CHAPTER-1

INTRODUCTION

Poison is a substance that causes injury or damage to the body and endangers the life of the person exposed by means of contact, inhalation or ingestion. Poisoning may be due to occupational, accidental, intentional exposure of such bio-hazardous substances to an intolerable quantity either at an instance or over a period of time.Among the reported cases of poisoning, the pesticide poisoning constitutes major chunk of the cases, which in turn have the highest fatal outcome. Approximately about 258,000 cases of fatal pesticide self - poisoning are reported each year globally, most of them are from Asia.However, the number of poisoned patients who were admitted at healthcare facilities is proportionately very high when compared to that of fatal cases. Data about the other kinds of poisonings are less and are quite variable depending on the socioeconomic, geographical area and cultural factors.

In one of a retrospective study from East Godavari District, the most common cause of poisoning was reported to be due to insecticide- organophosphorous compounds (OPC) **(45%)** and Herbicide-Paraquat dichloride **(45%)** and remaining 10% are other types of pesticides.

Over the last few decades agricultural pesticides have become a common household item in rural areas of the developing world.Due to their easy availability, pesticides have also become commonly used for intentional self-poisoning acute pesticide poisoning is now an important cause of morbidity and mortality worldwide. According to World Health Organization (WHO) estimates around **3 million** poisoning cases with **220,000** deaths occur annually. About 99% of these deaths occur in developing countries.

Pesticide poisoning is a significant problem in India. Organophosphorus (OP) compounds cause most self-poisoning deaths in southern and central India.

The state of Andhra Pradesh, southern India, is an area of intensive agricultural production. Pesticide use is high, and the state has one of the highest reported rates of pesticide poisoning in India. The resources for treating this number of cases in government hospitals are limited and likely have an impact on patient outcome. The present study was carried out to determine the impact, management and outcomes of pesticide poisoning in one hospital of the state.

1.1 PESTICIDES:

Pesticides are substances that are meant to control pests, including weeds. The term pesticide includes all of the following: Herbicide, Insecticides (which may include insect growth regulators, Termiticides, etc.) Rodenticide and Fungicide.

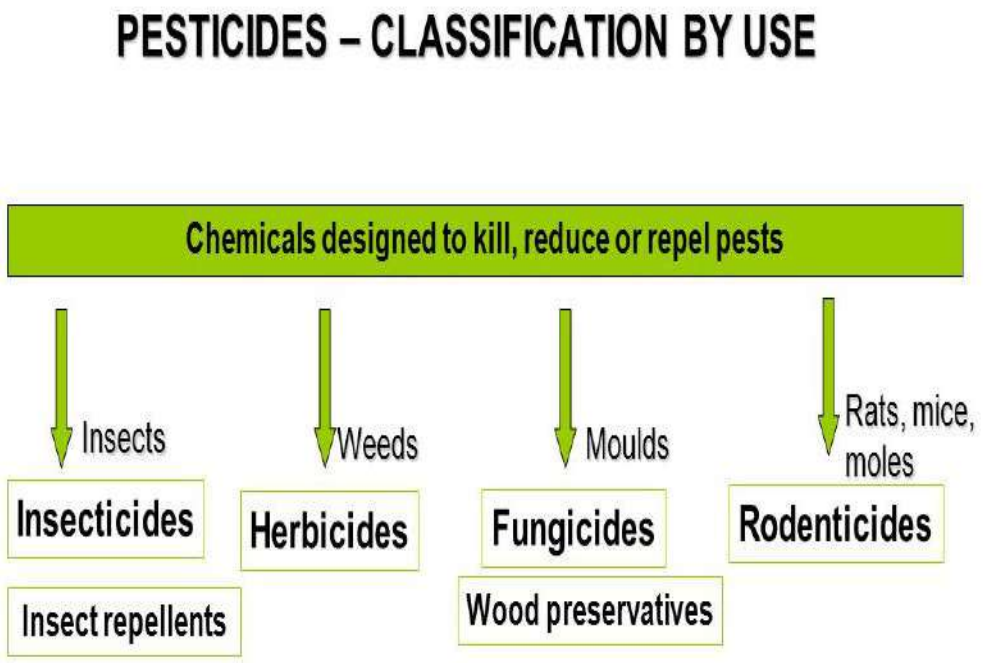


Fig.1.1 Classification of pesticides

From the above diagram, a brief description of Insecticides i.e., organophosphorous compound and Herbicide i.e., paraquat and rodenticide i.e., zinc phosphide.

1.1.1 INSECTICIDE:

- **ORGANOPHOSPHOROUS COMPOUNDS:-**

Organophosphorus poisoning occurs very commonly in southern India, where farmers form a significant proportion of the population who commonly use organophosphorus compounds like parathion as insecticides. Thus, due to the easy accessibility of these compounds, a large number of suicidal cases are encountered in this region.

