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REVIEW OF MECHANISM AND TOXICITY OF INSECTICIDES

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ABSTRACT

Insecticides are chemical substances that are widely used to kill insects in both Developing and Developed countries. African countries have also seen an increase in the use of these chemicals in order to increase yield of their crops and help improve their life. There are a number of insecticides that humans get exposed to as they operate in the anthroposphere. Most of them belong to some classes such as; Organophosphorus, Organochlorines, Carbamates, Neonicotinoids, and Pyrethroids.This classification is based on the chemical composition that members belonging to the class have. Each of these classes has individual members that when exposed to induce poisoning differently and they belong to different toxicological classes such as, extremely toxic, highly toxic, moderately toxic, slightly toxic and those that are unlikely to produce toxic effects. These chemical substances enter the body through inhalation, contact with the body where they are absorbed, ingestion in foods or accidentally drinking the chemical substance thinking it is a drink. They can also enter the body through the eyes and ears depending on the exposure. While in the body they bind to receptors which are mostly enzymes and proteins and transported to various organs where they cause acute toxicity and chronic toxicity. Tissue fluid, blood and lymph are also involved in their transport throughout the body. When humans get exposed and quickly report to the health facilities antidotes such as atropine, pralidoxime and Naloxone are used depending on which type. However, when the source is known toxicological risk assessment should be performed, the process of which involve identification of hazard, Dose-response assessment, Exposure assessment and finally risk characterization.

Key words: Insecticides, Mechanism of action, Health effects, Treatment, Toxicological Risk assessment

1.O. INTRODUCTION.

Increase in population of the world has led to development of the strategies that could help in coping up with the rising demand for food as a result of rising population. This has led to increase in the development of pesticides to assist in controlling insects and other organisms that are so destructive and interfere with the growth of different crops. Among the pesticides are the insecticides, fungicides, acaricides, Bactericides antivirals, growth regulators and many others though this chapter will focus much on insecticides. Despite helping in making sure that food is produced and the quality of life is improved, these chemical substances have negative effects to the environment and to the people who handle them and eat the food they produce. The effects of the mixtures and their mode of action in humans is a matter of continuous research up to now. The majority of insecticides are potentially toxic to organisms and human beings are not spared. Some being connected to disease development. In this milieu, the increase of chronic degenerative disease including cancer in humans, is of considerable concern [1]. Chemically insecticides may fall into Organochlorines containing chlorine molecule, Organophosphorus containing phosphorous element, Carbamates derived from Carbamic acids, neonicotinoids derived from nicotinic acids, Pyrethoids from pyrethrum plant and many others derived from inorganic elements such as Aluminium, Arsenic and mercury. While their use improves the quantity of agricultural products and human life, the health effects they cause is a matter of concern to almost everyone.

2.0. MATERIAL AND METHODS

The study **Design** that was used was Bibliographic review of the published studies on the mechanism and toxicity of insecticides. The study setting was Isoka district of Zambia. The **Inclusion criteria** in the study was all the publications covering mechanism and toxicity of insecticides Globally, in Africa and within Zambia. **Data extraction** was by means of comprehensive search on the following sites:www2.epa.gov, www.ncbi.nih.gov, mafiadoc.com, www.scribd.com, webcachegoogleusercontent.com, edis.ifas.ufi.edu, www.epa.gov, audre4088.blogspot.com, www.science.gov, pubs.rsc.org, www.docme.ru, PubMed, science citation Index. The World Health Organisation mechanism of action of insecticides (MOA) framework for data extraction and synthesis was used. Data was **analyzed** according to the toxicity issues, clinical effects of insecticides poisoning, year of publication and focus of the studies.

2.1.HOW INSECTICIDE TESTS ARE DONE ON PEOPLE.

When people are exposed to various chemicals that are suspected to be insecticides, various test are conducted depending on the group of insecticide. The table below gives a summary.

Table 1. Tests for detection of insecticides chemicals

chemicals	Primary Detection method	Other options
Organophosphorus	Cholinesterase	Urinary alkyl phosphates
Carbamates	Cholinesterase. (Specialized low dilution method)	Various Urinary metabolites
Pyrethroids	Urinary or serum levels by GC,GLC,HPLC	
Organochlorines	Plasma levels by GC-EC	Fat sampling by GC-EC

2.2. ORGANOPHOSPHOROUS AND MECHANISM OF TOXICITY

Organophosphorus insecticides were once promoted to be more ecological compared to the organochlorines and carbamates. They include variety of insecticides. Among the common members of this family glyphosate is the widely used. The other members of this family include; malathion, parathion and dimethoate, fernithion, diazinon, fenthion, phosalone, dichlorofenthion demton-methyl.

