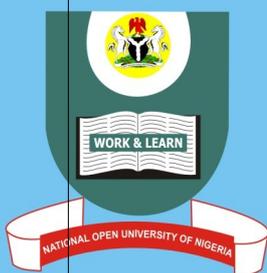


ESM 231

INTRODUCTORY TOXICOLOGY



NATIONAL OPEN UNIVERSITY OF NIGERIA



ESM 231
INTRODUCTORY TOXICOLOGY

Course Writer

Dr. Olusegun K. Abiola
Department of Chemistry
University of Lagos, Akoka
Lagos

Programme Leader

Prof. Afolabi Adebajo
National Open University of Nigeria



NATIONAL OPEN UNIVERSITY OF NIGERIA

National Open University of Nigeria
Headquarters
14/16 Ahmadu Bello Way
Victoria Island
Lagos

Abuja Office:
NOUN Building
No. 5, Dar es Sallam Street
Off Aminu Kano Crescent
Wuse II, Abuja
Nigeria.

e-mail: centralinfo@nou.edu.ng
URL: www.nou.edu.ng

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Introduction

Life for each of us is an ongoing series of chemical reactions which allow our bodies to function. The food we eat, the air we breathe and the water we drink provide the raw material for these chemical reactions and our bodies usually are efficient enough to expel most waste products.

Recently, there has been concern that our food, water and air are introducing toxic chemicals into our bodies. Are these concerns justified? What is a toxic chemical? Are there toxic chemicals in our environment polluting water and air? If so, can our bodies cope with these things? How do toxic chemicals differ from other chemicals?

The simple answer to the last question is that all chemicals can be toxic. An old cliché states that “the dose makes the poison” and that is true. Toxicology is the study of the adverse effects of chemicals or physical agents on living organisms.

These adverse effects may occur in many forms, ranging from immediate death to subtle changes not realised until months or years later. They may occur at various levels within the body, such as an organ, a type of cell or a specific biochemical.

The science of toxicology which overlaps with and incorporates aspect of other sciences including chemistry, biochemistry, physiology, microbiology, statistics, public health and pharmacology, studies the quantitative effects of chemicals on living things.

In the science of toxicology, the impact of external substance or condition and its deleterious effects on living things, organ systems, individual organs, tissues, cells, cellular units is the subject of study.

Organisms respond to toxic substances according to the amount or dose of the substance that gets into the body. This is one of the basic principles of toxicology that is with increasing dose or exposure to substances, you get more effects. This is easily illustrated with some examples from the home. Bread contains alcohol produced by the fermentation of sugars by yeast. The amount of alcohol in a slice of bread, or a loaf of bread, for that matter, is too small to cause a response (drunkenness) in humans. However, a bottle of liquor, also made by the fermentation of sugars by yeast contains a large enough dose of alcohol to make most people drunk or even, in some cases, to kill them.

If we are to live comfortably and safely in a chemical world, we need to be informed. We need to know the effects of certain chemicals and the associated risks.

This course will introduce you to the effects of certain chemicals and the associated risks on human body.

What You will Learn in this Course

The course consists of eight units on the history of toxicology, the field of toxicology and its history, basic principles of toxicology, toxicity, toxic agents, biotransformation, and the major classes of toxic agents, effects of toxic substances on the human body, carcinogenesis, mutagenesis, and tetraogenesis.

Course Aims

The aim of this course is to provide you with knowledge on the fundamental principles of toxicology, toxic agents, toxic effects, and factors affecting toxicity.

Course Objectives

After reading through this course material, you should be able to:

- Trace the history of toxicology
- Mention the field of toxicology
- Identify the major classes of toxic substances
- Explain the basic principles of toxicology
- Identify the different classes of environmental toxic substances
- Identify the routes of toxic substances and biotransformation in our body
- Explain the effects of different toxic substances on the organ systems and the whole body.
- Explain mutagenesis, carcinogenesis and tetraogenesis
- Explain the term “pesticide”
- Explain the fact that there are many different classes of pesticides
- Mention some pesticides that are very acutely toxic in humans.

Working through this Course

This course is learner driven, not teacher driven; assignments have been designed to create an active learning environment in the course. You will frequently be engaged in learning each unit independently You

should collaborate with your peers, when appropriate, to discuss and complete assignments.

Course Materials

You will be provided with the following materials:

- A course guide
- Study units

In addition, the course comes with a list of recommended textbooks which though are not compulsory for you to acquire or indeed read, are necessary as supplements to the course material.

Study Units

The following are the study units contained in this course:

Module 1

Unit 1	Background and Principles of Toxicology
Unit 2	Dose-Response Concepts
Unit 3	Toxicity
Unit 4	Routes of Entry of Toxic Agents and Bio Transformation of Toxic Agents
Unit 5	Toxic Inorganic Elements and Metals

Module 2

Unit 1	Toxic Organic Compounds
Unit 2	Teratogenesis, Mutagenesis, Carcinogenesis and Effects on the Immune and Reproductive Systems
Unit 3	Pesticides

Unit 1 serves as an introduction to the science of toxicology. This unit also traces the history of toxicology.

The second unit discusses the underlying principles of toxicology, the connection between doses, exposure and effects. It introduces you to toxicology terms such as threshold dose, effective dose, toxic dose, NOEL and LDSO.

Unit 3 introduces you to toxicity, factors that affect toxicity and types of toxicity. This unit also introduces you to physical form of toxic substances.

Unit 4 discusses the routes of entry of toxic agents, absorption of chemicals and biotransformation of toxic substances in the body. You will also learn about immunological reactions and immunotoxicity.

The fifth unit introduces you to toxicological aspects of inorganic elements and heavy metals. You will also learn about the toxicity and hazards of toxic heavy metals and inorganic elements, such as beryllium, lead, mercury, cadmium, arsenic, ozone, white phosphorus and chlorine.

Unit 6 is a continuation of Unit 5. This unit deals with the toxicity and hazards of some organic compounds, such as methane, ethane, methanol, ethanol, benzene, toluene, naphthalene, phenols, amines, ethers, ketenes and aldehydes.

Unit 7 discusses the interference of chemicals with the human body; teratogenesis, mutagenesis, carcinogenesis, and effects of chemical on the immune and reproductive systems. In this unit you will acquire basic knowledge on cancer and tumour development, and effects of chemicals on the immune and reproductive systems.

Unit 8 introduces you to the history and toxicology of pesticides.

Text books and References

Timbrell, John (2000). *Principles of Biochemical Toxicology*. UK: Taylor and Francis.

Timbrell, John (2002). *Introduction to Toxicology*, UK: Taylor and Francis.

Assignment File

There are two components of assessment for this course: The Tutor-Marked Assignment (TMA) and the end of course examination.

Tutor-Marked Assignment

The TMA is the continuous assessment component of your course. It accounts for 30% of the total score. You will be given four TMAs to answer; three of these must be answered before you are allowed to sit for the end of course examination. The TMAs would be given to you by

your facilitator. They should be returned after you have done the assignment.

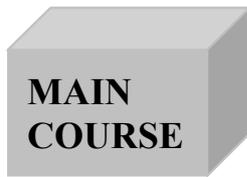
Final Examination and Grading

The examination concludes the assessment for the course. It constitutes 70% of the whole course. You will be informed of the time for the examination. It may or may not coincide with the university semester examination.

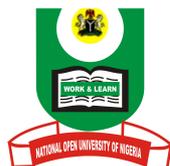
Summary

These eight study units are intended to provide you with basic the principles in the science of toxicology. By the time you complete studying them, you will be able to answer the following type of questions:

- Mention two scientists that were important in the development of toxicology
- What is toxicology?
- List the physical forms in which toxic substances can occur in our environment
- Using your own words, define the term “toxicity”
- What are the routes of human exposure to potentially toxic chemicals?
- What is the importance of body fat in relation to potential toxic substances?
- What are the Phase 1 reactions?
- Mention four metals that are toxic to human body
- What do you understand by the term Minamatal disease?
- Mention the stages in carcinogenic process
- Mention five organic compounds that are potentially toxic to human body
- What do you understand by the term tetratogenesis?
- Mention different classes of pesticides.



Course Code	ESM 231
Course Title	Introductory Toxicology
Course Writer	Dr. Olusegun K. Abiola Department of Chemistry University of Lagos, Akoka Lagos
Programme Leader	Prof. Afolabi Adebajo National Open University of Nigeria



NATIONAL OPEN UNIVERSITY OF NIGERIA

National Open University of Nigeria
Headquarters
14/16 Ahmadu Bello Way
Victoria Island
Lagos

Abuja Office
NOUN Building
5 Dar es Sallam Street
Off Aminu Kano Crescent
Wuse II, Abuja
Nigeria

e-mail: centralinfo@nou.edu.ng

URL: www.nou.edu.ng

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MODULE 1

Unit 1	Background and Principles of Toxicology
Unit 2	Dose-Response Concepts
Unit 3	Toxicity
Unit 4	Routes of Entry of Toxic Agents and Bio Transformation of Toxic Agents
Unit 5	Toxic Inorganic Elements and Metals

UNIT 1 BACKGROUND AND PRINCIPLES OF TOXICOLOGY

CONTENTS

1.0	Introduction
2.0	Objectives
3.0	Main Content
3.1	The History of Toxicology
3.2	What is Toxicology?
3.3	The Scope of Toxicology
3.3.1	Environmental Toxicology
3.3.2	Forensic Toxicology
3.3.3	Clinical Toxicology
3.3.4	Safety Toxicology
4.0	Conclusion
5.0	Summary
6.0	Tutor-Marked Assignment
7.0	References/Further Readings

1.0 INTRODUCTION

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

2.0 OBJECTIVES

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

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

3.0 MAIN CONTENT

3.1 The History of Toxicology

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

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

Paracelsus is often quoted for his statement:

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

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

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

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

3.2 What is Toxicology?

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

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

Wikipedia defines toxicology as the study of the adverse effects of chemicals on living organisms. It is the study of symptoms, mechanisms, treatments and detection of poisoning, especially the poisoning of people.

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

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

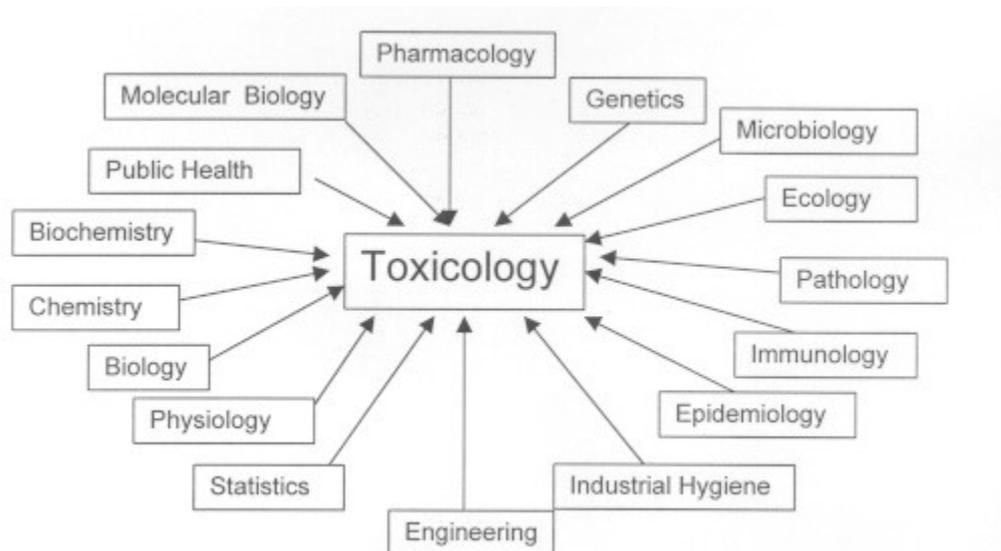


Figure 1: Toxicology as an inter-disciplinary science

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

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

3.3 The Scope of Toxicology

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

3.3.1 Environmental Toxicology

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

3.3.2 Forensic Toxicology

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

3.3.3 Clinical Toxicology

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

3.3.4 Safety Evaluation Toxicology

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

4.0 CONCLUSION

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

5.0 SUMMARY

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

6.0 TUTOR-MARKED ASSIGNMENT

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

7.0 REFERENCES/FURTHER READINGS

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

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

Wikipedia on - Line Dictionary

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

NURS 735- Applied Toxicology
<http://www.sis.nlm.nih.gov/Tox/ToxTutor.html>
<http://www.uoguelph.ca/cntc/educat/guide/intro.shtml>

UNIT 2 DOSE-RESPONSE CONCEPTS

CONTENTS

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main Content
 - 3.1 Doses -Response Concepts
 - 3.2 Dose Response
 - 3.3 Dose Estimates of Toxic Effects
 - 3.4 Effective Doses
 - 3.5 Toxic Doses
 - 3.6 No Observed Adverse Effect Level and Low Observed Adverse Effect Level
 - 3.7 Hazard and Risk assessment
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Readings

1.0 INTRODUCTION

Unit 2 will explain to you the underlying principles of toxicology, the connection between dose, exposure and effect. In this unit you will come across terms such as toxicant, threshold, dose response, effective doses, no observed effect level (NOEL) and LD₅₀.