Organophosphorous compounds are chemical agents in wide-spread use through out the world,mainly in agriculture.They are also used as nerve agents in chemical warfare (e.g.sain gas), and as therapeutic agents,such as ecothiopate used in the treatment of glaucoma.They comprise the ester,amide or rhiol derivatives of phosphoric acid and are most commonly used as pesticides in commercial agriculture,field sprays and as household chemicals.

There are no rules and regulations governing the purchase of these products,and they are therefore readily available "over the counter" despite them being a major cause of morbidity and mortality.

Exposure to organophosphates in an attempt to commit suicide is a key problem,particularly in the developing countries,and is a more common cause of poisoning than the chronic exposure experienced by farmers or sprayers in contact with the pesticides.

→ ***Synthesis:-***

Various routes exist for the synthesis of organophosphates

- **Esterification of Phosphoric acid**

$OP(OH)_3 + ROH \rightarrow OP(OH)_2(OR) + H_2O$

$OP(OH)_2(OR) + R'OH \rightarrow OP(OH)(OR)(OR') + H_2O$

$OP(OH)(OR)(OR') + R''OH \rightarrow OP(OR)(OR')(OR'') + H_2O$

Alcohols can be detached from phosphate esters by hydrolysis, which is the reverse of the above reactions. For this reason, phosphate esters are common carriers of organic groups in biosynthesis.

- **Oxidation of phosphite esters:**

Organophosphites can be readily oxidised to give organophosphates

$P(OR)_3 + [O] \rightarrow OP(OR)_3$

- **Alcoholysis of $POCl_3$**

Phosphorus oxychloride reacts readily with alcohols to give organophosphates.

$O{=}PCl_3 + 3\ ROH \rightarrow O{=}P(OR)_3 + 3\ HCl$

→ ***Classification:***

There are more than a hundred organophosphorous compounds in common use. These are classified according to their toxicity and clinical use:

- **Highly toxic organophosphates**

  (E.g. tetra-ethyl pyrophosphates, parathion)These are mainly used as agricultural insecticides

- **Intermediately toxic organophosphates**:

  (E.g.coumaphos, clorpyrifos, and trichlofon).These are used as animal insecticides.

- **Low toxicity:**

  (E.g. Diazinon, Malathion, and Dichlorvos).These is used for household application and field sprays.

→ ***Types of organophosphate:-***

Insecticide	**N**erve gases	**A**ntihelminthic agents
Malathion	Soman	**T**richlorfon
Parathion	**S**arin	
Diazinon	**T**abun	
Fenthion	**VX**	
Dichlorvos		
Chlorpyrifos		
Ethion		

Table.1.1 Types of Organophosphates

→ ***Absorption route:***

- **C**utaneous
- **I**ngestion(Accidental or suicidal)
- **I**nhalation
- **I**njection

→ ***Exposure:-***

Home Exposure	Occupational Exposure	Other Exposure
Accidental ingestion	**Farms and Farm worker**	**Dietary exposure-pesticide residues on crops**
Lawn and garden use	**Pesticide applicator**	**Leaching from soils to ground water**
Insect control	**Manufacture**	**Community exposure**
Food supply	**Mixing and handling**	**Airborne drift from commercial app**
Water supply	**Landscapers**	**Contaminated drinking water**

Table.1.2 Exposure

→ ***Pharmacokinetics:***

Most organophosphates are highly lipid soluble compounds and are well absorbed from intact skin, oral mucous membranes, conjunctiva and the gastrointestinal and respiratory tracts. They are rapidly redistributed to all body tissues. The highest concentrations are found in the liver and kidneys.

This high lipid solubility means that they easily cross the blood/brain barrier and therefore produce effects on the CNS.

Metabolism occurs principally by oxidation in the liver with conjugation and esterase hydrolysis producing a half-life of minutes-hours. The oxidative metabolites of Malathion and parathion (malaoxan and paraoxon) are active forms and are subsequently hydrolyzed into inactive metabolities.Elimination of organophosphorous compounds and its metabolites occur mainly via urine, bile and faeces.