Organophosphorus poison insects and other animals, including birds, amphibians and mammals, primarily by phosphorylation of the acetylcholinesterase enzyme (AChE) at nerve endings. Basically the role of the enzyme is to break the neurotransmitter acetyl choline into choline and acetic acid and prevent its accumulation. Organophosphorus results into a loss of available AChE so that the effector organ becomes overstimulated by the excess acetylcholine.

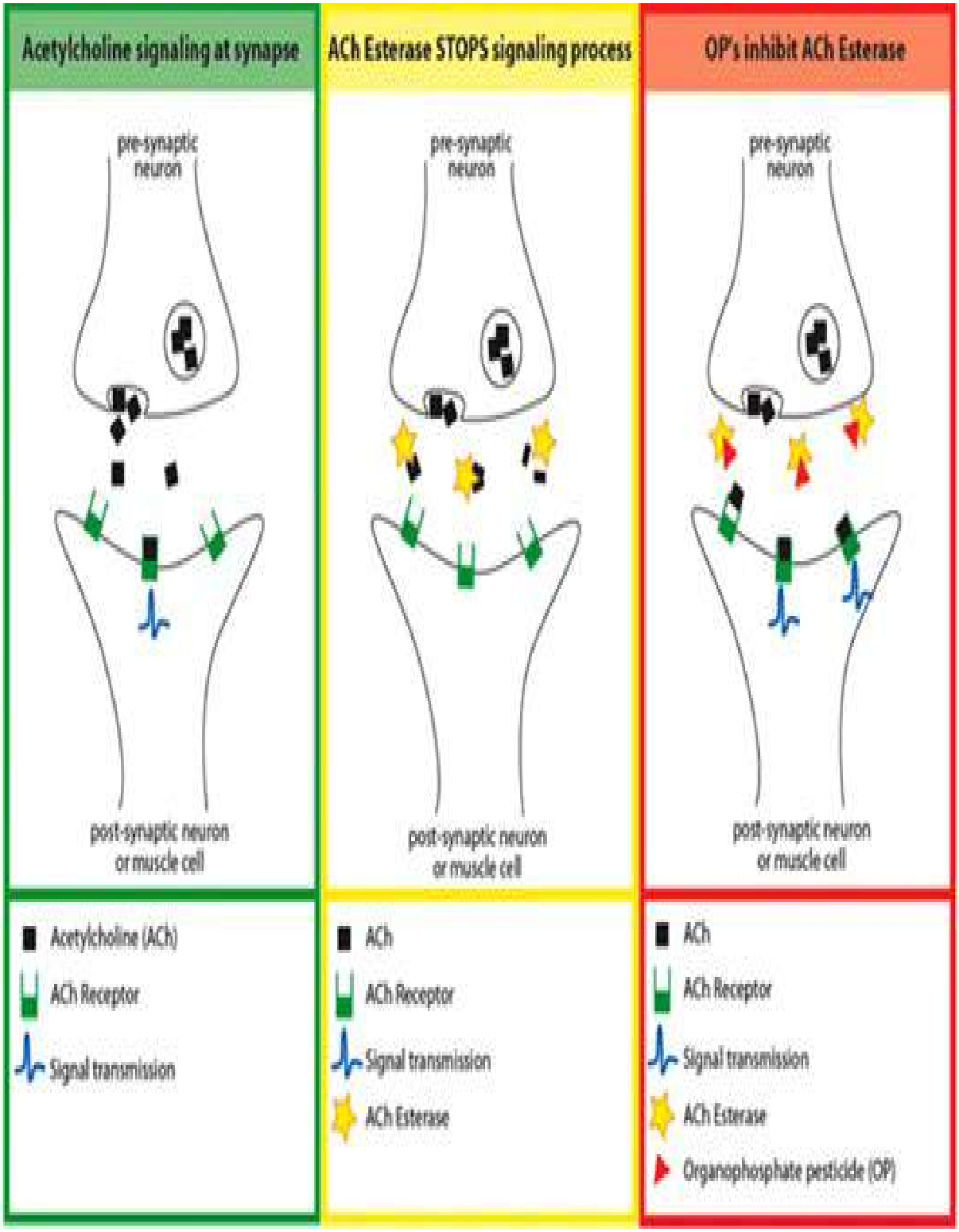

Figure.1. Mechanism of action of Organophosphorus.

