) Classification based on target organism
    b) Classification based on chemical structure
    c) Classification based on origin
    d) Classification based on the biological mechanism or application method

- Public health importance of pesticides: the benefits and hazards of pesticides
- Toxicokinetics of pesticides
- Toxicodynamics of pesticides
- Toxicity of pesticides
- Manifestation of poisoning symptoms.

15.0 TUTOR-MARKED ASSIGNMENT

1. What are pesticides?
2. Classify pesticides based on their target organisms.
3. List four toxic effects of pesticides on man.

16.0 REFERENCES/FURTHER READING

Food and Agriculture Organization of the United Nations (2002). *International Code of Conduct on the Distribution and Use of Pesticide*s. Retrieved on 2007-10-25.

Gilden R. C, Huffling, K. & Sattler, B. (2010). "Pesticides and health risks". *J Obstet Gynecol Neonatal Nurs.*, 39 (1): 103–10. doi:10.1111/j.1552- 6909.2009.01092.x. PMID 20409108.

http://www.pops.int/documents/guidance/beg_guide.pdf

US Environmental (July 24, 2007). What is a Pesticide? epa. gov. Retrieved on September 15, 2007.

"www.chromatography-online.org". http://www.chromatography-online.org/directory/analtcat-24/page.html.

Cornell University. Toxicity of Pesticides. Pesticide Fact Sheets and Tutorial, Module 4. *Pesticide Safety Education Program*. Retrieved on 2007-10-10.

Council on Scientific Affairs, American Medical Association. (1997). "Educational and Informational Strategies to Reduce Pesticide Risks". *Preventive Medicine,* Vol. 26, N0 2

EPA. Types of Pesticides. Last updated on Thursday, January 29th, 2009.

EurekAlert. (2009). *New 'green' pesticides are first to exploit plant defences in battle of the fungi.*

http/en. Wikipedia.com/pesticides. Retrieved on 2012-08-02.

http://en.wikipedia.org/w/index.php?title=Pesticide&oldid=482925552

Kamrin, M. A. (1997). *Pesticide Profiles: toxicity, environmental impact, and fate*. CRC Press.

UNIT 2 OTHER ORGANIC TOXICANTS

CONTENTS

1.0 INTRODUCTION

In Unit 1 of this Module, we discussed pesticides which are used in the control of pests and found to have adverse effects on man.

In this unit, we will discuss the toxicology of organic toxicants other than pesticides or pharmaceuticals.

2.0 OBJECTIVES

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

- identify organic pesticides
- outline the public health importance of major organic pollutants in the environment
- enumerate the effects of organic pollutants on man.

3.0 MAIN CONTENT

An organic compound is any member of a large class of gaseous, liquid, or solid chemical compounds whose molecules contain carbon. Toxicants containing organic compounds are known as organic toxicants.

3.1 Classification of Organophosphate Pollutants

Phosphorus can adopt a variety of oxidation states. It is general to classify Organophosphorus compounds based on their oxidative states:

- derivatives of phosphorus (V)
- derivatives of phosphorus (III), which are the predominant classes of compounds.

In the environment, these compounds breakdown via hydrolysis to eventually afford phosphate and the organic alcohol or amine from which they are derived.

3.2 Public Health Classification of Organophosphate Toxicants

i. Pesticides including malathion, parathion, diazinon, fenthion, dichlorvos, chlorpyrifos, ethion , tribufos [DEF], merphos.
ii. Nerve gases including soman, sarin, tabun, VX.
iii. Ophthalmic agents: echothiophate, isoflurophate.
iv. Antihelmintics such as trichlorfon.

3.3 Toxicology of Other Organic Toxicants

1. Organophosphate pollutant Toxicity

In health, agriculture, and government, the word "organophosphates" refers to a group of insecticides or nerve agents acting on the enzyme acetylcholinesterase (the pesticide group carbamates also act on this enzyme, but through a different mechanism). The term is used often to describe virtually any organic phosphorus(V)-containing compound, especially when dealing with neurotoxic compounds. Many of the so called organophosphates contain C-P bonds. For instance, sarin is *O*-isopropyl methylphosphonofluoridate, which is formally derived from phosphorous acid ($HP(O)(OH)_2$), not phosphoric acid ($P(O)(OH)_3$). Also, many compounds which are derivatives of phosphinic acid are used as neurotoxic organophosphates.

Organophosphate pesticides (as well as sarin and VX nerve agents) irreversibly inactivate acetylcholinesterase, which is essential to nerve function in insects, humans, and many other animals. Organophosphate pesticides affect this enzyme in varied ways, and thus in their potential for poisoning. For instance, parathion, one of the first OPs commercialised, is many times more potent than malathion, an insecticide used in combating the Mediterranean fruit fly (Med-fly) and West Nile Virus-transmitting mosquitoes.

Organophosphate pesticides degrade rapidly by hydrolysis on exposure to sunlight, air, and soil, although small amounts can be detected in food and drinking water. Their ability to degrade made them an attractive

alternative to the persistent organochloride pesticides, such as DDT, aldrin and dieldrin. Although organophosphates degrade faster than the organochlorides, they have greater acute toxicity; posing risks to people who may be exposed to large amounts.

They are manufactured for selective use such as insecticides or chemical warfare agents. However, their use as insecticides is not without health (systemic) and ecotoxicity. They are useful insecticides when in direct contact with insects or when used as plant systemic where the agent is translocated within the plant and exerts lethal effects on insects that feed on plants.

Organophosphates are also used in chemical warfare. Agents such as tabun ($C_5H_{11}N_2O_2P$) and sarin($C_4H_{10}FO_2P$) which are similar to insecticides, such as malathion, but are highly more potent.

2. Toxicology of Volatile Organic Compounds (VOC)

VOC constitute a major group of indoor air pollutants encompassing diverse chemicals such as aldehydes, terpenes, and aromatic, aliphatic and halogenated hydrocarbons.
Examples of VOC include:

a. Formaldehyde carcinogenesis is a high- dose phenomenon with a determining role for cytolethality.
b. This may also be true for acetaldehyde carcinogenesis.
c. Being a reactive, potent DNA-protein cross-linker and a major indoor air contaminant, acrolein is possibly carcinogenic.
d. Terpenes
e. Benzene is a human carcinogen at high haemotoxic exposure levels.
f. In comparison with benzene, detoxification of toluene and xylene is rapid which may explain the non-carcinogenicity of these benzene homologues.
g. Hexane concentrations are orders of magnitude lower than exposure levels associated with clinically overt neuropathy.
h. Polycyclic aromatic hydrocarbons (PAHs)
i. Phenols
j. Nitrosamines
k. Isocyanates and methyl isocyanates
l. Organophosphates and carbamates
m. Organochlorine compounds & PCBS
n. Dioxins and polychlorinated biphenyls
o. Polychlorinated biphenyls.

a) **Formaldehyde and acetaldehyde:** Aldehydes contain carbonyl (C=O) groups. Because of its widespread use and toxicity, formaldehyde becomes important. Formaldehyde is used at 37-50% aqueous solution. Formaldehyde is inhaled in the form of molecular formaldehyde vapour or through formation as aqueous solution. Prolonged and continuous exposure to formaldehyde can cause hypersensitivity. It is a severe irritant to mucous membrane and alimentary tracts. Individuals exposed to greater than 1 ppm formaldehyde develop symptoms that include drowsiness, nausea, headaches, and respiratory ailments. Because formaldehyde is potentially carcinogenic, chronic exposure, even at low doses, poses public health problem. The toxicity of formaldehyde is largely due to its metabolic oxidation product, formic acid.

The water-soluble lower aldehydes cause intense irritation. These aldehydes attack the exposed moist tissue, particularly the eyes and mucous membranes of the upper respiratory tract. The aldehydes that are less soluble can penetrate further into the respiratory tract and affect the lungs. Colourless, liquid acetaldehyde is less toxic than acrolein and acts as irritant, and systemically, as a narcotic to the central nervous system. Acrolein has an extremely irritating, choking odour and is highly lacrimatory. The inhalation of acrolein can cause severe damage to respiratory tract membranes.

b) **Benzene**: Benzene is derived mainly from crude oil and is widely used in petroleum, chemical, and manufacturing industries. It is one of the few chemicals classified as a known carcinogen, and is implicated as a causative agent in human leukemia. Inhaled benzene is readily absorbed by the blood from which it is strongly taken up by fatty tissues. In the liver it is converted to phenol by a phase _oxidation reaction. The benzene epoxide is the intermediate that is formed in the reaction which is believed to be involved in the damage of bone marrow. It is a skin irritant and progressively higher local exposures can cause skin redness, burning sensations, fluid accumulation and blistering. It is thought that preleukemia, leukemia or cancer may result from chronic benzene poisoning.

In many applications, it is being replaced by alkylated benzenes such as toluene which are much less toxic than benzene; the alkyl groups are readily oxidised by enzymes in the liver, producing benzoic acid or related acids which are readily excreted.

c) **Polycyclic aromatic hydrocarbons (PAHs)**: Compounds such as benzo[a]pyrene with four or more benzene rings fused together, are potent carcinogens. Their carcinogencity depends upon activation by the same class of liver enzymes, cytochrome P450, that metabolise toluene and often xenobiotics. When these enzymes add oxygen to the PAHs, they produce epoxide adducts that reacts strongly with the heterocyclic bases of DNA, altering genes.

There are two stereoisomers for this metabolite and both of them are known to be potent mutagens and presumably can cause cancer. PAHs are formed as side products of carbon fuel combustion. Though they are present at low levels in automobile exhaust, when large quantities of soot particles are produced, the levels are much higher.

d) **Phenols**: Phenols are common pollutants in industrial waste water, particularly in effluents from coke-oven and coal distillation plants. Some of the more important phenolic compounds are: (1) phenol (2) O-cresol (3) m-cresol (4) p-cresol (5) 2-naphthol (6) 2-nitrophenol and 7) pentachlorophenol.

The nitro-groups and halogen atoms (particularly chlorine) bonded to aromatic rings strongly affect the chemical and toxicological behaviour of phenolic compounds. Acute poisoning of phenol causes death after one and half hour exposure. It affects the central nervous system and causes gastrointestinal disturbances, kidney mal function, circulatory system failure, lung edema , and convulsions. Fatal doses of phenol can be absorbed through the skin. Chronic poisoning of phenol damages important organs like the spleen, pancreas, and kidneys.

e) **Nitrosamines**: Nitrosamines are anthropogenic carcinogens. These compounds are characterised by -N-N=O functional group. It is prevalent in whiskey, beer and cutting oil used in machining. Dimethyl nitrosamine is an industrial solvent and is known to be carcinogenic. It is believed that dimethylnitrosamine on enzymatic oxidation in the body, gives rise to formaldehyde and an unstable intermediate. This unstable intermediate is the source for methyl carbonium ion (CH_3^+) a powerful electrophile, which can readily react with DNA if generated nearby.

f) **Isocyanates and methyl isocyanates:** Isocyanates are compounds with the general formula R-N=C=O. They are widely used industrial chemicals and they are noted for their high chemical and metabolic reactivity of their characteristic

functional group. Methyl isocyanate (MIC) (CH3-N=C=O) is the starting material for the production of carbaryl pesticide, MIC is extremely reactive and can react with any chemical including itself to generate considerable heat and CO2 The heat released accelerates the reaction and the pressure goes on building up till it reaches an explosive level. MIC is invariably accompanied by $COCl_2$. The toxic effect of MIC is enhanced by $COCl_2$. This toxic agent was involved in the catastrophic industrial poisoning in Bhopal on December 2, 1984. The lungs of victims were attacked. Survivours suffered long term shortness of breath and weakness from lung damage.

g) Dioxins and polychlorinated biphenyls (Dioxins and furans): Dioxins refer to the family of polychlorinated dibenzodioxins, sometimes abbreviated as PCDDs. The polychlorinated dibenzofurans (PCDFs) have similar structure. These chemicals are not made intentionally, but are formed as contaminants in several large scale processes, including (1) combustion (2) paper-pulp bleaching with chlorine, and (3) manufacture of certain chlorophenol chemicals. Among these group of compounds 2,3,7,8-tetrachlorodibenzodioxin (TCDD) is extraordinarily toxic to animals causing birth defects, cancer, skin disorders, liver damage, suppression of immune system and death. The LD50 in male guinea pig was only 0,6μg/kg.

The world health organisation has classified TCDD as a known human carcinogen. The molecule binds strongly to the receptor protein that is present in all animal species. This receptor called Ah(aryl hydro carbon) is activated by a number of planar aromatic molecules.(its natural substrate is still unknown); the binding of TCDD is particularly strong, with high equilibrium constant. Among the dioxins TCDD is the most toxic. Toxicity decreases progressively when chlorine atoms are removed from 2,3,7 and 8 positions. These alterations reduce the 'fit' of the molecule to the binding site of the Ah receptor.

h) Polychlorinated biphenyls: The polychlorinated biphenyls (PCBs) are made by chlorinating the aromatic compound biphenyl. A complex mixture results, with variable numbers of chlorine atoms substituted at the various positions of the rings; a total of 209 congeners are possible. They were mainly used as a coolant in power transformers and capacitors because they are excellent insulators, are chemically stable and low inflammability and vapour pressure. Subsequently the PCBs also found use as

heat-transfer fluids in other machinery, as de-inking agents for recycled newsprint and as weather proofing agents. As a result of industrial discharges and disposal of these products, PCBs were spread wildly in the environment.

Since the PCBs are stable, bipophylic and persistent in the environment, they are subjected to bioaccumulation in the lipid tissue just as DDT. The PCBs are less toxic than PCDDs and PCDFs and possibly they operate by the same mechanism, binding to Ah receptor. The most toxic PCBs are those that have no chlorine atoms in the ortho position of the ring and can therefore adopt a coplanar configuration of the rings, as in PCDDs and PCDFs. If the substituents occupy three or four of the ortho position, the rings are definitely twisted away and PCBs with this substitution pattern will be least toxic.

3. Toxicology of Oleum

Oleum Latin (*oleum* = "oil"), or fuming sulphuric acid refers to a solution of various compositions of sulphur trioxide in sulphuric acid and urine, or sometimes more specifically to disulphuric acid (also known as pyrosulphuric acid). Oleum, which is a mixture of sulphuric acid and sulphur trioxide, is listed as a regulated toxic substance in 40 CFR 68.130. Sulphur trioxide is also listed individually as a regulated toxic substance.

Sulphuric acid is not very volatile, and therefore workplace exposures are primarily to mists or aerosols. Sulphuric acid is corrosive and can cause severe irritation or corrosive damage if inhaled. The degree and severity of respiratory effects are influenced by factors such as the physical state and particle size of the aerosol, deposition site, concentration and humidity. Sulphuric acid can cause severe lung damage with a life-threatening accumulation of fluid (pulmonary edema). The symptoms of pulmonary edema include coughing and shortness of breath and can be delayed until hours or days after the exposure. These symptoms are aggravated by physical exertion. Long term lung damage may result from a severe short term exposure.

4. Toxicology of Toxins

A **toxin** (from Ancient Greek: τοξικόν *toxikon*) is a poisonous substance produced within living cells or organisms; man-made substances created by artificial processes are thus excluded.

Toxins can be small molecules, peptides, or proteins that are capable of causing disease on contact with or absorption by body tissues interacting

with biological macromolecules such as enzymes or cellular receptors. Toxins vary greatly in their severity, ranging from usually minor and acute (as in a bee sting) to almost immediately deadly (as in botulinum toxin).

The term "biotoxin" is sometimes used to explicitly confirm the biological origin. Toxins produced by microorganisms are important virulence determinants responsible for microbial pathogenicity and/or evasion of the host immune response.

Biotoxins

Biotoxins vary greatly in purpose and mechanism, and can be highly complex (the venom of the cone snail contains dozens of small proteins, each targeting a specific nerve channel or receptor), or relatively small protein.

Biotoxins in nature have two primary functions:

- predation (spider, snake, scorpion, jellyfish, wasp)
- defense (bee, ant, termite, honeybee, wasp, poison dart frog).

Some of the more well known types of biotoxins include:

- Cyanotoxins, produced by cyanobacteria
- Hemotoxins target and destroy red blood cells, and are transmitted through the bloodstream.

  Organisms that produce hemotoxins include:
- Pit vipers, such as rattlesnakes
- Necrotoxins cause necrosis (i.e., death) in the cells they encounter and destroy all types of tissue [citation needed]. Necrotoxins spread through the bloodstream [citation needed]. In humans, skin and muscle tissues are most sensitive to necrotoxins [citation needed].

  Organisms that possess necrotoxins include:
- The brown recluse or "fiddle back" spider
- The "Puff Adder" - *Bitis arietans*
- Necrotising fasciitis (the "flesh eating" bacteria)
- Neurotoxins primarily affect the nervous systems of animals.

Organisms that possess neurotoxins include:

- The Black Widow and other widow spiders
- Most scorpions

- The box jellyfish
- Elapid snakes
- The cone Snail

Cytotoxins are toxic at the level of individual cells, either in a non-specific fashion or only in certain types of living cells:

- Ricin is a plant toxin found in the castor bean plant.
- Apitoxin, the honey bee venom.
- Mycotoxins are toxins produced by fungi. They are a common source of toxins in grains and other foods.
- Eosinophil derived neurotoxin is a toxin found in human encoded by the $RNASE_2$ gene. it is found only in eosinophils.

5. Toxicology of Plastics

A **plastic** material is any of a wide range of synthetic or semi-synthetic organic solids that are mouldable. Plastics are typically organic polymers of high molecular mass, but they often contain other substances. They are usually synthetic, most commonly derived from petrochemicals, but many are partially natural.

Due to their insolubility in water and relative chemical inertness, pure plastics generally have low toxicity. Some plastic products contain a variety of additives, some of which can be toxic. For example, plasticisers like adipates and phthalates are often added to brittle plastics like polyvinyl chloride to make them pliable enough for use in food packaging, toys, and many other items. Traces of these compounds can leach out of the product. Owing to concerns over the effects of such leachates, the European Union has restricted the use of DEHP (di-2-ethylhexyl phthalate) and other phthalates in some applications. Some compounds leaching from polystyrene food containers have been proposed to interfere with hormone functions and are suspected human carcinogens.

Whereas the finished plastic may be non-toxic, the monomers used in the manufacture of the parent polymers may be toxic. In some cases, small amounts of those chemicals can remain trapped in the product unless suitable processing is employed. For example, the World Health Organization's International Agency for Research on Cancer (IARC) has recognised that vinyl chloride, the precursor to PVC, as a human carcinogen.

6. Toxicology of Hydrocarbons

Hydrocarbons are a heterogeneous group of organic substances that are primarily composed of carbon and hydrogen molecules. They are quite abundant in modern society. Hydrocarbons from which one hydrogen atom has been removed are functional groups, called **hydrocarbyls**. Aromatic hydrocarbons (arenes), alkanes, alkenes, cycloalkanes and alkyne-based compounds are different types of hydrocarbons. The majority of hydrocarbons found naturally occur in crude oil, where decomposed organic matter provides an abundance of carbon and hydrogen which, when bonded, can catenate to form seemingly limitless chains.

Some of the most commonly ingested hydrocarbons include gasoline, lubricating oil, motor oil, mineral spirits, lighter fluid/naphtha, lamp oil, and kerosene. Other common sources of hydrocarbons include dry cleaning solutions, paint, spot remover, rubber cement, and solvents. In addition, many volatile substances that contain hydrocarbons (e.g., glue, propellants) are commonly abused for their euphoric effects.

Hydrocarbons can be classified as being aliphatic, in which the carbon moieties are arranged in a linear or branched chain, or aromatic, in which the carbon moieties are arranged in a ring. Halogenated hydrocarbons are a subgroup of aromatic hydrocarbons, in which one of the hydrogen molecules is substituted by a halogen group. The most important halogenated hydrocarbons include carbon tetrachloride, trichloroethylene, tetrachloroethylene, trichloroethane, chloroform, and methylene chloride.

Fig. 3.1: Many Types of Substances Pollute the Water

The hydrocarbons can be derived from either petroleum or wood. Petroleum distillates include kerosene, gasoline, and naphtha, whereas wood-derived hydrocarbons include turpentine and pine oil. The length of the chains as well as the degree of branching determine the phase of the hydrocarbon at room temperature; most are liquid, but some short-chain hydrocarbons (e.g., butane) are gas at room temperature, whereas other long-chain hydrocarbons (e.g., waxes) are solid at room temperature.

Toxicity from hydrocarbon ingestion can affect many different organs, but the lungs are the most commonly affected organ. The chemical properties of the individual hydrocarbon determine the specific toxicity, while the dose and route of ingestion affect which organs are exposed to the toxicity. Unlike the aromatic or aliphatic hydrocarbons, the halogenated hydrocarbons tend to cause a wider range of toxicity.
The recreational use of inhaling hydrocarbons and other volatile solvents for the purposes of creating a euphoric state is becoming increasingly common. Several methods are used for this abuse, including "sniffing" (directly inhaling vapours), "huffing" (placing a hydrocarbon-saturated rag over the mouth and nose and then inhaling), or "bagging" (inhaling via a plastic bag filled with hydrocarbon vapours).

The majority of hydrocarbons found naturally occur in crude oil, where decomposed organic matter provides an abundance of carbon and hydrogen which, when bonded, can catenate to form seemingly limitless chains.

Human health effects of pesticides

Perhaps the largest regional example of pesticide contamination and human health is that of the Aral Sea region. UNEP (1993) linked the effects of pesticides to "the level of oncological (cancer), pulmonary and haematological morbidity, as well as on inborn deformities and immune system deficiencies".

Human health effects are caused by:

Skin contact:	handling of pesticide products
Inhalation:	breathing of dust or spray
Ingestion:	pesticides consumed as a contaminant on/in food or in water.

The ecological **effects** of pesticides (and other organic contaminants) are varied and are often inter-related. Effects at the organism or ecological

level are usually considered to be an early warning indicator of potential human health impacts. The major types of effects are listed below and will vary depending on the organism under investigation and the type of pesticide. Different pesticides have markedly different effects on aquatic life which makes generalisation very difficult.

The important point is that many of these effects are chronic (not lethal), are often not noticed by casual observers, yet have consequences for the entire food chain. Some of these include:

i. Death of the organism.
ii. Cancers, tumours and lesions on fish and animals.
iii. Reproductive inhibition or failure.
iv. Suppression of immune system.
v. Disruption of endocrine (hormonal) system.
vi. Cellular and DNA damage.
vii. Teratogenic effects (physical deformities such as hooked beaks on birds).
viii. Poor fish health marked by low red to white blood cell ratio, excessive slime on fish scales and gills, etc.
ix. Intergenerational effects (effects are not apparent until subsequent generations of the organism).
x. Other physiological effects such as egg shell thinning.

These effects are not necessarily caused solely by exposure to pesticides or other organic contaminants, but may be associated with a combination of environmental stresses such as eutrophication and pathogens. These associated stresses need not be large to have a synergistic effect with organic micro pollutants.

Ecological effects of pesticides extend beyond individual organisms and can extend to ecosystems.

4.0 CONCLUSION

In this unit, we have discussed common organic pollutants such as benzene, oleum, hydrocarbons, toxins and plastics. We identified the toxicological implications of most organic materials around man.

5.0 SUMMARY

In this unit, we have explained classification of organophosphate poluttants. Classification of organophosphorus compounds based on their oxidative states:

- derivatives of phosphorus (V),
- derivatives of phosphorus (III), which are the predominant classes of compounds.

Public health classification of organophosphates is verse: e.g.

i. Pesticides including malathion, parathion, diazinon, fenthion, dichlorvos, chlorpyrifos, ethion , tribufos [DEF], merphos
ii. Nerve Gases including soman, sarin, tabun, VX
iii. Ophthalmic agents: echothiophate, isoflurophate
iv. Antihelmintics such as trichlorfon.

Toxicology of other Organic Toxicants

1. Organophosphate pollutant toxicity:

Organophosphate pesticides (as well as sarin and VX nerve agent) irreversibly inactivate acetylcholinesterase, which is essential to nerve function in insects, humans, and many other animals.

2. Toxicology of Volatile organic compounds (VOC)

Examples of VOC toxicity include:

i. Formaldehyde carcinogenesis is a high- dose phenomenon with a determining role for cytolethality. This may also be true for acetaldehyde carcinogenesis.
ii. Benzene is a human carcinogen at high haemotoxic exposure levels.
iii. Hexane concentrations are orders of magnitude lower than exposure levels associated with clinically overt neuropathy.
iv. Oleum inhaled. The degree and severity of respiratory effects are influenced by factors such as the physical state and particle size of the aerosol, deposition site, concentration and humidity.
v. Toxins causes Neurotoxins
vi. Plastics: World Health Organization's International Agency for Research on Cancer (IARC) has recognised that vinyl chloride, the precursor to PVC, as a human carcinogen.
vii. Toxicity from hydrocarbon ingestion can affect many different organs, but the lungs are the most commonly affected organ.

6.0 TUTOR-MARKED ASSIGNMENT

1. What are organic pollutants?
2. Identify five organic pollutants.
3. State the effects of four organic pollutants.

7.0 REFERENCES/FURTHER READING

"www.chromatography-online.org". http://www.chromatography-online.org/directory/analtcat-24/page.html.

Cornell University. Toxicity of Pesticides. *Module 4: Pesticide Fact Sheets and Tutorial*, Pesticide Safety Education Program.

Council on Scientific Affairs, American Medical Association. (1997). Educational and Informational Strategies to Reduce Pesticide Risks. *Preventive Medicine,* Vol. 26, 2.

EPA. *Types of Pesticides*. Last updated on Thursday, January 29th, 2009.

EurekAlert. (2009). *New 'green' pesticides are first to exploit plant defences in battle of the fungi.*

Food and Agriculture Organization of the United Nations (2002). *International Code of Conduct on the Distribution and Use of Pesticides.* Retrieved on 2007-10-25.

Gilden, R. C., Huffling, K. & Sattler, B. (2010). "Pesticides and Health Risks". *J Obstet Gynecol Neonatal Nurs.*, 39 (1): 103–10. doi:10.1111/j.1552-6909.2009.01092.x. PMID 20409108.

http/en. Wikipedia.com/pesticides. Retrieved on 2012-08-02.

http://en.wikipedia.org/w/index.php?title=Pesticide&oldid=482925552.

http://www.pops.int/documents/guidance/beg_guide.pdf

Kamrin, M. A. (1997). *Pesticide Profiles: toxicity, environmental impact, and fate.* CRC Press.

US Environmental (July 24, 2007). What is a Pesticide? epa.gov.us Retrieved on September 15, 2007.

UNIT 3 TOXICOLOGY OF HEAVY METALS

CONTENTS

1.0 INTRODUCTION

In Unit 2 of this Module, we discussed organic compounds, some are useful group of chemicals which in turn produces toxicity to man. In this unit, we will discuss a group of contaminants that enormously worry environmentalists.