→ ***Mechanism of action:***

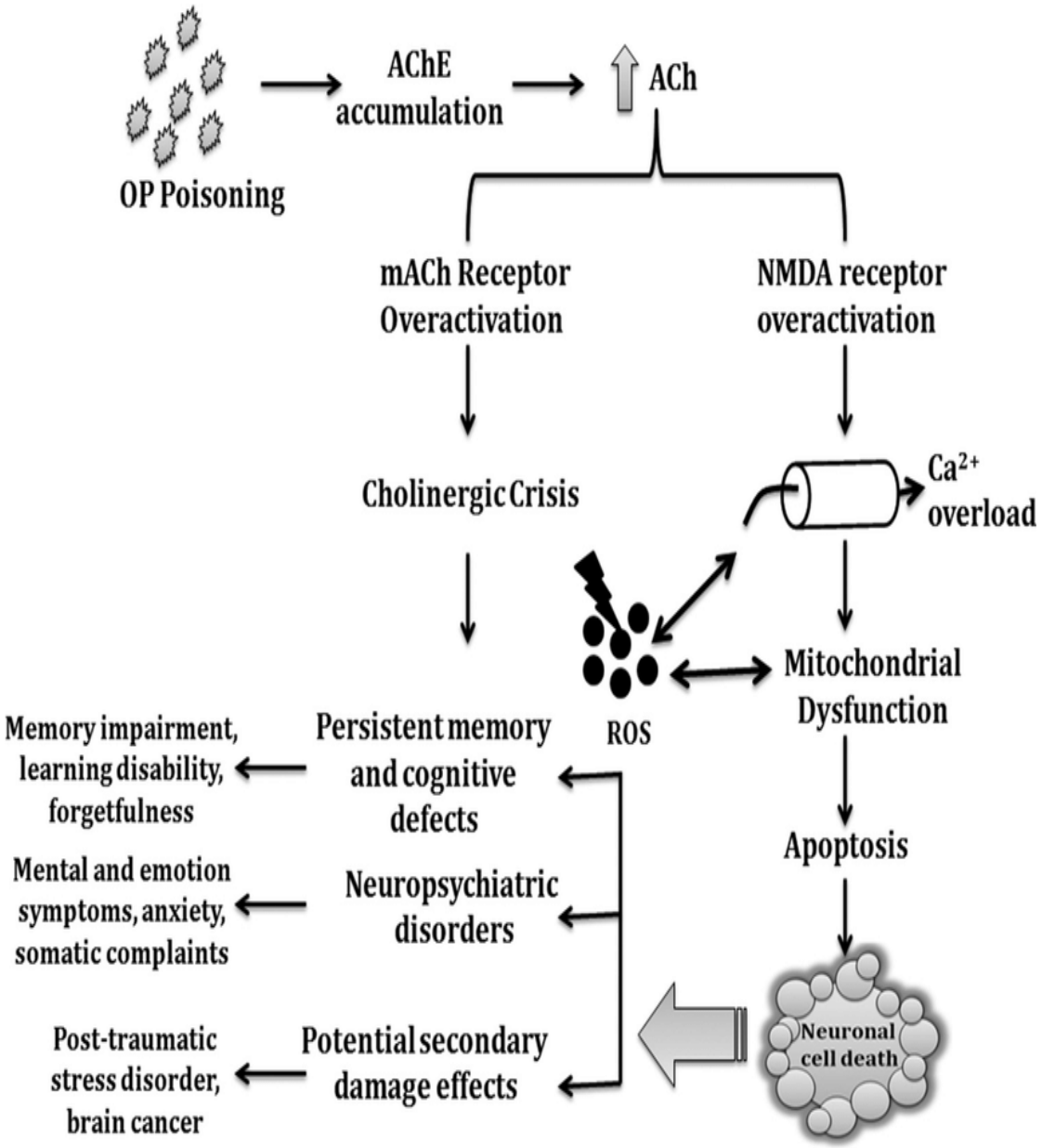


Fig.1.2 Mechanism of Action

- **O**P Inactivate Acetyl Cholinterase (Ach E).This results establishment of a covalent bond with AchE.
- **A**ch E is an enzyme that degrades the Neurotransmitter Acetylcholine (Ach) into Choline and Acetic Acid.
- **A**ch is found in CNS &PNS, NeuromuscularJunctions, and Red Blood Cells (RBCs).
- **O**nce Ach E- Inactivated, Ach accumulates throughout the Nervous System

⇒ **Overstimulation of Muscarinic and Nicotinic Receptors**

Once an organophosphate binds to AChE, the enzyme can undergo one of the following,

- **Endogenous hydrolysis** of the phosphorylated enzyme by esterases or paraoxonases.
- **Reactivation** by a strong nucleophile such as pralidoxime.
- **Irreversible binding** and **permanent enzyme inactivation** (aging).