EXPLANATION:

Acetylcholine (Ach) represented by **Black** in the diagram is a neurotransmitter that helps in transmission of information from one nerve ending to another. This is produced by pre-synaptic neuron and received by the post-synaptic neuron of the muscle cell.

The post-synaptic neuron has acetylcholine receptors (Ach-receptors) represented by Green on the diagram. As long as there is no enzyme to stop the signaling process, it continues.

The process of signaling is stopped by the Acetylcholine esterase enzyme represented by yellow on the diagram. The enzyme helps in the breaking down of acetylcholine into acetic acid and choline.

The organophosphorus insecticides represented by orange on the diagram binds to the enzyme and prevents it from breaking down the acetylcholine leading to the accumulation of the acetylcholine and therefore the process of signaling continues producing effects in both insects and human beings.

Table.2 signs and management of acute toxicity

Signs and symptoms	Treatment	Contraindications
Tachycardia and bradycardia	Ensure a clear airway	Morphine
Brochospasm and Brochorrhea	Administer atropine sulfate	succinylcholine
Respiratory depression	Administer glycopyrolate	theophylline
Loss of consciousness	Pralidoxime	phenothiazine
Miosis	Decontaminate concurentry	reserpine
Urination		
Diarrhea		
Diaphoresis		
Lacrimation		
Salivation		
CNS Excitation		

When there is no correction of the problem most of the clients develop: Neuromuscular transmission failure, Cardio respiration failure, Weakness of the respiratory muscles and even Death.

TREATMENT

When poisoned by organophosphorus insecticides, treatment can be done by using antagonists such as: Physostigmine and Plalidoxime.

Dosage of Pralidoxime Loading Dose: Adults and children over 12 years: 2.0 gm by intravenous infusion over a 30-minute period. Children under 12 years: 20-50 mg/kg body weight given intravenously (depending on severity of poisoning), mixed in 100 mL of normal saline and infused over 30 minutes.

GENERAL EFFECTS

Most of these chemical substances are known for their effect on the endocrine system where they induce some disrupting effect such as increasing or decreasing the level of the hormones produced by the glands of the endocrine system. This class of insecticides has been associated with effects on the function of cholinesterase enzymes where they bind into the enzyme and prevent it from breaking down acetylcholine into acetic acid and choline, this leads to the accumulation of the acetylcholine brings some excitation effects leading to tremors, convulsions and loss of muscular coordination**.** Organophosphates have been known to cause decrease in insulin secretion and when this happens carbohydrate metabolism disorders manifest. This process typically takes several years and is accompanied by the gradual destruction of β-cells. This might come as a result of chronic exposure to the organophosphates insecticides.

These chemical substances cause disruption of normal cellular metabolism of proteins that results into protein and amino acids metabolism disorders, a good number of other carbohydrates and fat metabolism diseases and also causing genotoxic effects and effects on mitochondrial function that is taken as a power house. Effects on the mitochondria cause cellular oxidative stress. Some of the members of the organophosphorus insecticides display endocrine-disrupting activity that affect human erythrocytes and promote carcinogenicity of the skin. They are considered to cause extreme disruption in shikimate pathway, that is a pathway found in plants and bacteria as well as in human gut bacteria. This disruption may affect the supply of human organism with essential amino acids and this results into amino acids deficient disorders. For example, glyphosates a member of the organophosphorus formulations are considered to be more toxic.

2.3. ORGANOCHLORINES AND MECHANISM OF TOXICITY

Organochlorine insecticides are made Aryls that can be carbocyclic or heterocyclic compounds having chlorine in their structures. There are four (4) classes that exist and these include:

1. DichloDiphenylTrichloroethane(DDT) and their Analogs.

2.Benzene hexachlorides

3.Cyclodiens

4.Toxaphenes.

Some countries have abandoned the use of organochlorines because when used they take long to be degraded or removed from the environment. Further theses class of insecticides have been known to be Endocrine System Disruptors an effect that leads into fertility problems in both males and females in Human beings.