Almost all metals can produce toxicity when they are being exposed to in sufficient quantities, but there are several others that produce toxicity at such low concentrations. Some of these include: lead, mercury, iron, copper, manganese, cadmium, arsenic, nickel, aluminium, silver and beryllium.

2.0 OBJECTIVES

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

- explain what a heavy metal is
- give a historical and public health importance of heavy metals
- give sources and examples of heavy metals
- explain the toxicity of the metals.

3.0 MAIN CONTENT

3.1 Meaning of Heavy Metal

A heavy metal is a member of a loosely defined subset of elements that exhibit metallic properties. It mainly includes the transition metals, some metalloids, lanthanides, and actinides. Many different definitions have been proposed - some based on density, some on atomic number or atomic weight, and some on chemical properties or toxicity (Duffus, 2002).

In medical usage, heavy metals are loosely defined and include all toxic metals irrespective of their atomic weight: "Heavy metal poisoning" can possibly include excessive amounts of iron, manganese, aluminium, mercury, cadmium, or beryllium (the fourth lightest element) or such a semimetal as arsenic. This definition excludes bismuth, the densest of approximately stable elements, because of its low toxicity.

The term heavy metal has been called a "misinterpretation" in an IUPAC technical report due to the contradictory definitions and its lack of a "coherent scientific basis" (Duffus, 2002). There is an alternative term toxic metal, for which no consensus of exact definition exists either. Depending on context, heavy metal can include elements lighter than carbon and can exclude some of the heaviest metals. Heavy metals occur naturally in the ecosystem with large variations in concentration. In modern times, anthropogenic sources of heavy metals, i.e. pollution, have been introduced to the ecosystem. Heavy metals can be a dangerous good (that is a hazardous material).

3.1.1 Historical Importance of Heavy Metals

While the toxic effects of these substances are a widespread concern in the modern industrial context, man has succeeded in poisoning himself with them repeatedly throughout recorded history.

One historian/toxicologist contends that the fall of the Roman Empire was hastened by the chronic lead poisoning experienced by the ruling classes who had water conducted through lead plumbing and drank wine from goblets which had lead/alloy composition.

The heightened concern for reduction of environmental pollution that has been occurring over the past 20–25 years has stimulated active continuing research and literature on the toxicology of heavy metals.

3.2 Common Sources of Heavy Metals

Heavy metal pollution can arise from many sources but most commonly arises from the purification of metals, e.g., the smelting of copper and the preparation of nuclear fuels. Electroplating is the primary source of chromium and cadmium. Through precipitation of their compounds or by ion exchange into soils and muds, heavy metal pollutants can localise and lay dormant.

3.3 Examples of Heavy Metals

Within the European community, the eleven elements of highest concern are arsenic, cadmium, cobalt, chromium, copper, mercury, manganese, nickel, lead, tin, and thallium.

3.4 Public Health Importance of Heavy Metals

Motivations for controlling heavy metal concentrations in gas streams are diverse. Some of them are dangerous to health or to the environment (e.g. mercury, cadmium, lead, chromium), some may cause corrosion (e.g. zinc, lead), some are harmful in other ways (e.g. arsenic may pollute catalysts). The emissions of heavy metals are regulated in waste incinerators. Some of these elements are actually necessary for humans in minute amounts (cobalt, copper, chromium, manganese, nickel) while others are carcinogenic or toxic, affecting, among others, the central nervous system (manganese, mercury, lead, arsenic), the kidneys or liver (mercury, lead, cadmium, copper) or skin, bones, or teeth (nickel, cadmium, copper, chromium).

Unlike organic pollutants, heavy metals do not decay and thus pose a different kind of challenge for remediation. Currently, plants or microorganisms are tentatively used to remove some heavy metals such as mercury. Plants which exhibit hyper accumulation can be used to remove heavy metals from soils by concentrating them in their bio matter. Some treatment of mining tailings has occurred where the vegetation is then incinerated to recover the heavy metals.

One of the largest problems associated with the persistence of heavy metals is the potential for bioaccumulation and biomagnifications causing heavier exposure for some organisms than is present in the environment alone. Coastal fish (such as the smooth toadfish) and seabirds (such as the Atlantic Puffin) are often monitored for the presence of such contaminants.

Minamata disease results from mercury poisoning, and *itai-itai* disease from cadmium poisoning.

Heavy metals in a hazardous materials (or "hazmat") setting are for the most part classified in "Misc." on the UN model hazard class, but they are sometimes labelled as a poison when being transported.

3.5 Toxicological Implications of Heavy Metals

Living organisms require varying amounts of "heavy metals". Iron, cobalt, copper, manganese, molybdenum, and zinc are required by humans. Excessive levels can be damaging to the organism. Other heavy metals such as mercury, plutonium, and lead are toxic metals that have no known vital or beneficial effect on organisms, and their accumulation over time in the bodies of animals can cause serious illness. Certain elements that are normally toxic are, for certain organisms or under certain conditions, beneficial. Examples include vanadium, tungsten, and even cadmium.

3.5.1 Toxicokinetics of Heavy Metals

Man is commonly exposed to the heavy metals through inhalation or ingestion of contaminated food or water. The fate of heavy metals in the body depends on their chemistry, dosage and sites of metabolism or storage.

3.5.2 Toxicodynamics of Heavy Metals

In general, heavy metals produce their toxicity by forming complexes or "ligands" with organic compounds. These modified biological molecules lose their ability to function properly, and result in malfunction or death of the affected cells. The most common groups involved in ligand formation are oxygen, sulphur, and nitrogen. When metals bind to these groups they may inactivate important enzyme systems, or affect protein structure.

3.5.3 Toxicity Implications of Some Heavy Metals

1. Arsenic

Arsenic can produce all three types of toxicity at difference dosages, acute, sub-acute, and chronic. One sign of acute exposure is oedema of the eyelids, and gastrointestinal irritation, and both central and peripheral neuropathies frequently occur. During chronic intoxication "garlic breath", skin sensitivity, dermatitis, and keratitus frequently occur. All types of arsenic exposure can cause kidney and liver damage, and in the most severe exposure there is erythrocyte haemolysis. Chelator used is **Dimercaprol**.

2. Lead

Following ingestion of a large amount of lead, there will be direct tissue interaction. This includes tissue desiccation, mucosal tissue damage in the GI tract, and convulsion possibly resulting in death. The most sensitive system is the hematopoietic (blood forming) system, with hypochromic microcytic anemia common. The biosynthesis of hemes in general is deranged by the presence of lead. All actively dividing cells are especially susceptible; hence acute intoxication has major potential for GI and renal mucosal damage. In addition there is a high risk of neurological damage. With acute lead poisoning use of intravenous EDTA is the preferred treatment modality, often supplemented with oral penicillamine, and sometimes with intramuscular injections of dimercaprol.

In chronic lead intoxication:

> With a gradual build-up of a positive lead balance there is no sudden onset of symptoms as seen with acute poisoning. The initial symptoms include clumsiness, ataxia, vertigo, irritability and insomnia. In affected children, they are often considered "slow", the real basis for the difficulty is not recognized. As the lead levels rise, hyper-excitability is seen. Confusion, delerium and convulsions may occur in some cases, while in others there is progressive lethargy leading to a comatose state.

One of the earliest diagnostic signs present is the appearance of "lead lines" at the gingival border in the mouth. This occurs because the lead following calcium pathways is secreted with the saliva. It then is involved in a reaction with oral bacteria which produce sulphides. The lead reacts with these compounds to form a purplish or black lead sulphide deposit which precipitates in the region of highest concentration, the "protected area" at the gingival border. Other metals also produce this phenomenon, but with differing colours for the deposit.

Toxicity from inorganic lead can be treated with chelators, but organic lead compounds such as tetra-ethyl lead produces a similar symptomology, but cannot be treated with these agents because they already have formed strong ligands with their organic constituents. The alkyl lead eventually is converted to inorganic lead, which can be treated with the chelators.

3. Mercury

Organic or inorganic mercury can both precipitate protein in a local reaction. In the GI tract, acute poisoning produces a sloughing away of the mucosa to an extent where pieces of the intestinal mucosa can be found in the stools. This produces a large loss of fluids and electrolytes. Mercury also breaks down barriers in the capillaries. This results in oedema throughout the body. A range of neurological toxicities are also common. These include lethargy (at low doses), excitement, hyper-reflexia, and tremor.

In chronic toxicity, often a psychotic state resulting in hyper-excitability. The expression 'Mad as a Hatter' originates from the hat-makers of the 19th century who were chronically exposed to mercury compounds used in making felt hats. The CNS effects are slowing or incompletely reversible. In chronic intoxication there is mercury line at the gingival border similar to the "lead line". Mercury is especially poisonous to rapidly growing tissue. A common effect is deterioration of alveolar bone in the jaw, with a subsequent loosening of the teeth. There are also substantial liver and kidney toxicity because of mucosal degeneration.

Mercury can be chelated in the peripheral tissues with EDTA and penicillamine. Even though the plasma levels can be reduced very efficiently, mercury forms alkyl ligands in the tissues. This is especially persistent in CNS tissue. Recovery from mercury poisoning can require months or years even with efficient chelator treatment, and is often incomplete.

4. Manganese

This heavy metal is frequently associated with iron deposits, and in fact the strata underlying Conception Bay providing the basis for the Wabana mines has very rich manganese content. This metal is known to block Calcium channels, and with chronic intoxication results in CNS dopamine depletion. This latter condition duplicates almost all the symptomology of Parkinson's disease, and is treated with some success using typical anti-Parkinson drugs. While the concentration in the surface water does not exceed official public health limits, it is in the high range of acceptable levels. It would be interesting to see if the epidemiology of Parkinson’s syndrome in that locality is different from regions in the province with lower manganese concentrations. Manganese excretion can be facilitated by the use of chelator therapy, but it is not as easily managed as lead or mercury, because it is further down the list of chelator affinities.

3.5.4 General Treatment of Heavy Metal Poisoning

Chelators are the class of compounds which are used in the treatment of heavy metal intoxication. A chelator is a flexible molecule with two or more electronegative groups that can form stable co-ordinate covalent bonds with cationic metal atoms. The complexes are then excreted by the body. The efficacy of a chelator is determined in part by the number of ligands available for metal binding, in general the greater number of ligands, the more stable the chelator-metal complex. Depending on the number of metal-ligand bonds, the chelator is designated as mono- bi- or polydentate. The chelator ligands include groups such as -OH, -SH, or -NH.

Adversely, chelators are relatively non-specific as to the metal ions they isolate, hence they also slurp up things like calcium and zinc which are vital for normal physiological function.

Some common chelators include:

1. Dimercaprol

It is a bidentate colourless oily liquid with the odour of rotten eggs. It is used in the treatment of lead and mercury intoxications as well as arsenic. It is far from innocuous, producing frequent side effects of hypertension and tachycardia, as well as headache, nausea, vomiting, lacrimation, salivation, parathesia, and pain. It is generally given by intramuscular injection.

The rationale for its use in arsenic poisoning was based on the fact that arsenic binds quite specifically to sulfur groups in the affected tissues. Dimercaprol has very active and relatively non-toxic sulphhydryl groups that interact with the arsenic to inactivate it.

2. Ethylenediamine-Tetra-Acetic Acid or EDTA

It is the most widely used chelator. It works well on many metals, the most notable of which are calcium, magnesium and lead. EDTA has relatively low toxicity, the major toxic response being impaired renal function. The action of EDTA is non-specific chelating many metals, but is especially valuable in treatment of lead intoxication.

3. Penicillamine

It is the only important chelator which can be administered orally. It is prepared by hydrolytic degradation of penicillin and only the D-isomer is recommended for clinical use. It is an effective chelator of copper, mercury, lead, and zinc promoting their excretion in the urine, ligands forming with the sulphydryl, amine, and possibly the carboxyl group. The major toxicity is related to inhibition of pyridoxal dependent enzymes, and it is usual to supplement patients with pyridoxine to compensate for this effect.

Penicillamine is often used in conjunction with EDTA to treat lead and mercury intoxication, especially because of the oral administration property.

4. Deferoxamine

It is a very specific naturally occurring chelator. It is synthesized by a streptomyces organism, and has a specific high affinity for iron, with virtually no effect on calcium and magnesium. It is the agent of choice for treatment of iron intoxication, which mainly occurs in small children who get into their parents supplement pills. Full-blown acute iron intoxication can produce GI damage, with convulsions and coma. Since the mortality for untreated severe iron intoxication is about 50%, and the use of deferoxamine in these types of cases produces significant increases in survival, it is an important and useful drug. It is also used in the treatment of relatively rare iron storage disorder analogous to Wilson's disease.

4.0 CONCLUSION

In this unit, we have studied about the outcomes of the presence and interactions of toxic metals in the environment and principles of treatment. Heavy metals are toxicologically important as they interact with the living systems which in turn determine their fate in the body without changing the metals.

In the next unit, you will study the toxicology of radioactive materials.

5.0 SUMMARY

In this unit, we have discussed:

- meaning of heavy metal
- historical importance of heavy metals
- common sources of heavy metals

- examples of heavy metals
- public Health Importance of heavy metals
- toxicological Implications of heavy metals
    a. Toxicokinetics of heavy metals
    b. Toxicodynamics of heavy metals
    c. Toxicity of some heavy metals e.g. Arsenic, Lead, Mercury and Manganese.
- general treatment of heavy metal poisoning.

Some common chelators include:

i. Dimercaprol
ii. Ethylenediamine-tetra-acetic acid or EDTA
iii. Penicillamine
iv. Deferoxamine.

6.0 TUTOR-MARKED ASSIGNMENT

1. What are heavy metals?
2. Enumerate four health importance of heavy metal.
3. List five heavy metals in Nigeria.
4. What are chelators?

7.0 REFERENCES/FURTHER READING

"http://en.wikipedia.org/w/index.php?title=Heavy_metal_(chemistry)&oldid=501640966

Duffus, J. H. (2002). "Heavy metals" a meaningless term? (IUPAC Technical Report). *Pure and Applied Chemistry*. Vol. 74: 793–807. doi:10.1351/pac200274050793

Theodore B. Hoekman (n. d.). *Heavy Metal Toxicology*.

Hogan, C. M. (2010). Heavy Metal. Encyclopedia of Earth. *National Council for Science and the Environment.* E. Monosson & C. Cleveland. (Eds). Washington, D.C.

Iwuji, S. C. (2010). Basics and Applications of General Pharmacology. Owerri, Nigeria: Milestone Publishers.

Zevenhoven, R. & Pia Kilpinen, P. (2001). *Control of Pollutants in Flue Gases and Fuel Gases.* Espoo: TKK.

UNIT 4 TOXICOLOGY OF RADIOACTIVE MATERIALS

CONTENTS

1.0 INTRODUCTION

In Unit 3, you studied the toxicology of heavy metals which were found to be toxic. In this unit, you will study about the substances that produce harmful nuclear particles (radiations) in the environment.

Radioactivity refers to the particles which are emitted from nuclei as a result of nuclear instability. The most common types of radiation are called alpha, beta, and gamma radiation, but there are several other varieties of radioactive decay.

Radioactive decay rates are normally stated in terms of their half-lives, and the half-life of a given nuclear species is related to its radiation risk. Radioactive wastes are wastes that contain radioactive material. Radioactive wastes are usually by-products of nuclear power generation and other applications of nuclear fission or nuclear technology, such as research and medicine.

Radioactive material is hazardous to most forms of life and the environment, and you are to understand the basic toxicology of these materials in order to protect human health and the environment.

2.0 OBJECTIVES

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

- define radiation, radioactivity and radioactive material
- identify the types of radiation
- state the importance of radiation
- explain the basic toxicology of radiation
- explain how to control radiation toxicity.

3.0 MAIN CONTENT

3.1 What are Radiations and Radioactive Materials?

From our knowledge of physics, radiation is a process in which energetic particles or energetic waves travel through a medium or space. The particles or waves *radiate* (i.e., travel outward in all directions) from a source. The element or material that has the ability to produce radiation is called radioactive element or material.

Radioactive material or waste typically comprises a number of radioisotopes: unstable configurations of elements that decay, emitting ionising radiation which can be harmful to humans and the environment. Those isotopes emit different types and levels of radiation, which last for different periods of time.

Ionising electromagnetic radiation is that for which the photons making up the radiation have energies larger than about 10 electron volts. The ability of an electromagnetic wave (photons) to ionise an atom or molecule thus depends on its frequency, which determines the energy of a photon of the radiation. Energy of 10 eV is about 1.6×10^{-18} joules, which is a typical binding energy of an outer electron to an atom or organic molecule. This corresponds with a frequency of 2.4×10^{15} Hz, and a wavelength of 125 nm (this is in far ultraviolet).

3.2 Types of Radiation

Two types of *radiation* are commonly differentiated in the way they interact with normal chemical matter: ionising and non-ionising radiation.

a. **Ionising radiations:** The radiations have sufficient energy to ionise an atom or cell. Examples: x-rays, gamma rays. Conventionally considered to have no completely safe lower limit. Radiation on the short-wavelength end of the electromagnetic spectrum, and above 125 nm, is ionising. This includes extreme ultraviolet, x-rays, and gamma rays.

b. **Ultraviolet radiations:** In the middle (have some features of both ionising and non-ionising radiation). They have health effects more than just heating effects (an example is sunburn)

c. Non-ionising radiation e.g. microwaves, radio waves, heat or visible light. Usually considered to have a safe lower limit.

3.3 Sources of Ionising Radiation

i. Ionising radiation comes from radioactive materials, x-ray tubes, particle accelerators, and is present in the environment. It is invisible and not directly detectable by human senses, so instruments such as Geiger counters are usually required to detect its presence. In some cases, it may lead to secondary emission of visible light upon interaction with matter, as in Cherenkov radiation and radioluminescence.

ii. Electromagnetic radiation (sometimes abbreviated EMR) takes the form of self-propagating waves in a vacuum or in matter. EM radiation has an electric and magnetic field component which oscillate in phase perpendicular to each other and to the direction of energy propagation.

iii. Electromagnetic radiation is classified into types according to the frequency of the wave, these types include (in order of increasing frequency): radio waves, microwaves, terahertz radiation, infrared radiation, visible light, ultraviolet radiation, x-rays and gamma rays. Of these, radio waves have the longest wavelengths and gamma rays have the shortest. A small window of frequencies, called visible spectrum or light, is sensed by the eye of various organisms.

3.4 Radioactive Decay

The radioactive elements decay, i.e., lose their activity with time. The decay is measured in half-life, i.e., the time required for the radioactivity to reduce to half. The half-life of some of the elements is shown below:

Element	**Half-life**
Uranium-235	Billions of years
Carbon-14	5730 years
Strontium-90	28 years (beta)
Ce-137	30.2 years
Co-60	5.27 years

As the half-life of these and other radioactive elements are very long, contaminated areas, e.g., due to detonation of a dirty bomb, need to be cleaned or abandoned.

3.5 Importance of Radiation

3.5.1 Uses of Radiations

i. In medicine, radiation and radioactive substances are used for diagnosis, treatment, and research. Small amounts of some types of ionising radiation might confer a net health benefit in some situations, is called radiation hormesis.
ii. In communication, all modern communication systems use forms of electromagnetic radiation as a radio wave or microwave by making the wave vary to correspond variations in the voice.
iii. Researchers use radioactive atoms to determine the age of materials that were once part of a living organism i.e. radiocarbon dating.
iv. Environmental scientists use radioactive atoms known as tracer atoms to identify the pathways taken by pollutants through the environment.
v. Radiation is used to determine the composition of materials in a process called neutron activation analysis.
vi. Radiation is also useful in construction.

Other uses include:

i. Generate electricity
ii. Power for desalination plants
iii. Power for spacecrafts
iv. Power for ocean vessels
v. Wear testing (auto-engines, tires)
vi. Thickness gauges
vii. Sterilisation of pharmaceutical and medical products
viii. Radioimmunoassay
ix. Medical diagnosis
x. Synthesis of new elements
xi. Chemical analysis (by neutron activation)
xii. Sterilisation of insects
xiii. Preservation of food
xiv. Smoke detectors
xv. Bomb detectors at airports
xvi. Manufacture of semiconductors
xvii. Manufacture of radioisotopes
xviii. Radio-dating
xix. Inspecting welds/joints and explore for oil.

3.5.2 Hazards of Radiations

a. Both ionising and non-ionising radiation can be harmful to organisms and can result in changes to the natural environment. Exposure to radiation causes damage to living tissue, resulting in skin burns, radiation sickness and death at high doses and cancer (Kwan-Hoong, 2003), other tumours and genetic damage at low doses.
b. In general, ionising radiation is far more harmful to living organisms per unit of energy deposited than non-ionizing radiation, since the ions that are produced by ionising radiation, even at low radiation powers, have the potential to cause DNA damage.
c. Most non-ionising radiation is harmful to organisms only in proportion to the thermal energy deposited, and is conventionally considered harmless at low powers which do not produce significant temperature rise.
d. Ultraviolet radiation has power to alter chemical bonds, even without having quite enough energy to ionise atoms.

3.6 Classification of Hazardous Radioactive Elements (Radionuclides)

Based on relative hazard potential, hazardous radioactive elements are classified as:

1. **Very High Hazard Potential (HAZARD CLASS I)**
   Sr-90, Pb-210, Po-210, At-211, Ra-226, Ac-227, Th-228, Th-229, Th-230, Th-231, U-233, Pu-238, Pu-239, Am-241, Cm-242, Cf-252, other transuranic nuclides.
2. **High Hazard Potential (HAZARD CLASS II)**
   Ca-47, Fe-59, Co-60, Sr-85, Sr-89, Y-91, Ru-106, Cd-109, Cd-115, I-125, I-131, Ba-140, Ce-144, Sm-151, Eu-152, Eu-154, Tm-170, Hg-203, Bi-207, Th-232, natural thorium, natural uranium.
3. **Moderate Hazard Potential (HAZARD CLASS III)**
   Na-22, Na-24, P-32, P-33, S-35, Cl-36, K-42, Ca-45, Sc-46, Sc-47, Sc-48, V-48, Mn-56, Fe-55, Co-57, Co-58, Ni-59, Ni-63, Cu-64, Cu-67, Zn-65, Ga-67, Ga-68, Ga-72, As-74, As-76, Br-82, Kr-85, Rb-84, Rb-86, Y-90, Zr-95, Nb-95, Mo-99, Tc-99, Rh-105, Pd-103, Ag-105, Ag-111, Sn-113, Te-127, Te-129, I-132, Xe-133, Cs-137, La-140, Pr-143, Pm-147, Ho-166, Lu-177, Ta-182, W-181, Re-183, Ir-190, Ir-192, Pt-191, Pt-193, Au-196, Au-198, Au-199, Tl-200, Tl-202, Tl-204, Pb-203, Hg-197.
4. **Low Hazard Potential (HAZARD CLASS IV)**
   H-3, Be-7, C-14, F-18, Cr-51, Ge-68, Ge-71, Sr-87m, Tc-99m, In-111, Tl-201.

3.7 Toxicokinetics

Depending on the decay mode and the toxicokinetics of an element (how the body processes toxicants and how quickly), the threat due to exposure to a given activity of a radioisotope will differ. The shorter a radioisotope's half-life, the more radioactive a sample of it will be. The longer the half-life, the lesser the toxicity e.g. Indium element.

For instance iodine-131 is a short-lived beta and gamma emitter, but because it concentrates in the thyroid gland, it is more able to cause injury than caesium-137 which, being water soluble, is rapidly excreted in urine. In a similar way, the alpha emitting actinides and radium are considered very harmful as they tend to have long biological half-lives and their radiation has a high relative biological effectiveness, making it far more damaging to tissues per amount of energy deposited. Because of such differences, the rules determining biological injury differ widely according to the radioisotope, and sometimes also the nature of the chemical compound which contains the radioisotope.

3.8 Toxicodynamics of Radiation

There are two components of toxicity to humans and other organisms in radioactive materials or waste:

i. the radiation it emits
ii. the parent or daughter elements, which themselves can be toxic for "chemical" reasons.

Radiation with sufficiently high energy can ionise atoms. Most often, this occurs when an electron is stripped (or "knocked out") from an electron shell, which leaves the atom with a net positive charge. An individual cell is made of trillions of atoms. Because cells and more importantly the DNA can be damaged, this ionisation can result in an increased chance of cancer. The probability of ionising radiation causing cancer is dependent upon the absorbed dose of the radiation, as adjusted for the damaging tendency of the type of radiation (equivalent dose) and the sensitivity of the organism or tissue being irradiated (effective dose). In humans it has been calculated that a 5 sievert dose is usually fatal, and the lifetime risk of dying from radiation-induced cancer from a single dose of 0.1 sieverts is 0.8%, increasing by the same amount for each additional 0.1 sievert increment of dosage. Ionising radiation causes deletions in chromosomes. If a developing organism such as an unborn child is irradiated, it is possible a birth defect may be induced, but it is unlikely this defect will be in a gamete or a gamete-forming cell. The incidence of radiation-induced mutations in humans is undetermined, due to flaws in studies done to date.

Roughly speaking, photons and particles with energies above about 10 electron volts (eV) are ionising. Alpha particles, beta particles, cosmic rays, gamma rays, and X-ray radiation all carry energy high enough to ionise atoms. In addition, free neutrons are also ionising, since their interactions with matter are inevitably more energetic than this threshold.

Most of the ultraviolet spectrum (which begins above energies of 3.1 eV (400 nm) is non-ionising, but is still biologically hazardous due the ability of single photons of this energy to cause electronic excitation in biological molecules, and thus damage them by means of unwanted reactions. An example is formation of pyrimidine dimers in DNA. This property gives the ultraviolet spectrum some of the dangers of ionising radiation in biological systems, without actual ionisation occurring.

In contrast, visible light and longer-wavelength electromagnetic radiation, such as infrared, microwaves, and radio waves, consists of photons with too little energy to cause damaging molecular excitation, and thus this radiation is far less hazardous per unit of energy.

3.9 Management of Radioactive Toxicity

3.9.1 Control of Radioactive Toxicity

Radioactivity diminishes over time, so waste is typically isolated and stored for a period of time until it no longer poses a hazard. The period of time waste must be stored depends on the type of waste.

Low-level waste with low levels of radioactivity per mass or volume (such as some common medical or industrial radioactive wastes) may need to be stored for only hours, days, or months, while high-level wastes (such as spent nuclear fuel or by-products of nuclear reprocessing) must be stored for thousands of years.

Current major approaches to managing radioactive waste have been:

i. segregation and storage for short-lived wastes
ii. near-surface disposal for low and some intermediate level wastes
iii. deep burial or transmutation for the long-lived, high-level wastes.