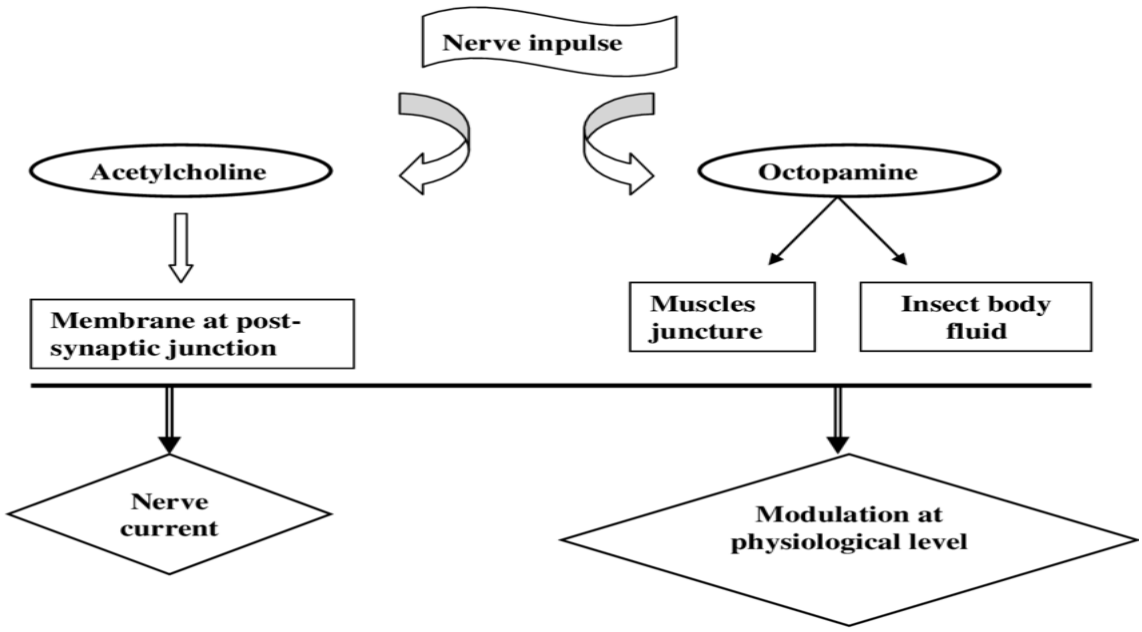


Fig.1.3 Route of exposure

The onset and severity of symptoms depend on the specific compound, amount, route of exposure, and rate of metabolic degradation.

→ ***Clinical Feautures:***

Following exposure to organophosphorous compounds, the toxic features are usually obvious within 30 minutes to 3 hours.

- **T**his may be delayed in some cases depending on the rate and amount of systemic absorption.
- **T**he majority of patients give a history of intentional or accidental ingestion of organophosphorous compounds.
- **T**oxicity is produced by the rapid absorption of the compound through the gastrointestinal, respiratory tracts and skin.
- **T**he clinical symptoms and signs are non-specific and will depend on the specific agent, the quantity and the route of entry.
- **S**ome patients present with vomiting, diarrhoea and abdominal pain, while others may be unconscious on arrival at the hospital.A high index of suspicion istherefore needed to make an early diagnosis.
- **T**he clinical features can be broadly classifies as secondary to the
  a) **M**uscarinic Effects
  b) **N**icotinic Effects
  c) **C**entral receptor stimulation
- **E**arly cases present predominantly with Para-sympathetic over-activity, and a characteristic garlic smell.
- **T**he end result may be a multi-system manifestation involving the gastrointestinal, respiratory, and cardiovascular and nervous systems, as well as involvement of skeletal muscle, other organs and metabolic effects such as hypo-or-hyperglycemia.
- **M**ost fatalities occur within 24 hours and those who recover usually do so within 10 days.

→ ***Respiratory Manifestations:***

- **R**espiratory manifestations of acute organophosphorous poisoning include bronchorrhoea, rhinorrhoea, bronchospasm and laryngeal spasm.
- **T**his is due to the action of the organophosphate on muscarinic receptors.
- **T**he integrity of the airway may be compromised by excessive secretions.
- **T**he nicotinic effects lead to weakness and subsequent paralysis of respiratory and oropharngeal muscles.
- **T**his increase the likelihood of both airway obstruction and aspiration of gastric contents.
- **F**inally, central neurological depression may lead to respiratory arrest.

→ ***Neurological Manifestations:***

Three different types of paralysis are recognized based largely on the time of occurrence and their differing pathophysiology:

▪ **Type I- Paralysis or acute paralysis**
▪ **Type II-Paralysis or Intermediate syndrome**
▪ **Type III--Paralysis or Organophosphate induced delayed Polyneuropathy**

Table.1.3 Paralysis

- ***Type I Paralysis Or Acute Paralysis:***

– **I**t is seen during the initial cholinergic phase.

– **T**his is when large numbers of both muscarinic and nicotinic receptors are occupied by acetylcholine, leading to persistent depolarization at the neuromuscular junction.

- ***Clinical Features:***

– **I**t includes muscle fasciculation, cramps, twitching and weakness.