Mechanism of Action

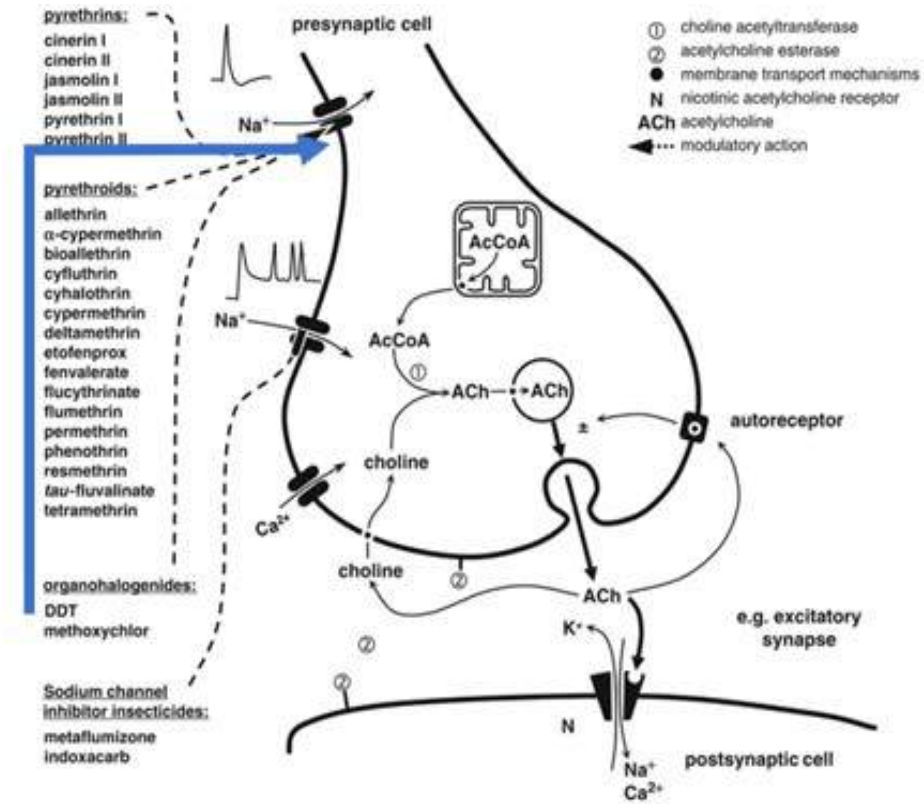

Figure.2. Mechanism of action of Organochlorines

Explanation:

Organochlorines insecticides are known to work by interfering with the inactivation of the sodium channels in the in the excitable membrane. This results into rapid repetitive firing in most neurons. The inhibition of sodium ions and calcium ions prevent the repolarization of the pre-synaptic cell. Acetylcholine then continues to be released.

Table 3. signs, symptoms and management

Signs and symptoms of acute toxicity	Treatment	Contraindicated
Hyperesthesia	Administer oxygen	Epinephrine
Paresthesia	Decontaminate the skin	atropine
Headache and hypertension	Monitor cardiac	Vegetable oil
Dizziness	Monitor pulmonary status	Animal oil
Nausea and vomiting	GI decontamination	atropine
respiratory depression	Administer oxygen	epinephrine
Confusion	Manage convulsions	Vegetable or animal oil
Tremor		

2.4. CARBAMATES AND MECHANISM OF TOXICITY

The class of insecticides called Carbamates are structurally and Mechanistically similar to the organophosphorus insecticides. They are derived from carbamic acid, Aryl and Alkyl ester derivatives of carbamic acid.

Classification by toxicity

These insecticides can be classified into four (4) with some examples as follows

1.Extremely toxic (LD_{50}:1 to 50mg/kg)

2.Highly toxic (LD_{50}: 51 to 500mg/kg)

Examples

Aminocarb, Bendiocarb, Benfuracarb, Carbaryl, Carbofuran, Dimetan, Dimetilan, Dioxacarb, Formetanate,Methiocarb,Methomyl,Oxamyl and Propoxur

3.Moderately toxic (LD_{50}: 501 TO 5000mg/kg

4.Slightly toxic (LD_{50}:5000mg/kg or more.

Examples

Aldicarb, Bufencarb,Isoprocarb and Pirimicarb.