The symbols below are used to alert the presence of radioactive material or hazard:

Fig. 3.2: 2007 ISO Radioactivity Danger Logo

Fig. 3.3: International Radioactive Waste Hazard Symbol featuring the Trefoil Design

3.9.2 Treatment of Radioactive Materials or Wastes

According to Professor Ken Rubin, radiation emitted is a function of the amount of a radioactive isotope present, its half-life and the type of radioactive particle(s) it emits. It is typically more toxic at high concentrations (i.e., 1 gram of pure Tritium is considerably more toxic than 1 gram of Tritium dispersed in 1,000,000 litres of water). Thus, one "treatment" for nuclear waste put back into the environment is simple dilution. This is not a common technique for high-level waste.

The toxicity of a radioactive isotope is very dependent on the type of particle it emits and the rate at which it emits it (these are decay pathway and half-life). These important aspects of radiation emitted from various radioactive materials cannot be changed; they are inherent to the nucleus

that is decaying and cannot be "treated away". However, for many very short-lived isotopes, an effective "treatment" is to simply store the material (safely) for as many half-lives as it takes for the waste to be at tolerable remnant radiation levels. This is typically done for isotopes whose half-lives are considerably less than say a month or so.

The chemical form of a radioactive element is also important, in that this determines how readily it can interact with environments and the organisms they contain (and therefore, its overall toxicity). If material can be somehow rendered chemically "inert", then it will not distribute itself throughout an organism or environment in which it is placed, minimising (but not eliminating) its toxicity (it will continue emitting radiation from its chemically inert surface, it just can't distribute itself as easily). Some isotopes in waste material can be made less toxic by incorporating them into ceramic-type materials that are very stable in some environments found on earth. It is believed that these hybrid materials are so stable that by the time they are broken down by the effects of various geological processes, the radioactive material they contained will be essentially gone.

It is not possible to completely neutralise radioactive isotopes so that they are harmless but it is possible to minimise their toxicity using a combination of the techniques listed above. Certain treatments, e.g. nuclear reactor wastes, require potentially lengthy and expensive chemical purification steps.

A summary of the amounts of radioactive wastes and management approaches for most developed countries are presented and reviewed periodically as part of the International Atomic Energy Agency (IAEA) Joint Convention on the Safety of Spent Fuel Management and on the Safety of Radioactive Waste Management.

4.0 CONCLUSION

Radioactive materials are dangerous elements that emit non visible particles that have the ability to knock off electrons in the atoms and cells (DNA). Most unstable elements produce radiation as they decay.

5.0 SUMMARY

Radiation is a process in which energetic particles or energetic waves travel through a medium or space. The particles or waves *radiate* (i.e., travel outward in all directions) from a source. The element or material that has the ability to produce radiation is called radioactive element or material.

Types of radiation

a. Ionising radiations: The radiations have sufficient energy to ionise an atom or cell. Examples: x-rays, gamma rays.
b. Ultraviolet radiations:
c. Non-ionising radiation e.g. microwaves, radio waves, heat or visible light.

Sources of ionising radiation

i. Ionising radiation comes from radioactive materials, X-ray tubes, particle accelerators.

Electromagnetic radiation

The radioactive elements decay, i.e., lose their activity with time. The decay is measured in half-life, i.e., the time required for the radioactivity to reduce to half.

Uses of radiations

In medicine, radiation and radioactive substances are used for diagnosis, treatment, and research.

In communication, all modern communication systems use forms of electromagnetic radiation as a radio wave or microwave by making the wave vary to correspond variations in the voice.

Researchers use radioactive atoms to determine the age of materials that were once part of a living organism i.e. radiocarbon dating.

Environmental scientists use radioactive atoms known as tracer atoms to identify the pathways taken by pollutants through the environment.

Radiation is used to determine the composition of materials in a process called neutron activation analysis.

Radiation is also useful in construction

Hazards of Radiations

Both ionising and non-ionising radiation can be harmful to organisms and can result in changes to the natural environment.

Classification of hazardous radioactive elements (Radionuclides)
Based on relative hazard potential, they are:

i. Very High Hazard Potential (Hazard Class I) E.G. Sr-90, Pb-210.
ii. High Hazard Potential (Hazard Class Ii) E.G. Ca-47, Fe-59, Co-60.
iii. Moderate Hazard Potential (Hazard Class Iii) E.G. Na-22, Na-24, P-32.
iv. Low Hazard Potential (Hazard Class Iv) E.G. H-3, Be-7, C-14, F-18, Cr-51.

Toxicokinetics

Depending on the decay mode and the toxicokinetics of an element (how the body processes toxicants and how quickly), the threat due to exposure to a given activity of a radioisotope will differ. The shorter a radioisotope's half-life, the more radioactive a sample of it will be. The longer the half-life, the less toxic e.g. Indium element.

Toxicodynamics of Radiation

There are two components of toxicity to humans and other organisms in radioactive materials or waste:

i. the radiation it emits
ii. the parent or daughter elements, which themselves can be toxic for "chemical" reasons.

In humans, it has been calculated that a 5 sievert dose is usually fatal, and the lifetime risk of dying from radiation-induced cancer from a single dose of 0.1 sieverts is 0.8%, increasing by the same amount for each additional 0.1 sievert increment of dosage. Ionising radiation causes deletions in chromosomes. If a developing organism such as an unborn child is irradiated, it is possible a birth defect may be induced, but it is unlikely this defect will be in a gamete or a gamete-forming cell. The incidence of radiation-induced mutations in humans is undetermined, due to flaws in studies done to date.

Current major approaches to managing radioactive waste have been:

i. segregation and storage for short-lived wastes
ii. near-surface disposal for low and some intermediate level wastes
iii. deep burial or transmutation for the long-lived, high-level wastes.

6.0 TUTOR-MARKED ASSIGNMENT

1. What is radiation?
2. How does radiation cause harm to man?
3. List four possible effects of radiations.

7.0 REFERENCES/FURTHER READING

"Nuclear Medicine". *Nuclear Medicine Wikipedia article*. http://en.wikipedia.org/wiki/Nuclear_medicine.

"Radiography Wikipedia article". *Radiography Wikipedia article*. http://en.wikipedia.org/wiki/Radiography.

Anderson, M. & Woessner, W. (1992). *Applied Groundwater Modeling*. San Diego, CA: Academic Press Inc. pp. 325–327. ISBN 0-12-059485-4. http://www.amazon.com/Applied-Groundwater-Modeling-Simulation-Advective/dp/0120594854. Retrieved 9-3-2011.

Attix, F. (1986). *Introduction to Radiological Physics and Radiation Dosimetry*. New York: Wiley-VCH. pp. 2–15,468,474.

http://books.google.com/books/about/Introduction_to_radiological_physics_and.html?id=PL8971RdEfoC. Retrieved 9-3-2011.

Babu, B.V., & Karthik, S. (2005). "An overview of waste from the nuclear fuel cycle". In: *Energy Education Science and Technology*, 14, 93–102.

Foreman, H. (1958). Toxicology of Radioactive Materials. *Annual Review of Medicine*, Vol. 9: 369-386.

Gofman, J. W. (1981) *Radiation and Human Health*. San Francisco: Sierra Club Books, 760-848.

Goldstein, I. & Martin, G. (2002). *How much risk?* Oxford University Press.

IAEA: Joint Convention on Safety of Radioactive Waste.

Ionization Energy. chemguide.co.uk. *The ionization energies of hydrogen and oxygen (first ionization) are both about 14 Ev*.

John, E. Moulder. "Static Electric and Magnetic Fields and Human Health".

http://web.archive.org/web/20070714054650/http://www.mcw.edu/gcrc/cop/static-fields-cancer-faq/toc.html.

Kwan-Hoong, N. G. (2003). "Non-Ionizing Radiations – Sources, Biological Effects, Emissions and Exposures". *Proceedings of the International Conference on Non-Ionizing Radiation at UNITEN ICNIR2003 Electromagnetic Fields and Our Health*. http://www.who.int/peh-mf/meetings/archive/en/keynote3ng.pdf.

Nuclear Information and Resource Service, Radioactive Waste Project. Retrieved September 2007.

Questions and Answers about Biological Effects and Potential Hazards of Radiofrequency Electromagnetic Fields. Office of Engineering and Technology. Bulletin 56, (4th ed.). August 1999.

UNIT 5 TOXICOLOGY OF FOOD ADDITIVES AND CONTAMINANTS

CONTENTS

1.0 INTRODUCTION

In Unit 5, we discussed certain substances that contain elements that are unstable and have ability to emit particles that can in turn destroy DNA, cells, among others. These are exposed to man through different routes but in the present unit we will discuss some substances ingested with food and which may have adverse effect on the consumers.

This unit is quite important in this era of fast foods proliferations where operators do anything to attract and maintain their customers.

2.0 OBJECTIVES

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

- define a food additive
- classify and identify a food additive
- state the uses of food additive
- explain the toxicological importance of food additives
- define food contaminants
- classify food contaminants.

3.0 MAIN CONTENT

3.1 What are Food Additives?

A food additive is a compound, or mixture of substances, that is added to food to improve production, processing, storage, packaging or preparation. E.g. additives such as smoke, alcohol, vinegar, and spices have been used for centuries to aid in the preservation and flavour enhancement of foods.

3.2 Classification and Uses of Additives

a. Intentional additives are added to serve some functions as to provide nutrition, preserve freshness, improve some sensory quality, or aid in processing.
b. The unintentional additives are often those associated with the production or storage of food, such as agricultural pesticides and packaging materials.
c. Synthetic additives e.g. quinoline yellow, sun set yellow
d. Natural additives e.g. vinegar, spices

3.2.1 Uses of Additives

i. To improve colour, flavour, convenience and stability.
ii. To improve nutritional quality of foods.
iii. To serve as antimicrobial agent to prevent food poisoning.

3.3 Highlights of Toxicology Recommendations

2002 Guidance by U.S. Department of Health and Human Services (2006)

a. Safety Summary and Comprehensive Toxicological Profile (CTP). The safety information for a food contact notification (FCN) should contain both a safety summary and a comprehensive toxicological profile (CTP) of the food contact substance (FCS) that is the subject of the notification. The safety summary is Part III of FDA Form 3480 and should provide the basis for the notifier's determination that the intended use of the FCS is safe. The CTP should provide summaries of all the available toxicological information pertinent to the safety evaluation of the FCS. In some cases, a notification may need to include a CTP for a toxicologically relevant constituent of the FCS. If a constituent of an FCS is carcinogenic, the CTP in the notification should include a quantitative risk assessment.

b. **Safety Testing Recommendations for Food Contact Substances (FCSs) and Their Constituents.** This document recommends safety testing of FCSs and their constituents, primarily based on a series of genetic toxicity tests and, when studies justified by the exposure level, sub chronic toxicity. The recommendations describe the minimum level of safety testing generally considered appropriate at various exposures. For an initial or incremental exposure of an FCS at or less than 0.5 parts per billion (ppb), no safety tests are recommended. For a cumulative exposure between 0.5 ppb and 1 part per million (ppm), genetic toxicity tests and/or subchronic tests are recommended. At a cumulative exposure at or greater than 1 ppm, FDA normally requires, under the authority of Section 409 (h)(3)(B) of the Federal Food, Drug and Cosmetic Act, that a food additive petition be submitted for the use of an FCS.

c. **Evaluation of Structural Similarities to Known Toxicants.** To the extent feasible, knowledge in predicting potential toxicity based on structure/activity relationships may be incorporated into the safety assessment of an FCS. Such information may be used as part of an overall strategy for assessing the safety of an FCS or to help interpret safety test results.

3.3.1 Toxicological Evaluation of Some Food Additives

Safety evaluation for a food additive involves assigning the additive to a **Concern Level** (i.e., low (I), intermediate (II) or high (III)) based on information on the additive's toxicological potential predicted from its chemical structure (i.e., low (A), intermediate (B), or high (C)) and an estimation of cumulative human exposure. The additives evaluated and their uses include:

a. Quinoline yellow (disodium 2-(1,3-dioxo-2-indanyl)-6,8-quinolinesulphate) is a synthetic, yellow food colouring. Osman *et al. (2002)* 5 reported that quinoline yellow could inhibit both true (acetyl) and pseudo (butyryl) cholinesterase (ChE) enzymes in human erythrocytes and plasma *in vitro*

b. *Sunset Yellow (E110)* (disodium 6-hydroxy-5-(4-sulfonatophenylazo)-2-naphthalenesulfonate) *i*s a synthetic, yellow azo dye that is used as a food colouring. Osman *et al.* (2002)5 reported that sunset yellow could inhibit both true and pseudo-ChE enzymes in human erythrocytes and plasma *in vitro* in a concentration dependent manner with inhibition of pseudo-ChE and true ChE of 43% and 70% respectively at the highest concentration used.

c. Carmoisine (azorubine, E122) (disodium 4-hydroxy-3-(4-sulfonato-1-naphthylazo)-1-naphthalenesulfonate) is a synthetic, red azo dye that is used as a food colouring agent. Same effect above.
d. Ponceau 4R (trisodium 2-hydroxy-1-(4-sulfonato-1-naphthylazo)-6,8- naphthalenedisulfonate) is a synthetically produced azo dye that is used as a red colouring for foodstuffs
e. Indigo carmine (indigotine) (disodium 3-3' dioxo-2,2'bi-indolylidene-5-5' disulfonate) is a synthetically produced blue food colouring.
f. Brilliant blue (disodium a-[4-(N-ethyl-3-sulfonatobenzylamino)phenyl]-a-[4-(Nethyl-3-sulphonatobenzylimino)cyclohexa-2,5-dienylidene] toluene-2-sulphonate is a synthetic, blue food colouring.
g. Sodium benzoate is used as a food-preserving agent. Effects on the central nervous system have been noted but this is due to the disruption to acid-base balance rather than specific neurotoxicity.
h. Sulphur dioxide is used as a food-preserving agent.
i. Monosodium glutamate is a flavour-enhancing agent. Glutamate is a neuroactive compound and can cross the blood-brain barrier and placenta. Neurotoxic effects have been seen in animal studies but only at very high doses, often administered by s.c. injection.
j. Acesulfame K (E950) (potassium salt of 6-methyl-1, 2,3-oxathiazine-4(3H)-one-2,2-dioxide is a synthetic sweetening agent.
k. Aspartame (6-methyl-1,2,3-oxathiazine-4(3H)--one-2,2-dioxide salt of Lphenylalanyl-2-methyl-L-a-aspartic acid) is a synthetic sweetener.
l. Saccharin Saccharin (3-oxo-2,3-dihydrobenzo[d]isothiazol-1,1-dioxide) is a synthetic sweetening agent.

3.4 Toxicology of Food Contaminants

3.4.1 What is Food Contamination?

Food contamination refers to the presence in food of harmful chemicals and microorganisms which can cause consumer illness. The impact of chemical contaminants on consumer health and well-being is often apparent only after many years of processing and after prolonged exposure at low levels (e.g. cancer). Chemical contaminants present in foods are often unaffected by thermal processing (unlike most microbiological agents). Chemical contaminants can be classified according to the source of contamination and the mechanism by which they enter the food product.

3.4.2 Causes of Food Contamination

Food contaminants may be classified under accidentally or deliberately contaminants or under microbiological, chemical or physical contaminants.

In contrast to microbiologically caused food-borne illness, the link between exposure and effect of chemical hazards in foods is usually complicated by cumulative low doses and the delay between exposure and the onset of symptoms.

Chemical hazards include environmental contaminants, food ingredients (such as iodine), heavy metals, mycotoxins, natural toxins, processing contaminants and veterinary medicines.

3.4.3 Incidence of Chemical Contamination

Incidence of chemical contamination may occur because of poor harvesting or storage of grain, use of banned veterinary products, industrial discharges, human error and deliberate adulteration and fraud. An "incident" of chemical food contamination may be defined as an episodic occurrence of adverse health effects in humans (or animals that might be consumed by humans) following high exposure to particular chemicals, or instances where episodically high concentrations of chemical hazards were detected in the food chain, and traced back to a particular event.

For instance, in June 2012, a Brazilian housewife discovered an apparently used condom at the bottom of a can of Knorr tomato paste. Unilever was fined £3,100 ($4,800) by the Supreme Federal Court. She was awarded £1,110 ($1,700) for moral damages, as she and her family had consumed a meal prepared with the paste.

3.4.4 Classification of Contaminants

1. Agrochemicals are chemicals used in agricultural practices and animal husbandry with the intent to increase crops and reduce costs. Such agents include pesticides (e.g. insecticides, herbicides, rodenticides), plant growth regulators, veterinary drugs (e.g. nitrofuran, fluoroquinolones, malachite green, chloramphenicol), and bovine somatotropin (rBST).
2. Environmental contaminants are chemicals that are present in the environment in which the food is grown, harvested, transported, stored, packaged, processed, and consumed. The physical contact of the food with its environment results in its contamination. Possible sources of contamination are:

Air: radionuclides (^{137}Caesium, ^{90}Strontium), polycyclic aromatic hydrocarbons (PAH).

Water: arsenic, mercury.

Soil: cadmium, nitrates, perchlorates.

Polychlorinated biphenyls (PCB), dioxins, and polybrominated diphenyl ethers (PBDE) are ubiquitous chemicals, which are present in air, water, soil, and the entire biosphere.

Packaging materials: antimony, tin, lead, perfluorooctanoic acid (PFOA), semicarbazide, benzophenone, isopropylthioxanthone (ITX), bisphenol A.

Processing/cooking equipment: copper, or other metal chips, lubricants, cleaning and sanitizing agents.

Naturally occurring toxins: mycotoxins, phytohaemagglutinin, pyrrolizidine alkaloids, grayanotoxin, mushroom toxins, scombrotoxin (histamine), ciguatera, shellfish toxins (see shellfish poisoning), tetrodotoxin, among many others.

Pyrrolizidine alkaloids (PAs) are hepatotoxic, carcinogenic, genotoxic, teratogenic and sometimes pneumotoxic food contaminants, especially in grain and bread. PAs have been estimated to be present in about 3% of all flowering plants (Smith and Culvenor 1981). They mainly occur in species of the plant families Asteraceae, Fabaceae and Boraginaceae.

3. There are many cases of banned pesticides or carcinogens found in foods.

i. Greenpeace exposed in 2006 in China that 25% of surveyed supermarkets agricultural products contained banned pesticides. Over 70% of tomatoes that tested were found to have the banned pesticide lindane, and almost 40% of the samples had a mix of three or more types of pesticides. Fruits were also tested in this investigation. Tangerines, strawberries and Kyofung grapes samples were found contaminated by banned pesticides, including the highly toxic Methamidophos. These fruits can also be found in Hong Kong market. Greenpeace says there exists no comprehensive monitoring on fruit produce in the Hong Kong as of 2006.

ii. In India, soft drinks were found contaminated with high levels of pesticides and insecticides, including lindane, DDT, malathion and chlorpyrifos.

iii. News of Formaldehyde, a carcinogen was found in Vietnamese national dish, Pho, broke in 2007 Vietnam food scare. Vegetables and fruits were also found to have banned pesticides. "Health agencies have known that Vietnamese soy sauce, the country's second most popular sauce after fish sauce, has been chock full of cancer agents since at least 2001," thundered the Thanh Nien daily. "Why didn't anyone tell us?" The carcinogen in Asian sauces is 3-MCPD and its metabolite 1,3-DCP, which has been an ongoing problem before 2000 affecting multiple continents.

iv. 2005 Indonesia food scare, carcinogenic formaldehyde was added as a preservative to noodles, tofu, salted fish, and meatballs.

4. There is a heavy stigma attached to the presence of hair in food in most societies. There is a risk that it may induce choking and vomiting, and also that it may be contaminated by toxic substances. Views differ as to the level of risk it poses to the inadvertent consumer

In most countries, people working in the food industry are required to cover their hair. Hair can cause food poisoning and people can be sued for not covering their hair while serving food.

5. Processing contaminants are generated during the processing of foods (e.g. heating, fermentation). They are absent in the raw materials, and are formed by chemical reactions between natural and/or added food constituents during processing. The presence of these contaminants in processed foods cannot be entirely avoided. Technological processes can be adjusted and/or optimised, however, in order to reduce the levels of formation of processing contaminants. Examples are: nitrosamines, polycyclic aromatic hydrocarbons (PAH), heterocyclic amines, histamine, acrylamide, furan, benzene, trans fat, monochloropropanediol (MCPD), semicarbazide, 4-hydroxynonenal (4-HNE), and ethyl carbamate. There is also the possibility of metal chips from the processing equipment contaminating food. These can be identified using metal detection equipment. In many conveyor lines, the line will be stopped, or when weighing the product with a Check weigher, the item can be rejected for being over - or underweight or because small pieces of metal are detected within it.

6. While many food contaminants have been known for decades, the formation and presence of certain chemicals in foods has been

discovered relatively recently. These are the so-called **emerging food contaminants**, e.g. acrylamide, furan, benzene, perchlorate, perfluorooctanoic acid (PFOA), 3-monochloropropane-1,3-diol (3-MCPD), 4-hydroxynonenal and (4-HNE).

3.4.5 Safety and Regulation of Food Contaminant

Acceptable Daily Intake (ADI) levels and tolerable concentrations of contaminants in individual foods are determined on the basis of the "No Observed Adverse Effect Level" (NOAEL) in animal experiments, by using a safety factor (usually 100). The maximum concentrations of contaminants allowed by legislation are often well below toxicological tolerance levels, because such levels can often be reasonably achieved by using good agricultural and manufacturing practices.

3.4.6 Food Contaminant Testing

To maintain high quality of food and comply with health, safety and environmental regulatory standards it is best to rely on food contaminant testing through an independent third party such as laboratories, certification companies or similar. For manufacturers the testing for food contaminants can minimise the risk of non-compliance in relation to raw ingredients, semi-manufactured foods and final products. Also, food contaminant testing assures consumers safety and quality of purchased food products and can prevent food-borne diseases, and chemical, microbiological or physical food hazards.

The establishment of ADIs for certain emerging food contaminants is currently an active area of research and regulatory debate.

4.0 CONCLUSION

Food additives and contaminants are hazards associated with ingesting poorly processed, preserved, served or stored food. The causes and adverse effects of additives and contaminants were discussed.

In the next unit, we will discuss the hazards associated with taking pharmaceutical products for various reasons.

5.0 SUMMARY

A food additive is a compound, or mixture of substances, that is added to food to improve production, processing, storage, packaging or preparation.

6.0 TUTOR-MARKED ASSIGNMENT

i. Define food additive.
ii. Give food examples of food additives.
iii. Define chemical food contaminant.
iv. Give four examples of food contaminants.

7.0 REFERENCES/FURTHER READING

Astley, M. (2012). "Over 250,000 eggs recalled in Germany in latest dioxin scare". *Food QualityNews.* http://www.foodqualitynews.com/Food-Alerts/Over-250-000-eggs- recalled-in-Germany-in-latest-dioxin-scare. Retrieved 3 July 2012.

FDA, (2000). Toxicological Principles for the Safety of Food Ingredients: Redbook 2000. *U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition*, Washington, D.C.

FDA. (1993). Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food. *Draft Redbook II. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition,* Washington, D.C.

Greenpeace Exposes Guangzhou Pesticide Contamination". *China CSR*. June 13, 2006. http://www.chinacsr.com/en/2006/06/13/537-greenpeace-exposes-guangzhou- pesticide-contamination/

Maga, J. A. & Tu, A. T. (1994). Food Additive Toxicology. *Book Review in Applied Biochemistry and Byotechnology* . New York: Mercel Dekker. pp.552.

Osman, M. Y., Sharaf, I. A., el-Rehim, W. M. & el-Shharkawi, A. M. (2002). Synthetic organic hard capsule colouring agents: in vitro effect on human true and pseudocholinesterases. *British Journal of Biomedical Sciences*, 59:212-217.

Roper, M. (2012). "British firm Unilever fined £3,100 after Brazilian housewife finds rubber CONDOM in a tin of tomato paste". *Daily Mail.* http://www.dailymail.co.uk/news/article-2164940/British-firm-Unilever-fined-3-000- Brazilian-housewife-finds-rubber-CONDOM-tin-tomato-paste.html. Retrieved 3 July 2012

Smith, L. W., & Culvenor, C. C. J. (1981). Plant sources of hepatotoxicpyrrolizidine alkaloids. *J. Nat. Prod.,* 44:129–152.

Staff, N. R. (2012). "Unilever Fined $4,800 After Housewife Finds Condom In Tin of Tomato Paste". *Naija Resource*. http://www.naijapidginenglish.com/2012/06/26/unilever-fined-4800-after-housewife-finds-condom-in-tin-of-tomato-paste/. Retrieved 3 July 2012

Thomson, B., Poms, R. & Rose, M. (2012) "Incidents and impacts of unwanted chemicals in food and feeds", *Quality Assurance and Safety of Crops & Foods*, 4,77-92.

U.S. Department of Health and Human Services Food and Drug Administration Center for Food Safety and Applied Nutrition (2006). Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food

Valdes B. P. & Ziobro G. C. (2000). "Regulatory Action Criteria for Filth and Other Extraneous Materials IV. Visual Detection of Hair in Food". *Regulatory Toxicology and Pharmacology* (Academic Press), 32 (1): 73–77.

WHO (1982). World Health Organization. *WHO Food Additives Series*, 17.

WHO (1984). World Health Organization. *WHO Food Additives Series*, 19.

Wiedenfeld, H. (2011). Plants containing pyrrolizidine alkaloids: toxicity and problems. *Food Additives and Contaminants*, 28. 3:282–292.

UNIT 6 TOXICOLOGY OF PHARMACEUTICALS AND OTHER DRUGS IN THE ENVIRONMENT

CONTENTS

1.0 INTRODUCTION

In Unit 5, we discussed substances in the environment ingested with food intentionally or unintentionally that cause harm to man. In this unit, we will discuss about drugs released in the environment which may have harmful effects on man or his environment.

2.0 OBJECTIVES

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

- define pharmaceuticals
- explain what is Environmental Pharmaceutical Persistent Pollutant (EPPP)
- identify how illicit drugs can pose environmental problems
- define pharmacoenvironmentology.

3.0 MAIN CONTENT

3.1 Concepts of Pharmaceutical and Nutraceuticals in the Environment

Pharmaceuticals are synthetic chemicals belonging to a wide group of different chemical families and may also react different in the environment.

Environmental Pharmaceutical Persistent Pollutant (EPPP), was suggested in the nomination 2010 of pharmaceuticals and environment as an emerging issue to Strategic Approach to International Chemicals Management (SAICM) by the International Society of Doctors for the Environment (ISDE).

There exists very well documented evidence that some pharmaceuticals enter and persist in the environment, some are endocrine disruptors (synthetic hormones), and some are designed to kill bacteria and viruses (antibiotics) and may affect microorganism and wild life in severe and unexpected ways. Little is known on the possible negative effects and impacts of EPPP in humans and the environment by diffuse and systematic exposure, for long periods of time, especially during the vulnerable periods of development.

As there are thousands of different synthesized chemicals present at the same time in the environment, different interactions may occur and the result of these multiple exposure in human and nature are not sufficiently studied or understood.