– **A**t this stage the patient may require ventilatory support due to the weakness of the respiratory muscles leading to respiratory depression and arrest.

→ ***Type II Paralysis/Intermediate Syndrome:***

– **T**he intermediate syndrome is a distinct clinical entity that occurs 24 to 96 hours after the ingestion of an OP compound.

– **A**pproximately 10-40% of patients treated for acute poisoning develop this illness.

– **T**he onset of the IMS is often rapid, with progression of muscle weakness from the

  - **Ocular Muscles**
  - **Neck Muscle** (the patient cannot raise their head from the pillow)
  - **Proximal Limbs**
  - **Respiratory Muscles** (intercostals and diaphragm) over the course of 24 hours.

- ***Clinical Features :***

– **C**linical manifestations of IMS typically occur within 24 to 96 hours, and affect conscious patients without fasciculation or other cholinergic signs

– **M**arked weakness of neck flexion and varying degree of proximal limb muscle weakness, manifesting as weakness of shoulder abduction and hip flexion, are the constant clinical features.

– **R**espiratory insufficiency is common and frequently draws medical attention to the onset of the syndrome.

– **O**ther possible manifestations are involvement of muscles innervated by motor cranial nerves and decreased deep tendon reflexes.

– **S**ensory impairment is not a clinical manifestation of IMS.

→ ***Type III Paralysis Or Organophosphate- Induced Delayed Polyneuropathy. (OPIDP) :***

- **I**t is a sensory-motor distal axonopathy that usually occurs after ingestion of large doses of an organophosphorus compound.
- **T**he neuropathy presents as weakness and ataxia following a latent period of 2-4 weeks.
- **I**nitial stimulation causes excitatory fasciculation, which then progresses to an inhibitory paralysis. The cardinal symptoms are distal weakness of the hands and feet.
- **T**his is often preceded by calf pain, and in some cases, parasthesia of the distal part of the limbs. Delayed CNS signs include tremor, anxiety and coma.

▪ ***Test For Organophosphate Poisoning In Labs by Forensic Toxicologists:***

In general, intact organophosphates cannot be detected in the blood due to rapid hydrolysis by the liver. Therefore, the most commonly used test to confirm acute organophosphate poisoning is measurement of plasma cholinesterase activity. Plasma cholinesterase levels usually decline to less than 50% of the normal value before any symptoms of poisoning are observed. As a rough guide, plasma cholinesterase levels of 20-50% of the normal value are found with mild poisoning, 10-20% with moderate poisoning, and less than 10% in cases of severe toxicity.

A follow-up test that evaluates RBC cholinesterase levels may also be useful in certain circumstances. For example, plasma cholinesterase activity may be decreased by a number of conditions besides organophosphate poisoning. In contrast, depression of RBC cholinesterase activity is more specific for organophosphate poisoning. If both plasma and RBC cholinesterase activities are significantly decreased, the clinical symptoms may be attributed to organophosphate poisoning.

It is important to note, however, that some organophosphates selectively inhibit plasma cholinesterase and, therefore, would yield normal RBC cholinesterase results. Measurement of RBC cholinesterase levels may also be useful when organophosphate poisoning is suspected but plasma cholinesterase levels remain

normal. Certain organophosphates selectively inhibit RBC cholinesterase, and observation of a decrease in RBC cholinesterase activity is critical to confirm poisoning by such insecticides.

Because organophosphate metabolites, such as alkyl phosphates and phenols, are excreted by the kidneys, urinalysis may aid in identifying and quantifying the parent compound. Typically, metabolites can be detected up to 48 hours after exposure and can demonstrate organophosphate absorption at lower dosages than is required to produce symptoms or to depress cholinesterase activities. For this reason, urinalysis may also be useful in confirming low-dosage chronic exposure to this group of chemicals.

Plasma cholinterase	**RBC cholinterase**
< 3 U/mL	**< 8 U/mL**

Table.1.4 Levels of Plasma and RBC Cholinterase

→ ***Factors May Affect The Lab Results:***

Several preanalytical variables may affect laboratory results. In the presence of organophosphate or pralidoxime, the inhibition or reactivation of cholinesterase in blood may continue after sample collection. Therefore, the appropriate sampling and storage of blood is crucial to obtaining accurate test results.

Reference ranges for cholinesterase results are method dependent and different for plasma versus RBC cholinesterase. The reference range for RBC cholinesterase depends on the method of normalization of RBC cholinesterase activity: reported values may refer to hematocrit, hemoglobin, erythrocyte volume, or whole blood volume. The reference range for plasma cholinesterase is lower for women than for men, and lower for infants than adults. The use of an incorrect

reference range may lead to misinterpretation of an abnormal result as being normal or vice versa.