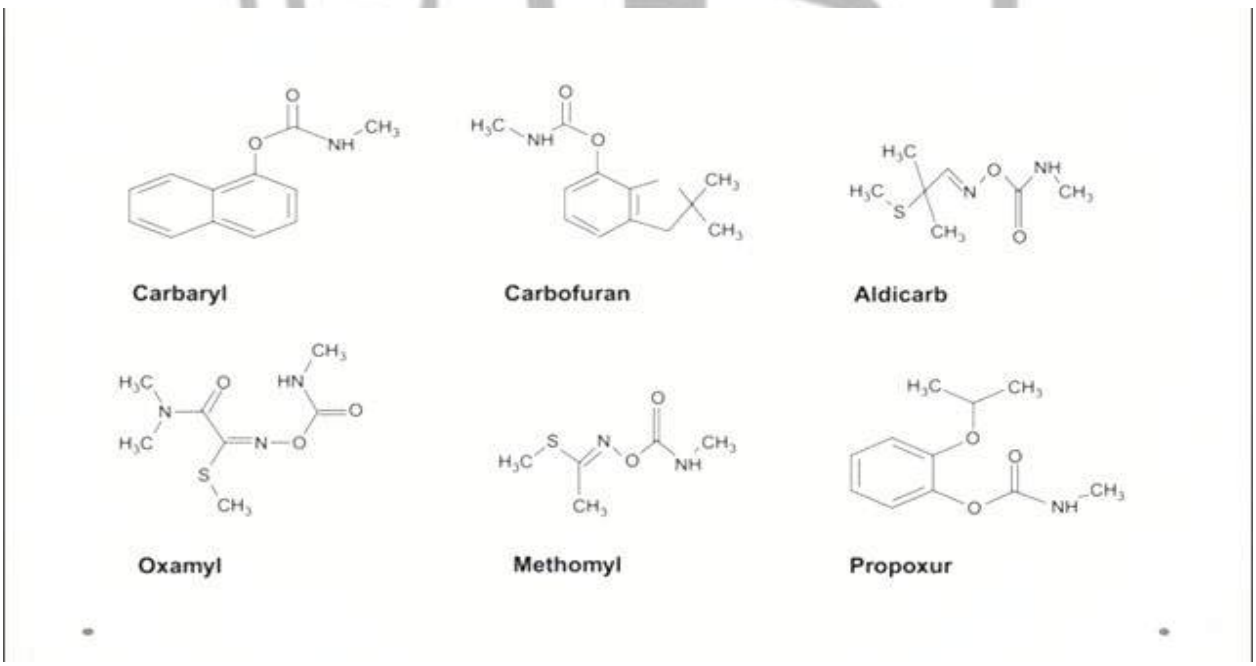

Figure.3. Some examples of members of carbamates

Mechanism of Action

The Mechanism of Action of carbamates is by binding to the enzyme acetylcholinesterase and preventing it from converting Acetylcholine to acetic acid and choline just like the organophosphorus but the difference is that the binding of carbamates is rapidly reversed than that of organophosphorus. Because of this both Mortality and morbidity are limited when we compare with organophosphorus insecticides.

Table 4. Signs, Symptoms and Management of Acute poisoning

Signs and symptoms	Treatment	contraindication
Malaise and muscle weakness	Ensure clear airway	Hypotension
Dizziness and sweating	Administer atropine	Hypotension
Blurred vision	Decontaminate concurrently	Hypotension
Incoordination	pralidoxime	Hypotension
Headache and salivation	Consider GI decontamination	Hypotension
Nausea and vomiting	Administer atropine	Hypotension
Abdominal and diarrhea	GI decontamination	Hypotension
Coma and seizures	pralidoxime	Hypotension
Hypertension	Ensure clear airway	Hypotension
respiratory depression.	Administer atropine	Hypotension

2.5. PYRETHROIDS AND MECHANISM OF TOXICITY

Pyrethroid insecticides are a synthetic alteration of the pyrethrins that are naturally removed from the flowers of chrysanthemum species. Sometimes they are said to be ion channel poisons because they interfere with the way the nervous system work. Mechanism of Action

Pyrethroid insecticides colored purple on top of the sodium channels colored green on the diagram below are sodium channel modulators that work by keeping the sodium channels open. When this happens there is a continuous flow of the sodium ions into the neurons and this results into the disruption of the normal balance of the electrical charges inside the nerve cells. Because there is no change in polarity all the impulses stop and the effect that follows is called paralysis.