2.0 OBJECTIVES

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

- explain the use of dose – response relationships to quantify toxicity
- demonstrate the use of concentration – response relationships to quantify toxicity
- show that the shape and slope of the dose-response curve is extremely important
- explain the meaning of LD₅₀, LC₅₀, NOEL and toxic dose

3.0 MAIN CONTENT

3.1 Doses-Response Concepts

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

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

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

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

Knowledge of the dose-response relationship:

- Establishes causality that the chemical has induced the observed effects
- Establishes the lowest dose where an induced effect occurs the threshold effect
- Determines the rate at which injury builds up the slope for the dose-response.

3.2 Dose-Response

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

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

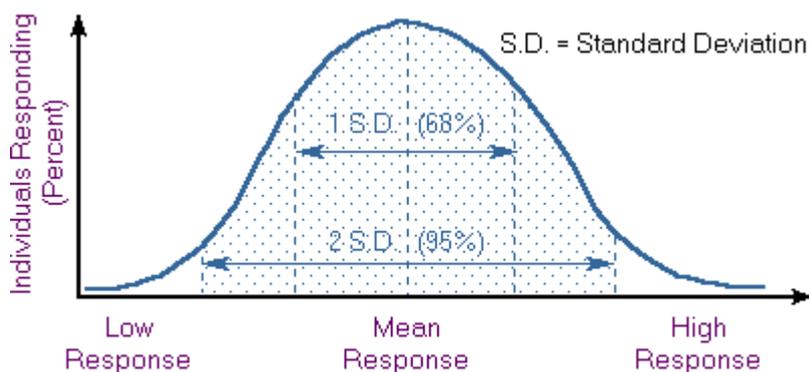


Figure 2.1: The dose-response curve

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

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

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

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

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

The dose-response curve normally takes the form of a sigmoid curve; see Figure 2.2 below. It conforms to a smooth curve as close as possible to the individual data points. For most effects, small doses are not toxic.

The point at which toxicity first appears is known as the threshold dose level. From that point, the curve increases with higher dose levels. In Figure 2.2, no toxicity occurs at 10.mg whereas at 35mg 100% of the individuals experience toxic effects.

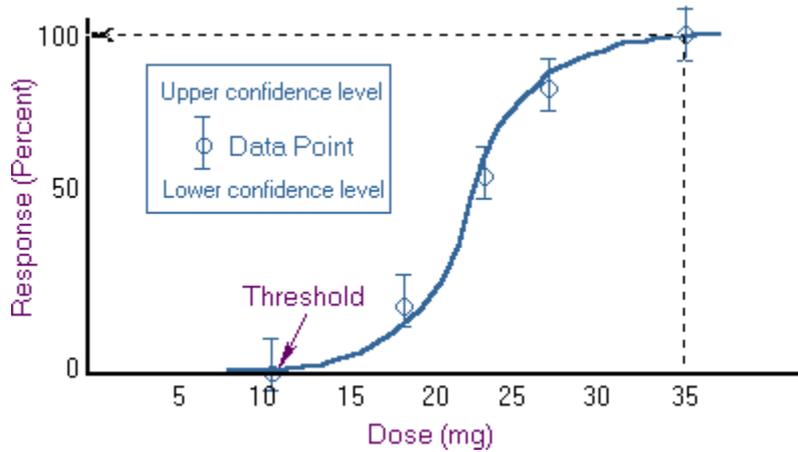


Figure 2.2: Shape of dose-response curve

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

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

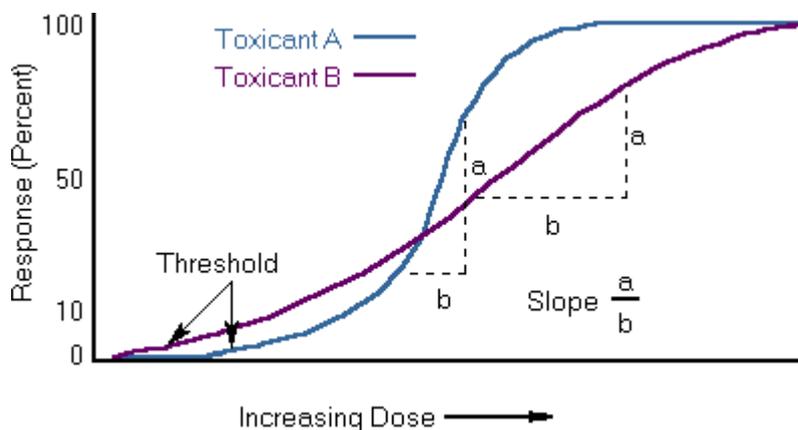


Figure 2.3: Dose-response curve for two-toxicants

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

Dose-response curves are used to derive dose estimates of chemical substances. A common dose estimate for acute toxicity is the LD₅₀ (Lethal Dose 50%). This is a statistically derived dose at which 50% of the individuals will be expected to die.

Other dose estimates also may be used: 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 LC₅₀ (which stands for lethal concentration 50%) is utilized to denote the calculated concentration of a gas lethal to 50% of a group.

3.4 Effective Doses

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

ED ₀	Effective for 0% of the population
ED ₁₀	Effective for 10% of the population
ED ₅₀	Effective for 50% of the population
ED ₉₀	Effective for 90% of the population

3.5 Toxic Doses (TDs)

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

TD ₀	Toxic to 0% of the population
TD ₁₀	Toxic to 10% of the population
TD ₅₀	Toxic to 50% of the population
TD ₉₀	Toxic to 90% of the population

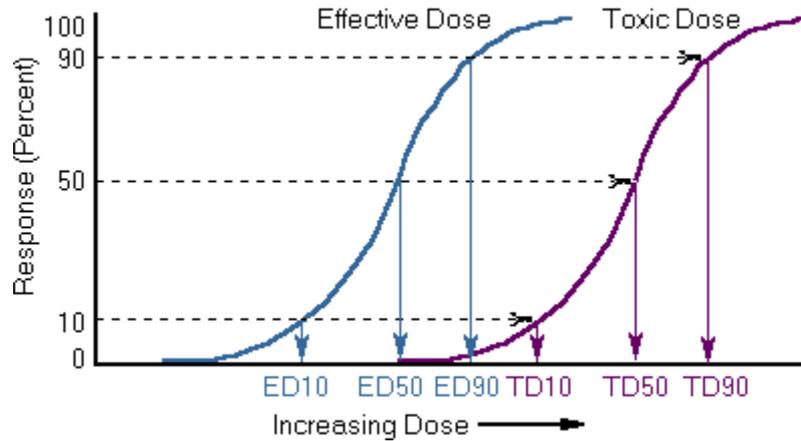


Figure 2.4: The dose-response curve explanation for effective and toxic doses

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

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

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

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

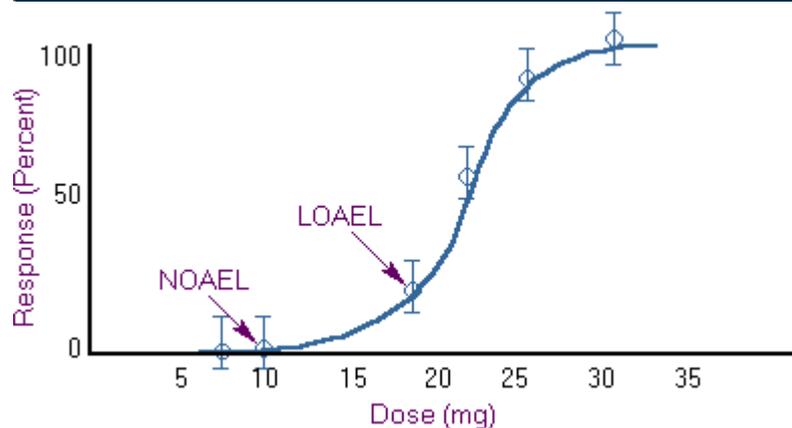


Figure 2.5: Curve dose-response for NOEL

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

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

3.7 Hazard and Risk assessment

Another important role of the dose-response relationship is its use in the extrapolation of toxic effects seen at high dose to lower dose in order to undertake hazard and risk assessment. For some types of toxic effect, there will be a threshold dose below which there is no detectable response. This is referred to as No Observed Effect Level (NOEL) (Figure 2.6).

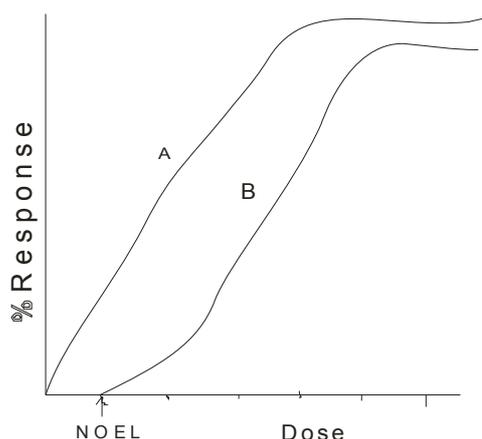


Figure 2.6: The Curve dose-response for two compounds NOEL (Curled from Timbrel 2000)

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

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

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

4.0 CONCLUSION

This unit has taught the dose - response relationship which is central to toxicology. From the dose – response curve, it is possible for you to determine the LD₅₀, ED₅₀ and NOEL. Also, you should be able to mention at least two assumptions on the dose – response relationship and the importance of this concept in risk and hazard assessment.

5.0 SUMMARY

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

6.0 TUTOR-MARKED ASSIGNMENT

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

7.0 REFERENCES/FURTHER READINGS

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

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

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

UNIT 3 TOXICITY

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- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main Content
 - 3.1 What is Toxicity?
 - 3.2 Types of Toxicity
 - 3.3 Classes of Toxic Substances
 - 3.3.1 Gases
 - 3.3.2 Vapours
 - 3.3.3 Dusts
 - 3.3.4 Mists
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Readings

1.0 INTRODUCTION

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

2.0 OBJECTIVES

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

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

3.0 MAIN CONTENT

3.1 What is Toxicity?

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

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

3.2 Types of Toxicity

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

- **Acute exposures:** This term refers to exposure 'of short duration'. As applied to materials which are inhaled or absorbed through the skin, it refers to a single exposure of a duration measured in seconds, minutes, or hours. As applied to materials which are ingested, it refers generally to a single quantity or dose.
- **Sub-acute exposure:** This refers to exposures of intermediate duration, i.e., between acute and chronic durations up to about 90 days.
- **Chronic exposure:** This term will be used in contrast to acute exposure and it is of long duration. As applied to materials which are inhaled or absorbed through the skin, it refers to prolonged or repeated exposures of a duration measured in days, months or years. As applied to materials which are ingested, it refers to repeated doses over a period of days, months, or years. The term 'chronic' will not refer to severity of symptoms but will carry the implication of exposures or dose which would be relatively harmless unless extended or repeated over a long period of time (days, months or years).