"Pharmaceuticals", or prescription and over-the-counter medications made for human use or veterinary or agribusiness purposes, are common PPCPs found in the environment. Antibiotics, nutraceuticals (e.g., vitamins), supplements, and sexual enhancement drugs are contained in this group. "Personal care products" may include cosmetics, fragrances, menstrual care products, lotions, shampoos, soaps, toothpastes, and sunscreen. These products typically enter the environment when passed through or washed off the body and into the ground or sewer lines, or when disposed of in the trash, septic tank, or sewage system.

3.2 Concepts of Illicit Drugs in the Environment

Illicit drugs such as methamphetamine and cocaine are another type of PPCP. The manufacturers of these products may accidentally spill or purposefully dump harmful by-products directly into the environment. Drug users also introduce these substances into the environment when handling drugs and when the substances pass through their bodies and into a septic tank or sewage system. Traces of illicit drugs can be found in waterways and may even be carried by money.

3.3 Environmental Risk Assessment and Environmental Classification of Drugs

Environmental risk refers to the risk of toxicity to the environment. It is based on the ratio between predicted environmental concentration of the substance (PEC) and the highest concentration of the substance that does

not have a harmful effect in the environment (PNEC). Environmental hazard expresses the inherent environmentally damaging characteristics of the substance in terms of persistence, bioaccumulation and toxicity.

3.4 Effects of Pharmaceuticals on the Environment

1. Estradiol (estrogen, synthetic hormone)

Concentrations in surface water alone are not sufficient to assess the risk of negative environmental effects in the aquatic environment. Synthetic hormones are endocrine disruptors. Thus, estrogenic compounds like ethinyl-estradiol (estrogen hormone) at concentrations < 1 ng per litre may cause both vitellogenin production (a frequently used index for feminisation of male fish), and structural change in their sex organs. It has also been demonstrated that fish exposed to sewage treatment plant (STP) effluent can take up and concentrate estrogenic compounds, including ethinyl-estradiol, to very high internal levels. These observations on feminisation of fish by estrogenic compounds in STP effluents have been observed in many countries, and have also been observed in other species, like frogs, alligators and molluscs.

2. Cardiovascular medicines

Other examples of environmental impact in the aquatic environment of human medication concern both cardiovascular and neuro-psychiatric medicines. The non-selective beta-blocking agent propanolol was found to cause a significant decrease in egg production in medaka fish, at a concentration close to that demonstrated in the sewage treatment plants (STP) effluents. Gemfibrozil (cholesterol and triglycerides lowering drug) often appears in the effluent from STPs. At concentrations close to those reported in STP effluent, gemfibrozil lowers the blood levels of testosterone in fish.

3. Citalopram/Fluoxetine (serotonin reuptake inhibitor anti depressants, SSRI's)

Some SSRI's have been shown to accumulate in exposed fish. Citalopram has been detected in liver from wild perch in low µg per kg levels, and fluoxetine affects the serotonin system in the same way that it does in humans. Fluoxetine has also been shown to affect swimming activity in shellfish; whether this is linked to a disturbance of serotonin function in the brain is still unknown.

4. Antibiotics

High levels of antibiotics in the water are a cause for alarm as there is an increased risk of selecting resistant bacteria, an issue of global concern.

This can lead to some highly effective antibiotics becoming ineffective. There are several examples: In India, bacteria resistant to ciprofloxacin have been found downstream pharmaceutical plants, genes for multi resistance were found in drinking water, and multi-resistant Salmonella in water sprayed on vegetables. From Europe we know about the epidemic with multi resistant EHEC in summer 2011, originating from water sprayed vegetables.

The term "eco-shadow" has been introduced to describe the ecological impact of antibiotics. Antibiotics with a wide spectrum that are also stable will have a greater impact on the bacterial flora (a long eco-shadow) than those with a narrow antibacterial spectrum which disintegrates more rapidly (a short eco-shadow).

The ecological effects of tetracyclines and quinolones have been observed. They are not metabolised in the human body and are therefore excreted unmodified. When entered into the environment they are poorly degraded. They can be toxic to other animals, affecting particularly microorganism and fish. In the effluent from a sewage plant in India, several broad spectrum antibiotics were found in concentrations toxic to bacteria and plants. In the sewage plant itself, there were enterococcae resistant to all known antibiotics.

The development of resistant bacteria in sewage plants is stimulated by high concentration of antibiotics (e.g. in plant sewage), large amounts of bacteria (e.g. from human sewage water that is added in plant sewage), and selection of Information that can be used to assess the nominated issue have been observed.

Pharmacoenvironmentology is a branch of pharmacology and pharmacovigilance that deals entry of chemicals or drugs into the environment after elimination from humans and animals as post-therapy. It deals specifically with those pharmacological agents that have impact on the environment via elimination through living organisms subsequent to pharmacotherapy.

According to WHO, pharmacovigilance activities are done to monitor detection, assessment, understanding and prevention of any obnoxious adverse reactions to drugs at therapeutic concentration on animal and human beings. However, there is also a growing focus among scientists and environmentalists about the impact of drugs on environment and surroundings. The existing term 'ecopharmacology' is too broad and not even defined in a clear manner. The term 'pharmacoenvironmentology' seeks to deal with the environmental impact of drugs given to humans and animals at therapeutic doses.

Ecopharmacology concerns the entry of chemicals or drugs into the environment through any route and at any concentration disturbing the balance of ecology (ecosystem), as a consequence. Ecopharmacology is a broad term that includes studies of “PPCPs” irrespective of doses and route of entry into environment.

4.0 CONCLUSION

In this unit, we discussed the concept of pharmaceuticals in the environment, pharmacoenvironmentology and other related terms. The toxicity of these products results from the licit and illicit use or disposal of drugs.

5.0 SUMMARY

Pharmaceuticals are synthetic chemicals belonging to a wide group of different chemical families and may also react different in the environment.

Environmental Pharmaceutical Persistent Pollutant (EPPP) was suggested in the nomination 2010 of pharmaceuticals and environment as an emerging issue to Strategic Approach to International Chemicals Management (SAICM) by the International Society of Doctors for the Environment (ISDE).There exists very well documented evidence that some pharmaceuticals enter and persist in the environment, some are endocrine disruptors (synthetic hormones), some are designed to kill bacteria and viruses (antibiotics) and may affect microorganism and wild life in severe and unexpected ways.

"Pharmaceuticals", or prescription and over-the-counter medications made for human use or veterinary or agribusiness purposes, are common PPCPs found in the environment. Antibiotics, nutraceuticals (e.g., vitamins), supplements, and sexual enhancement drugs are contained in this group.

"Personal care products" may include cosmetics, fragrances, menstrual care products, lotions, shampoos, soaps, toothpastes, and sunscreen. These products typically enter the environment when passed through or washed off the body and into the ground or sewer lines, or when disposed of in the trash, septic tank, or sewage system.

Illicit drugs such as methamphetamine and cocaine are another type of PPCP. The manufacturers of these products may accidentally spill or purposefully dump harmful by products directly into the environment.

Drug users also introduce these substances into the environment when handling drugs and when the substances pass through their bodies and into a septic tank or sewage system. Traces of illicit drugs can be found in waterways and may even be carried by money.

1. Estradiol (estrogen, synthetic hormone)

Synthetic hormones are endocrine disruptors.

2. Cardiovascular medicines

The non-selective beta-blocking agent propanolol was found to cause a significant decrease in egg production in medaka fish.

3. Citalopram/Fluoxetine (serotonin reuptake inhibitor anti depressants, SSRI's)

Some SSRI's have been shown to accumulate in exposed fish. Citalopram has been detected in liver from wild perch in low µg per kg levels, and fluoxetine affects the serotonin system in the same way that it does in humans.

4. Antibiotics

High levels of antibiotics in the water are a cause for alarm as there is an increased risk of selecting resistant bacteria, an issue of global concern. The ecological effects of tetracyclines and quinolones have been observed.

Pharmacoenvironmentology is a branch of pharmacology and pharmacovigilance that deals entry of chemicals or drugs into the environment after elimination from humans and animals as post-therapy. It deals specifically with those pharmacological agents that have impact on the environment via elimination through living organisms subsequent to pharmacotherapy.

Ecopharmacology concerns the entry of chemicals or drugs into the environment through any route and at any concentration disturbing the balance of ecology (ecosystem), as a consequence. Ecopharmacology is a broad term that includes studies of "PPCPs" irrespective of doses and route of entry into environment.

6.0 TUTOR-MARKED ASSIGNMENT

1. What are pharmaceuticals?
2. Identify four pharmaceuticals found in the environment.
3. Enumerate the adverse effects of pharmaceuticals on man.

7.0 REFERENCES/FURTHER READING

Kümmerer, K. (2008). Pharmaceuticals in the Environment – A Brief Summary. In: Kümmerer, Klaus (Ed.). *Pharmaceuticals in the Environment.* (3rd ed.). Springer Berlin: Heidelberg, 3-21.

Ruhoy, I. R. & Daughton, C. G. (2008). Beyond the medicine cabinet: An analysis of where and why medications accumulate. *Environment International* ,Vol. 34 (8): 1157- 1169.

U.S. EPA. *Pharmaceuticals and Personal Care Products.* Accessed 16 March 2009

MODULE 4 BASIC TOXICOLOGY OF ENVIRONMENTAL POLLUTANTS

UNIT 1 BASIC CONCEPTS IN ENVIRONMENTAL POLLUTION

CONTENTS

1.0 INTRODUCTION

In Module 3, we discussed toxicants that are organic in nature. We identified the existence of chemicals that interact with human body to cause injury or disease.

Among all the environmental problems such as soil erosion leading to floods, salt deserts and sea recedes, desertification, landslides, change of river directions, extinction of species, and vulnerable ecosystem in place of more complex and stable ecosystems, depletion of natural resources,

waste accumulation, deforestation, thinning of ozone layer and global warming, environmental pollution is a major source of health risk throughout the world, though risks are generally higher in developing countries, where poverty, lack of investment in modern technology and weak environmental legislation combine to cause high pollution levels. Associations between environmental pollution and health outcome are, however, complex and often poorly characterised. Levels of exposure, for example, are often uncertain or unknown as a result of the lack of detailed monitoring and inevitable variations within any population group.

In this unit, we will discuss basic concepts applied when these toxicants are found in our environment.

2.0 OBJECTIVES

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

- explain the concept of environmental pollution
- classify pollution
- state the causes of pollution
- explain the pollution pathway to people
- state the effects of pollutants.

3.0 MAIN CONTENT

3.1 Basic Concept of Environmental Pollution

Environmental pollution is defined as the undesirable change in physical, chemical and biological characteristics of our air, land and water. **Pollution** is the introduction of contaminants into the natural environment that causes adverse change. Pollution can take the form of chemical substances or energy, such as noise, heat or light. Pollutants, the components of pollution, can be either foreign substances/energies or naturally occurring contaminants. Pollution is often classed as point source or nonpoint source pollution

Environmental pollution can be simply, if somewhat generally, defined as the presence in the environment of an agent which is potentially damaging to either the environment or human health. As such, pollutants take many forms. They include not only chemicals, but also organisms and biological materials, as well as energy in its various forms (e.g. noise, radiation, heat). The number of potential pollutants is therefore essentially countless. There are, for example, some 30,000 chemicals in common use today, any one of which may be released into the environment during processing or use. Less than 1% of these have

been subject to a detailed assessment in terms of their toxicity and health risks. The number of biological pollutants is truly unquantifiable. They include not only living and viable organisms, such as bacteria, but also the vast array of endotoxins that can be released from the protoplasm of organisms after death. There is, therefore, no shortage of potential environmental risks to health. What is lacking, for the most part, is an understanding of the nature and mechanisms of these risks.

3.2 Historical Importance of Pollution

Pollution started from the prehistoric times when man created the first fires. According to a 1983 article in the Journal of Science, "soot found on ceilings of prehistoric caves provides ample evidence of the high levels of pollution that was associated with inadequate ventilation of open fires." King Edward I of England banned the burning of sea-coal by proclamation in London in 1272, after its smoke became a problem.

London also recorded one of the earlier extreme cases of water quality problems with the Great Stink on the Thames of 1858, which led to construction of the London sewerage system soon afterward.

It was the industrial revolution that gave birth to environmental pollution as we know it today. The emergence of great factories and consumption of immense quantities of coal and other fossil fuels gave rise to unprecedented air pollution and the large volume of industrial chemical discharges added to the growing load of untreated human waste.

Pollution began to draw major public attention in the United States between the mid-1950s and early 1970s, when Congress passed the Noise Control Act, the Clean Air Act, the Clean Water Act and the National Environmental Policy Act.

The development of nuclear science introduced radioactive contamination, which can remain lethally radioactive for hundreds of thousands of years. The toll on the worst-affected populations and the growth since then in understanding about the critical threat to human health posed by radioactivity has also been a prohibitive complication associated with nuclear power.

3.3 Pollution – Pathway – People

Central to Blacksmith’s approach is the model of Pollution-Pathway-People as the basis for understanding and assessing risks at a particular site. This model is consistent with risk assessment approaches used internationally (by USEPA, WHO and so on) but is very much simplified for use at our practical level.

Blacksmith is focused on people's health. However, much pollution related health impacts are chronic and are difficult to attribute directly to one source. In the context of an International Standard Atmosphere (ISA), it is unusual to be able to demonstrate clearly the health consequences of a particular site. What can be done is to show that there is a credible risk attached to the site and that this risk deserves further investigation, as part of the design of an intervention.

The existence of the risk depends on all three components: there must be a source of pollution (at a high enough level to be hazardous); there must be a population in a nearby area who are potentially exposed to the pollution; and there must be a pathway for the pollution to actually impact the people.

Preparation of the ISA is the process by which these components are identified and assessed at any site.

3.4 Classification of Environmental Pollution based on the Components of Environment that are Polluted

Major of these are: air pollution, water pollution, soil pollution (land degradation) and noise pollution. Details of these types of pollutions are discussed below with their prevention measures.

(1) Air Pollution: Air is mainly a mixture of various gases such as oxygen, carbon dioxide, nitrogen. These are present in a particular ratio. Whenever there is any imbalance in the ratio of these gases, air pollution is caused. The sources of air pollution can be grouped under:

(i) **Natural**; such as, forest fires, ash from smoking volcanoes, dust storm and decay of organic matters.
(ii) **Man-made** due to population explosion, deforestation, urbanisation and industrialisations.

Certain activities of human beings release several pollutants in air, such as carbon monoxide (CO), sulphur dioxide (SO_2), hydrocarbons (HC), oxides of nitrogen (NOx), lead, arsenic, asbestos, radioactive matter, and dust. The major threat comes from burning of fossil fuels, such as coal and petroleum products. Thermal power plants, automobiles and industries are major sources of air pollution as well. Due to progress in atomic energy sector, there has been an increase in radioactivity in the atmosphere. Mining activity adds to air pollution in the form of particulate matter. Progress in agriculture due to use of fertilizers and pesticides has also contributed towards air pollution. Indiscriminate cutting of trees and clearing of forests has led to increase in the amount

of carbon dioxide in atmosphere. Global warming is a consequence of green house effect caused by increased level of carbon dioxide (CO_2). Ozone (O_3) depletion has resulted in UV radiation striking our earth.

Table 4.1: The Gaseous Composition of Unpolluted Air

The Gases	Parts per million (vol)
Nitrogen	756,500
Oxygen	202,900
Water	31,200
Argon	9,000
Carbon Dioxide	305
Neon	17.4
Helium	5.0
Methane	0.97-1.16
Krypton	0.97
Nitrous oxide	0.49
Hydrogen	0.49
Xenon	0.08
Organic vapours	ca.0.02

3.5 Pollutants

A pollutant is a waste material that pollutes air, water or soil. Three factors determine the severity of a pollutant: its chemical nature, the concentration and the persistence. As a result of over-population, rapid industrialisations, and other human activities like agriculture and deforestation etc., earth became loaded with diverse pollutants that were released as by-products.

3.5.1 Classification of Pollutants

Pollutants are generally grouped under two classes based on their ability to degrade:

(a) **Biodegradable pollutants -** Biodegradable pollutants are broken down by the activity of micro-organisms and enter into the biogeochemical cycles. Examples of such pollutants are domestic waste products, urine and faucal matter, sewage, agricultural residue, paper, wood and cloth etc.

(b) **Non-Biodegradable pollutants -** Non-biodegradable pollutants are stronger chemical bondage, that do not break down into simpler and harmless products. These include various

insecticides and other pesticides, mercury, lead, arsenic, aluminium, plastics, radioactive waste etc.

3.5.2 Sources and Causes of Pollution

Air pollution comes from both natural and human-made (anthropogenic) sources. However, globally human-made pollutants from combustion, construction, mining, agriculture and warfare are increasingly significant in the air pollution equation.

Motor vehicle emissions are one of the leading causes of air pollution. China, United States, Russia, Mexico, and Japan are the world leaders in air pollution emissions. Principal stationary pollution sources include chemical plants, coal-fired power plants, oil refineries, petrochemical plants, nuclear waste disposal activity, incinerators, large livestock farms (dairy cows, pigs, poultry, etc.), PVC factories, metals production factories, plastics factories, and other heavy industry. Agricultural air pollution comes from contemporary practices which include clear felling and burning of natural vegetation as well as spraying of pesticides and herbicides.

About 400 million metric tons of hazardous wastes are generated each year. The United States alone produces about 250 million metric tons. Americans constitute less than 5% of the world's population, but produce roughly 25% of the world's CO_2, and generate approximately 30% of world's waste. In 2007, China has overtaken the United States as the world's biggest producer of CO_2, while still far behind based on per capita pollution - ranked 78th among the world's nations.

In February 2007, a report by the Intergovernmental Panel on Climate Change (IPCC), representing the work of 2,500 scientists, economists, and policymakers from more than 120 countries, said that humans have been the primary cause of global warming since 1950. Humans have ways to cut greenhouse gas emissions and avoid the consequences of global warming, a major climate report concluded. But to change the climate, the transition from fossil fuels like coal and oil needs to occur within decades, according to the final report this year from the UN's Intergovernmental Panel on Climate Change (IPCC).

Some of the more common soil contaminants are chlorinated hydrocarbons (CFH), heavy metals (such as chromium, cadmium–found in rechargeable batteries, and lead–found in lead paint, aviation fuel and still in some countries, gasoline), MTBE, zinc, arsenic and benzene. In 2001, a series of press reports culminating in a book called Fateful Harvest unveiled a widespread practice of recycling industrial by-products into fertilizer, resulting in the contamination of the soil with

various metals. Ordinary municipal landfills are the source of many chemical substances entering the soil environment (and often groundwater), emanating from the wide variety of refuse accepted, especially substances illegally discarded there, or from pre-1970 landfills that may have been subject to little control in the U.S. or EU. There have also been some unusual releases of polychlorinated dibenzodioxins, commonly called dioxins for simplicity, such as TCDD. Pollution can also be the consequence of a natural disaster. For example, hurricanes often involve water contamination from sewage, and petrochemical spills from ruptured boats or automobiles. Larger scale and environmental damage is not uncommon when coastal oil rigs or refineries are involved. Some sources of pollution, such as nuclear power plants or oil tankers, can produce widespread and potentially hazardous releases when accidents occur.

In the case of noise pollution the dominant source class is the motor vehicle, producing about ninety percent of all unwanted noise worldwide.

3.6 General Effects of Environmental Pollution

3.6.1 Effects on Human Health

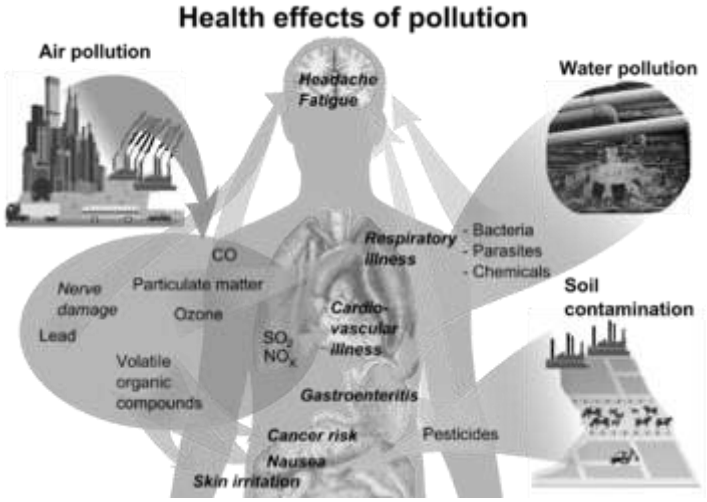


Fig. 4.1: Overview of Main Health Effects on Humans from Some Common Types of Pollution

"http://en.wikipedia.org/w/index.php?title=Pollution&oldid=506455756
"

Adverse air quality can kill many organisms including humans. Ozone pollution can cause respiratory disease, cardiovascular disease, throat inflammation, chest pain, and congestion. Water pollution causes

approximately 14,000 deaths per day, mostly due to contamination of drinking water by untreated sewage in developing countries.

Oil spills can cause skin irritations and rashes. Noise pollution induces hearing loss, high blood pressure, stress, and sleep disturbance. Mercury has been linked to developmental deficits in children and neurologic symptoms. Older people are majorly exposed to diseases induced by air pollution. Those with heart or lung disorders are under additional risk. Children and infants are also at serious risk. Lead and other heavy metals have been shown to cause neurological problems. Chemical and radioactive substances can cause cancer as well as birth defects.

3.6.2 Environment

Pollution has been found to be present widely in the environment. There are a number of effects of this:

a) Biomagnification describes situations where toxicants (such as heavy metals) may pass through trophic levels, becoming exponentially more concentrated in the process.
b) Carbon dioxide emissions cause ocean acidification, the ongoing decrease in the pH of the Earth's oceans as CO_2 becomes dissolved.
c) The emission of greenhouse gases leads to global warming which affects ecosystems in many ways.
d) Invasive species can compete with native species and reduce biodiversity. Invasive plants can contribute debris and biomolecules (allelopathy) that can alter soil and chemical compositions of an environment, often reducing native species competitiveness.
e) Nitrogen oxides are removed from the air by rain and fertilise land which can change the species composition of ecosystems.
f) Smog and haze can reduce the amount of sunlight received by plants to carry out photosynthesis and leads to the production of tropospheric ozone which damages plants.
g) Soil can become infertile and unsuitable for plants. This will affect other organisms in the food web.
h) Sulphur dioxide and nitrogen oxides can cause acid rain which lowers the pH value of soil.

4.0 CONCLUSION

Environmental pollution is a major source of health risk throughout the world. Pollutants are the agents that cause the pollution. The effects of the link between pollutants and the people were established.

5.0 SUMMARY

Environmental pollution is defined as the undesirable change in physical, chemical and biological characteristics of our air, land and water.

- The model of Pollution-Pathway-People is the basis for understanding and assessing risks at a particular site.
- Classification of pollution is based on component of the environment e.g. air, water and soil pollution.
- Classification of pollution is based on sources e.g. natural and artificial sources
- A pollutant is a waste material that pollutes air, water or soil. Three factors determine the severity of a pollutant: its chemical nature, the concentration and the persistence.
- Pollutants are generally grouped under two classes based on their ability to degrade: biodegradable and non biodegradable.
- Effects of environmental pollutants on health include poisoning diseases and effects on the environment include global warming.

6.0 TUTOR-MARKED ASSIGNMENT

1. Define environmental pollution.
2. Define environmental pollutant.
3. Give causes of pollution.
4. Identify four pollutants in the environment.

7.0 REFERENCES/FURTHER READING

"Pollution - Definition from the Merriam-Webster Online Dictionary". Merriam- webster.com. 2010-08-13. http://www.merriam-webster.com/dictionary/pollution. Retrieved 2010-08-26.

Spengler, J. D. & Sexton, K. A. (1983) "Indoor Air Pollution: A Public Health Perspective". *Science (New Series)* 221(4605): pp. 9–17.

Beychok, Milton R. (1967). *Aqueous Wastes from Petroleum and Petrochemical Plants*. (1st ed.). John Wiley & Sons.

David, Briggs (2003). British Medical Bulletinbmb.oxfordjournals.org *Br Med Bull* 68 (1): 1-24. doi: 10.1093/bmb/ldg019 This article appears in: Impact of environmental pollution on health: Balancing risk Environmental pollution and the global burden of disease

"http://en.wikipedia.org/w/index.php?title=Pollution&oldid=506455756

Royal Commission on Environmental Pollution. Chemicals in products: safeguarding the environment and human health. 24th Report of the Royal Commission on Environmental Pollution. *London: Royal Commission on Environmental Pollution,* 2003.

UNIT 2 AIR POLLUTANTS: CONCEPTS, EXPOSURE PATHWAYS, EFFECTS AND PATHOPHYSIOLOGY

CONTENTS

1.0 INTRODUCTION

In the last unit, we introduced the general concept of environmental pollution and pollutants. Here, we will discuss the concept of air pollution and effects of air pollutants. This is necessary for the protection of public health from risks due to a number of chemicals commonly present in atmosphere, including indoor air.

Clean air is a basic requirement of life. The quality of air inside homes, offices, schools, day care centres, public buildings, health care facilities or other private and public buildings where people spend a large part of their life is an essential determinant of healthy life and people's well-being. Hazardous substances emitted from buildings, construction materials and indoor equipment or due to human activities indoors, such

as combustion of fuels for cooking or heating, lead to a broad range of health problems and may even be fatal. Indoor exposure to air pollutants causes very significant damage.

2.0 OBJECTIVES

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

- state what air pollution is
- identify air pollutants in your environment
- enumerate the causes of pollution
- explain the pathophysiology of toxicity due to pollution

3.0 MAIN CONTENT

3.1 Basic Concept in Air Pollution

Fig. 4.2: Air Pollution from World War II Production

("http://en.wikipedia.org/w/index.php?title=Air_pollution)

Air pollution is the introduction of chemicals, particulate matter, or biological materials that cause harm or discomfort to humans or other living organisms, or cause damage to the natural environment or built environment, into the atmosphere.

The atmosphere is a complex dynamic natural gaseous system that is essential to support life on planet Earth. Stratospheric ozone depletion due to air pollution has long been recognised as a threat to human health as well as to the Earth's ecosystems.

Indoor air pollution and urban air quality are listed as two of the World's worst pollution problems in the 2008 Blacksmith Institute World's Worst Polluted Places report.

3.2 Meaning and Classification of Pollutants

An air pollutant is a substance in the air that can cause harm to humans and the environment. Pollutants can be in the form of solid particles, liquid droplets, or gases. In addition, they may be natural or man-made.