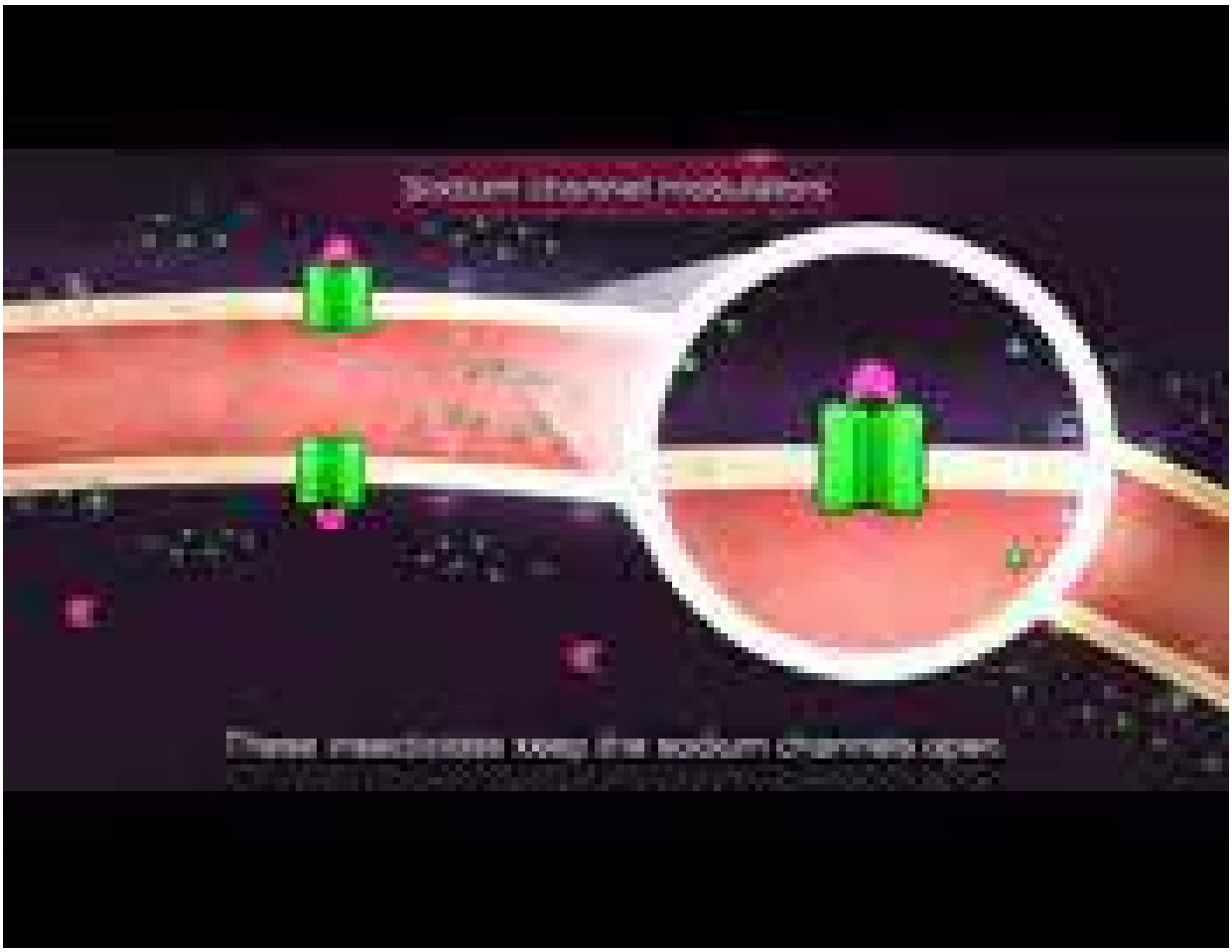

Figure.4. Nerve cell and Pyrethroid insecticide on sodium channels

Table 5. The toxic effects of parathyroid range from mild to moderate to severe.

Mild effects	Moderate effects	Severe effects
Paresthesia	CNS depression	Seizures
Nausea	Increased salivation	Coma
Headache	fasciculation	Pulmonary edema
Vomiting	diaphoresis	Respiratory failure
Dizziness	fever	Convulsions
Fatigue	Blurred vision	Loss of site

2.6. NEONICOTINOIDS

Neonicotinoid insecticides such as imidacloprid, thiacloprid, and guadipyr, are relatively new and also the most extensively used insecticides that were promoted for their low risk for non-target organisms. However, there is plenty of evidence to the contrary that they have effects on bees.

MECHANISM OF TOXICITY

Neonicotinoids elicit toxicity by acting on nicotinic acetylcholine receptors (nAChRs) in exposed organisms [4]. This produces fasculation, sweating, hypertension and tarchycardia in human beings. As agonist-gated ion channels, localized in post-synaptic membranes of neuronal or neuromuscular junctions nAChRs are responsible for rapid excitatory neurotransmission at cholinergic synapses. In vertebrates nAChRs are located in both the central nervous system (CNS) and the peripheral nervous system (PNS). In invertebrates, which display varying degrees of nervous system complexities, nAChRs are either similarly dispersed or exclusively located in diffuse neuropil regions.