The normal range of plasma and RBC cholinesterase activities is wide, and day-to-day variations may be as large as 10-20%, making test result interpretation difficult. For example, a plasma cholinesterase activity considered normal based on a population-based reference range might actually be abnormally low for a particular patient. To alleviate this problem, baseline measurements prior to organophosphate exposure should be made for all persons with a high risk of organophosphate exposure (e.g., workers in agriculture and in organic chemical industries).

Despite suspicion of organophosphate poisoning, plasma cholinesterase levels may appear normal in several instances. The elevated activities observed in some obese and diabetic patients, for example, may balance the decreased levels that would arise because of organophosphate poisoning, resulting in normal plasma Cholinesterase levels. Certain organophosphates selectively inhibit RBC cholinesterase, and, in these instances, the plasma cholinesterase activity would also be normal. It should be noted that the opposite may also occur: certain organophosphates that selectively inhibit plasma cholinesterase yield normal RBC cholinesterase values.

Decreased plasma cholinesterase activity is not unique to organophosphate poisoning. It may also present in certain types of liver disease, malnutrition, chronic alcoholism, dermatomyositis, and congestive heart failure. Pregnancy, oral contraceptives, and metoclopramide may also cause depression of plasma cholinesterase activity. A number of exogenous substances may reduce plasma cholinesterase activity, including cocaine, carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines. In addition, 3% of the healthy population has atypical genetic variants of the enzyme and, as a result, show low normal activities in plasma cholinesterase tests.

Although a depression of RBC cholinesterase activity is more specific for organophosphate poisoning, decreases in RBC cholinesterase activity may be seen in patients receiving antimalarial therapy or in patients with pernicious anemia, paroxysmal nocturnal hemoglobinuria, or certain other rare conditions that damage the RBC membrane. Establishing a history of exposure to an insecticide or pesticide along with a thorough clinical evaluation can aid in ruling out causes unrelated to organophosphate poisoning.

The most common complicating factor in the urinalysis of organophosphate metabolites is the dietary ingestion of low levels of organophosphates.

→ ***Postmortem Appearances:-***

- Signs of asphyxia are found
- The face is congested and there is cyanosis of the lips, fingers and toes.
- Blood strained froth is seen at the mouth and nose.
- The stomach contents may smell of kerosene.
- The mucosa of the stomach is congested with sub mucous petechial haemorrhage.
- Respiratory passages are congested and contain frothy, haemorrhagic exudate.
- The lungs show gross congestion, excessiveoedema.
- The internal organs, brain and meninges are congested.

1.1.2 HERBICIDE:

→ ***Classification of Herbicide Poisoning:***

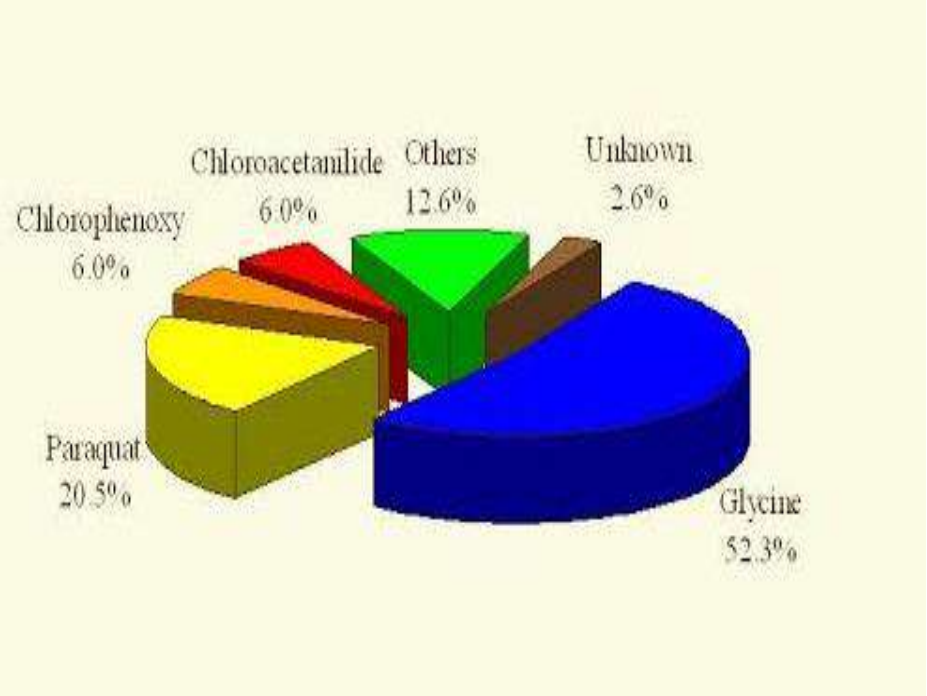
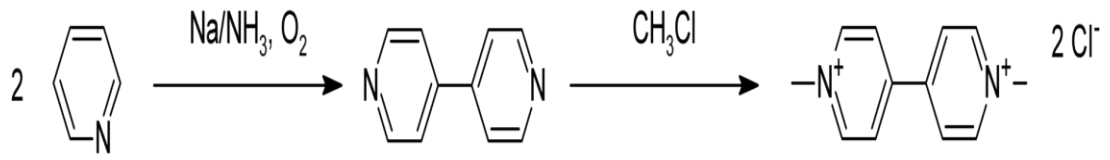