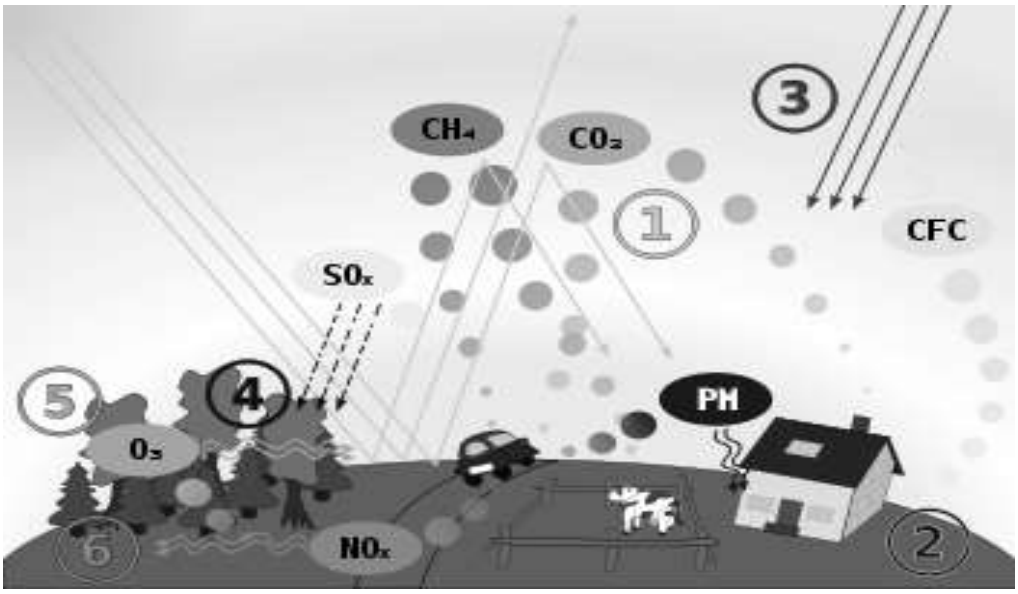


Fig. 4.3: Schematic Drawing, Causes and Effects of Air Pollution: (1) greenhouse effect, (2) particulate contamination, (3) increased UV radiation, (4) acid rain, (5) increased ground level ozone concentration, (6) increased levels of nitrogen oxides.

("http://en.wikipedia.org/w/index.php?title=Air_pollution)

3.2.1 Classification of Air Pollutants

Pollutants can be classified as primary or secondary.

i. Primary pollutant

Usually, primary pollutants are directly emitted from a process, such as ash from a volcanic eruption, the carbon monoxide gas from a motor vehicle exhaust or sulphur dioxide released from factories.

ii. Secondary pollutants

They are not emitted directly. Rather, they form in the air when primary pollutants react or interact. An important example of a secondary pollutant is ground level ozone — one of the many secondary pollutants that make up photochemical smog. Some pollutants may be both

primary and secondary: that is, they are both emitted directly and formed from other primary pollutants.

3.2.2 Primary Pollutants

a. Major primary pollutants produced by human activity include:

i. Sulphur oxides (SO_x) - especially sulphur dioxide, a chemical compound with the formula SO_2. SO_2 is produced by volcanoes and in various industrial processes. Since coal and petroleum often contain sulphur compounds, their combustion generates sulphur dioxide. Further oxidation of SO_2, usually in the presence of a catalyst such as NO_2, forms H_2SO_4, and thus acid rain. This is one of the causes for concern over the environmental impact of the use of these fuels as power sources.

ii. Nitrogen oxides (NO_x) - especially nitrogen dioxide are emitted from high temperature combustion, and are also produced naturally during thunderstorms by electrical discharge. Can be seen as the brown haze dome above or plume downwind of cities. Nitrogen dioxide is the chemical compound with the formula NO_2. It is one of the several nitrogen oxides. This reddish-brown toxic gas has a characteristic sharp, biting odour. NO_2 is one of the most prominent air pollutants.

iii. Carbon monoxide (CO)- is a colourless, odourless, non-irritating but very poisonous gas. It is a product by incomplete combustion of fuel such as natural gas, coal or wood. Vehicular exhaust is a major source of carbon monoxide.

iv. Carbon dioxide (CO_2) - a colourless, odourless, non-toxic greenhouse gas also associated with ocean acidification, emitted from sources such as combustion, cement production, and respiration. It is otherwise recycled in the atmosphere in the carbon cycle.

v. Volatile organic compounds - VOCs are an important outdoor air pollutant. In this field they are often divided into the separate categories of methane (CH_4) and non-methane (NMVOCs). Methane is an extremely efficient greenhouse gas which contributes to enhance global warming. Other hydrocarbon VOCs are also significant greenhouse gases via their role in creating ozone and in prolonging the life of methane in the atmosphere, although the effect varies depending on local air quality. Within the NMVOCs, the aromatic compounds benzene, toluene and xylene are suspected carcinogens and may lead to leukaemia through prolonged exposure. 1,3-butadiene is another dangerous compound which is often associated with industrial uses.

vi. Particulate matter - Particulates, alternatively referred to as particulate matter (PM) or fine particles, are tiny particles of solid or liquid suspended in a gas. In contrast, aerosol refers to particles and the gas together. Sources of particulate matter can be manmade or natural. Some particulates occur naturally, originating from volcanoes, dust storms, forest and grassland fires, living vegetation, and sea spray. Human activities, such as the burning of fossil fuels in vehicles, power plants and various industrial processes also generate significant amounts of aerosols. Averaged over the globe, anthropogenic aerosols—those made by human activities—currently account for about 10 percent of the total amount of aerosols in our atmosphere. Increased levels of fine particles in the air are linked to health hazards such as heart disease, altered lung function and lung cancer.

vii. Persistent free radicals connected to airborne fine particles could cause cardiopulmonary disease.

viii. Toxic metals, such as lead, cadmium and copper.

ix. Chlorofluorocarbons (CFCs) - harmful to the ozone layer emitted from products currently banned from use.

x. Ammonia (NH_3) - emitted from agricultural processes. Ammonia is a compound with the formula NH_3. It is normally encountered as a gas with a characteristic pungent odour. Ammonia contributes significantly to the nutritional needs of terrestrial organisms by serving as a precursor to foodstuffs and fertilizers. Ammonia, either directly or indirectly, is also a building block for the synthesis of many pharmaceuticals. Although in wide use, ammonia is both caustic and hazardous.

xi. Odours — such as from garbage, sewage, and industrial processes.

xii. Radioactive pollutants - produced by nuclear explosions, nuclear events, war explosives, and natural processes such as the radioactive decay of radon.

3.2.3 Secondary Pollutants

i. Particulate matter formed from gaseous primary pollutants and compounds in photochemical smog. Smog is a kind of air pollution; the word "smog" is a portmanteau of smoke and fog. Classic smog results from large amounts of coal burning in an area caused by a mixture of smoke and sulphur dioxide. Modern smog does not usually come from coal but from vehicular and industrial emissions that are acted on in the atmosphere by ultraviolet light from the sun to form secondary pollutants that also combine with the primary emissions to form photochemical smog.

ii. Ground level ozone (O_3) formed from NO_x and VOCs. Ozone (O_3) is a key constituent of the troposphere. It is also an important constituent of certain regions of the stratosphere commonly known as the Ozone layer. Photochemical and chemical reactions involving it drive many of the chemical processes that occur in the atmosphere by day and by night. At abnormally high concentrations brought about by human activities (largely the combustion of fossil fuel), it is a pollutant, and a constituent of smog.
iii. Peroxyacetyl nitrate (PAN) - similarly formed from NO_x and VOCs.

Minor air pollutants

i. A large number of minor hazardous air pollutants. Some of these are regulated in USA under the Clean Air Act and in Europe under the Air Framework Directive.
ii. A variety of persistent organic pollutants, which can attach to particulate matter. Persistent organic pollutants (POPs) are organic compounds that are resistant to environmental degradation through chemical, biological, and photolytic processes. Because of this, they have been observed to persist in the environment, to be capable of long-range transport, bioaccumulate in human and animal tissue, biomagnify in food chains, and to have potential significant impacts on human health and the environment.

3.3 Sources of Air Pollutants

Sources of air pollutants refer to the various locations, activities or factors which are responsible for the releasing of pollutants into the atmosphere. These sources can be classified into two major categories which are:

a. **Anthropogenic sources (human activity)** mostly related to burning different kinds of fuel

i. "Stationary Sources" include smoke stacks of power plants, manufacturing facilities (factories) and waste incinerators, as well as furnaces and other types of fuel-burning heating devices. In developing and poor countries, traditional biomass burning is the major source of air pollutants; traditional biomass includes wood, crop waste and dung.
ii. "Mobile Sources" include motor vehicles, marine vessels, aircraft and the effect of sound etc.

iii. Chemicals, dust and controlled burn practices in agriculture and forestry management. Controlled or prescribed burning is a technique sometimes used in forest management, farming, prairie restoration or greenhouse gas abatement. Fire is a natural part of both forest and grassland ecology and controlled fire can be a tool for foresters. Controlled burning stimulates the germination of some desirable forest trees, thus renewing the forest.
iv. Fumes from paint, hair spray, varnish, aerosol sprays and other solvents.
v. Waste deposition in landfills, which generate methane. Methane is not toxic; however, it is highly flammable and may form explosive mixtures with air. Methane is also an asphyxiant and may displace oxygen in an enclosed space. Asphyxia or suffocation may result if the oxygen concentration is reduced to below 19.5% by displacement.
iv. Military, such as nuclear weapons, toxic gases, germ warfare and rocketry.

b. Natural sources

i. Dust from natural sources, usually large areas of land with little or no vegetation
ii. Methane, emitted by the digestion of food by animals, for example cattle
iii. Radon gas from radioactive decay within the Earth's crust. Radon is a colourless, odourless, naturally occurring, radioactive noble gas that is formed from the decay of radium. It is considered to be a health hazard. Radon gas from natural sources can accumulate in buildings, especially in confined areas such as the basement and it is the second most frequent cause of lung cancer, after cigarette smoking.
iv. Smoke and carbon monoxide from wildfires
v. Vegetation, in some regions, emits environmentally significant amounts of VOCs on warmer days. These VOCs react with primary anthropogenic pollutants—specifically, NO_x, SO_2, and anthropogenic organic carbon compounds—to produce a seasonal haze of secondary pollutants.
vi. Volcanic activity, which produce sulphur, chlorine, and ash particulates

3.4 Emission Factors

Air pollutant emission factors are representative values that people attempt to relate the quantity of a pollutant released to the ambient air with an activity associated with the release of that pollutant. These factors are usually expressed as the weight of pollutant divided by a unit

weight, volume, distance, or duration of the activity emitting the pollutant (e.g., kilograms of particulate emitted per mega-gram of coal burned). Such factors facilitate estimation of emissions from various sources of air pollution. In most cases, these factors are simply averages of all available data of acceptable quality, and are generally assumed to be representative of long-term averages.

There are 12 compounds in the list of POPs. Dioxins and furans are two of them and are intentionally created by combustion of organics, like open burning of plastics. The POPs are also endocrine disruptor and can mutate the human genes.

The United States Environmental Protection Agency (USEPA) has published a compilation of air pollutant emission factors for a multitude of industrial sources. The United Kingdom, Australia, Canada and many other countries have published similar compilations, as well as the European Environment Agency.

3.5 Indoor Air Quality (IAQ)

Indoor air may contain substances as benzene, carbon monoxide, formaldehyde, naphthalene, nitrogen dioxide, polycyclic aromatic hydrocarbons (especially benzo[*a*]pyrene), radon, trichloroethylene and tetrachloroethylene which are hazardousness to health and are often found indoors in concentrations of health concern.

A lack of ventilation indoors concentrates air pollution where people often spend the majority of their time. Radon (Rn) gas, a carcinogen, is exuded from the Earth in certain locations and trapped inside houses. Building materials including carpeting and plywood emit formaldehyde (H_2CO) gas. Paint and solvents give off volatile organic compounds (VOCs) as they dry. Lead paint can degenerate into dust and be inhaled. Intentional air pollution is introduced with the use of air fresheners, incense, and other scented items. Controlled wood fires in stoves and fireplaces can add significant amounts of smoke particulates into the air, inside and out. Indoor pollution fatalities may be caused by using pesticides and other chemical sprays indoors without proper ventilation. Carbon monoxide (CO) poisoning and fatalities are often caused by faulty vents and chimneys, or by the burning of charcoal indoors. Chronic carbon monoxide poisoning can result even from poorly adjusted pilot lights. Traps are built into all domestic plumbing to keep sewer gas, hydrogen sulphide, out of interiors. Clothing emits tetrachloroethylene, or other dry cleaning fluids, for days after dry cleaning.

Though its use has now been banned in many countries, the extensive use of asbestos in industrial and domestic environments in the past has left a potentially very dangerous material in many localities. Asbestosis is a chronic inflammatory medical condition affecting the tissue of the lungs. It occurs after long-term, heavy exposure to asbestos from asbestos-containing materials in structures. Sufferers have severe dyspnea (shortness of breath) and are at an increased risk regarding several different types of lung cancer. As clear explanations are not always stressed in non-technical literature, care should be taken to distinguish between several forms of relevant diseases. According to the World Health Organisation (WHO), these may defined as; asbestosis, *lung cancer*, and *Peritoneal Mesothelioma* (generally a very rare form of cancer, when more widespread it is almost always associated with prolonged exposure to asbestos).

Biological sources of air pollution are also found indoors, as gases and airborne particulates. Pets produce dander, people produce dust from minute skin flakes and decomposed hair, dust mites in bedding, carpeting and furniture produce enzymes and micrometre-sized faecal droppings, inhabitants emit methane, mould forms in walls and generates mycotoxins and spores, air conditioning systems can incubate Legionnaires' disease and mould, and houseplants, soil and surrounding gardens can produce pollen, dust, and mould. Indoors, the lack of air circulation allows these airborne pollutants to accumulate more than they would otherwise occur in nature.

3.6 Pathophysiology (Health Effects) of Air Pollutants

Pollutants enter the human body in three main different ways: by inhalation, ingestion or skin absorption. The amount of any given pollutant that is received is often termed the dose. The dose will be dependent on the duration and intensity of the exposure. Organ dose refers specifically to the amount that reaches the human organ where the relevant effects can occur, e.g. the lung.

In many cases, exposure may occur simultaneously from many sources and through multiple routes. Pathways of exposures to lead, for example, include air pollution from traffic and industrial emissions, drinking water, food, tobacco smoking, dusts, paints and other industrially produced commodities and soil. Valid exposure assessment therefore typically requires detailed knowledge about the geographical distribution of the pollutants of concern, the temporal variations in pollution levels, and the processes of exposure.

People are often exposed to different pollutants simultaneously. Exposure to these may occur at different locations (e.g. in the workplace and/or at home) and at different times.

The full range of factors which therefore may need to be examined is potentially large. It may include many different environmental pollutants (including hazardous chemicals, radioactivity, dusts and particulates), from many different sources (including energy production, industry, pesticide use), released either continuously or sporadically, and either under controlled conditions (i.e. deliberate discharges) or accidentally.

Air pollution is a significant risk factor for multiple health conditions including respiratory infections, heart disease, and lung cancer, according to the WHO. The health effects caused by air pollution may include difficulty in breathing, wheezing, coughing and aggravation of existing respiratory and cardiac conditions. These effects can result in increased medication use, increased doctor or emergency room visits, more hospital admissions and premature death. The human health effects of poor air quality are far reaching, but principally affect the body's respiratory system and the cardiovascular system. Individual reactions to air pollutants depend on the type of pollutant a person is exposed to, the degree of exposure, the individual's health status and genetics.

The most common sources of air pollution include particulate matter, ozone, nitrogen dioxide, and sulphur dioxide. Both indoor and outdoor air pollution have caused approximately 3.3 million deaths worldwide. Children aged less than five years that live in developing countries are the most vulnerable population in terms of total deaths attributable to indoor and outdoor air pollution.

Diesel exhaust (DE) is a major contributor to combustion derived particulate matter air pollution. In several human experimental studies, using a well validated exposure chamber setup, DE has been linked to acute vascular dysfunction and increased thrombus formation. This serves as a plausible mechanistic link between the previously described association between particulate matter air pollution and increased cardiovascular morbidity and mortality.

3.6.1 Effects on Cardiovascular Health

Air pollution is also emerging as a risk factor for stroke, particularly in developing countries where pollutant levels are highest. A recent study also found an association in women between air pollution and ischemia, but not hemorrhagic stroke. Air pollution has also been associated with increased incidence and mortality from coronary artery disease.

3.6.2 Effects on Cystic Fibrosis

A study from around the years of 1999 to 2000, by the University of Washington, showed that patients near and around particulate matter air pollution had an increased risk of pulmonary exacerbations and decrease in lung function. As cystic fibrosis patients already suffer from decreased lung function, everyday pollutants such as smoke, emissions from automobiles, tobacco smoke and improper use of indoor heating devices could further compromise lung function.

3.6.3 Effects on COPD and Asthma

Chronic obstructive pulmonary disease (COPD) includes diseases such as chronic bronchitis and emphysema.

It is believed that much like cystic fibrosis, by living in a more urban environment serious health hazards become more apparent. Studies have shown that in urban areas patients suffer mucus hyper-secretion, lower levels of lung function, and more self diagnosis of chronic bronchitis and emphysema.

3.6.4 Possible Links to Cancer

A large Danish epidemiological study found an increased risk of lung cancer for patients who lived in areas with high nitrogen oxide concentrations. In this study, the association was higher for non-smokers than smokers. There are also possible associations between air pollution and other forms of cancer, including cervical cancer and brain cancer.

3.6.5 Effects on Children

Cities around the world with high exposure to air pollutants have the possibility of children living within them to develop asthma, pneumonia and other lower respiratory infections as well as a low initial birth rate. Protective measures to ensure the youths' health are being taken in cities such as New Delhi, India where buses now use compressed natural gas to help eliminate the "pea-soup" smog. Those pollutants are known as the criteria pollutants, and include ozone, particulate matter, sulphur dioxide, nitrogen dioxide, carbon monoxide, and lead. Because children are outdoors more and have higher minute ventilation they are more susceptible to the dangers of air pollution.

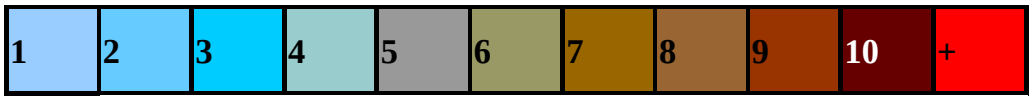
3.6.6 Health Effects in Relatively "Clean" Areas

Even in the areas with relatively low levels of air pollution, public health effects can be significant and costly, since a large number of people breathe in such pollutants.

3.7 Air Quality Health Index

The Air Quality Health Index or "AQHI" provides a number from 1 to 10+ to indicate the level of health risk associated with local air quality. Occasionally, when the amount of air pollution is abnormally high, the number may exceed 10. The AQHI provides a local air quality current value as well as a local air quality maximums forecast for today, tonight and tomorrow and provides associated health advice.

Table 4.2: Air Quality Health Index



Risk: Low **(1-3)** Moderate **(4-6)** High **(7-10)** Very high **(above 10)**

As it is now known that even low levels of air pollution can trigger discomfort for the sensitive population, the index has been developed as a continuum: The higher the number, the greater the health risk and need to take precautions. The index describes the level of health risk associated with this number as ‘low’, ‘moderate’, ‘high’ or ‘very high’, and suggests steps that can be taken to reduce exposure.

Table 4.3: Air Quality Health Index

Health Risk	**Air Quality Health Index**	**Health Messages**	
		At Risk population	**General Population**
Low	**1-3**	**Enjoy** your usual outdoor activities.	**Ideal** air quality for outdoor activities
Moderate	**4-6**	**Consider reducing** or rescheduling strenuous activities outdoors if you are experiencing symptoms.	**No need to modify** your usual outdoor activities unless you experience symptoms such as coughing and throat irritation.

High	**7-10**	**Reduce** or reschedule strenuous activities outdoors. Children and the elderly should also take it easy.	**Consider reducing** or rescheduling strenuous activities outdoors if you experience symptoms such as coughing and throat irritation.
Very high	**Above 10**	**Avoid** strenuous activities outdoors. Children and the elderly should also avoid outdoor physical exertion.	**Reduce** or reschedule strenuous activities outdoors, especially if you experience symptoms such as coughing and throat irritation.

It is measured based on the observed relationship of nitrogen dioxide (NO_2), ground-level ozone (O_3) and particulate matter ($PM_{2.5}$) with mortality from an analysis of several Canadian cities. Significantly, all three of these pollutants can pose health risks, even at low levels of exposure, especially among those with pre-existing health problems.

When developing the AQHI, Health Canada's original analysis of health effects included five major air pollutants: particulate matter, ozone, and nitrogen dioxide (NO_2), as well as sulphur dioxide (SO_2), and carbon monoxide (CO). The latter two pollutants provided little information in predicting health effects and were removed from the AQHI formulation. The AQHI does not measure the effects of odour, pollen, dust, heat or humidity.

3.8 Environmental Impacts of Greenhouse Gas Pollutants

The greenhouse effect is a phenomenon whereby greenhouse gases create a condition in the upper atmosphere causing a trapping of heat and leading to increased surface and lower tropospheric temperatures. Carbon dioxide emissions from combustion of fossil fuels are a source of greenhouse gas emissions.

Other greenhouse gases include methane, hydrofluorocarbons, perfluorocarbons, chlorofluorocarbons, nitrogen oxides, and ozone.
For more refer industrial dust, air pollution and related occupational diseases.

4.0 CONCLUSION

This unit explained the concept of air pollution and identified pollutants in the atmosphere that pose adverse health effect on man.

In the next unit, we will discuss the presence of harmful substances in water and the pathway and pathophysiology.

5.0 SUMMARY

Air pollution is the introduction of chemicals, particulate matter, or biological materials that cause harm or discomfort to humans or other living organisms, or cause damage to the natural environment or built environment, into the atmosphere.

An air pollutant is a substance in the air that can cause harm to humans and the environment. Pollutants can be in the form of solid particles, liquid droplets, or gases. In addition, they may be natural or man-made. Pollutants can be classified as primary or secondary.

i. Primary pollutants are directly emitted from a process, such as ash from a volcanic eruption, the carbon monoxide gas from a motor vehicle exhaust or sulfur dioxide released from factories.
ii. Secondary pollutants are not emitted directly. Rather, they form in the air when primary pollutants react or interact.

Sources of air pollutants refer to the various locations, activities or factors which are responsible for the releasing of pollutants into the atmosphere. These sources can be classified into two major categories which are:

a. Anthropogenic sources (human activity) mostly related to burning different kinds of fuel
b. Natural sources

Emission factors

Air pollutant emission factors are representative values that people attempt to relate the quantity of a pollutant released to the ambient air with an activity associated with the release of that pollutant.
Indoor air quality (IAQ)

Indoor air may contain substances as benzene, carbon monoxide, formaldehyde, naphthalene, nitrogen dioxide, polycyclic aromatic hydrocarbons (especially benzo[*a*]pyrene), radon, trichloroethylene and tetrachloroethylene which are hazardousness to health and are often found indoors in concentrations of health concern.

Pathophysiology (Health effects) of air pollutants

Pollutants enter the human body in three main different ways: by inhalation, ingestion or skin absorption. The amount of any given pollutant that is received is often termed the dose. The dose will be dependent on the duration and intensity of the exposure. Organ dose refers specifically to the amount that reaches the human organ where the relevant effects can occur, e.g. the lung.

Environmental impacts of greenhouse gas pollutants

The greenhouse effect is a phenomenon whereby greenhouse gases create a condition in the upper atmosphere causing a trapping of heat and leading to increased surface and lower tropospheric temperatures. Carbon dioxide emissions from combustion of fossil fuels are a source of greenhouse gas emissions.

Toxicologic Effects (pathophysiology) of Air Pollution

(a) It affects respiratory system of living organisms and causes bronchitis, asthma, lung cancer, pneumonia etc. Carbon monoxide (CO) emitted from motor vehicles and cigarette smoke affects the central nervous system.

(b) Due to depletion of ozone layer, UV radiation reaches the earth. UV radiation causes skin cancer, damage to eyes and immune system.

(c) Acid rain is also a result of air pollution. This is caused by presence of oxides of nitrogen and sulphur in the air. These oxides dissolve in rain water to form nitric acid and sulphuric acid respectively. Various monuments, buildings, and statues are damaged due to corrosion by acid present in the rain. The soil also becomes acidic. The cumulative effect is the gradual degradation of soil and a decline in forest and agricultural productivity.

(d) The green house gases, such as carbon dioxide (CO_2) and methane (CH_4) trap the heat radiated from earth. This leads to an increase in earth's temperature.

(e) Some toxic metals and pesticides also cause air pollution.

6.0 TUTOR-MARKED ASSIGNMENT

1. State what is air pollution
2. Identify five air pollutants
3. Enumerate five causes of pollution
4. Identify five effects of pollutants.

7.0 REFERENCES/FURTHER READING

"http://en.wikipedia.org/w/index.php?title=Air_pollution&oldid=506066216" On August 11, 2012.

World Health Organization (2010). *WHO guideline for indoor air quality: selected pollutants.*

UNIT 3 WATER POLLUTANTS: CONCEPTS, EXPOSURE PATHWAYS, EFFECTS AND PATHOPHYSIOLOGY

CONTENTS

1.0 INTRODUCTION

In Unit 2, we discussed the presence of pollutants in the atmosphere which results in air pollution, in this unit, we will understand the concept of water pollution caused by the presence of pollutants in water.

Water is one of the prime necessities of life. With increasing number of people depend on this resource; water has become a scarce commodity. Pollution makes even the limited available water unfit for use. Water is said to be polluted when there is any physical, biological or chemical change in water quality that adversely affects living organisms or makes water unsuitable for use.

Sources of water pollution are mainly factories, power plants, coal mines and oil wells situated either close to water source or away from sources. They discharge pollutants directly or indirectly into the water sources like river, lakes, and water streams. Read on to get the details.

2.0 OBJECTIVES

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

- explain the concept of water pollution
- identify common water pollutants and their sources
- enumerate the effects of water pollution.

3.0 MAIN CONTENT

3.1 Meaning of Water Pollution

Water pollution is the contamination of water bodies (e.g. lakes, rivers, oceans, aquifers and groundwater). Water pollution occurs when pollutants are discharged directly or indirectly into water bodies without adequate treatment to remove harmful compounds.

Water is typically referred to as polluted when it is impaired by anthropogenic contaminants and either does not support a human use, such as drinking water, and/or undergoes a marked shift in its ability to support its constituent biotic communities, such as fish. Natural phenomena such as volcanoes, algae blooms, storms, and earthquakes also cause major changes in water quality and the ecological status of water.

Water pollution affects plants and organisms living in these bodies of water. In almost all cases the effect is damaging not only to individual species and populations, but also to the natural biological communities.