Neonicotinoids elicit toxicity by binding to nAChRs and interfering with neural transmission [5]. Normally, nAChRs are activated by the endogenous neurotransmitter acetylcholine (ACh) . Upon ACh binding, nAChRs open ion channels, allowing for an influx of extracellular ions typically sodium (Na+) or calcium (Ca2+) and an efflux of intracellular ions typically potassium (K+), which acts to propagate an action potential in post-synaptic neurons or myocytes. Once the nervous signal is transmitted, acetylcholinesterase (AChE) is released, hydrolyzing ACh at

nAChR surfaces, inhibiting ion flow and terminating impulse transmission at cholinergic synapses. Neonicotinoids have key structural similarities to Ach, nitrogen atoms, and hydrogen bond acceptors, allowing them to bind to the ACh binding site and activate nAChRs . However, these insecticides are not degraded by AChE , thus once bound, neonicotinoids can continuously excite cholinergic neurons, causing a biphasic response. First, neonicotinoid binding excites the cholinergic neuron or myocyte, increasing the frequency of spontaneous discharge, resulting in uncontrollable muscle tremors, cell energy exhaustion, and cell death. This is then followed by neural desensitization to ACh, blocking nerve impulse propagation, resulting in paralysis, loss of normal neuronal or neuromuscular function, and then death. Therefore, following exposure to neonicotinoid, toxicity manifests as seizures, immobility, and then eventual death.

Toxicity of neonicotinoids can also be influenced by metabolic processes. Neonicotinoids are metabolized in two phases. Phase I, carried out by cytochrome P-450 enzymes (CYP 450), involves structural alterations by the process of hydroxylation that involves ring opening or olefin production, demethylation, nitro reduction, cyano-hydrolysis, and dechlorination at multiple sites, either detoxifying the compound or producing metabolites that can be more toxic than the parent compounds for example the metabolism of TMX to CLO [5]. Phase II, carried out by a variety of conjugation enzymes dependent on organism of interest and neonicotinoid of exposure), involves conjugation of the Phase I metabolites, and often leads to the production of less toxic products that are subsequently excreted [5]. Therefore, any alteration of the expression or activity of Phase I or II enzymes can influence metabolic pathways, changing the magnitude of toxic effect elicited by neonicotinoid exposure.

3.0. **CHRONIC TOXICITY OF MOST INSECTICIDES**

Measure of chronic toxicity.

There is no standard measure like the LD50 for chronic toxicity. The chronic toxicity is studied depending on the adverse reactions being studied. Chronic effects may include Carcinogenic effects, teratogenic effects, mutagenicity effects, hem toxicity effect, endocrine disruption and reproductive toxicity which may result into infertility and sterility**.**

Carcinogenicity effect.

Epidemiological data support associations for both adult and childhood cancer [2,3] with occupational exposure playing a role in cancer development for both adults and children. However, the most common types of cancer vary for children and adult. Several meta-analyses and systematic reviews have been published on the association between insecticide exposure and cancer. In most instances, these analyses and reviews serve as the primary source of information for the childhood and adult cancers.

There is sufficient evidence that endocrine disruptors altered mammary gland morphogenesis in humans, making them more prone to neoplastic development.

Teratogenicity effect.

Teratogenicity is the production of birth defects. Any substance that is capable of producing changes in the structure and function of an embryo exposed before birth is said to be a teratogen. Insecticides have been known to produce teratogenic effects.

Mutagenicity effects

Mutagenicity is the production changes in the genetic structure. Substances that because genetic changes are said to be mutagens. Most of the substances that are mutagenic are oncogenes, that is to say they cause tumors as well. Most of the oncogenic substances are also mutagenic**.**

Reproductive Toxicity.

Some chemicals have effects on the fertility or reproduction rates of animals on both males and females. DDE has been linked to precocious puberty in one study of immigrant females in Belgium and estrogenic pesticides have been proposed as a contributor to this effect.

4.0. Toxicological Hazard and risk assessment.

- Risk Assessment: Is defined as the process of determining the short and long term adverse consequences to humans or ecosystems from the use of a particular chemical, mixture, substance or technology.
- A hazard is the inherent capacity of a substance or chemical to cause adverse effects (injury, disease, death, economic loss or environmental deterioration) on man or the environment under the conditions of exposure.

- Risk is the probability of the occurrence of an adverse effect on man or the environment resulting from a given exposure to a chemical or mixture.
- Risk assessment therefore involves, hazard identification, effects assessment, exposure assessment and risk characterization.