It is important to differentiate between acute and chronic exposure and acute and chronic effects. Although the expression "chronic toxicity" is sometimes used to indicate the result of repeated exposure to a chemical or to ionising radiation; it would be much clearer if 'chronic toxicity' were equated with chronic illness resulting from these agents without any commitment regarding the duration of exposure. The fact is that some compounds have a strong tendency to produce chronic illness even though the exposure may be acute (i.e., only a single dose). Such compounds include the heavy metals and most carcinogens. Of course, their tendency to produce chronic sickness is accentuated if they are absorbed in repeated dose. At the opposite extreme are compounds such as CN^- with which it is virtually impossible to produce chronic illness—even though a single excessive dose may produce acute poisoning and rapid death. Most compounds lie somewhere between the two extremes.

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

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

- **Local effect:** This means that the action takes place at the point or area of contact. The site may be skin, mucous membranes of the eyes, nose, mouth, throat, or anywhere along the respiratory or gastrointestinal system. Absorption does not necessarily occur.
- **Systemic effect:** This refers to a site of action other than the point of contact and presupposes that absorption has taken place. It is possible, however, for toxic agents to be absorbed through a channel (skin, lungs, or intestinal canal) and produce later manifestations on one of those channels which are not a result of the original direct contact. Thus, it is possible for some agents to produce harmful effects on a single organ or tissue as a result of both local and systemic actions.

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

The dosage concept leads to the condition that no chemical safe and that is none is entirely harmful. Compounds vary tremendously in their toxicity. In comparing the toxicity of different compounds standardised notation are used for describing the toxic level. The commonly used notation is the median lethal doses or LD_{50} . The LD_{50} is a statistical estimate of the dosage necessary to kill 50% of an infinite population of the test animals. The LD_{50} is usually expressed in terms of the weight of poison /unit of body weight (mg) of different species regardless of their size. The LD_{50} is a special case of a more general measure of effect, the median effective dosage (ED_{50}). The ED_{50} is the dosage necessary to produce any specified effect in 50% of the test animals. The effect can

be anything that can be observed (i.e., degree of inhibition of an enzyme or the production of tumour. These measures of effect (ED_{50} or LD_{50}) for a particular compound have meaning only if experimental conditions are defined, including the species, age and sex of experimental animal, the number of dose and the route of administration.

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

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

2. Threshold Limit Values

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

TLV represents an arbitrarily set value on the basis of experimental and other available data while LD₅₀ represents an experimentally derived value. The acute oral LD₅₀ value is most useful if one is dealing with an ingestion case while TLV is useful for industrial and occupational exposure restrictions.

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

- (a) undesirable changes in body biochemistry;
- (b) undesirable functional reactions that may have no discernible effects on health; and
- (c) irritation or other adverse sensory effects.

For gases and vapours, the TLV is usually expressed in parts per million (ppm); that is, parts of the gas or vapour per million parts of air. For fumes and mists and for some dusts, the TLV is usually given as milligrams per cubic meter (mg/m³) or per 10m³ of air. For some dusts particularly those containing SiO₂, the TLV is usually expressed as millions of particles per cubic foot air (mppcf).

3.3 Classes of Toxic Substances

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

3.3.1 Gases

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

3.3.2 Vapours

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

3.3.3 Dusts

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

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

3.3.4 Mists

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

4.0 CONCLUSION

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

You should now be able to explain the following:

- Acute exposure
- Chronic exposure
- Threshold limit values (TLV)
- LD₅₀

5.0 SUMMARY

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

6.0 TUTOR-MARKED ASSIGNMENT

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

7.0 REFERENCES/FURTHER READINGS

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UNIT 4 ROUTES OF ENTRY OF TOXIC AGENTS AND BIO TRANSFORMATION OF TOXIC AGENTS

CONTENTS

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main Content
 - 3.1 Absorption of chemicals
 - 3.1.1 Membrane Structure
 - 3.2 Distribution and metabolism of chemicals
 - 3.3 Immunological reactions
 - 3.4 Biotoxification
 - 3.5 Toxicodynamics
 - 3.6 Immunotoxicity
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Readings

1.0 INTRODUCTION

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

2.0 OBJECTIVES

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

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

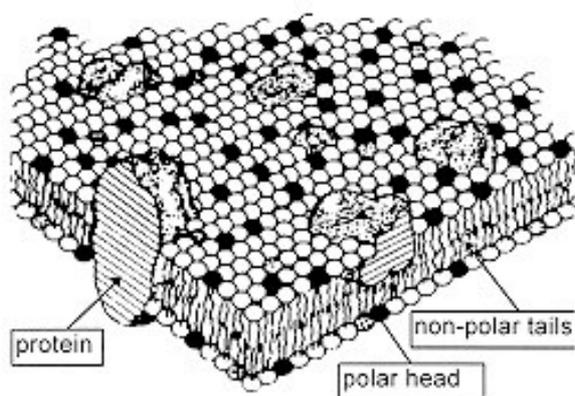
3.0 MAIN CONTENT

3.1 Absorption of Chemicals

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

3.1.1 Membrane Structure

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



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

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

Figure 4.1 shows what happens to xenobiotics absorbed by these routes. The severity of the effects produced by any given dose, amount or concentration of a chemical or chemical formulation is related to the route of absorption, among other things. Usually absorption is most rapid from the lungs, less rapid from the gastro intestinal tract and least rapid through the skin. The lungs evolved for efficient exchange of gases and present little resistance to the uptake of chemicals in the vapour state.

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

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

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

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

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

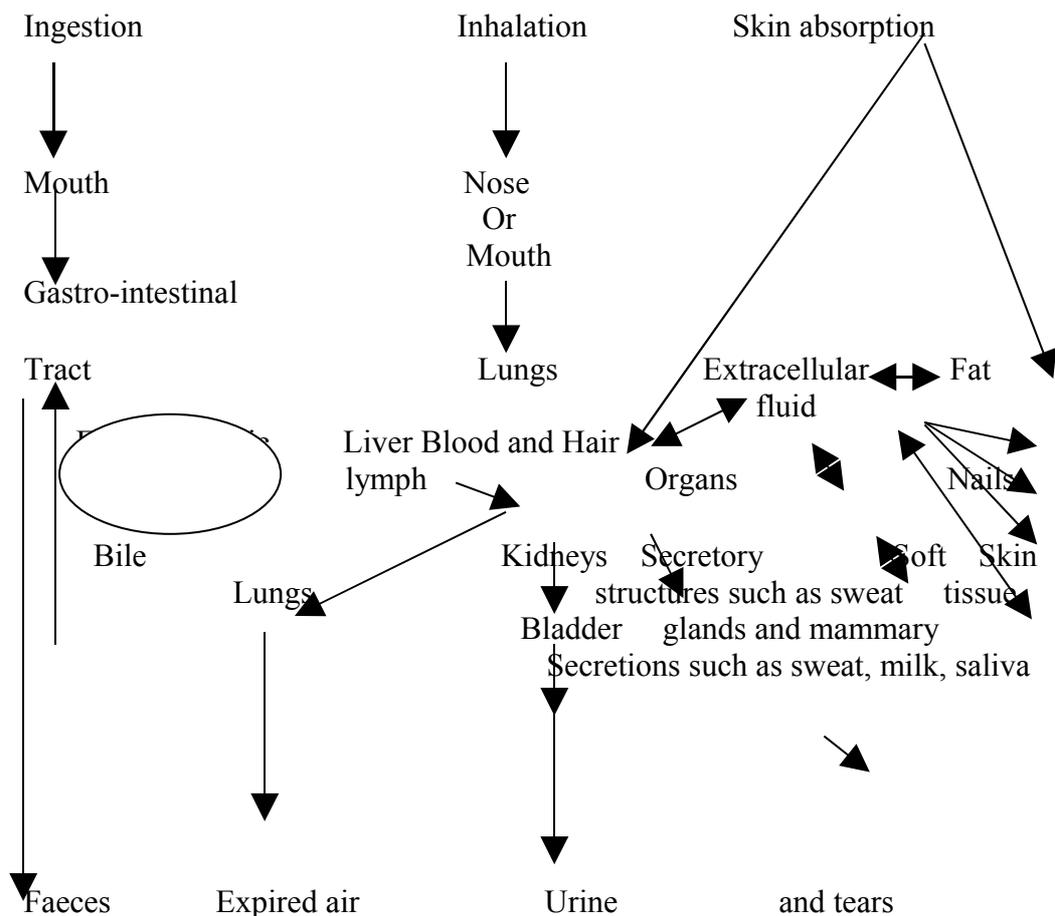


Figure 4.1: Routes of absorption, distribution and excretion of potentially toxic substances (Culled from Edintox on-line Toxicology course).

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

1. Passive diffusion
2. Specialised transport

Passive diffusion: Most toxicants enter this way; through.

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

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

- Lipid solubility
- Molecular size
- Degree of ionization

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

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

Molecular size: Small particles absorbed more readily.

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

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

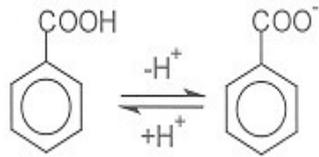
The degree of ionisation is dependent upon:

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

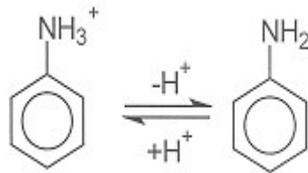
For acids: $pK_a - pH = \log \frac{[\text{nonionised}]}{[\text{ionised}]}$ Acids such as R-COOH, etc.

For bases: $pK_a - pH = \log \frac{[\text{ionised}]}{[\text{nonionised}]}$ Bases such as R-NH₂

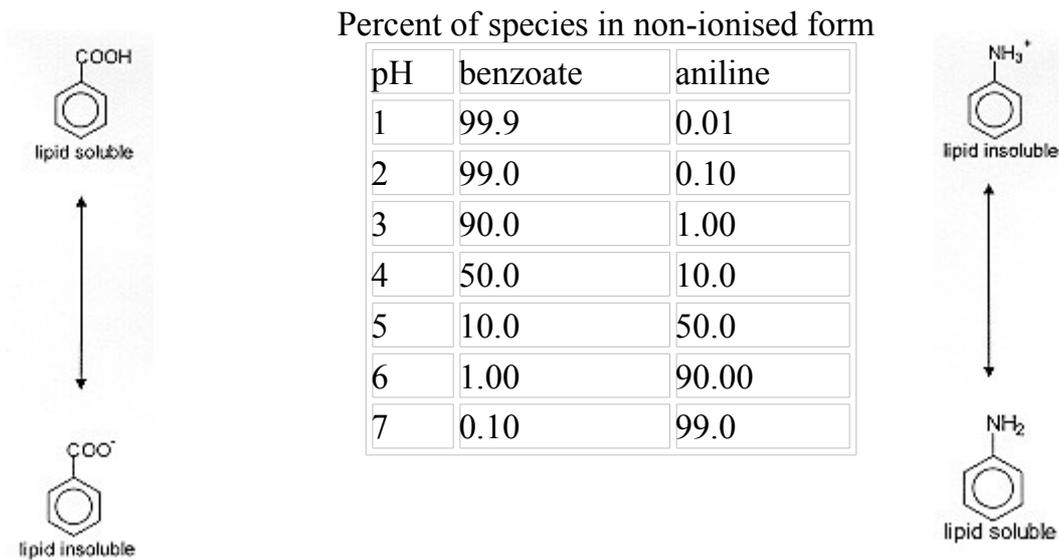
Consider the ionisation of two compounds:



benzoic acid (weak acid: $pK_a=4$)



aniline (weak base: $pK=5$)



