NATIONAL OPEN UNIVERSITY OF NIGERIA

ESM 231

Introductory Toxicology

Module 2

ESM 231 Introduction to Toxicology
Module 2

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Module 2

Unit 1 Toxic Organic Compounds

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 characterized 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 clothing (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, heamoglobin, and hematocrit in individuals exhibiting enteric susceptibility to these conditions. Naphthalene causes skin irritation or severe dermatitis in sensitized 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 irons (I) in haemoglobin to iron (III). This causes a condition called methemoglobinaemia, characterized 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, H_3C-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 characterized 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 acetylcholinestrase 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, $CC1_{4,}$ 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 Self-Assessment Exercise

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 Reading

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

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

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

Unit 2 Teratogenesis, Mutagenesis, Carcinogenesis and Effects on the Immune And Reproductive Systems

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, cyutonine, 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 characterized by the uncontrolled replication and growth of the body's own somatic cells. Carcinogenic agents may be categorized 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-naphthalamine 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 recognized that cancer is multistage processes, with at least three easily recognizable stages:

- Initiation
- Promotion
- 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 characterized 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 characterized 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 recognized 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 pestricides, resins, and plasticizers.

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.

60 Self-Assessment Exercise

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 Reading

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

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Unit 3 Pesticides

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

16th 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

17th century Water extract of tobacco leaves was sprayed on plants to kill insect.

19th Century:

- Insecticides isolated from plants included rotenone from the root of *derris eliptica* and *pyrethrum* extracted from flowers of chrysanthemums.
- Arsenic trioxide was used as a weed killer, especially dandelions.
- Copper arsenite (Paris green) was used for control of Colorado beetle.
- 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,

- Insecticides target harmful or destructive insects
- Herbicides target weeds
- Fungicides target fungi
- Rodenticides target rodents
- 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 recognize 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 LD_{50} 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
- Organophosphates
- Carbamates Esters
- Pyrethroids
- Botanical Insecticides

Fungicides

- Hexachlorobenzene
- Organomercurials
- Pentachlorophenol
- Phthalimides
- Dithiocarbamates

Herbicides

- Chlorophenoxyl Compounds
- Bipyridyl derivatives

Fumigants

- Phosphine
- Ethylene dibromide
- Dibromochloropropane

Rodenticides

- Zinc Phosphide
- Fluoroacetic acid and derivatives
- α-Napthyl 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 are 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.

Organophosophate 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 pesticides and is also one of the oldest.

Mammalian Toxicity of DDT

- DDT is a Class II Pesticide: Oral LD_{50} 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 LD_{50} 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, have 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 metabolized 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 mobilize 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 I 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 I pesticides (extremely hazardous) by WHO based on their LD_{50} values (see WHO Classification chart) while the OC pesticides are generally Class II.

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 Inseticides

Pyrethroids fall into two categories based on their acute toxicity:

Type I	Peripherial 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 tocicity 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.

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

Chorophenoxy 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 metabolized 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: LD_{50} 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 characterized by dermal blistering and epidemiolysis, infection with pigmented scars and photosensivity.

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 Self-Assessment Exercise

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

7.0 Reference/Further Reading

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