- Risk assessment related to human beings tended to receive more attention due to the immediacy of human effects on man.
- However various human activities such as deforestation and the production and use of chemicals has begun to threaten biological diversity and ecosystem integrity
- Risk Assessment is the central theme in chemical control

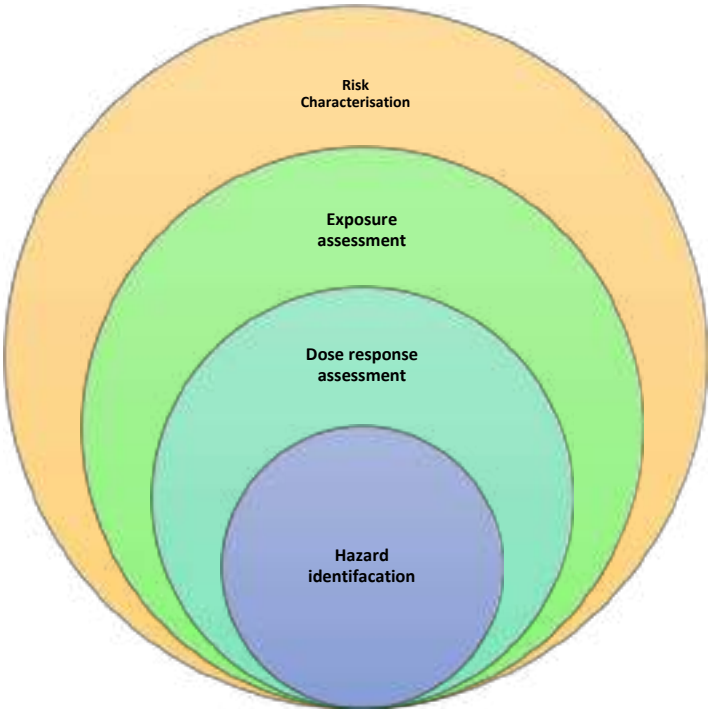

Figure 5. Toxicological Risk Assessment process

Due to an increase in the use of pesticides such as insecticides that has led to the increase in the cervical cancers, prostate cancers, lung cancers, liver cancers and other problems associated with reproduction such as infertility as a result of weak erection and low sperm count, it is important to conduct toxicological risk assessment. It is therefore one of the solutions to try and reduce or eliminate the use of chemical insecticides. Risk assessment involves the following steps.

1.Hazard Identification

This involves identifying toxic substances that may pose health hazard. It also involves quantification of the concentration at which they are present in the environment and description of the resultant forms of toxicity.

2.Dose-Response assessment.

This involves evaluating the conditions under which the toxic properties of the chemical might be manifested in exposed populations. The assessments are based on observed data using test animals.

3.Exposure assessment.

This involves the determination of the magnitude frequency and duration of exposure that is characteristic of the exposed population, sources of the toxic agents and exposure pathway.

4.Risk characterization.

This involves the expression of risk assessment results and the probability of occurrence, severity given population and attendant uncertainties.

As risk assessment is conducted, there is need for the balance between the risk and benefit. Toxicological risk assessment provides the much needed solutions.

When risk assessment is conducted, management of the risk then follows. This involves looking at the context of the problem, size of the risk, options available, decision, action and evaluation of the action.

4.CONCLUSION

Today both developed and developing countries have witnesses an increase in the use of insecticides. This phenomenon has resulted into high level exposure to insecticides. Empirically in most developing countries there is decrease in the use of Personal Protective Equipment(PPE), low level of education about the acute and chronic effects of insecticides to the sellers and the users**.** There is need however to appeal for the development of effective public health strategies to improve awareness and safe use of PPE. In addition, there is a need to inform farmers about integrated pest management to prevent severe health complications, which may occur as a result of unsafe and inappropriate use of pesticides such as the cancers, reproduction effect, mutagenesis and others. Where need arises Toxicological risk management should be conducted so that options and good decisions are made.

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6.NOTES

Pesticide incidents are underreported for several reasons. It is very important for primary health care providers to have good knowledge about pesticide poisoning. Today there is an increase in pesticide use and their effects cause signs and symptoms that make them miss the diagnosis and give wrong medications which end up producing side effects some of which are irreversible. Good knowledge will also help these primary health care providers to assist the general public in preventive care. The environmental management agencies in both developing and developed countries should help in educating the people who handle pesticides, those who sale and the farmers who do the sprays so that exposure levels are minimized and correct personal protective

equipment (PPEs) are used correctly. They should be given knowledge about acute and chronic toxicity of the insecticides and advise them to report to the nearest health facilities in order to reduce on the mortality and morbidity. Important information should be toxicity symbols, colours coding, diluting and concentration and first aid information. Further entry and re-entry policy of the sprayed fields especially to the farmers of different crops who use pesticides throughout.

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