Toxicological consequences of interaction between pH and pK :

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

b. Specialised transport

1. Characteristics of active transport:

- absorption against concentration gradient
- saturable

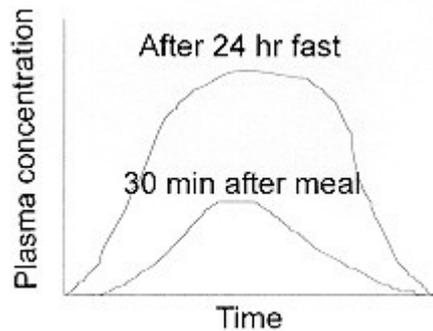
- selective
 - requires energy
2. Carrier-mediated
 3. Endocytosis: pinocytosis/phagocytosis:
 - requires energy
 - for small amounts of compounds: peptides, AG:AB complexes
- c. Absorption of chemicals by specific routes
1. Percutaneous route (skin is a good barrier)
 - A. transepidermal: (most here)
 - B. transfollicular: via sweat glands and follicles (Pb)

Absorption of chemicals through the skin is promoted by:

- high lipid solubility and non-ionisation
 - sweaty, hot skin
 - wrapping of skin
 - abrasion, injury, rash
 - presence of solvents
2. Pulmonary route: rapid since epithelium is 1-2 cells thick
 - principal route of absorption for gases, vapours, aerosols
 3. Gastrointestinal route
 - epithelial linings are only one cell thick
 - extremely large surface area in many areas (the stomach is not as good an absorptive surface and is continually emptying)
 - due to tremendous pH ranges, diffusion of drug occurs where it is present in most lipid soluble form:
 - weak acids diffuse best at lower pH (stomach--pH 2)
 - weak bases diffuse best at higher pH (intestines--pH 6)
 - some compounds are absorbed well, regardless of pH/pK characteristics:
 - paraquat (has two positive charges), 2-PAM

- factors promoting absorption: ulceration, GI irritation, starvation
factors decreasing absorption: food in gut, vomiting

Effect of meal on plasma concentration of a chemical:



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

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

d. Distribution

Factors affecting distribution:

(i). Binding to charged particles:

The blood contains charged proteins to which chemicals will bind (such as albumin, globulins, and proteins) chemical bound chemical (crosses membranes) (does not cross membranes)

(ii) Fat storage:

Depends on lipophilicity of compound:

3. Volume of distribution (Vd):

- That volume that would exist in the body if all parts of the body had the same drug concentration as the plasma.

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

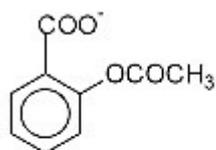
Type of water	% of total	Volume (L)
Plasma	4	3
Interstitial	13	9
Intracellular	41	28

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

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

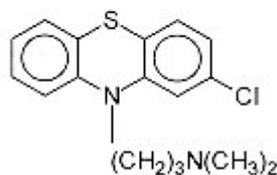
V_d will be greater than 3L.

Examples:



Acetylsalicylic acid

$V_d = 0.15L$



Chlorpromazine (thorazine)

$V_d = 21 L$

3.2 Distribution and Metabolism of Chemicals

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

Location of biotransformation reaction: Liver is by far the most important organ in which most of the biotransformation reactions are carried out. Most of the enzymes which catalysed biotransformation reactions have been shown to be present in the cells of the liver on

endoplasmic reticulum which is a network of inter-connected structures made up of lipoproteins.

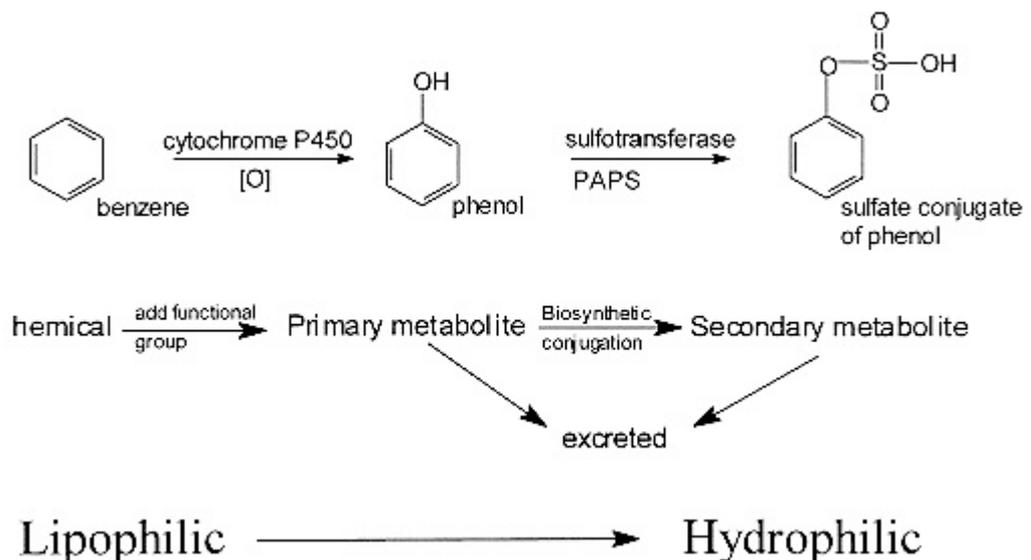
Toxic agents are metabolised in the liver cells by unique pathways which appear to exist mainly for the purpose and are capable of dealing with a tremendous variety of compounds.

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

3.2.1 Phase I Reactions

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

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



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

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

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

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

Mechanism and sequence of cytochrome P-450 catalysis:

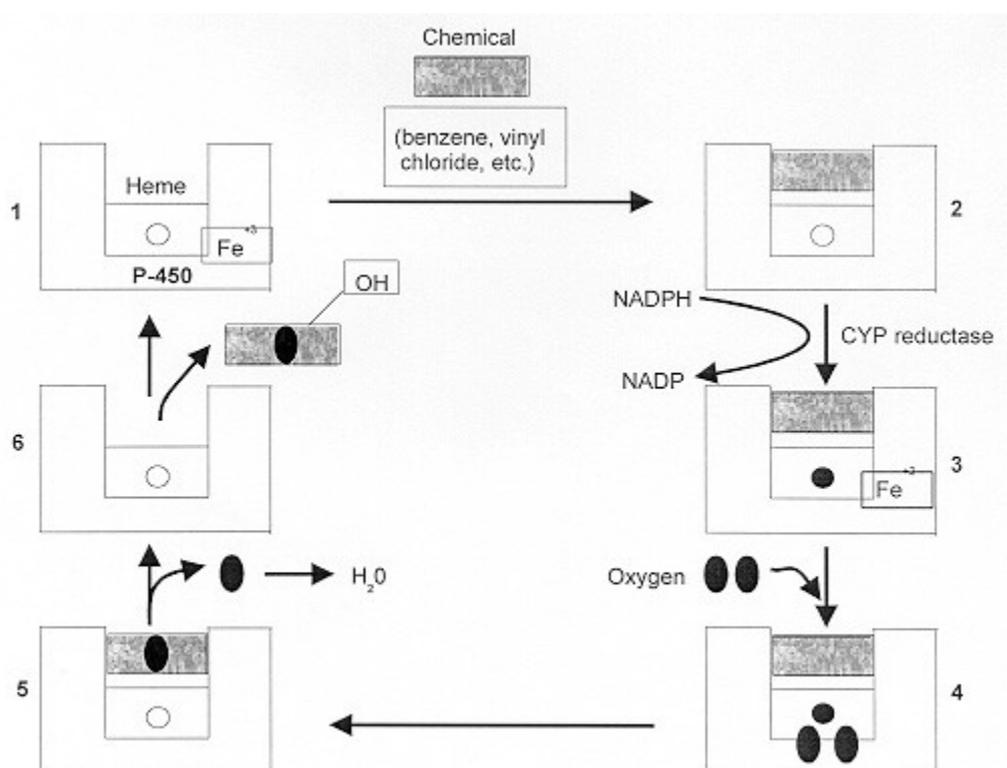
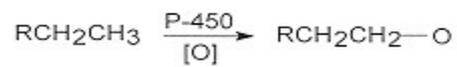
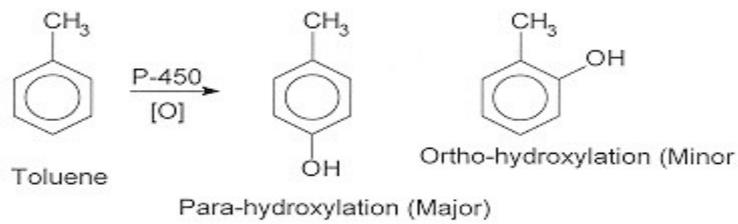
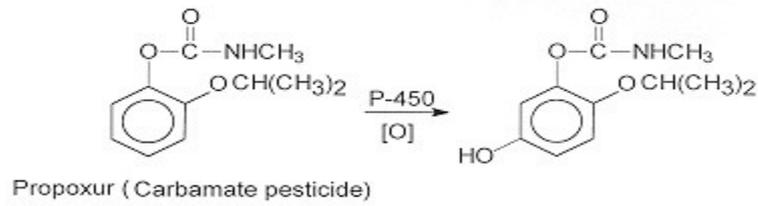


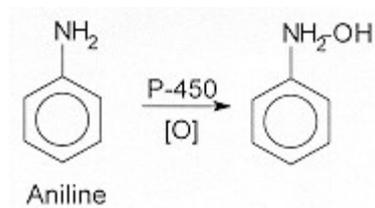
Figure 4.2 Phase I biotransformation.

P-450 mediated reactions:

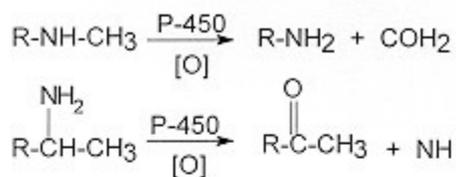
Aliphatic and aromatic hydroxylations



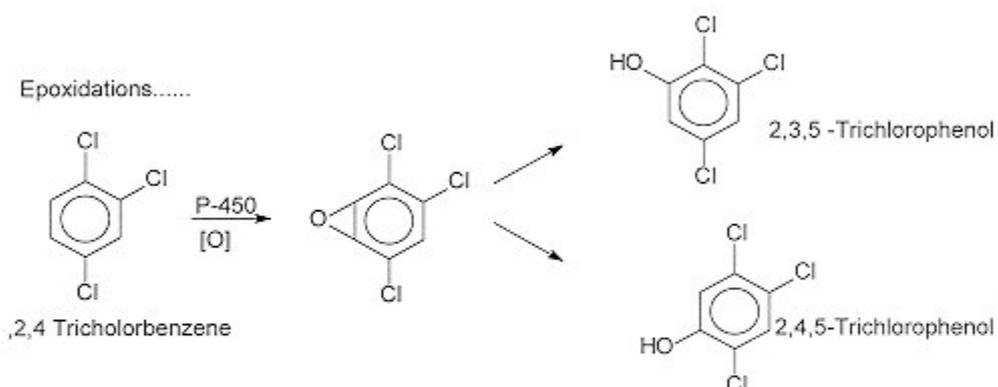
Nitrogen hydroxylation:



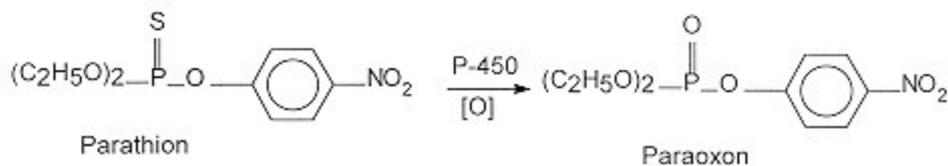
Dealkylations and deaminations



Epoxidations.....