Fig.1.4 Classification of Herbicide Poisoning

PARAQUAT:

→ ***Introduction:-***

Paraquat or ***N*, *N*-dimethyl-4, 4-bipyridinium dichloride** (systematic name) also known as **Methyl Viologen.** It is Organic compound with the chemical formula $[(C_6H_7N)_2]$ Cl2. It is classified as aviologen; a family of redox active heterocycles of similar structure.Paraquat was manufactured by chevron. This salt is one of the most widely used herbicides. It is quick-acting and non-selective, Killing green plant tissue on contact. It is also toxic to human beings and animals due to its redox activity, which produces superoxide anions.



Pyridine is coupled by treatment with sodium in ammonia followed by oxidation to give 4, 4′-bipyridine. This chemical is then dimethylated with chloromethane to give the final product as the dichloride salt.

→ ***Causes:***

Breathing in paraquat may cause lung damage and can lead to a disease called paraquat lung. Paraquat causes damage to the body when it touches the lining of the mouth, stomach, or intestines. You can get sick if paraquat touches a cut on your skin. Paraquat may also damage the kidneys, liver, and esophagus (the tube that food goes down from your mouth to your stomach).

If paraquat is swallowed, death can quickly occur. Death may occur from a hole in the esophagus, or from severe inflammation of the area that surrounds the major blood vessels and airways in the middle of the chest.

Long-term exposure to paraquat may cause scarring of the lungs called pulmonary fibrosis. This makes it hard to breathe.

→ **Symptoms:**

- Burns and pain in the throat
- Coma
- Difficulty breathing
- Nosebleed
- Seizures
- Shock

- Shortness of breath
- Stomach pain
- Vomiting, including vomiting blood

Severity of intoxication	Ingested amount (mL)	Symptoms	Signs
Mild	< 10	No specific symptom	No specific sign
Moderate	10-40	Sore tongue Shortness of breath Agitation Abdominal discomfort Head lightness	Tachypnea Tachycardia Increased serum creatinine Oral mucosa necrosis
Severe	> 40	Sore tongue Shortness of breath Hiccup* Agitation Confusion†	Tachypnea Tachycardia Increased serum creatinine Oral mucosa necrosis Jaundice

Table.1.5 Symptoms

→ ***Mechanism of Paraquat Poisoning:***

Several pathways are identified as causative factors of critical toxicity of paraquat in the human body. Firstly, the lungs are vulnerable to paraquat intoxication. Paraquat concentration within the lungs increases continuously during the first several hours' post-paraquat ingestion despite decreasing plasma paraquat levels. Many scientists attribute this phenomenon to high affinity of paraquat to alveolar cells. Injury to pneumocytes is initiated by nicotinamide adenine dinucleotide

(NADH)-dependent reduction of paraquat to mono cation radicals ($paraquat^{+}$). Spontaneous reaction with molecular oxygen yields the superoxide radical (O_2^{-}) and

Reversibly forms paraquat, which can be reduced again. Paraquat intoxication thus frequently causes death due to respiratory failure.