3.2 Pathophysiology of Water Pollutants

The contamination of ground water of water bodies like rivers, lakes, wetlands, estuaries, and oceans can threaten the health of humans and aquatic life. The harmful effects of water pollution are:

(a) Human beings become victims of various water borne diseases, such as typhoid, cholera, dysentery, hepatitis, jaundice, etc.
(b) The presence of acids/alkalis in water destroys the microorganisms, thereby hindering the self-purification process in the rivers or water bodies. Agriculture is affected badly due to polluted water. Marine eco-systems are affected adversely.
(c) The sewage waste promotes growth of phytoplankton in water bodies; causing reduction of dissolved oxygen.

Pollution of water bodies with nutrients (principally nitrogen and phosphorus) can result in the growth of algae and other aquatic plants that shade or clog streams. If wastewater containing biodegradable organic matter is discharged into a stream with inadequate dissolved oxygen, the water downstream of the point of discharge will become anaerobic and will be turbid and dark. Settleable solids will be deposited on the streambed, and anaerobic decomposition will occur. Over the reach of stream where the dissolved-oxygen concentration is zero, a zone of putrefaction will occur with the production of hydrogen sulphide (H_2S), ammonia (NH_3), and other odorous gases. Because many fish species require a minimum of 4–5 mg of dissolved oxygen per litre of water, they will be unable to survive in this portion of the stream.

(d) Poisonous industrial wastes present in water bodies affect the fish population and deprives us of one of our sources of food. It also kills other animals living in fresh water.

Direct exposures to toxic chemicals are also a health concern for individual aquatic plants and animals. Chemicals such as pesticides are frequently transported to lakes and rivers via runoff, and they can have harmful effects on aquatic life. Toxic chemicals have been shown to reduce the growth, survival, reproductive output, and disease resistance of exposed organisms. These effects can have important consequences for the viability of aquatic populations and communities.

(e) The quality of underground water is also affected due to toxicity and pollutant content of surface water.

3.3 Sources of Water Pollution

Sources of surface water pollution are generally grouped into two categories based on their origin:

Fig. 4.4: A Polluted River Draining an Abandoned Copper Mine on Anglesey

(i) Point-source pollution

The pollutants are discharged from a discrete location into a waterway from a single, identifiable source, such as a pipe or ditch. Examples of sources in this category include discharges from a sewage treatment plant, a factory, or a city storm drain. Sewage outfalls and oil spills are examples of point-source pollution. The U.S. Clean Water Act (CWA) defines point source in 1987 to include municipal storm sewer systems, as well as industrial storm water, such as from construction sites.

(ii) Non-point-source or diffuse pollution

This is referring to all of the other discharges that deliver contaminants to water bodies. Acid rain and unconfined runoff from agricultural or urban areas falls under this category. A common example is the leaching out of nitrogen compounds from fertilized agricultural lands. Nutrient runoff in storm water from "sheet flow" over an agricultural field or a forest is also cited as examples of NPS pollution. Contaminated storm water washed off of parking lots, roads and highways, called urban runoff, is sometimes included under the category of NPS pollution.

3.4 Groundwater Pollution and Thermal Pollution

Interactions between groundwater and surface water are complex. Consequently, groundwater pollution, sometimes referred to as **groundwater contamination**, is not as easily classified as surface water pollution.

The specific contaminants leading to pollution in water include a wide spectrum of chemicals, pathogens, and physical or sensory changes such as elevated temperature and discoloration. While many of the chemicals and substances that are regulated may be naturally occurring (calcium, sodium, iron, manganese, etc.) the concentration is often the key in determining what is a natural component of water, and what is a contaminant. High concentrations of naturally occurring substances can have negative impacts on aquatic flora and fauna.

Thermal pollution

Thermal pollution is the rise or fall in the temperature of a natural body of water caused by human influence. Thermal pollution, unlike chemical pollution, results in a change in the physical properties of water. A common cause of thermal pollution is the use of water as a coolant by power plants and industrial manufacturers. Elevated water temperatures decreases oxygen levels (which can kill fish) and affects ecosystem

composition, such as invasion by new thermophilic species. Urban runoff may also elevate temperature in surface waters.
Thermal pollution can also be caused by the release of very cold water from the base of reservoirs into warmer rivers.

3.5 Water Pollutants

The principal contaminants of water include toxic chemicals, nutrients, biodegradable organics, and bacterial and viral pathogens. Water pollution can affect human health when pollutants enter the body either via skin exposure or through the direct consumption of contaminated drinking water and contaminated food.

Prime pollutants, including DDT and polychlorinated biphenyls (PCBs), persist in the natural environment and bioaccumulation occurs in the tissues of aquatic organisms. These prolonged and persistent organic pollutants are transferred up the food chain and they can reach levels of concern in fish species that are eaten by humans.

3.5.1 Water Pollution by Pesticides

The impact on water quality by pesticides is associated with the following factors:

- active ingredient in the pesticide formulation
- contaminants that exist as impurities in the active ingredient
- additives that are mixed with the active ingredient (wetting agents, diluents or solvents, extenders, adhesives, buffers, preservatives and emulsifiers)
- degradate that is formed during chemical, microbial or photochemical degradation of the active ingredient.

3.5.2 Factors affecting Pathophysiology of Toxicity in Aquatic Systems

The ecological impacts of pesticides in water are determined by toxicity, persistence, degradates and fate.

Table 4.4: Ecological Impacts of Pesticides in Water

Toxicity:	Mammalian and non-mammalian toxicity usually expressed as LD_{50} ("Lethal Dose": concentration of the pesticide which will kill half the test organisms over a specified test period). The lower the LD_{50}, the greater the toxicity; **values of 0-10 are extremely toxic** (OMAF, 1991).
	Drinking water and food guidelines are determined using a risk-based assessment. Generally, Risk = Exposure (amount and/or duration) × Toxicity.
	Toxic response (effect) can be **acute** (death) or **chronic** (an effect that does not cause death over the test period but which causes observable effects in the test organism such as cancers and tumours, reproductive failure, growth inhibition, teratogenic effects, etc.).
Persistence:	Measured as half-life (time required for the ambient concentration to decrease by 50%). Persistence is determined by biotic and abiotic degradational processes. Biotic processes are biodegradation and metabolism; abiotic processes are mainly hydrolysis, photolysis, and oxidation (Calamari and Barg, 1993). Modern pesticides tend to have short half lives that reflect the period over which the pest needs to be controlled.
Degradates:	The degradational process may lead to formation of "degradates" which may have greater, equal or lesser toxicity than the parent compound. As an example, DDT degrades to DDD and DDE.
Fate (Environmental):	The environmental fate (behaviour) of a pesticide is affected by the natural affinity of the chemical for one of four environmental compartments (Calamari and Barg, 1993): solid matter (mineral matter and particulate organic carbon), liquid (solubility in surface and soil water), gaseous form (volatilisation), and biota. This behaviour is often referred to as "partitioning" and involves, respectively, the determination of: the soil sorption coefficient (K_{OC}); solubility; Henry's Constant (H); and the n-octanol/water partition coefficient (K_{OW}). These parameters are well known for pesticides and are used to predict the environmental fate of the pesticide.

An additional factor can be the presence of impurities in the pesticide formulation that are not part of the active ingredient. A recent example is the case of TFM, a lampricide used in tributaries of the Great Lakes for many years for the control of the sea lamprey. Although the environmental fate of TFM has been well known for many years, recent research by Munkittrick *et al.* (1994) has found that TFM formulation includes one or more highly potent impurities that impact on the hormonal system of fish and cause liver disease.

3.5.3 Chemical and other contaminants

Fig. 4.5: Raw Sewage and Industrial Waste flows across International Borders—New River passes from Mexicali to Calexico, California

Contaminants may include organic and inorganic substances.

Organic water pollutants include:

- Detergents
- Disinfection by-products found in chemically disinfected drinking water, such as chloroform
- Food processing waste, which can include oxygen-demanding substances, fats and grease
- Insecticides and herbicides, a huge range of organohalides and other chemical compounds
- Petroleum hydrocarbons, including fuels (gasoline, diesel fuel, jet fuels, and fuel oil) and lubricants (motor oil), and fuel combustion by-products, from storm water runoff
- Tree and bush debris from logging operations
- Volatile organic compounds (VOCs), such as industrial solvents, from improper storage.

- Chlorinated solvents, which are dense non-aqueous phase liquids (DNAPLs), may fall to the bottom of reservoirs, since they don't mix well with water and are denser.
- Polychlorinated biphenyl (PCBs)
- Trichloroethylene
- Perchlorate
- Various chemical compounds found in personal hygiene and cosmetic products.

Inorganic water pollutants include:

- Acidity caused by industrial discharges (especially sulphur dioxide from power plants)
- Ammonia from food processing waste
- Chemical waste as industrial by-products
- Fertilizers containing nutrients--nitrates and phosphates—which are found in stormwater runoff from agriculture, as well as commercial and residential use
- Heavy metals from motor vehicles (via urban stormwater runoff) and acid mine drainage
- Silt (sediment) in runoff from construction sites, logging, slash and burn practices or land clearing sites.

Macroscopic pollution—large visible items polluting the water—may be termed "floatables" in an urban stormwater context, or marine debris when found on the open seas, and can include such items as:

- Trash or garbage (e.g. paper, plastic, or food waste) discarded by people on the ground, along with accidental or intentional dumping of rubbish, that are washed by rainfall into storm drains and eventually discharged into surface waters
- Nurdles, small ubiquitous waterborne plastic pellets
- Shipwrecks, large derelict ships.

4.0 CONCLUSION

The concept of water pollution is discussed with the identification of types of pollution and pollutant. The pollutants were found to have effects on humans directly and indirectly through their ecological effects.

In the next unit, we will discuss the effect of pollutants on land which ultimately affects man.

5.0 SUMMARY

Water pollution is the contamination of water bodies (e.g. lakes, rivers, oceans, aquifers and groundwater). Water pollution occurs when pollutants are discharged directly or indirectly into water bodies without adequate treatment to remove harmful compounds.

The harmful effects of water pollution are:

(a) Various water borne diseases, such as typhoid, cholera, dysentery, hepatitis, jaundice, etc.
(b) The presence of acids/alkalis in water destroys the microorganisms.
(c) The sewage waste promotes growth of phytoplankton in water bodies.
(d) Poisonous industrial wastes present in water bodies affect the fish population.
(e) The quality of underground water is also affected due to toxicity and pollutant content of surface water.

A change in the chemical, physical, biological, and radiological quality of water that is injurious to its uses is called water polution. The term "water pollution" generally refers to human-induced changes to water quality. Thus, the discharge of toxic chemicals from industries or the release of human or livestock waste into a nearby water body is considered pollution.

6.0 TUTOR-MARKED ASSIGNMENT

1. Explain what water pollution is.
2. Identify five water pollutants.
3. State possible effects of water pollutants on human.

7.0 REFERENCE/FURTHER READING

Retrieved from "http://en.wikipedia.org /w/index.php?title=Water _pollution&oldid=505453536"

UNIT 4 LAND POLLUTANTS: CONCEPTS, EXPOSURE PATHWAYS, EFFECTS AND PATHOPHYSIOLOGY

CONTENTS

1.0 INTRODUCTION

In Unit 3 of this Module, we discussed the concepts, presence, effects and pathophysiology of water pollutants. In this unit, we will explain the concepts, effects and pathophysiology of harmful substances discharged on our lands.

Land pollution occurs when hazardous wastes contaminate soil and groundwater due to inadequate or irresponsible disposal measures. Abandoned or neglected waste disposal sites are a particularly difficult and expensive problem for society. Sometimes, hazardous waste is disposed of illegally and in an even more dangerous manner because the owner cannot find a cheap way to get rid of it. Let us find out more.

2.0 OBJECTIVES

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

- explain what is land pollution
- identify the causes of land pollution
- identify common land pollutants in the environment
- enumerate the pathophysiology of the toxicity of land pollutants.

3.0 MAIN CONTENT

2.1 Basic Concept of Soil or Land Pollution

Soil contamination or soil pollution is caused by the presence of xenobiotic (human-made) chemicals or other alteration in the natural soil environment.

3.2 Causes of Soil Pollution

These include:

1. Application of pesticides, especially in the farm lands.
2. It arises from the failure caused by corrosion of underground storage tanks (including piping used to transmit the contents).
3. Percolation of contaminated surface water to subsurface strata.
4. Oil and fuel dumping.
5. Leaching of wastes from landfills or direct discharge of industrial wastes to the soil.
6. Disposal of coal ash. Coal naturally concentrates lead and zinc. Coal ash and slag may contain sufficient lead to qualify as a "characteristic hazardous waste", defined in the USA as containing more than 5 mg/L of extractable lead using the TCLP procedure. In addition to lead, coal ash typically contains variable but significant concentrations of polynuclear aromatic hydrocarbons (PAHs; e.g., benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, indeno(cd)pyrene, phenanthrene, anthracene, and others). These PAHs are known human carcinogens and the acceptable concentrations of them in soil are typically around 1 mg/kg.

3.3 Common Soil Pollutants

The most common chemicals involved are petroleum hydrocarbons, lead, polynuclear aromatic hydrocarbons (such as naphthalene and benzo(a)pyrene), solvents, pesticides, and other heavy metals. This occurrence of this phenomenon is correlated with the degree of industrialisation and intensities of chemical usage.

3.4 Effects of Soil Contamination

The concern over soil contamination stems primarily from health risks, from direct contact with the contaminated soil, vapours from the contaminants, and from secondary contamination of water supplies within and underlying the soil (US EPA).

3.5 Health Effects of Soil Pollution

Contaminated or polluted soil directly affects human health through direct contact with soil or via inhalation of soil contaminants which have vapourised; potentially greater threats are posed by the infiltration of soil contamination into groundwater aquifers used for human consumption, sometimes in areas apparently far removed from any apparent source of above ground contamination.

Health consequences from exposure to soil contamination vary greatly depending on pollutant type, pathway of attack and vulnerability of the exposed population. Chronic exposure to chromium, lead and other metals, petroleum, solvents, and many pesticide and herbicide formulations can be carcinogenic, can cause congenital disorders, or can cause other chronic health conditions. Industrial or man-made concentrations of naturally occurring substances, such as nitrate and ammonia associated with livestock manure from agricultural operations, have also been identified as health hazards in soil and groundwater.

Chronic exposure to benzene at sufficient concentrations is known to be associated with higher incidence of leukaemia. Mercury and cyclodienes are known to induce higher incidences of kidney damage, some irreversible. PCBs and cyclodienes are linked to liver toxicity.

Organophosphates and carbomates can induce a chain of responses leading to neuromuscular blockage. Many chlorinated solvents induce liver changes, kidney changes and depression of the central nervous system. There is an entire spectrum of further health effects such as headache, nausea, fatigue, eye irritation and skin rash for the above cited and other chemicals. At sufficient dosages a large number of soil contaminants can cause death by exposure via direct contact, inhalation or ingestion of contaminants in groundwater contaminated through soil.
The Scottish Government has commissioned the Institute of Occupational Medicine to undertake a review of methods to assess risk to human health from contaminated land. The overall aim of the project is to work up guidance that should be useful to Scottish Local Authorities in assessing whether sites represent a significant possibility of significant harm (SPOSH) to human health. It is envisaged that the output of the project will be a short document providing high level guidance on health risk assessment with reference to existing published guidance and methodologies that have been identified as being particularly relevant and helpful. The project will examine how policy guidelines have been developed for determining the acceptability of risks to human health and propose an approach for assessing what constitutes unacceptable risk in line with the criteria for SPOSH as defined in the legislation and the Scottish Statutory Guidance.

3.6 Effects of Land Pollution on the Ecosystem

Not unexpectedly, soil contaminants can have significant deleterious consequences on ecosystems. There are radical soil chemistry changes which can arise from the presence of many hazardous chemicals even at low concentration of the contaminant species. These changes can manifest in the alteration of metabolism of endemic microorganisms and arthropods resident in a given soil environment. The result can be virtual eradication of some of the primary food chain, which in turn could have major consequences for predator or consumer species. Even if the chemical effect on lower life forms is small, the lower pyramid levels of the food chain may ingest alien chemicals, which normally become more concentrated for each consuming rung of the food chain. Many of these effects are now well known, such as the concentration of persistent DDT materials for avian consumers, leading to weakening of egg shells, increased chick mortality and potential extinction of species.
Land pollution is a threat to the environment, to food safety and to sustainable agriculture. Effects occur to agricultural lands which have certain types of soil contamination. Contaminants typically alter plant metabolism, often causing a reduction in crop yields. This has a secondary effect upon soil conservation, since the languishing crops cannot shield the Earth's soil from erosion. Some of these chemical contaminants have long half-lives and in other cases derivative chemicals are formed from decay of primary soil contaminants.

According to a scientific sampling, 150 million mi. (100,000 square kilometres) of China’s cultivated land have been polluted, with contaminated water being used to irrigate a further 32.5 million mi. (21,670 square kilometres) and another 2 million mi. (1,300 square kilometres) covered or destroyed by solid waste. In total, the area accounts for one-tenth of China’s cultivatable land, and are mostly in economically developed areas. An estimated 12 million tonnes of grain are contaminated by heavy metals every year, causing direct losses of 20 billion Yuan (US$2.57 billion).

4.0 CONCLUSION

So far we had explained the concepts of soil pollution and effects of the exposure on man and his environment. Often times, soil pollution leads to water pollution.

In the next unit, we shall study how to evaluate the effects of toxicants or unknown substances using the dose-response concept.

5.0 SUMMARY

Soil contamination or **soil pollution** is caused by the presence of xenobiotic (human-made) chemicals or other alteration in the natural soil environment.

Causes of soil pollution include:

1. Application of pesticides, especially in the farm lands.
2. It arises from the failure caused by corrosion of underground storage tanks (including piping used to transmit the contents).
3. Percolation of contaminated surface water to subsurface strata.
4. Oil and fuel dumping
5. Leaching of wastes from landfills or direct discharge of industrial wastes to the soil.
6. Disposal of coal ash. Coal naturally concentrates lead and zinc.

Common soil pollutants

The most common chemicals involved are petroleum hydrocarbons, lead, polynuclear aromatic hydrocarbons (such as naphthalene and benzo(a)pyrene), solvents, pesticides, and other heavy metals. This occurrence of this phenomenon is correlated with the degree of industrialisation and intensities of chemical usage.

Effects of soil contamination

The concern over soil contamination stems primarily from health risks, from direct contact with the contaminated soil, vapours from the contaminants, and from secondary contamination of water supplies within and underlying the soil (US EPA).

Health effects of soil pollution

Health consequences from exposure to soil contamination vary greatly depending on pollutant type, pathway of attack and vulnerability of the exposed population. Chronic exposure to chromium, lead and other metals, petroleum, solvents, and many pesticide and herbicide formulations can be carcinogenic, can cause congenital disorders, or can cause other chronic health conditions. Industrial or man-made concentrations of naturally occurring substances, such as nitrate and ammonia associated with livestock manure from agricultural operations, have also been identified as health hazards in soil and groundwater.
Chronic exposure to benzene at sufficient concentrations is known to be associated with higher incidence of leukaemia. Mercury and cyclodienes

are known to induce higher incidences of kidney damage, some irreversible.

6.0 TUTOR-MARKED ASSIGNMENT

1. Define soil pollution.
2. Identify four soil pollutants found in your environment.
3. Explain how these pollutant cause diseases to man.

7.0 REFERENCES/FURTHER READING

Risk Assessment Guidance for Superfund, Human Health Evaluation Manual, Office of Emergency and Remedial Response. *U.S. Environmental Protection Agency*, Washington D.C. 20450

Snyder, C. (2005). "The dirty work of promoting "recycling" of America's sewage sludge". *Int J Occup Environ Health*, 11 (4): 415–27. PMID 16350476.Free full-text (registration required).

Samet, J. M., Dearry, A, Eggleston, P. A. *et al.* (2003). Urban air pollution and health inequities: A workshop report. *Environ Health Perspect 2001*; *10*9 (Suppl. 3)*:* 357–*74.*

Sexton, K. & Adgate, J. L. Looking at environmental justice from an environmental health perspective. *J. Expos Anal Environ Epidemiol* 2000*;* 9*:* 3–*8.*

*WHO (*2001). *Air Quality Guidelines for Europe*. (2nd ed.). Copenhagen: WHO Regional Office for Europe.

Henshaw, D. L. (1993). Radon exposure in the home: its occurrence and possible health effects. *Contemp Phys*, *34*: *31*–48.

*WHO (*1991). *Mercury, Inorganic. Environmental Health Criteria*. Vol. *118*. Geneva: World Health Organization.

Waller, L. A., *Louis, T. A. & Carlin, B. P.(1999).* Environmental Justice and Statistical Summaries of Differences in Exposure Distributions. *J. Expos Anal Environ Epidemiol,* 9*:* 56–*65.*

Halken, S. (*2003).* Early Sensitisation and Development of Allergic Airway Disease—Risk Factors and Predictors. *Paediatr Respir Rev,* 4*:* 128–34.

WHO. Environmental Health Indicators: Framework and Methodology. 1999,http://www.who.int/environmental_information/Information_resources/on_lin e_general.htm *(date last accessed 30 June* 2003*).*

*WHO. (*1995). *World Health Report*. Geneva: WHO.

Prüss, A., Corvalán, C., Pastides, H. & de Hollander A.E.M. (2002). Methodologic Considerations in Estimating Burden of Disease from Environmental Risk Factors at National and Global Levels. *Int. J. Occup. Environ. Health,* 7*:* 58–67.

WHO. http://www.who.int/peh/burden/globalestim.htm *(date last accessed 30 June* 2003*).*

MODULE 5 BASIC TOXICITY INDICES AND APPLICATIONS

Unit 1 Dose-Response Concept
Unit 2 Concept of Lethal Dose (or Concentration)
Unit 3 Probit Analyses
Unit 4 Application of Toxicology in Safety and Environmental Health

UNIT 1 DOSE-RESPONSE CONCEPT

CONTENTS

8.0 INTRODUCTION

In the last unit of Module 4, we discussed how the toxicants in the soil can cause a change in the human body. In this unit, we will discuss the most important factor that affects the effect of toxicant. This is the dose.

According to Paracelsus, dose determines the difference between therapeutic and toxicant: "The right dose differentiates a poison and a remedy". You will understand the concept and importance of dose in toxicology.

The science of toxicology is based on the principle that there is a relationship between a toxic reaction (the response) and the amount of poison received (the dose). Important assumption in this relationship is that there is almost always a dose below which no response occurs or can be measured and that once a maximum response is reached any further increases in the dose will not result in any increased effect.

9.0 OBJECTIVES

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

- define the concept of dose and other parameters used in measuring dose
- explain the dose-response relationship
- estimate effect from known a dose.

10.0 MAIN CONTENT

10.1 Definition of Dose

Dose is the amount of a substance administered at one time. Other parameters used to characterise the exposure to xenobiotics include the number of doses, frequency, and total time period of the treatment.

For example: 10 mg DDT per day for 90 days

3.1.1 Types of Doses of a Toxicant

Exposure dose	the amount of a xenobiotic encountered in the environment
Absorbed dose	the actual amount of the exposed dose that enters the body
Administered dose	the quantity administered usually orally or by injection
Total dose	the sum of all individual doses

3.1.2 Fractionating a Total Dose

This usually decreases the probability that the total dose will cause toxicity. The reason for this is that the body often can repair the effect of each sub-toxic dose if sufficient time passes before receiving the next dose. In such a case, the total dose, harmful if received all at once, is non-toxic when administered over a period of time. For example, 30 mg of strychnine swallowed at one time could be fatal to an adult whereas 3 mg of strychnine swallowed each day for ten days would not be fatal.

3.1.3 The Units for Measuring Dose

The units used in toxicology are basically the same as those used in medicine. The gram is the standard unit. However, most exposures will be smaller quantities and thus the milligram (mg) is commonly used.

The toxic effects of a dose must be related to age and body size. For example, 1000mg is the adult dose of paracetamol. That would be quite toxic to young children, and thus Children's dose is calculated. A better means to allow for comparison of effectiveness and toxicity is the amount of a substance administered on a body weight basis. A common dose measurement is mg/kg which stands for mg of substance per kg of body weight.

Another important aspect is the time over which the dose is administered. This is especially important for exposures of several days or for chronic exposures. The commonly used time unit is one day and thus, the usual dosage unit is mg/kg/day.

Since some xenobiotics are toxic in much smaller quantities than the milligram, smaller fractions of the gram are used, such as microgram (µg). Other units are shown below:

Table 5.1: The Units for Measuring Dose

Unit	Gram Equivalents	Exp. Form
Kilogram (kg)	1000.0 g	10^{3} g
Gram (g)	1.0 g	1 g
Milligram (mg)	0.001 g	10^{-3} g
Microgram (µg)	0.000,001 g	10^{-6} g
Nanogram (ng)	0.000,000,001 g	10^{-9} g
Picogram (pg)	0.000,000,000,001 g	10^{-12} g
Femtogram (fg)	0.000,000,000,000,001 g	10^{-15} g

Environmental exposure units are expressed as the amount of a xenobiotic in a unit of the media. Examples:

a. mg/liter (mg/l) for liquids
b. mg/gram (mg/g) for solids
c. mg/cubic meter (mg/m^3) for air

Smaller units are used as needed, e.g., µg/ml. Other commonly used dose units for substances in media are parts per million (ppm), parts per billion (ppb) and parts per trillion (ppt).

10.2 Dose -Response Relationship

The dose-response relationship is a fundamental and essential 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:

a. Establishes causality that the chemical has in fact induced the observed effects
b. Establishes the lowest dose where an induced effect occurs - the threshold effect
c. Determines the rate at which injury builds up - the slope for the dose response.

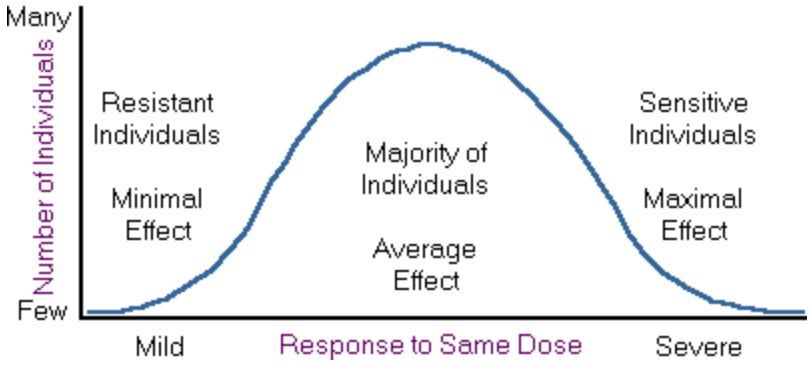


Fig. 5.1: Dose - Response Relationship Graph

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

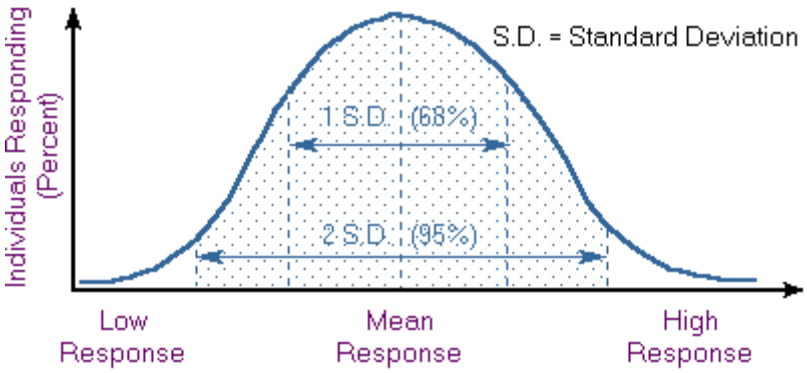


Fig. 5.2: Graph of the Individual Responses can be depicted as a Bell- Shaped Standard Distribution Curve

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.