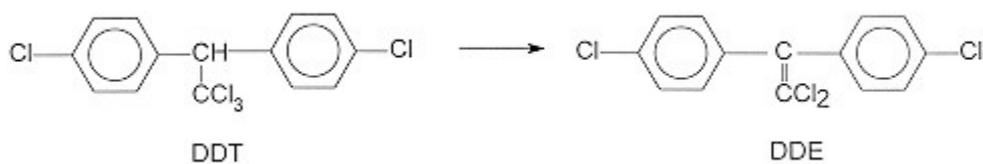
De-sulfuration...



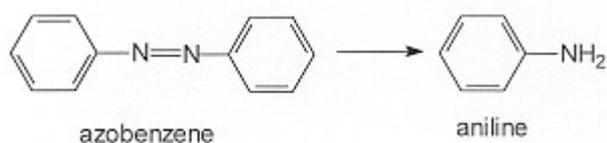
(paraoxon is more toxic than parathion)

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

Reductive dehalogenation.



azo reduction:

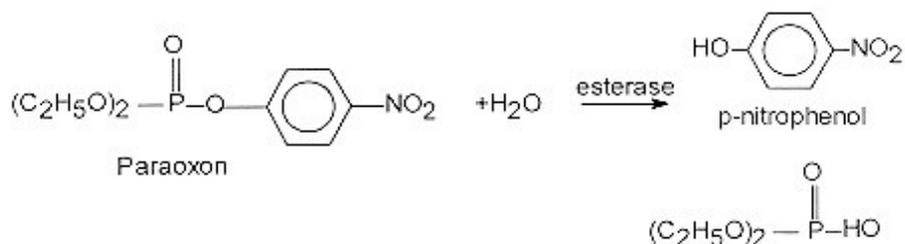


nitro reduction:

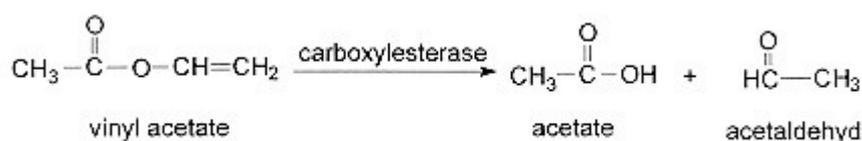


3.2.1.2 Hydrolysis Reactions (add H₂O to ester Groups)

Phosphoric acid ester:

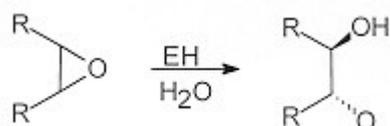


Carboxylic acid ester:

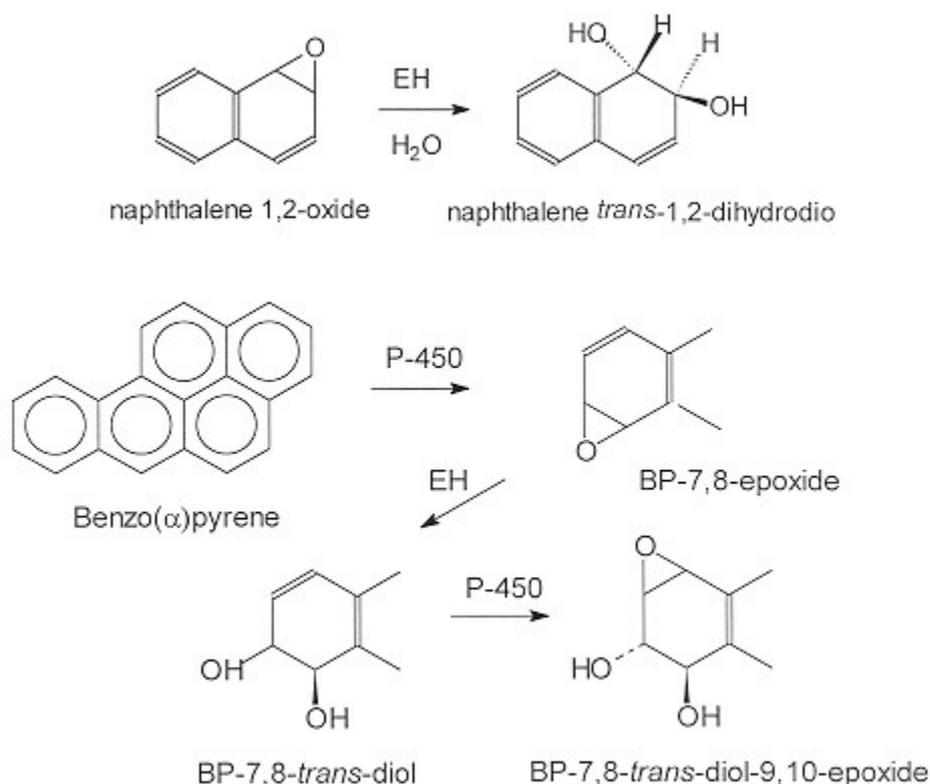


Epoxide Hydrolase:

- A hydrolytic enzyme in microsomes and soluble cellular fractions.
- Mainly in liver, but also in lung, kidney and intestines.
- Catalyses the transital addition of H₂O to epoxides to produce transaldriols.



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



3.2.2 Phase II Reactions

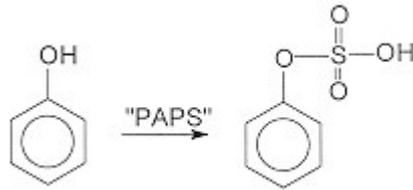
Phase II reactions are called conjugation reactions in which enzymes attach conjugating agent to xenobiotics, their phase I reaction products, and non-xenobiotic compounds: the conjugation product of such a reaction is usually less toxic than the original xenobiotic compound, less lipid soluble, more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

Chemicals modified by phase I reactions can be further metabolised by a variety of secondary, or "phase II" reactions.

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

Products of phase II reactions are generally detoxified.
Products of phase II reactions are called "conjugates".

Chemicals may be conjugated to the following compounds:



I. Sulfate

Enzyme: Sulfotransferase

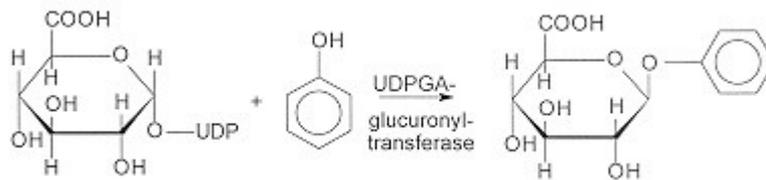
Coenzyme: Phosphoadenosine-5'-Phosphosulfate ("PAPS")

II. Glucuronic Acid

Enzyme: UDP-Glucuronyl Transferase

Coenzyme: Uridine diphosphoglucuronic acid (UDPGA)

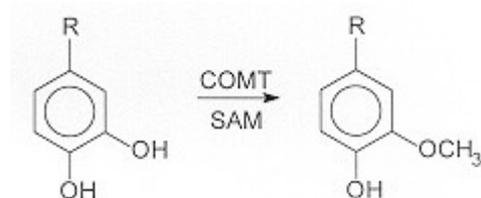
(During conjugation UDPGA is interconverted from β to α configuration)



III. Methyl Group

Enzyme: O-Methyltransferase

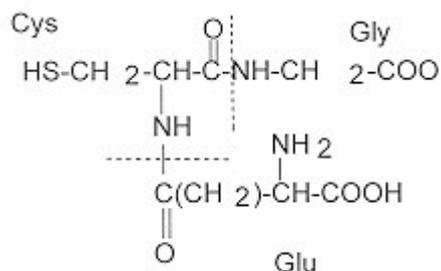
Coenzyme: S-Adenosyl Methionine ("SAM")



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

Enzyme: glutathione S-transferase (GST)

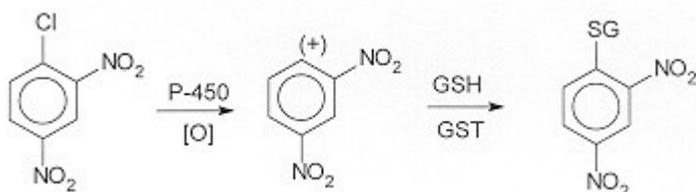
Coenzyme: glutathione (γ -glutamyl L-cysteinyl glycine; GSH)
glutathione is a tripeptide with a backwards or γ peptide bond.



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

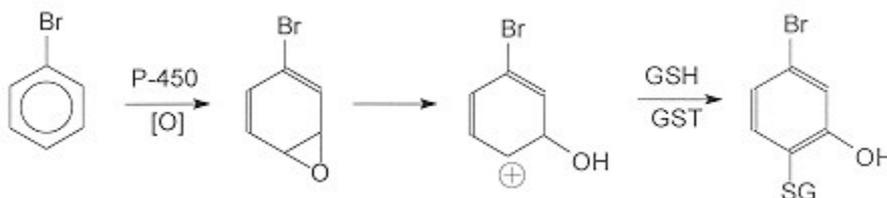
GSH conjugates are subsequently cleaved to cysteine derivatives in the kidney.

Dinitrochlorobenzene



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

Bromobenzene



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

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

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

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

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

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

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

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

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

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

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

3.3 Immunological Reactions

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

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

3.4 Biotoxification

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

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

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

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

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

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

3.5 Toxicodynamics

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

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

If such mutations occur in gametes (eggs or sperm), they are heritable and may affect future generations. If mutations occur in other body

cells, they are called somatic mutations and may cause benign or malignant tumour development.

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

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

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

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

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

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

3.6 Immunotoxicity

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

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

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

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

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

4.0 CONCLUSION

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

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

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

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

5.0 SUMMARY

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

6.0 TUTOR-MARKED ASSIGNMENT

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

7.0 REFERENCES/FURTHER READINGS

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

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

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

UNIT 5 TOXIC INORGANIC ELEMENTS AND METALS

CONTENTS

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main Content
 - 3.1 Toxic Elements
 - 3.1.1 Ozone
 - 3.1.2 White Phosphorus
 - 3.1.3 Elemental Halogens
 - 3.2 Heavy Metals
 - 3.2.1 Sources of Metallic Toxicants
 - 3.2.2 Beryllium
 - 3.2.3 Mercury
 - 3.2.4 Lead
 - 3.2.5 Cadmium
 - 3.2.6 Arsenic
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Readings

1.0 INTRODUCTION

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

2.0 OBJECTIVES

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

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

3.0 MAIN CONTENT

3.1 Toxic Elements

3.1.1 Ozone

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

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

3.1.2 White Phosphorus

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

3.1.3 Elemental Halogen

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

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

3.2 Heavy Metals

Heavy metals are toxic and their toxicity varies with chemical form. Metallic toxicants in the cell membrane attack the proteins (enzymes) in the body; the sites of attack are the sulphur atoms, the free amino (-NH₂) and carboxyl (-COOH) groups of the enzymes.

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

3.2.1 Sources of Metallic Toxicants

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

Table 1: Metallic Toxicants from industries and business (Ademoroti, 1996)

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

3.2.2 Beryllium

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

3.2.3 Mercury

Mercury can exist in three forms: elemental, inorganic and organic forms, and all are toxic. Elemental mercury may be absorbed by biological system as a vapour; it readily passes across the blood-brain

barrier into the central nervous system and also to the foetus. All the forms of mercury will cross the placenta and gain access to the foetus, although elemental mercury and organic mercury show greater uptake.

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

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

3.2.4 Lead

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

3.2.5 Cadmium

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

3.2.6 Arsenic

Arsenic is a metalloid which forms a number of toxic compounds. The toxic trioxide, As_2O_3 is absorbed through the lungs and intestines. Arsenic can affect the blood system and interfere with the porphyrin biosynthesis and affect blood cells. It causes spontaneous abortion and loss of hearing. Arsenic affects the skin causing skin cancer and has also been implicated in lung cancer.

4.0 CONCLUSION

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

5.0 SUMMARY

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

6.0 TUTOR-MARKED ASSIGNMENT

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

7.0 REFERENCES/FURTHER READINGS

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

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

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

MODULE 2

Unit 1	Toxic Organic Compounds
Unit 2	Teratogenesis, Mutagenesis, Carcinogenesis and their Effects on the Immune and Reproductive Systems
Unit 3	Pesticides

UNIT 1 TOXIC ORGANIC COMPOUNDS

CONTENTS

1.0	Introduction
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3.0	Main Content
3.1	Alkane Hydrocarbons
3.1.1	Alkene and Alkyne Hydrocarbons
3.1.2	Benzene and Aromatic Hydrocarbons
3.1.3	Toluene
3.1.4	Naphthalene
3.1.5	Polycyclic Aromatic Hydrocarbons
3.1.6	Alcohols
3.1.7	Phenols
3.1.8	Aliphatic Amines
3.1.9	Carbon Cyclic Aromatic Amines
3.2	
3.2.1	Pyridine
3.2.2	Nitro Compounds
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3.2.4	Isocyanates Methyl Isocyanate
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3.2.6	Alkyl Halides
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5.0	Summary
6.0	Tutor-Marked Assignment
7.0	References/Further Readings

1.0 INTRODUCTION

This unit is a continuation of Unit 5. It discusses the toxicology aspects of some common organic compounds.

The unit will help you to acquire basic knowledge about the toxicity and hazards of organic compounds such as methane, ethane, methanol, ethanol, benzene, toluene, naphthalene, phenols, amines, ethers, ketones and aldehydes.

2.0 OBJECTIVES

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

- describe the effects of toxic organic compounds
- mention the health hazards of some industrial organic compounds.

3.0 MAIN CONTENT

3.1 Alkane Hydrocarbons

The most common toxicological occupational problem associated with the use of hydrocarbon liquids is dermatitis, caused by dissolution of the fat portions of the skin and characterised by inflamed, dry, scaly skin. Inhalation of volatile liquid of n-alkanes and branched chain alkanes may lead to the depression of the central nervous system, manifested by dizziness and loss of coordination. Exposure to n-hexane and cyclohexane results in loss of myelin and degeneration of axons; and this may lead to multiple disorders of the nervous system including muscle weakness and impaired sensory function of the hands and feet in the body.

3.1.1 Alkene and Alkyne Hydrocarbons

Ethylene, a widely used colorless gas, acts as an anesthetic to animals and is toxic to plants. The toxicological properties of propylene are very similar to those of ethylene. Colourless, odourless, gaseous 1,3-butadiene is an irritant to the eyes, respiratory system and mucous membranes; at higher levels it can lead to unconsciousness and even death. Acetylene is a colourless gas with a garlic odour. It acts as an asphyxiant and narcotic, causing headache, dizziness and gastric disturbances.

3.1.2 Benzene and Aromatic Hydrocarbons

Inhaled benzene is readily absorbed by the blood from which it is taken up by fatty tissues. Benzene is a skin irritant, and progressively higher local exposure can cause skin redness, burning sensations, fluid accumulation (edema) and blistering. Inhalation of air containing about 7g/m^3 of benzene causes acute poisoning within an hour because of a narcotic effect upon the central nervous system manifested progressively by excitation, depression, respiratory system failure and death. Inhalation of air containing more than about 60g/m^3 of benzene can be fatal within a few minutes.

Chronic benzene poisoning causes blood abnormalities, including a lowered white cell count and abnormal increase in blood lymphocytes, anaemia, a decrease in the number of blood platelets required for clotting (thrombocytopenia) and damage to bone marrow.

3.1.3 Toluene

Toluene, a colourless liquid, is classified as moderately toxic through inhalation or ingestion. Massive exposure to toluene has a narcotic effect which can lead to coma.

3.1.4 Naphthalene

Exposure to Naphthalene can cause anaemia and marked reductions in red cell count, haemoglobin, and hematocrit in individuals exhibiting enteric susceptibility to these conditions. Naphthalene causes skin irritation or severe dermatitis in sensitised individuals. Headaches, confusion and vomiting may result from inhalation or ingestion of naphthalene. Death from kidney failure occurs in severe instances of poisoning.

3.1.5 Polycyclic Aromatic Hydrocarbons

Benzo[a]pyrene is the most studied of the polycyclic aromatic hydrocarbons (PAHs). Some metabolites of PAH compounds, particularly the 7,8-diol-9,10-epoxide of benzo[a]pyrene are known to cause cancer.

3.1.6 Alcohols

Human exposure to methanol, ethanol and ethylene glycol is common because they are widely used industrially and in consumer products. In addition to causing acidosis, these products affect the central nervous system and the optic nerve. Acute exposure to lethal doses causes an initially mild inebriation followed in about 10-20 hours, by unconsciousness, cardiac depression and death. Sub-lethal exposures can cause blindness from deterioration of the optic nerve and retinal ganglion cells. Inhalation of methanol fumes may result in chronic low-level exposure.

Ethanol has numerous acute effects resulting from central nervous system depression. These range from decreased inhibitions and slowed reaction times at 0.05% blood ethanol, through intoxication, stupor and, at more than 0.5% blood ethanol-death. Ethanol also has a number of chronic effects of which the addictive condition of alcoholism and cirrhosis of the liver are the most prominent.

Inhalation of droplets of ethylene glycol can be very dangerous. In the body, ethylene glycol initially stimulates the central nervous system, and then depresses it. Of the higher alcohols 1-butanol is an irritant but its toxicity is limited by its low vapour pressure.

3.1.7 Phenols

The acute toxic toxicological effects of phenol are largely upon the central nervous system and death can occur as soon as one and a half hours after exposure. Acute poisoning by phenol can cause severe gastro-intestinal disturbances, kidney malfunction, circulatory system failure, lung edema and convulsions. Key organs damaged by chronic phenol exposure include the spleen, pancreas and kidneys. The toxicity of other phenols resembles those of phenol.

3.1.8 Aliphatic Amines

The lower amines, such as the methylamines, are rapidly and easily taken into the body by all common exposure routes. They are basic and react with water in tissue raising the pH of the tissue to harmful level, acting as corrosive poisons (especially to sensitive eye tissue) and causing tissue necrosis at the point of contact. Among the system effects of amines are necrosis of the liver and kidneys, lung haemorrhage and edema and sensitisation of the immune system. The lower amines are among the more toxic substances in routine large-scale use.

3.1.9 Carbon Cyclic Aromatic Amines

Some of the carbon cyclic aromatic amines have been shown to cause cancer in the human bladder, urethra, and pelvis, and are suspected of being lung, liver and prostate carcinogens. A very toxic colourless liquid with an oily constituency and distinct odour, aniline, readily enters in the body by inhalation, ingestion and through the skin. Metabolically, aniline converts iron (II) in haemoglobin to iron (III). This causes a condition called methemoglobinemia, characterised by cyanosis and a brown-black colour of the blood in which the haemoglobin can no longer transport oxygen in the body. This condition is not reversed by oxygen therapy.

3.2

3.2.1 Pyridine

Pyridine, a colourless liquid with a sharp, penetrating terrible odour, is an aromatic amine in which an N-atom is part of a 6-membered ring. This widely used industrial chemical is only moderately toxic with a toxicity rating of 3. Symptoms of pyridine poisoning include anorexia, nausea, fatigue and, in cases of chronic poisoning, mental depression.

3.2.2 Nitro Compounds

The simplest of the nitro, compounds, nitro methane H_3CNO_2 , is an oily liquid that causes anorexia, diarrhea, nausea, and vomiting, and damages the kidneys and liver, Nitrobenzene, a pale yellow, oily liquid with an odour of bitter almond or shoe polish, can enter the body by all routes. It has a toxic action much like that of aniline; converting haemoglobin to met- haemoglobin, which cannot carry oxygen to the body tissue.

3.2.3 Nitrosamines

Nitroso compounds (nitrosamines) contain the N-N=O functional group and have been found in a variety of materials to which humans may be exposed including beer, whiskey, and cutting oils used in machining. Cancer may result from exposure to a single large dose or from chronic exposure to relatively small doses of some nitrosamines.

3.2.4 Isocyanates Methyl Isocyanate

Compounds with the general formula R-N=C=O , isocyanates, are widely used industrial chemicals noted for the high chemical and metabolic reactivity of their characteristic functional group. Methyl isocyanate, $\text{H}_3\text{C-N=C=O}$, was the toxic agent involved in the catastrophic industrial poisoning in Bhopal. India, on December 2, 1984, the worst industrial accident in history. In this incident several tons of methyl isocyanate was released, killing 2000 people and affecting about 100,000 others. The lungs of victims were attacked; survivors suffered long-term shortness of breath and weakness from lung damage, as well as numerous other toxic effects including nausea and bodily pain.

3.2.5 Organonitrogen Pesticides

Pesticidal carbamates are characterised by the structural skeleton of carbamic acid. Widely used on lawns and gardens, insecticidal carbaryl has a low toxicity to mammals. Highly water soluble carbofuran is a systemic insecticide in that it is taken up by the roots and leaves of plants; insects that feed on the leaves are poisoned. The toxic effects on animals of carbamates are due to the fact that they inhibit acetylcholinesterase directly without the need to first undergo biotransformation. This effect is relatively reversible because of metabolic hydrolysis of the carbamate ester.

Paraquat is a systemic poison that affects enzyme activity and is devastating to a number of organs. Pulmonary fibrosis results in animals that have inhaled paraquat aerosols and the lungs are also adversely affected by non-pulmonary exposure. Acute exposure may cause variations in the levels of catecholamine, glucose, and insulin. The most prominent initial symptom of poisoning is vomiting, followed, with a few days, by dyspnea, cyanosis, and evidence of impairment of the kidneys, liver, and heart. Pulmonary fibrosis, often accompanied by pulmonary edema and haemorrhaging, is observed in fatal cases.

3.2.6 Alkyl Halides

The toxicities of alkyl halides, such as carbon tetrachloride, CCl_4 , vary a great deal with the compound. Most of these compounds cause depression of the central nervous system, and individual compounds exhibit specific toxic effects.

CCl_4 is a systemic poison that affects the nervous system when inhaled, and the gastro-intestinal tract, liver, and kidneys, when ingested. The biochemical mechanism of carbon tetrachloride toxicity involves reactive radical species. The most damaging of such reaction occurs in the liver.

4.0 CONCLUSION

This unit has treated the toxicological effects of some common organic compounds such as methanol, ethanol, benzene, amines and some aromatic organic compounds. You should, by now, be able to describe the toxic effects of methanol, ethanol, amines, alkanes, pyridine and aniline.

5.0 SUMMARY

This unit has focused on the toxicological effects of alcohols, alkanes, amines, organic halide compounds and some aromatic organic compounds on organs of the body.

6.0 TUTOR-MARKED ASSIGNMENT

1. List three alcohols that are toxic to the organs in the human body.
2. Mention five organic compounds that are potentially toxic to human body.