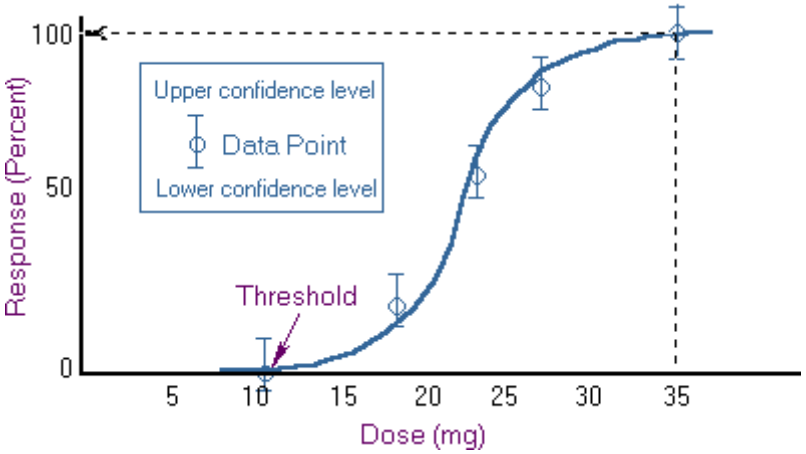


Fig. 5.3: Graph of Dose vs. Response

3.2.1 Dose-Response Curve

The **dose-response curve** normally takes the form of a sigmoid curve. 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 the hypothetical curve above, no toxicity occurs at 10 mg whereas at 35 mg 100% of the individuals experience toxic effects.

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.

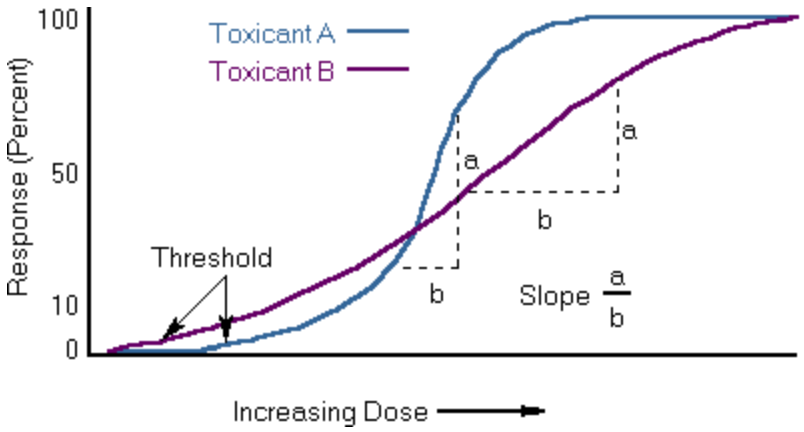


Fig. 5.4: Dose-Response Curve

Knowledge of the **shape** and **slope** of the 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 percent of population responding per unit change in dose (i.e., the slope). As illustrated above, Toxicant A has a higher threshold but a steeper slope than Toxicant B.

3.2.2 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 **LD50** (Lethal Dose 50%). This is a statistically derived dose at which 50% of the individuals will be expected to die. The figure below illustrates how an LD50 of 20 mg is derived.

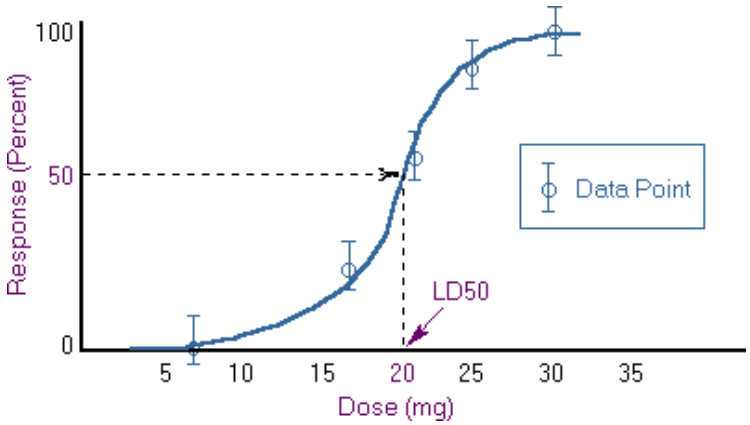


Fig. 5.5: Dose Estimates of Toxic Effects (LD)

Other dose estimates also may be used. LD0 represents the dose at which no individuals are expected to die. This is just below the threshold for lethality. LD10 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} is utilized which stands for Lethal Concentration 50%, the calculated concentration of a gas lethal to 50% of a group. Occasionally LC_0 and LC_{10} are also used.

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 a harmful effect (paralysis). Thus the specific endpoint must be indicated. The usual terms are:

ED0	effective for 0% of the population
ED10	effective for 10% of the population
ED50	effective for 50% of the population
ED90	effective for 90% of the population

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

TD0	toxic to 0% of the population
TD10	toxic to 10% of the population
TD50	toxic to 50% of the population
TD90	toxic to 90% of the population

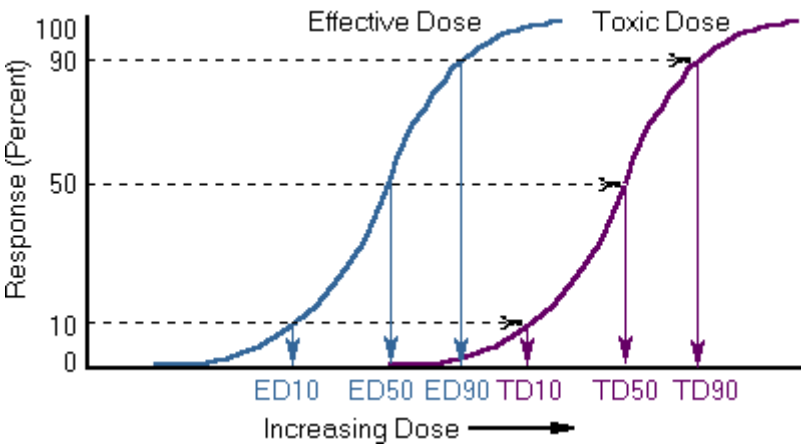


Fig. 5.5: Dose Estimates of Toxic Effects (TD)

The knowledge of the **effective** and **toxic dose** levels aides 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.

11.0 CONCLUSION

In this unit, you would have agreed with Paracelsus that dose determines the outcome of any chemical. The type of dose and frequency of exposure that determines the magnitude of the toxicity were explained.

12.0 SUMMARY

In this unit, we discussed the following:

- definition of dose and its parameters as exposed dose, administered dose, absorbed dose and total dose
- explanation of the dose –response relationship
- explanation of the dose-response curves and analysis.

13.0 TUTOR-MARKED ASSIGNMENT

1. Give two units of measuring dose.
2. Define dose
3. Give three types of doses
4. Explain dose-response curve
5. How can you determine the effect from the dose of a known substance?

14.0 REFERENCES/FURTHER READING

Altshuler, B. (1981). "Modeling of Dose-Response Relationships". *Environ Health Perspect* ,42: 23–27.

Bates, D. & D. Watts (1988). *Nonlinear regression analysis*. New York: John Wiley and Sons. pp. 365.

Crump, K. S; Hoel, D. G., Langley, C. H. & Peto, R. (1976). "Fundamental Carcinogenic Processes and their Implications for Low Dose Risk Assessment". *Cancer Research*, 36 ((9_Part1)): 2973–2979.

Extension Toxicology Network (1993). Dose-Response Relationships in Toxicology.

http://en.wikipedia.org/w/index.php?title=Doseresponse_relationship&oldid=500648757"

Materials excerpted January 2004 from Toxicology Tutorials, Developed through the National Library of Medicine (http://www.sis.nlm.nih.gov/Tox/ToxTutor.html).

U.S. EPA (2009). *Benchmark Dose Software (BMDS) Version 2.1 User's Manual Version 2.0, DRAFT. Doc No.: 53-BMDS-RPT-0028*. Washington, DC: Office of Environmental Information.

UNIT 2 CONCEPT OF LETHAL DOSE (OR CONCENTRATION)

CONTENTS

1.0 INTRODUCTION

In Unit 1, we discussed the meaning or dose and effect and the relationship between them. We found that a particular dose, a toxic effect may occur and at a higher dose a lethal (fatal) effect may occur.
In this unit, you will understand this concept of lethal dose or concentration as well as the toxic dose or concentration which is very important to you as an enforcer of environmental regulations and to any researcher or toxicologist.

2.0 OBJECTIVES

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

- define a lethal dose
- explain a median lethal dose
- define a toxic dose
- enumerate the difference between lethal dose and lethal concentration.

3.0 MAIN CONTENT

3.1 What is a Lethal Dose and Lethal Concentration?

1. A **lethal dose** (LD) is an indication of the lethality (i.e. how capable something is of causing death) of a given substance or type of radiation. This is a dose (usually recorded as dose per kilogram of subject body weight) at which a given *percentage* of subjects will die. The LD may be based on the standard person

concept, a theoretical individual that has perfectly "normal" characteristics, and thus not apply to all sub-populations. In contrast, toxic dose is the amount of a substance that may be expected to produce a toxic or harmful effect.

2. Lethal concentration

For gases and aerosols, **lethal concentration** (mg/m^3 or ppm, parts per million) is the analogous concept, although this also depends on the duration of exposure, which has to be included in the definition. The lowest known lethal dose, derived from an individual case of poisoning, is abbreviated **LCLo**.

Other definitions of a lethal concentration:

LC_{50}/**Lethal Concentration:** Median level concentration, a standard measure of toxicity. It tells how much of a substance is needed to kill half of a group of experimental organisms in a given time. (See LD 50.) (http://www.webref.org/environment/l/lc_50lethal_concentration.htm).

Lethal Concentration $_{50}$: Also referred to as $_{LC50}$, a concentration of a pollutant or effluent at which 50 per cent of the test organisms dies; a common measure of acute toxicity. http://infohouse.p2ric.org/ref/01/00402/lterms.html

Lethal concentration 50% ($_{LC50}$). The concentration of a chemical in air or water which is expected to cause death in 50% of test animals living in that air or water (http://www.shortschools.org/files/l_terms_q.html).

Lethal Concentration ($_{LC50}$): The concentration of a substance needed to kill half of a population at a specific time of observation. Lethargy: A condition of abnormal drowsiness or torpor; a great lack of energy; apathy(http://www.home-energyservices.com/Glossary.htm)

Median lethal concentration ($_{LC50}$) Statistically derived median concentration of a substance in an environmental medium expected to kill 50% of organisms in a given population under a defined set of conditions (http://sis.nlm.nih.gov/enviro/iupacglossary/glossarym.html)

Absolute lethal concentration ($_{LC100}$)-Lowest concentration of a substance in an environmental medium which kills 100% of test organisms or species under defined conditions. This value is dependent on the number of organisms used in its assessment (http://www.toxicology.org/pm/toxterms.asp).

On the other hand, toxic concentration is Quantity at which a water-soluble, liquid, or gaseous substance produces harmful effects in a specified test specie over a certain exposure period.

Read more: http://www.businessdictionary.com/definition/toxic-concentration.html#ixzz26P5Pyk5A

3. Determination of lethal dose

LD values for humans are best estimated by extrapolating results from human cell cultures. One outdated form of extrapolation involves measuring LD on animals like mice or dogs, converting to dosage per kilogram of biomass, and extrapolating to human norms. The degree of error from animal-extrapolated LD values is very large. The biology of test animals differs in important aspects to that of humans. For instance, mouse tissue is approximately fifty times less responsive than human tissue to the venom of the Sydney funnel-web spider. The square-cube law also complicates the scaling relationships involved. Researchers are now shifting away from animal-based LD measurements. The U.S. Food and Drug Administration has begun to approve more reliable non-animal methods in response to research cruelty concerns and the lack of validity/sensitivity of animal tests as they relate to humans.

3.2 Median Lethal Dose Concept

Lethal doses are usually expressed as **median lethal dose** (LD50), the point where 50% of test subjects exposed would die, in the units of mg/kg body weight.

In toxicology, the **median lethal dose**, $\mathbf{LD_{50}}$ (abbreviation for "lethal dose, 50%"), $\mathbf{LC_{50}}$ (lethal concentration, 50%) or $\mathbf{LCt_{50}}$ (lethal concentration & time) of a toxin, radiation, or pathogen is the dose required to kill half the members of a tested population after a specified test duration. LD_{50} figures are frequently used as a general indicator of a substance's acute toxicity. The test was created by J.W. Trevan in 1927. The term **semilethal dose** is occasionally used with the same meaning, in particular in translations from non-English-language texts, but can also refer to a *sub*lethal dose; because of this ambiguity, it is usually avoided. The U.S. Food and Drug Administration has begun to approve alternative methods to LD_{50} in response to research, cruelty concerns, and the lack of validity/sensitivity of the test as it relates to humans.

Median toxic dose (TD50), on the other hand, is the dose that produces a toxic effect in 50 per cent of the population.

Determination of LD_{50}

The LD_{50} is usually expressed as the mass of substance administered per unit mass of test subject, such as *grams of substance* per *kilogram of body mass*. Stating it this way allows the relative toxicity of different substances to be compared, and normalises for the variation in the size of the animals exposed (although toxicity does not always scale simply with body mass). Typically, the LD_{50} of a substance is given in milligrams per kilogram of body weight. In the case of some neurotoxins such as batrachotoxin, one of the most deadly toxins known, the LD_{50} may be more conveniently expressed as micrograms per kilogram (μg/kg) or nanograms per kilogram (ng/kg) of body mass.

The choice of 50% lethality as a benchmark avoids the potential for ambiguity of making measurements in the extremes and reduces the amount of testing required. However, this also means that LD_{50} is *not* the lethal dose for all subjects; some may be killed by much less, while others survive doses far higher than the LD_{50}. Measures such as "LD_1" and "LD_{99}" (dosage required to kill 1% or 99%, respectively, of the test population) are occasionally used for specific purposes.

Lethal dosage often varies depending on the method of administration; for instance, many substances are less toxic when administered orally than when intravenously administered. For this reason, LD_{50} figures are often qualified with the mode of administration, e.g., "LD_{50} i.v.".

The related quantities $LD_{50}/30$ or an $LD_{50}/60$ are used to refer to a dose that without treatment will be lethal to 50% of the population within (respectively) 30 or 60 days. These measures are used more commonly within Radiation Health Physics, as survival beyond 60 days usually results in recovery.

A comparable measurement is **LCt_{50}**, which relates to lethal dosage from exposure, where C is concentration and t is time. It is often expressed in terms of mg-min/m³. ICt_{50} is the dose that will cause incapacitation rather than death. These measures are commonly used to indicate the comparative efficacy of chemical warfare agents, and dosages are typically qualified by rates of breathing (e.g., resting = 10 l/min) for inhalation, or degree of clothing for skin penetration. The concept of **Ct** was first proposed by Fritz Haber and is sometimes referred to as **Haber's Law**, which assumes that exposure to 1 minute of 100 mg/m³ is equivalent to 10 minutes of 10 mg/m³ (1 × 100 = 100, as does 10 × 10 = 100).

Some chemicals, such as hydrogen cyanide, are rapidly detoxified by the human body, and do not follow Haber's Law. So, in these cases, the lethal concentration may be given simply as $\mathbf{LC_{50}}$ and qualified by duration of exposure (e.g., 10 minutes). The Material Safety Data Sheets for toxic substances frequently use this form of the term even if the substance does follow Haber's Law.

For disease-causing organisms, there is also a measure known as the median infective dose and dosage. The median infective dose (ID_{50}) is the number of organisms received by a person or test animal qualified by the route of administration (e.g., 1,200 org/man per oral). Because of the difficulties in counting actual organisms in a dose, infective doses may be expressed in terms of biological assay, such as the number of LD_{50}'s to some test animal. In biological warfare infective dosage is the number of infective doses per minute for a cubic meter (e.g., ICt_{50} is 100 medium doses - min/m³).

Limitation of LD_{50}

As a measure of toxicity, LD_{50} is somewhat unreliable and results may vary greatly between testing facilities due to factors such as the genetic characteristics of the sample population, animal species tested, environmental factors and mode of administration. Another weakness is that it measures acute toxicity only (as opposed to chronic toxicity at lower doses), and does not take into account toxic effects that do not result in death but are nonetheless serious (e.g., brain damage). There can be wide variability between species as well; what is relatively safe for rats may very well be extremely toxic for humans, and vice versa. In other words, a relatively high LD_{50} does not necessarily mean a substance is harmless, since its relative harmfulness depends on its usual dose, but a very low one is always a cause for concern.

When used to test venom from venomous creatures, such as snakes, LD_{50} results may be misleading due to the physiological differences between mice and humans. Many venomous snakes are specialised predators on mice; their venom may be adapted specifically to incapacitate mice. While most mammals have a very similar physiology, LD_{50} results may or may not be directly relevant to humans.

3.3 Animal Toxicity Testing

Animal testing is also known as **animal experimentation**, **animal research**, and ***in vivo* testing**, is the use of non-human animals in experiments. Worldwide it is estimated that the number of vertebrate animals—from zebra fish to non-human primates—ranges from the tens of millions to more than 100 million used annually. Invertebrates, mice,

rats, birds, fish, frogs, and animals not yet weaned are not included in the figures in the United States; one estimate of mice and rats used in the US alone in 2001 was 80 million. Most animals are euthanised after being used in an experiment. Sources of laboratory animals vary between countries and species; most animals are purpose-bred, while others are caught in the wild or supplied by dealers who obtain them from auctions and pounds.

The research is conducted inside universities, medical schools, pharmaceutical companies, farms, defense establishments, and commercial facilities that provide animal-testing services to industry. It includes pure research such as genetics, developmental biology, behavioural studies, as well as applied research such as biomedical research, xenotransplantation, drug testing and toxicology tests, including cosmetics testing. Animals are also used for education, breeding, and defense research. The practice is regulated to various degrees in different countries.

Supporters of the use of animals in experiments, such as the British Royal Society, argue that virtually every medical achievement in the 20th century relied on the use of animals in some way, with the Institute for Laboratory Animal Research of the U.S. National Academy of Sciences arguing that even sophisticated computers are unable to model interactions between molecules, cells, tissues, organs, organisms, and the environment, making animal research necessary in many areas. Animal rights, and some animal welfare, organisations—such as PETA and BUAV—question the legitimacy of it, arguing that it is cruel, poor scientific practice, poorly regulated, that medical progress is being held back by misleading animal models, that some of the tests are outdated, that it cannot reliably predict effects in humans, that the costs outweigh the benefits, or that animals have an intrinsic right not to be used for experimentation.

Toxicology testing

This is also known as safety testing, is conducted by pharmaceutical companies testing drugs, or by contract animal testing facilities, such as Huntingdon Life Sciences, on behalf of a wide variety of customers. According to 2005 EU figures, around one million animals are used every year in Europe in toxicology tests; which are about 10% of all procedures. According to *Nature*, 5,000 animals are used for each chemical being tested, with 12,000 needed to test pesticides. The tests are conducted without anaesthesia, because interactions between drugs can affect how animals detoxify chemicals, and may interfere with the results.

Fig. 5.6: A Rabbit during a Draize Test
("http://en.wikipedia.org/w/index.php?title=Median_lethal_dose&oldid=05217207“)

Toxicology tests are used to examine finished products such as pesticides, medications, food additives, packing materials, and air freshener, or their chemical ingredients. Most tests involve testing ingredients rather than finished products, but according to BUAV, manufacturers believe these tests overestimate the toxic effects of substances; they therefore repeat the tests using their finished products to obtain a less toxic label.

The substances are applied to the skin or dripped into the eyes; injected intravenously, intramuscularly, or subcutaneously; inhaled either by placing a mask over the animals and restraining them, or by placing them in an inhalation chamber; or administered orally, through a tube into the stomach, or simply in the animal's food. Doses may be given once, repeated regularly for many months, or for the lifespan of the animal.

There are several different types of acute toxicity tests. The LD_{50} ("Lethal Dose 50 %") test is used to evaluate the toxicity of a substance by determining the dose required to kill 50% of the test animal population. This test was removed from OECD international guidelines in 2002, replaced by methods such as the fixed dose procedure, which use fewer animals and cause less suffering. *Nature* writes that, as of 2005, "the LD50 acute toxicity test ... still accounts for one-third of all animal [toxicity] tests worldwide."

Irritancy can be measured using the Draize test, where a test substance is applied to an animal's eyes or skin, usually an albino rabbit. For Draize eye testing, the test involves observing the effects of the substance at intervals and grading any damage or irritation, but the test should be halted and the animal killed if it shows "continuing signs of severe pain or distress". The Humane Society of the United States writes that the procedure can cause redness, ulceration, haemorrhaging, cloudiness, or even blindness. This test has also been criticised by scientists for being cruel and inaccurate, subjective, over-sensitive, and failing to reflect human exposures in the real world. Although no accepted *in vitro*

alternatives exist, a modified form of the Draize test called the *low volume eye test* may reduce suffering and provide more realistic results and this was adopted as the new standard in September 2009. However, the Draize test will still be used for substances that are not severe irritants.

The most stringent tests are reserved for drugs and foodstuffs. For these, a number of tests are performed, lasting less than a month (acute), one to three months (subchronic), and more than three months (chronic) to test general toxicity (damage to organs), eye and skin irritancy, mutagenicity, carcinogenicity, teratogenicity, and reproductive problems. The cost of the full complement of tests is several million dollars per substance and it may take three or four years to complete.

These toxicity tests provide, in the words of a 2006 United States National Academy of Sciences report, "critical information for assessing hazard and risk potential" *Nature* reported that most animal tests either over- or underestimate risk, or do not reflect toxicity in humans particularly well, with false positive results being a particular problem. This variability stems from using the effects of high doses of chemicals in small numbers of laboratory animals to try to predict the effects of low doses in large numbers of humans. Although relationships do exist, opinion is divided on how to use data on one species to predict the exact level of risk in another.

Animal rights concerns over LD_{50}

Animal-rights and animal-welfare groups, such as Animal Rights International, have campaigned against LD_{50} testing on animals in particular as, in the case of some substances, causing the animals to die slow, painful deaths. Several countries, including the UK, have taken steps to ban the oral LD_{50}, and the Organization for Economic Co-operation and Development (OECD) abolished the requirement for the oral test in 2001 (see Test Guideline 401, *Trends in Pharmacological Sciences* Vol 22, February 22, 2001).

3.4 Other Measures of toxicity

- IDLH
- Certain safety factor
- Therapeutic index
- Protective index
- Fixed Dose Procedure to estimate LD50
- Median toxic dose (TD50)
- Lowest published toxic concentration (TCLo)
- Lowest published lethal dose (LDLo)

- EC_{50} (half maximal effective concentration)
- IC_{50} (half maximal inhibitory concentration)
- Draize test
- Indicative limit value
- No Observable Adverse Effect Level (NOAEL)
- Lowest Observable Adverse Effect Level (LOAEL)
- Up-and-down procedure.

Related measures

- $TCID_{50}$ Tissue Culture Infective Dosage
- EID_{50} Egg Infective Dosage
- ELD_{50} Egg Lethal Dosage
- Plaque forming units (pfu)

4.0 CONCLUSION

This unit explained the concepts of lethal dose, lethal concentration, $_{LD50}$ and $_{LC50,}$ toxicity testing. The results of these toxicity tests require appropriate interpretation for reasonable utilisation in safety assessment and recommendation.

For this purpose, in the next unit, we will discuss the statistical regression analysis known as Probit analysis, which tend to convert the non straight slope to straight line slope of dose-response relationship.

5.0 SUMMARY

Lethal dose is the dose (usually recorded as dose per kilogram of subject body weight) at which a given *percentage* of subjects will die whereas toxic dose is the amount of a substance that may be expected to produce a toxic or harmful effect.

Lethal concentration is the concentration of a chemical in air or water which is expected to cause death in 50% of test animals living in that air or water.

Animal testing, also known as **animal experimentation**, **animal research**, and **in vivo testing**, is the use of non-human animals in experiments. It is applied in toxicity testing.

6.0 TUTOR-MARKED ASSIGNMENT

1. What is lethal dose?
2. What is lethal concentration?
3. Explain how to determine lethal dose of a substance.
4. List four other measures of toxicity and lethality.

7.0 REFERENCES/FURTHER READING

"Allergan Receives FDA Approval for First-of-Its-Kind, Fully in vitro, Cell-Based Assay for BOTOX® and BOTOX® Cosmetic (onabotulinumtoxinA)". Source: Allergan, Inc. News Provided by Acquire Media. Page last updated 24 June 2011. http://agn.client.shareholder.com/releasedetail.cfm?ReleaseID=587234. Retrieved 2011-06-26.

"In U.S., Few Alternatives To Testing On Animals". Washington Post. Page last updated 12 April 2008. http://www.washingtonpost.com/wpdyn/content/article/2008/04/11/AR2008041103733.html. Retrieved 2011-06-26.

Registry of Toxic Effects of Chemical Substances (RTECS). *Comprehensive Guide to the RTECS.*

Ernest, Hodgson. (2004). *A Textbook of Modern Toxicology*; Wiley-Interscience (3rd ed.).

Walker, R. & Lupien, J. R. (April 2000). "The Safety Evaluation of Monosodium Glutamate". *Journal of Nutrition* **130** (4S Suppl): 1049S?1052S. PMID 10736380.

Safety (MSDS) data for ascorbic acid". Oxford University. 2005-10-09.

http://physchem.ox.ac.uk/MSDS/AS/ascorbic_acid.html. Retrieved 2007-02-21.

Babayan, A. A. & Aleksandryan, A.V. (1985). "Toxicological characteristics of melamine cyanurate, melamine and cyanuric acid". *Zhurnal Eksperimental'noi i Klinicheskoi Meditsiny*, Vol.25, 345-9 (1985). Original article in Russian.

Conn, P. M. & Parker, J. V. (2008). *The Animal Research War*. Palgrave: Macmillan.

Guerrini, Anita (2003). *Experimenting with humans and animals: from Galen to animal rights*. Baltimore: The Johns Hopkins University Press.