7.0 REFERENCES/FURTHER READINGS

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

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UNIT 2 TERATOGENESIS, MUTAGENESIS, CARCINOGENESIS AND EFFECTS ON THE IMMUNE AND REPRODUCTIVE SYSTEMS

CONTENTS

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main Content
 - 3.1 Teratogenesis
 - 3.2 Mutagenesis
 - 3.3 Carcinogenesis
 - 3.3.1 The Carcinogenic Process
 - 3.4 Immune System Response
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Readings

1.0 INTRODUCTION

This unit discusses the interference of chemicals with the human body; teratogenesis, mutagenesis, carcinogenesis and effects of chemicals on the immune and reproductive systems. The unit will help you to acquire basic knowledge on cancer and the effects of foreign chemicals (xenobiotic) on immune and reproductive systems.

2.0 OBJECTIVES

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

- explain teratogenesis, mutagenesis and carcinogenesis
- mention the process that are involved in tumour and cancer development.

3.0 MAIN CONTENT

3.1 Teratogenesis

Teratogenes are chemical species that cause birth defects. These usually arise from damage to embryonic or foetal cells. However, mutations in germ cells (egg or sperm cells) may cause birth defects, such as Down's syndrome.

The biochemical mechanisms of teratogenesis are varied. These include enzyme inhibition by xenobiotics; deprivation of the foetus of essential substrates, such as vitamins; interference with energy supply; or alteration of the permeability of the placental membrane.

3.2 Mutagenesis

Mutagens alter DNA to produce inheritable traits. Although mutation is a natural process that occurs even in the absence of xenophobic substances, most mutations are harmful. The mechanisms of mutagenicity are similar to those of carcinogenicity, and mutagens often cause birth defects as well. Therefore, mutagenic hazardous substances are of major toxicological concern.

To understand the biochemistry of mutagenesis, it is important to recall that DNA contains the nitrogenous bases adenine, guanine, cytosine, and thymine. The order in which these bases occur in DNA determines the nature and structure of newly produced RNA, a substance generated as a step in the synthesis of new proteins and enzymes in cells. Exchange, addition, or deletion of any of the nitrogenous bases in DNA alters the nature of RNA produced and **can endanger vital** life processes, such as the synthesis of an important enzyme. This phenomenon

3.3 Carcinogenesis

Cancer is a condition characterised by the uncontrolled replication and growth of the body's own somatic cells. Carcinogenic agents may be categorised as follows:

1. Chemical agents, such as nitrosamines and polycyclic aromatic hydrocarbons;
2. Biological agents, such as viruses or retroviruses;
3. Ionizing radiation such as X-rays and
4. Genetic factors such as selective breeding.

However, in some cases, cancer is the result of the action of synthetic and naturally occurring chemicals. The role of xenobiotic chemicals in causing cancer is called chemical carcinogenesis. It is often regarded as the single most important facet of toxicology and is clearly the one that receives the most publicity.

Chemical carcinogenesis has a long history. Around 1900 a German surgeon, Ludwig Rehn, reported elevated incidences of bladder cancer in dye workers exposed to chemicals extracted from coal-tar; 2-naphthylamine was shown to be responsible. Other historical examples of carcinogenesis include observations of cancer from tobacco juice

(1915), oral exposure to radium from painting luminescent watch dials (1929), and tobacco smoke (1939), asbestos (1960).

Large expenditures of time and money on the subject in recent years have yielded a much better understanding of the biochemical bases of chemical carcinogenesis. The overall processes for the induction of cancer may be quite complex, involving numerous steps.

3.3.1 The Carcinogenic Process

It is now generally recognised that cancer is multistage processes, with at least three easily recognisable stages :

1. Initiation
2. Promotion
3. Progression

The first stage, initiation stage, is a rapid, irreversible change which is believed to involve a change in genetic material of the cell.

Promotion is the second stage of the carcinogenic process. This stage is characterised by an alteration in the genetic expression, and the growth of the clone from the initiated cell. Promoters can act in several ways and lead to several effects.

Progression is the stage in which the neoplastic (cancerous) cells become a malignant tumour and may involve changes in the phenotype. This is characterised by changes in the number and/or arrangement of chromosomes. The result is an increased growth rate, invasion of healthy tissues and formation of metastases.

3.4 Immune System Response

The immune system acts as the body's natural defense system to protect it from xenobiotic chemicals; infectious agents, include viruses or bacteria and neoplastic cells, which give rise to cancerous tissue. Adverse effects on the body's immune system are being increasingly recognised as important consequences of exposure to hazardous substances. Toxicants can cause immunosuppression, which is the impairment of the body's natural defense mechanisms. Xenobiotics can also cause the immune system to lose its ability to control cell proliferation, resulting in leukemia or lymphoma.

Another major toxic response of the immune system is allergy or hypersensitivity. This kind of condition results when the immune system overreacts to the presence of a foreign agent or its metabolites in a self-

destructive manner. Among the xenobiotic materials that can cause such reactions are beryllium, Chromium, nickel, formaldehyde, some kinds of pesticides, resins, and plasticisers.

4.0 CONCLUSION

This unit has dealt with mutagenesis, teratogenesis, carcinogenesis and effects of chemicals on the reproductive system. You should by now be able to explain the terms mutagenesis, teratogenesis and carcinogenesis. You should also be able to explain the processes that are involved in cancer and tumour development.

5.0 SUMMARY

This unit has focused on different types of toxic responses such as teratogenesis, mutagenesis and carcinogenesis. Cancer is the unrestrained, malignant proliferation of somatic cell. Cancer is also a multistage process, involving three stages; initiation, promotion and progression.

6.0 TUTOR-MARKED ASSIGNMENT

1. List the different types of toxic responses caused by chemicals.
2. Mention the stages in carcinogenic process.
3. What do you understand by the term teratogenesis?

7.0 REFERENCES/FURTHER READINGS

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UNIT 3 PESTICIDES

CONTENTS

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main content
 - 3.1 History of Pesticides
 - 3.2 Definition of Pesticides
 - 3.3 Toxicity of Pesticides
 - 3.4 Basic Classes of Pesticides
 - 3.4.1 Insecticides
 - 3.5 Pyrethroid Insecticides
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1.0 INTRODUCTION

Unit 3 explains the toxicology of pesticides. It also introduces you to the groupings of insecticides, rodenticides and acaricides.

2.0 OBJECTIVES

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

- trace the history of pesticides
- define the term pesticide
- identify the different classes of pesticides
- show that some pesticides are very acutely toxic in humans
- explain that the toxicity of herbicides in mammals is generally low, but specific compounds show high toxicity due to their unique structure
- explain that the acute toxicity of fungicides is generally low in mammals; however, health effects have been observed in cases of human exposure.

3.0 MAIN CONTENT

3.1 The History of Pesticides

1000 BC	The Chinese used sulphur as a fumigant
1800s	Europeans used sulphur as a fungicide to control powdery mildew on fruit
2001	Sulfur still in use in California till today
16 th century	The Japanese mixed poor quality whale oil with vinegar to spray on rice paddies to prevent development of insect larvae by weakening the cuticle
17 th century	Water extract of tobacco leaves was sprayed on plants to kill insect.
19th Century	<ol style="list-style-type: none"> 1. Insecticides isolated from plants included rotenone from the root of <i>derris elliptica</i> and <i>pyrethrum</i> extracted from flowers of chrysanthemums. 2. Arsenic trioxide was used as a weed killer, especially dandelions. 3. Copper arsenite (Paris green) was used for control of Colorado beetle. 4. Bordeaux mixture (copper, sulphur, lime and water) was used to combat vine downy mildew.

In the 19th century a number of metal compounds were found to be useful for controlling insects and mildew.

The key to a good pesticide is to find a chemical that selectively kills the unwanted plant, animal or fungus without causing damage to the surrounding environment. Sulphur has been used in many ways over the past 3000 years. Many other pesticides were obtained from plant materials.

3.2 Definition of Pesticides

Pesticides are chemicals that are used to kill pests. For example,

1. Insecticides target harmful or destructive insects
2. Herbicides target weeds
3. Fungicides target fungi
4. Rodenticides target rodents
5. Acaricides target acarose (mites)

Toxicity to humans can vary widely within each group because chemical structures differ within the categories as well as between categories.

Different pesticides have been developed over the years, some of which are highly toxic to human while others have relatively low toxicity. Pesticides can be marketed under different trade names; it is therefore often difficult to recognise which class a specific pesticide belongs to without reading the fine print on the label.

3.3 Toxicity of Pesticides

There are many pesticides in use with very different modes of action and levels of toxicity.

When considering the toxicity of pesticides, it is important to remember that these chemicals were developed to kill organisms, and thus they are inherently acutely toxic. To protect the public, WHO developed a hazard classification system which was used to label all pesticides containers to warn users of the acute hazards associated with each product? This hazard system was based on the LD₅₀ for the pesticides in rats under either oral or dermal exposure conditions.

Table 1 The WHO Recommended Classification of Pesticides by Hazard

		LD ₅₀ for the rat (mg/kg body weight)			
		Oral		Dermal	
Class		Solids	Liquids	Solids	Liquids
1a	Extremely hazardous	≤ 5	≤ 20	≤ 10	≤ 40
1b	Highly hazardous	5-50	20-200	10-100	40-400
II	Moderately hazardous	50-500	200-2000	100-1000	400-4000
III	Slightly hazardous	>500	>2000	>1000	>4000
III+	Unlikely to present hazard in normal use	>2000	>3000	-	-

Source: From Copplestone, 1988

Pesticide poisonings do occur as a result of accidental exposures in pesticide application or in agricultural workers. Dose is an important factor in determining the severity of the response.

3.4 Basic Classes of Pesticides

Insecticides

Organochlorines	Fungicides
Organophosphates	Hexachlorobenzene
Carbamates Esters	Organomercurials
Pyrethroids	Pentachlorophenol
Botanical Insecticides	Phthalimides
	Dithiocarbamates

Herbicides

Chlorophenoxy Compounds	Fumigants
Bipyridyl derivatives	Phosphine
	Ethylene dibromide
	Dibromochloropropane

Rodenticides

- Zinc Phosphide
- Fluoroacetic acid and derivatives
- α -Naphthyl Thiourea (ANTU)
- Anticoagulants

Insecticides can be divided into three main groups: the organochlorines, the acetylcholine sterases and the pymethrins (or natural) insecticides. New generation pesticides are also being designed which target systems that are specific to insects in order to make these more selectively toxic.

3.4.1 Insecticides

Insecticides act by poisoning the nervous system of target organisms-including man if dose is sufficiently high.

The basic mechanisms of action for most pesticide is an alteration in the transfer of a signal along a nerve fibre and across the synapse from one nerve to another or from a nerve to a muscle fiber. The transfer of a signal along a nerve occurs by changes in the electrical potential across the nerve cell membrane which is created by the movement of ions in and out of the cell. At the terminal end of a nerve, the signal is transferred across the synapse to the next nerve cell of a nerve of neurotransmitters such as acetylcholine (ACH). Different classes of pesticides inhibit this process in different ways, but the end result is an alteration in normal nerve signal propagation.

Organochlorine pesticides act primarily by altering the movement of ions across the nerve cell membrane, thus changing the ability of the nerve to fire.

Organophosphate and carbamate pesticides act primarily at the synapses, altering the regulation of the transmission of the signal from one cell to the next.

There are three major classes of organochlorine insecticides. All of these are organic compounds with chlorine (Cl) atoms attached to the ring structures. The Cl atoms prevent the organic compounds from being rapidly degraded in the environment, thus these pesticides “persistent” and are active for long periods of time after application.

Table 2: Categories of organochlorine pesticides and toxic potential

DDT and analogues	Low to moderate
DDT	Low
Methoxychlor	
Benzene hexachloride	
Gamma-hexachlorbenzene (Lindane)	Moderate
Cyclodienes and related compounds	
Aldrin	High
Chlordane	Moderate
Chlordecone (kepone)	Moderate
Dieldrin	High
Endosulfan (Thiodan)	High
Endrin	High
Heptachlor	Moderate
Isobenzan	High
Mirex (Dechlorane)	Low
Toxaphene and related compounds	
Toxaphene	Moderate

The acute toxicity of the different organochlorine pesticides differs significantly. This information is important for pesticide applicators and agricultural workers.

Organochlorine: DDT

DDT, (1,1,1-trichloro-2,2-bis (P-chlorophenyl) ethane)

- First synthesised in 1874
- Used to kill moths and carpet beetles in 1939
- Used on humans to control typhus epidemic by killing lice in Italy in winter of 1943-1944.
- Used extensively from 1940s to 1960s in agriculture and forestry, building and structural protection from termites, and disease prevention in humans.

DDT is one of the most well known organochlorine pesticide and is also one of the oldest.

Mammalian Toxicity of DDT

- DDT is a Class II Pesticide: Oral LD₅₀ is 250mg/kg
- As little as 10mg/kg will produce signs of poisoning in man.
- DDT causes repetitive discharge of axonal action potentials in response to a single stimulus.

The WHO has designated DDT as a Class II pesticide based on its LD₅₀ of 250mg/kg. The mechanism by which DDT causes neurotoxicity is well studied. This is by causing repetitive discharge of nerve cells; the cells eventually are unable to fire in response to a signal.

Organochlorine Toxicity

- DDT produces tremors and incoordination at low doses and convulsions at higher doses through effects on Na channels.
- HCH and cyclodienes produce convulsions as first sign of intoxication and fever, through a central nervous system effect.

The tremors and coordination produced by DDT exposure results from the repetitive discharge (over-firing) of the nerves. The additional effects seen in HCH and cyclodiene exposures may involve a mechanism of action of these pesticides at the synapses

Effects of chronic exposures to organochlorine insecticides are difficult to identify because they are general nervous system alterations that can occur through many causes.

The carcinogenicity of organochlorine insecticides is not well established. There have been some epidemiological studies in agricultural workers that suggest an association between organochlorine pesticide uses and non- Hodgkin's lymphoma, but the studies are not robust.

As mentioned previously, the Cl atoms on the organic moieties in the OC pesticides make these compounds very stable in the environment. This persistence can be advantageous for the control of pests such as termites around buildings. The lack of biodegradation and the high lipid solubility of these OC pesticides, however, has led to problems of accumulation of these compounds in animal tissues. In fish, for example, the concentrations of chlordane are much higher in fish tissues than they are in the water in which the fish are living. This is called bioconcentration. Because OC compounds are not metabolised and

excreted by the fish, they “biomagnify” up the food chain, which means that larger, older fish have higher body burdens of OC pesticides than smaller fish. These smaller fish have higher concentrations than the food sources, the zooplankton. Birds that eat fish have been shown to have very high concentrations of OC pesticides such as DDT in their tissues.

Ecological effects: Interference with reproductive system of organisms high on the food chain, especially fish-eating birds (Osprey, Pelicans, falcons and eagles).

Ortho and para isomers of DDT have estrogenic effects competing with estradiol for binding to estrogen receptors in uterin cytosol.

Estrogenic and enzyme-inducing properties of DDT cause changes in steroid metabolism, alters ability of birds to mobilise Ca to produce strong egg shells.

Thus, these persistent chlorinated compounds can cause adverse health effects in organisms that are high in the food chain, such as birds.

Organochlorine pesticides have been banned in North America and Europe, but still in use in developing countries because they are:

- inexpensive to manufacture
- highly effective
- relatively safe to humans
- Risk/benefit weighted in favour of control of insects for better food production and disease control in developing countries.

Acetylcholinesterase inhibitors:

- Organophosphates and carbamates

Degrade relatively rapidly in the environment, but Class 1 in toxicity rating in humans.

Many fatal poisonings were recorded in 1950s as parathion replaced DDT due to improper training of pesticide applicators.

The organophosphate and carbamate insecticides which were developed to replace the organochlorine insecticides, breakdown in the same mechanism or more quickly. These two classes of insecticides have the same mechanism of action: they inhibit the enzyme, acetylcholinesterase, which breakdown the neurotransmitter, acetylcholine. These insecticides have less of an ecological impact due to their rapid breakdown after application. They are, however, much more toxic to humans. They are classified as Class 1 pesticides

(extremely hazardous) by WHO based on their LD₅₀ values (see WHO Classification chart) while the OC pesticides are generally Class 11.

The active part of the OP (organophosphate) insecticides is the phosphate group sharing a double bond with either an oxygen or a sulphur group. The carbamate active moiety is the carbamate ester shown in this slide.

In order to understand the mechanism of action of these OP and carbamate insecticides, we need to review the role of neurotransmitters in normal nervous system function. Remember that there are small molecules (such as acetylcholine, glutamate, and (GABA) that are released from the presynaptic neuron that interact with the nerve impulse to then travel down the second nerve axon. When these transmitters are released, the postsynaptic nerve fires until the transmitter molecules in the synapse are degraded. Acetylcholine, a major neurotransmitter in animals, is normally rapidly deactivated by an enzyme called acetylcholinesterase.

Both OP and carbamate insecticides bind to the active site and inhibit the action of acetylcholinesterase as mentioned. When this happens, the acetylcholine remains in the synapse and the nerves continue to be stimulated for much longer periods of time than they normally would.

3.5 Pyrethroid Insecticides

Pyrethroids fall into two categories based on their acute toxicity:

- Type 1 Peripheral CNS effects
- Type 11 Primarily CNS effects

A third, newer class of insecticides is the synthetic pyrethroids. These were developed because of their toxicity than OP and carbamates. These chemicals alter normal neuronal function by inhibiting ion movements across the nerve cell membrane, alterations in intracellular calcium ion concentrations and possibly by binding to GABA receptors.

Synthetic pyrethroids that were available in the 1980s rapidly accounted for 30% of the worldwide market due to lower toxicity. It replaced natural pyrethroid preparations which often caused allergic reactions such as contact dermatitis or asthma.

Human toxicity:

- Cutaneous paresthesia observed in workers spraying V-cyano type pyrethroid. Stinging or burning sensation on skin, progressing to tingling and numbness lasting 12-18 hours.
- Occupational exposure has resulted in dizziness in addition to burning skin. At higher doses, can lead to convulsions and loss of consciousness. Seizures can last up to 2 to 3 weeks.

Although less toxic to humans, exposures to pyrethroid insecticides can cause peripheral effects at low doses and central nervous system effects at higher doses.

The lower toxicity of pyrethroid insecticides is due in large part to their rapid metabolism by non-specific carboxyl esterases.

3.6 Botanical insecticides

Nicotine	Sold as Black Leaf 40 Extremely toxic: Oral LD ₅₀ is 50-60 mg/kg Is readily absorbed through skin Mimics the action of acetylcholine
Rotenone	Isolated from derris root Toxicity varies greatly in different species Very toxic to fish – used to paralyze fish for capture and consumption Blocks nerve conduction by inhibiting electron transport in mitochondria Low acute toxicity in humans, but causes allergic reactions.

Other insecticides that have been derived from plants include nicotine from tobacco leaves. Unlike the botanical pyrethroids, nicotine is extremely toxic to humans. Rotenone is very toxic to fish as well as insects, but is relatively low in toxicity in humans.

3.7 Herbicides

- Generally low toxicity to mammals.
- Mechanisms of action toward plants primarily involve phyto-processes.
- Can be dermal irritants
- Can cause contact dermatitis in sub-populations of sensitive people.

Because the physiology of plants is so different from that of animal physiology, it is possible to design herbicides with toxicity in humans.

Chlorophenoxy Compounds: Mimic the action of auxins, plant hormones that stimulate growth.

Chlorophenoxy herbicides such as 2,4-D and 2,4,5-T kill plants by over stimulating growth. The primary risk associated with 2,4-D and 2,4,5-T was due to the presence of small amounts of dioxin compounds such as 2,3,7,8-TCDD which are formed during the production process. 2,3,7,8-TCDD is a known carcinogen and developmental toxin. Agent Orange, used during the Vietnam War, was a mixture of 2,4-D and 2,4,5-T which was shown to contain 2,3,7,8-TCDD. Studies of Vietnam soldiers have shown an association between exposure to Agent Orange and incidence of Non-Hodgkin's lymphoma, Hodgkin's disease, soft-tissue sarcoma and chloracne. Newer processing methods for chlorophenoxy herbicides have decreased the formation of dioxin by-products.

Paraquat is a herbicide that is much more acutely toxic in humans than most other herbicides. It is a specific pulmonary toxicant because it is selectively accumulated by alveolar cells in the lung by a specific diamine/polyamine transport system. Once in the alveolar cells, paraquat is metabolised to a reactive free radical compound. Diquat, though similar in structure, is not transported by the diamine transport system into the cells.

3.8 Fungicides

Acute toxicity generally very low in mammals: LD₅₀ range from 800-10,000 mg/kg. However, most (>90%) fungicides test positive in mutagenicity assays, raising concerns about carcinogenicity.

Most cases of human poisonings have resulted from consumption of feed grain. Ingestion of hexachlorobenzene, for example, caused "black sore" syndrome in Turkey. This syndrome was characterised by dermal blistering and epidermolysis, infection with pigmented scars and photosensitivity.

Although acute toxicity from most fungicides is not a great concern, chronic exposures to lower concentrations can cause adverse health effects. Though not well characterised in human, fungicides have the potential to be carcinogenic based on their mutagenic activity. There have also been case reports from the consumption of fungicides when treated grains were ingested by accident. Hexachlorobenzene studies in rats also provide evidence of immunosuppression and dose-dependent

increase in hepatic and thyroid tumours. Also perinatal exposure causes enlarged kidneys, hepatomegaly and possible immune system effects.

Organomercurials: Used to treat seed grain

Peripheral and central nervous system effects seen in two cases:

- Iraq – people consumed seed grain
- New Mexico – people consumed meat from hogs fed treated grain

As discussed in the lecture on mercury, organomercurials used as fungicides have been consumed accidentally through the misuse of treated seed grain. To help prevent this in the future, organomercurial fungicide preparations now include a bright pink dye to show that the seed has been treated.

Phthalimides:

- Low acute toxicity, but similar in structure to thalidomide
- Captan is a weak initiator of benign squamous cell paillomas

Dithiocarbamaes:

- Low acute toxicity, but teratogenic and causes tumours in animals.
- Suggestion that exposure can cause Parkinson-type syndrome. Possible breakdown to carbon disuphide which is a known neurotoxicant.

The toxicity of other fungicides has also been studied in animals. The toxicity of most fungicides is generally unique since the structures of these compounds vary significantly.

4.0 CONCLUSION

This unit has dealt with the history, and the toxicology of pesticides. It has also show that pesticides include the broad groupings of insecticides, herbicides, fungicides, rodenticides and acaricides.

You should be able to trace the history of pesticides and explain the term “pesticides” and grouping of pesticides. Also, you should be able to explain the mechanism of action of different classes of pesticides.

5.0 SUMMARY

This unit has introduced you to the history, definition and toxicology of pesticides. The term “pesticides” includes chemicals that are insecticides, herbicides, fungicides and rodenticides. There are many different classes of pesticides with different structures, mechanisms of action and levels of toxicity.

There are large numbers of different types of pesticides which differ in their mechanisms of action. Some pesticides are very acutely toxic in humans, while others have low acute toxicity but may cause long-term health effects in chronically exposed individuals.

Each pesticide class has to be considered individually when predicting effects

6.0 TUTOR-MARKED ASSIGNMENT

1. Explain the term “pesticides”.
2. Biochemically, what do organophosphosphate esters such as parathion do that could classify them as “nerve poisons”?

7.0 REFERENCES/FURTHER READINGS

Katherine Squibb, *Applied Toxicolot.* (NURS 735) Pesticides.