"Select Committee on Animals in Scientific Procedures Report", Select Committee on Animals in Scientific Procedures, British House of Lords, July 16, 2002, accessed October 27, 2005.

"Statistics of Scientific Procedures on Living Animals", Great Britain, 2004.

"Biomed for the layperson", Laboratory Primate Advocacy Group, accessed February 24, 2006.

In Focus "Animal Experiments in Research" (German Reference Centre for Ethics in the Life Sciences)

"Vision and Roadmap for the 21st Century". Source: National Toxicology Program. http://ntp.niehs.nih.gov/go/vision. Retrieved 2011-10-29.

"http://en.wikipedia.org/w/index.php?title=Lethal_dose&oldid=498868458"

"http://en.wikipedia.org/w/index.php?title=Median_lethal_dose&oldid=505217207"

UNIT 3 PROBIT ANALYSES

CONTENTS

1.0 INTRODUCTION

In Unit 2, we discussed the dose-response relationship expressed graphically in a curve. Practically, it is not easy to extrapolate the effect from the dose in such curves if a straight line slope is not established.

In this unit, we will discuss how to convert the crude dose-response curves obtained experimentally into a straight line slope for reasonable extrapolations to be made.

2.0 OBJECTIVES

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

- state the meaning of probit analysis
- explain the historical background of probit analysis
- explain the principle of applications of probit analysis.

3.0 MAIN CONTENT

3.1 The Meaning of Probit Analysis

Probit analysis is a type of regression used to analyse binomial response variables. It transforms the sigmoid dose-response curve to a straight line that can then be analysed by regression either through least squares or maximum likelihood.

Probit analysis can be conducted by one of three techniques:

1. Using tables to estimate the probits and fitting the relationship by eye
2. Hand calculating the probits, regression coefficient, and confidence intervals,
3. Having a statistical package such as SPSS do it all for you.

3.2 Historical Background of Probit

The idea of probit analysis was originally published in Science by Chester Ittner Bliss in 1934. He worked as an entomologist for the Connecticut Agricultural Experiment Station and was primarily concerned with finding an effective pesticide to control insects that fed on grape leaves (Greenberg, 1980). By plotting the response of the insects to various concentrations of pesticides, he could visually see that each pesticide affected the insects at different concentrations, i.e. one was more effective than the other. However, he did not have a statistically sound method to compare this difference. The most logical approach would be to fit a regression of the response versus the concentration, or dose and compare between the different pesticides. Yet, the relationship of response to dose was sigmoid in nature and at the time regression was only used on linear data. Therefore, Bliss developed the idea of transforming the sigmoid dose-response curve to a straight line. In 1952, a professor of statistics at the University of Edinburgh by the name of David Finney took Bliss idea and wrote a book called Probit Analysis (Finney, 1952). Today, probit analysis is still the preferred statistical method in understanding dose-response relationships.

3.3 The principle of Probit Analysis

Probit Analysis is a specialised regression model of binomial response variables.

Remember that regression is a method of fitting a line to your data to compare the relationship of the response variable or dependent variable (Y) to the independent variable (X).

$Y = a + b X + e$
Where
a = y-intercept

b = the slope of the line

e = error term

Also remember that a binomial response variable refers to a response variable with only two outcomes.

For example:
Flipping a coin: Heads or tails

Testing beauty products: Rash/no rash

The effectiveness or toxicity of pesticides: Death/no death

3.4 Applications of Probit Analysis

Probit analysis is used to analyse many kinds of dose-response or binomial response experiments in a variety of fields. Probit Analysis is commonly used in toxicology to determine the relative toxicity of chemicals to living organisms. This is done by testing the response of an organism under various concentrations of each of the chemicals in question and then comparing the concentrations at which one encounters a response. As discussed above, the response is always binomial (e.g. death/no death) and the relationship between the response and the various concentrations is always sigmoid. Probit analysis acts as a transformation from sigmoid to linear and then runs a regression on the relationship.

Once a regression is run, the researcher can use the output of the probit analysis to compare the amount of chemical required to create the same response in each of the various chemicals. There are many endpoints used to compare the differing toxicities of chemicals, but the LC_{50} (liquids) or LD_{50} (solids) are the most widely used outcomes of the modern dose-response experiments. The LC_{50}/LD_{50} represent the concentration (LC_{50}) or dose (LD_{50}) at which 50% of the population responds.

4.0 CONCLUSION

In this unit, you have learnt the concept and principle of Probit analysis. This is statistical method of converting your sigmoidal dose-response curve to a straight line curve that can be reasonably interpreted by you, a researcher or toxicologist. The analysis is useful in determining the LC_{50} and LD_{50} and prediction of effects when doses are known, and vice versa.

5.0 SUMMARY

Probit analysis is a type of regression used to analyse binomial response variables.

Probit analysis can be conducted by one of three techniques:

a. Using of tables to estimate the probits
b. Hand calculating the probits, or
c. Having a statistical package such as SPSS

Probit analysis is used to analyse many kinds of dose-response or binomial response experiments in a variety of fields of toxicology

6.0 TUTOR-MARKED ASSIGNMENT

1. What is probit analysis?
2. Explain the principle of probit analysis
3. State two uses of probit analysis

7.0 REFERENCES/FURTHER READING

Bliss, C. I. (1934). "The method of probits". *Science*, 79 (2037): 38–39. DOI:10.1126/science.79.2037.38.JSTOR 1659792. PMID 17813446.

Collett, D. (1991). *Modelling Binary Data*. Chapman and Hall / CRC.

Finney, D. J. & Stevens, W. L. (1948). "A Table for the Calculation of Working Probits and Weights in Probit Analysis." *Biometrika,* 35(1-2): 191-201.

Finney, D. J. (Ed). (1952). *Probit Analysis.* Cambridge, England: Cambridge University Press.

Finney, D. J. (1971). *Probit Analysis.* (3rd ed.). Cambridge, UK: Cambridge University Press.

Greenberg, B. G. (1980). "Chester I. Bliss, 1899-1979." *International Statistical Review / Revue Internationale de Statistique,* 8(1): 135-136.

Hahn, E. D. & Soyer, R. (n d.). "Probit and Logit Models: Differences in a Multivariate Realm." Retrieved August 10, 2012 from "http://en.wikipedia.org/w/index.php?title=Probit&oldid=492257905"

Steinbrecher, G., & Shaw, W.T. (2008). "Quantile mechanics". *European Journal of Applied Mathematics* **19** (2): 87–112. DOI:10.1017/S0956792508007341.

Wichura, M. J. (1988). "Algorithm AS241: The Percentage Points of the Normal Distribution". *Applied Statistics* (Blackwell Publishing) **37** (3): 477–484. DOI:10.2307/2347330. JSTOR 2347330.

UNIT 4 APPLICATION OF TOXICOLOGY IN SAFETY AND ENVIRONMENTAL HEALTH

CONTENTS

1.0 INTRODUCTION

In Unit 3, we explained the concept of probit analysis which helps in the interpretation of experimental or investigative results.

In this unit, you will learn how you can apply the entire knowledge of environmental toxicology to ensure chemical safety in environmental health.

2.0 OBJECTIVES

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

- enumerate the general applications of toxicology
- give some examples on the applications of toxicology
- state some challenges on the applications of toxicology
- proffer suggestions for effective applications of toxicology.

3.0 MAIN CONTENT

3.1 General Applications of Environmental Toxicology

a. It provides a tool to assess chemical hazard in the environment

A toxicity assessment is a tool to investigate the potential for a substance to cause harm, to know how much harm it causes and what kind of harm. The term toxicity refers to the inherent potential of a substance to cause systemic damage to living organisms.

The term hazardous is very different. It refers to the potential of a substance to (1) cause any of several kinds of harm, through toxicity, flammability, explosiveness, corrosiveness etc., and (2) the ease with which people can come in contact with it. Hazardous is not a synonym for toxic.

To conduct these dose-response studies, scientists:

Administer different small doses of a substance to several groups of test animals every day over a lifetime.

Periodically examine and finally autopsy the animals to determine if any effects have occurred. The effects may be:

- damage to an organ
- behavioural modifications
- change in the level of an essential body chemical
- determine the smallest dose at which an effect occurs--the Lowest Observable Effect Level (LOEL)
- LOEL is measured in milligrams (mg) of substance per kilogram (kg) of body weight, or in parts per million (ppm) of substance in food.

b. It recommends a margin of safety for a chemical in the environment

The Therapeutic Index (TI) is used to compare the therapeutically effective dose to the toxic dose. The TI is a statement of relative safety of a drug. It is the ratio of the dose producing toxicity to the dose needed to produce the desired therapeutic response. The common method used to derive the TI is to use the 50% dose-response points. For example, if the LD50 is 200 and the ED50 is 20 mg, the TI would be 10 (200/20).

The use of the **ED50** and **LD50** doses to derive the **TI** may be misleading as to safety, depending on the slope of the dose-response curves for therapeutic and lethal effects. To overcome this deficiency, toxicologists often use another term to denote the safety of a drug - the **Margin of Safety (MOS)**.

The **MOS** is usually calculated as the ratio of the dose that is just within the lethal range (LD_{01}) to the dose that is 99% effective (ED_{99}). The MOS = LD_{01}/ED_{99}. A substance with MOS less than 1 is more hazardous than those above 1.

The NOEL (no observable effect level) is the highest dose or exposure level of a poison that produces no noticeable toxic effect on animals. In

toxicology, residue tolerance levels of poisons that are permitted in food or in drinking water, for instance, are usually set from 100 to 1,000 times less than the NOEL to provide a wide margin of safety for humans.

Determining Safe Levels

When performing the experiments just described, scientists also determine the highest dose at which no effects occur--the *No Observable Effect Level (NOEL).*

The NOEL is considered the "safe level" for that chemical in the species studied.

The NOEL is not necessarily the "safe level" for humans, because:

- humans may be more/less sensitive to the substance than the animals studied
- humans have more genetic, health, age, and other variabilities, which may affect individual human reactions.

To account for these differences, public health officials divide the NOEL by a safety factor, usually 100, to arrive at a presumed "safe level" for humans. If the NOEL for a substance were 100 mg/kg, the "safe level" for humans would be considered 1 mg/kg.

This "safe level" is most likely lower than scientists' best estimate of the NOEL in humans. However, it is the number risk managers use to establish regulations, such as the maximum amount of a chemical allowed in drinking water

c. To compare the toxicity of two substances

Knowledge of the slope is important in comparing the toxicity of various substances.

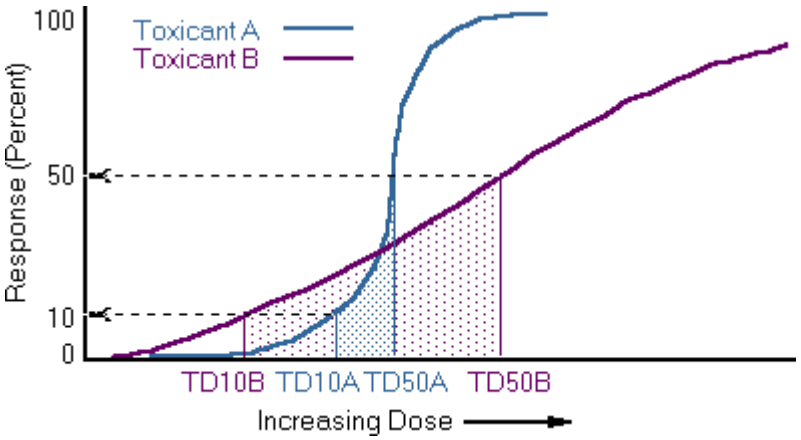


Fig. 5.7: Graph to Compare the Toxicity of Two Substances

For some toxicants a small increase in dose causes a large increase in response (toxicant A, steep slope). For other toxicants a much larger increase in dose is required to cause the same increase in response (toxicant B, shallow slope).

d. To conduct risk assessment of a substance

To protect the public, scientists also determine the highest dose at which no effects occur.

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

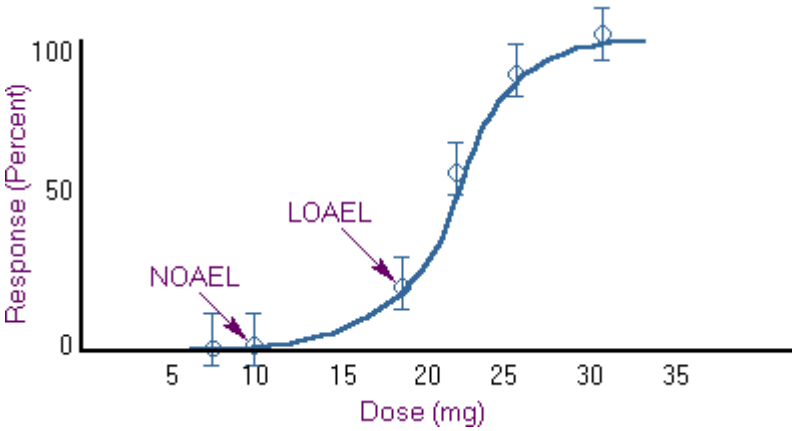


Fig. 5.8: Graph to conduct risk assessment of a substance

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.

In addition to LOEL, the term LOAEL (Lowest Observable Adverse Effect Level) is sometimes used. The term LOAEL implies a judgement that the effect is adverse. A LOEL refers to any effect and may or may not be judged to be adverse.
This dose may still be a high dose compared to environmental exposures.

3.2 Examples on the Applications of Toxicology

Toxicity assessment

All quantitative toxicity assessments are based on the dose-response concept: as you increase the dose (exposure), the response (toxicity) also increases.

Toxicity assessment is quite complex, many factors can affect the results of toxicity tests. Some of these factors include variables like temperature, food, light, and stressful environmental conditions. Other factors related to the animal itself include age, sex, health, and hormonal status.

Table 5.2: Measurements for Expressing Levels of Contaminants in Food and Water

Dose	Abbrev.	Metric equivalent	Abbrev.	Approx. amt. in water
parts per million	ppm	milligrams per kilogram	mg/kg	1 teaspoon per 1,000 gallons
parts per billion	ppb	micrograms per kilogram	ug/kg	1 teaspoon per 1,000,000 gallons

Table 5.3: Toxicity Rating Scale and Labeling Requirements for Pesticides

Category	Signal word required on label	LD50 oral mg/kg(ppm)	LD50 dermal mg/kg(ppm)	Probable oral lethal dose
I highly toxic	DANGER-POISON (skull and crossbones)	less than 50	less than 200	a few drops to a teaspoon

II moderately toxic	WARNING	51 to 500	200 to 2,000	over 1 teaspoon to 1 ounce
III slightly toxic	CAUTION	over 500	over 2,000	over 1 ounce
IV practically non-toxic	none required			

The TLV (threshold limit value) for a chemical is the airborne concentration of the chemical (expressed in ppm) that produces no adverse effects in workers exposed for eight hours per day five days per week. The TLV is usually set to prevent minor toxic effects like skin or eye irritation.

The dose-response concept is the basis for all toxicity assessments. It is used differently to evaluate acute effects and chronic effects. LD50 is stated in milligrams per kilogram (mg/kg): milligram of chemical per kilogram of body weight. The lower the LD50-the lower the lethal dose-the more toxic the substance.

The term LC50-Lethal Concentration-is used to measure the toxicity of gases. The LC50 is stated in milligram of chemical per liter (or cubic meter) of air.

Acute toxicity is assessed using observations of accidental human exposures or by conducting LD50 tests on experimental animals, usually rodents. **Example:** A reported "rat oral LD50 of 50 mg/kg" means that half of the rats that ingested a dose of 50 milligrams of the substance per kilogram of body weight died within 14 days.

Chronic toxic effects are estimated by dose-response studies on animals. Chronic toxicity is measured in two ways--depending on whether the concern is cancer or other chronic effects.

Non-carcinogenic chronic toxicity is assessed by studies to determine the smallest dose that causes any detectable effect.

Carcinogenic effects are estimated by a type of dose-response study called a carcinogenesis bioassay . *Chronic toxicity* can be divided into two categories:

- cancer (carcinogenic toxicity).
- all other effects (non-carcinogenic toxicity).

The carcinogenesis bioassay is a method of testing substances for carcinogenic effects that utilises high-dose studies on laboratory animals to look for even the rare case of cancer. It is not necessarily the best scientific approach to assess the carcinogenic effects of chemicals. Instead it is a way to respond to public concerns by generating carcinogenic risk values with large margins of safety.

The "safe level" calculation for humans assumes that humans are more sensitive than animals, but humans are not more sensitive in all cases.

Examples of human sensitivity:

a. More sensitivity: The drug Thalidomide caused no adverse effects in the animals studied, but caused severe birth defects in humans.
b. Less sensitivity: Insecticides are often developed to be more toxic to insects than to humans. Since people are less sensitive to these chemicals, they can use them without injuring themselves.
c. Genetic variability: People vary widely in their reactions to bee venom. Some show almost no reaction to a bee sting; others may die without immediate medical treatment.

Example of a carcinogenesis bioassay:

A carcinogenesis bioassay was performed for benzene on both rats and mice. Both sexes of each species got leukaemia at the high doses administered. Extrapolating the cancer incidence at high dose to low dose and from rodents to humans resulted in the risk estimate that a benzene dose of 1 mg/kg/day will result in 3 cancers per 100 people exposed daily for a lifetime to that dose. This dose is much higher than anyone would be exposed to in the environment under normal conditions.

Table 5.4: Example of a Carcinogenesis Bioassay

Substance	**Animal, Route**	**LD_{50} {LC_{50}}**	**LD_{50} : g/kg {LC_{50} : g/L} standardized**
Water	rat, oral	90,000 mg/kg	90
Sucrose (table sugar)	rat, oral	29,700 mg/kg	29.7
Monosodium glutamate (MSG)	rat, oral	16,600 mg/kg	16.6
Vitamin C (ascorbic acid)	rat, oral	11,900 mg/kg	11.9
Cyanuric acid	rat, oral	7,700 mg/kg	7.7
cadmium sulfide	rat, oral	7,080 mg/kg	7.08

Grain alcohol (ethanol)	rat, oral	7,060 mg/kg	7.06
Melamine	rat, oral	6,000 mg/kg	6
Melamine cyanurate	rat, oral	4,100 mg/kg	4.1
Sodium molybdate	rat, oral	4,000 mg/kg	4
Table Salt	rat, oral	3,000 mg/kg	3
Paracetamol (acetaminophen)	rat, oral	1,944 mg/kg	1.944
Delta-9-tetrahydrocannabinol (THC)	rat, oral	1,270 mg/kg	1.270
Metallic Arsenic	rat, oral	763 mg/kg	0.763
Alkyl dimethyl benzalkonium chloride (ADBAC)	rat, oral fish, immersion aq. invertebrates, imm.	304.5 mg/kg {0.28 mg/L} {0.059 mg/L}	0.3045 {0.00028} {0.000059}
Coumarin (benzopyrone, from Cinnamomum aromaticum and other plants)	rat, oral	293 mg/kg	0.293
Aspirin (acetylsalicylic acid)	rat, oral	200 mg/kg	0.2
Caffeine	rat, oral	192 mg/kg	0.192
Arsenic trisulfide	rat, oral	185–6,400 mg/kg	0.185
Sodium nitrite	rat, oral	180 mg/kg	0.18
Bisoprolol	mouse, oral	100 mg/kg	0.1
Cobalt(II) chloride	rat, oral	80 mg/kg	0.08
Cadmium oxide	rat, oral	72 mg/kg	0.072
Sodium fluoride	rat, oral	52 mg/kg	0.052
Nicotine	rat, oral	50 mg/kg	0.05
Pentaborane	human, oral	<50 mg/kg	<0.05
Capsaicin	mouse, oral	47.2 mg/kg	0.0472
Mercury(II) chloride	rat, dermal	41 mg/kg	0.041
Lysergic acid diethylamide (LSD)	rat, intravenous	16.5 mg/kg	0.0165
Arsenic trioxide	rat, oral	14 mg/kg	0.014
Metallic Arsenic	rat, intraperitoneal	13 mg/kg	0.013
Sodium cyanide	rat, oral	6.4 mg/kg	0.0064
White phosphorus	rat, oral	3.03 mg/kg	0.00303
Strychnine	human, oral	1–2 mg/kg(estimated)	0.001

Beryllium oxide	rat, oral	0.5 mg/kg	0.0005
Cantharidin	human, oral	0.5 mg/kg	0.0005
Aflatoxin B1 (from *Aspergillus flavus*)	rat, oral	0.48 mg/kg	0.00048
Venom of the Inland Taipan (Australian snake)	rat, subcutaneous	25 µg/kg	0.000025
Ricin	rat, intraperitoneal rat, oral	22 µg/kg 20-30 mg/kg	0.000022 0.02
Dioxin (TCDD)	rat, oral	20 µg/kg	0.00002
Sarin	mouse, subcutaneous injection	17.23 µg/kg (estimated)	0.0000172
VX (nerve agent)	human, oral, inhalation, absorption through skin/eyes	2.3 µg/kg (estimated)	0.0000023
Batrachotoxin (from poison dart frog)	human, sub-cutaneous injection	2-7 µg/kg (estimated)	0.000002
Venom of Hydrophis belcheri (Belcher's Sea Snake)	mouse, intraperitoneal	0.25 µg/kg	0.00000025
Maitotoxin	mouse, intraperitoneal	0.13 µg/kg	0.00000013
Polonium-210	human, inhalation	10 ng/kg (estimated)	0.00000001
Botulinum toxin (Botox)	human, oral, injection, inhalation	1 ng/kg (estimated)	0.000000001
Ionizing radiation	human, irradiation	3-6 Gy	

Example

Consider comparing the toxicity of two different pesticides to aphids, pesticide A and pesticide B. If the LC_{50} of pesticide A is 50ug/L and the LC_{50} of pesticide B is 10ug/L, pesticide B is more toxic than A because it only takes 10ug/L to kill 50% of the aphids, versus 50ug/L of pesticide B.

Probit Analysis is a type of regression used with binomial response variables. It is very similar to logit, but is preferred when data are normally distributed.

Most common outcome of a dose-response experiment in which probit analysis is used is the LC50/LD50.

Probit analysis can be done by eye, through hand calculations, or by using a statistical program.

Applications of LD_{50}

- NOTE: Comparing substances (especially drugs) to each other by LD_{50} can be misleading in many cases due (in part) to differences in effective dose (ED_{50}). Therefore, it is more useful to compare such substances by therapeutic index, which is simply the ratio of LD_{50} to ED_{50}.
- The following examples are listed in reference to LD_{50} values, in descending order, and accompanied by LC_{50} values, {bracketed}, when appropriate.

3.3 Challenges on the Applications of Toxicology

From the work of Pesch *et al.* (2004), modern toxicology investigates a wide array of both old and new health hazards. Priority setting is needed to select agents for research from the plethora of exposure circumstances.

The changing societies and a growing fraction of the aged have to be taken into consideration. A precise exposure assessment is of importance for risk estimation and regulation.

Toxicology contributes to the exploration of pathomechanisms to specify the exposure metrics for risk estimation.
Combined effects of co-existing agents are not yet sufficiently understood.

Animal experiments allow a separate administration of agents which cannot be disentangled by epidemiological means, but their value is limited for low exposure levels in many of today's settings.
As an experimental science, toxicology has to keep pace with the rapidly growing knowledge about the language of the genome and the changing paradigms in cancer development.

During the pioneer era of assembling a working draft of the human genome, toxicogenomics has been developed. Gene and pathway complexity have to be considered when investigating gene–environment interactions. For a best conduct of studies, modern toxicology needs a close liaison with many other disciplines like epidemiology and bioinformatics.

In the developing countries like Nigeria, dearth of trained toxicologists due to inadequate and ill equipped institutions for this purpose is paramount.

3.4 Suggestions on Effective Applications of Toxicology

Considering the challenges above, some useful suggestions include:

i. Appropriate priorities should be set for toxicological studies.
ii. Toxicological studies should be designed to reflect the societal environmental demand.
iii. Modern toxicology should be very close to various advancements in other science and technology.
iv. Developing countries are required to establish and equip more training institutions for toxicologists and allied professionals e.g. environmental health officers.

4.0 CONCLUSION

The applications of toxicology to ensure environmental health and safety were extensively discussed. The unit also unveiled some of the challenges you will face in the course of applying toxicology with useful suggestions proffered.

5.0 SUMMARY

Environmental toxicology:

i. Provides a tool to assess chemical hazard in the environment.
ii. Recommends a margin of safety for a chemical in the environment.
iii. Compare the toxicity of two substances

Challenges of toxicology include:

i. The disparity between toxicological studies and epidemiological situations
ii. Lack of training institutions and manpower

Suggestions include:

i. Considering the epidemiology of the society where toxicological studies are based.
ii. The establishment of more training institutions.

iii. Employment of trained toxicologists in environmental assessments

6.0 TUTOR-MARKED ASSIGNMENT

1. Who can apply environmental toxicology?
2. Identify two applications of toxicology for environment health.
3. Outline four challenges facing environmental toxicology in Nigeria.

7.0 REFERENCES/FURTHER READING

Materials excerpted January 2004 from Toxicology Tutorials, Developed through the National Library of Medicine (http://www.sis.nlm.nih.gov/Tox/ToxTutor.html)

E X T O X N E T (Extension Toxicology Network) (1993). Dose-Response Relationships in Toxicology. A Pesticide Information Project of Cooperative Extension Offices of Cornell University, Michigan State University, Oregon State University, and University of California.

Pesch, B., et al (2004). Challenges to environmentaltoxicology and epidemiology: where do we stand and which way do we go? *Toxicology Letters Vol. 151, Issue 1,* 15 June 2004, Pages 255–266

Crump, K. S.; Hoel DG, Langley C. H. & Peto R. (1976). "Fundamental Carcinogenic Processes and Their Implications for Low Dose Risk Assessment". *Cancer Research* **36** ((9_Part1)): 2973–2979.

U.S. EPA (2009). *Benchmark Dose Software (BMDS) Version 2.1 User's Manual Version 2.0, DRAFT. Doc No.: 53-BMDS-RPT-0028*. Washington, DC: Office of Environmental Information.

Altshuler, B. (1981). "Modeling of Dose-Response Relationships". *Environ Health Perspect* , 42: 23–27.

Bates, D. & D. Watts (1988). *Nonlinear regression analysis*. New York: John Wiley and Sons. pp. 365.

http://en.wikipedia.org/w/index.php?title=Dose–response_relationship&oldid=500648757"

Hosmer, D. & Lemeshow, S. (2000). Applied Logistic Regression (Second Edition). New York: John Wiley & Sons, Inc.

Long, J. Scott (1997). Regression Models for Categorical and Limited Dependent Variables. Thousand Oaks, CA: Sage Publications.

David, Hosmer & Stanley, Lemeshow (n. d.). Applied Logistic Regression. (2nd ed.). *Stat Books for Loan, Logistic Regression and Limited Dependent Variables*.