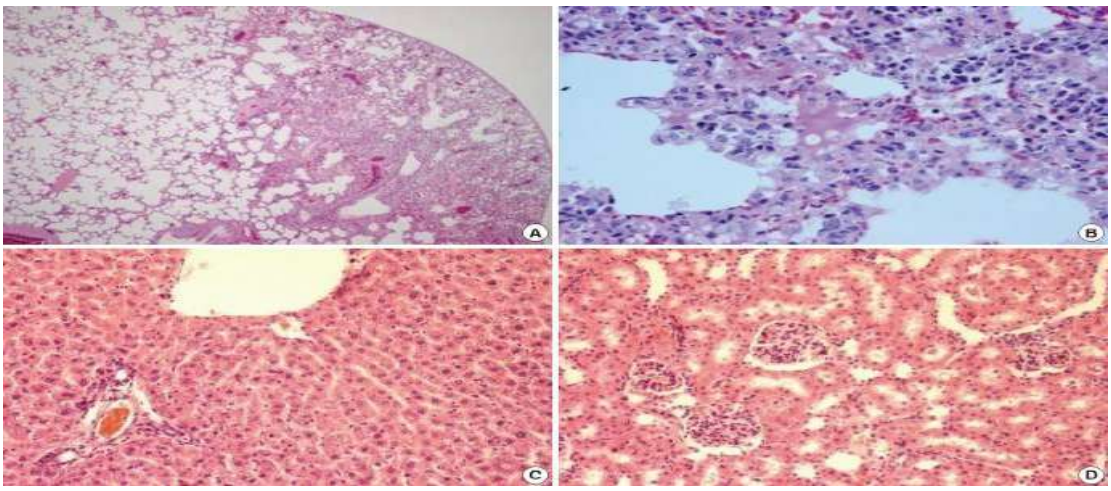


Fig.1.5 Mechanism of Paraquat Poisoning

Lung is a vulnerable organ in acute paraquat intoxication. Lethal dose of paraquat (25 mg/kg) was injected intraperitoneally in mice and 3 days later, the mice were sacrificed. The lung, liver and kidney were obtained and examined by light microscopy.

(**A**) **T**he lung parenchyma show interstitial widening and inflammatory infiltrates predominantly in the sub-pleural area.

(**B**) **H**igh power examination of the lung reveals dense infiltration of lymph plasma cells.

(C) And Kidney

(D) Are Histologically unremarkable.

Secondly, **Reactive Oxygen Species (ROS)** mediated cell signal transduction causes inflammation. Consequently, the initial pathologic finding is characterized by inflammatory cell infiltration. Many physicians thus attempt anti-inflammatory drugs as a treatment modality in patients with acute paraquat intoxication. This topic is further addressed in the following paragraphs. Thirdly, mitochondria damage by paraquat. Finally, paraquat releases free form iron from ferritin, aggravating ROS production.

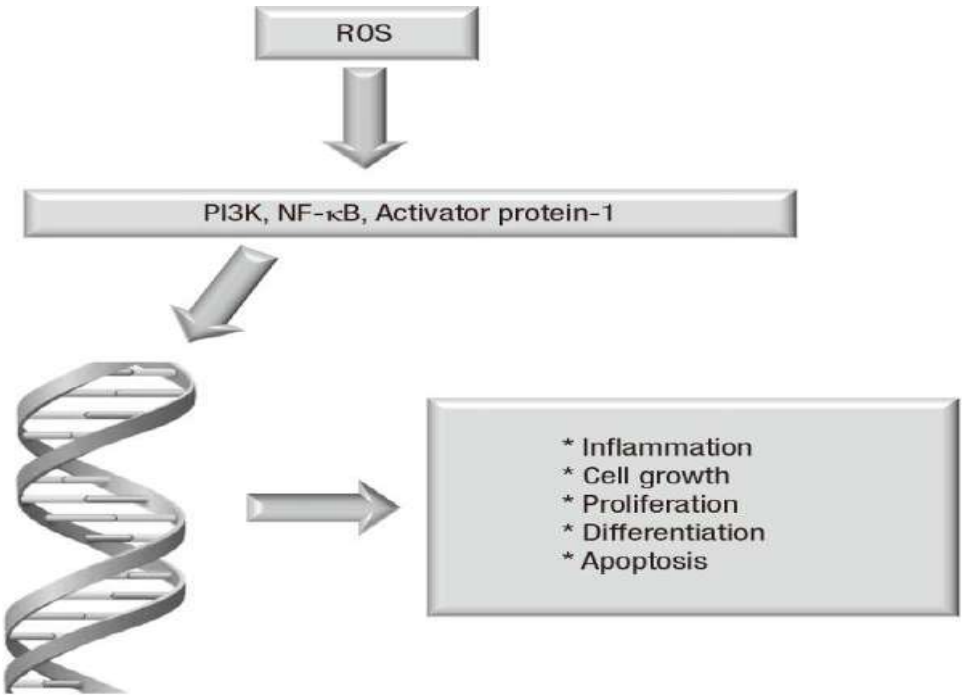


Fig.1.6 Reactive oxygen of species

ROS mediated signal transduction in inflammation. Free radicals stimulate protein complexes, such as **PI3K, NF-be,** and Activator protein-1 which control transcription of DNA, involved in cellular functions such as cell growth, proliferation, and differentiation.

→ ***DIAGNOSIS:***

- **Detection And Interpretation Of Paraquat In A Body Fluid:**

The detection of paraquat in a body fluid (e.g., serum, plasma, urine) is necessary and sufficient to confirm paraquat intoxication. Paraquat levels are to be interpreted with reference to the time lag after paraquat ingestion in keeping with the toxicokinetics of paraquat. The kinetics of paraquat distribution is best described by a 3-compartment model:

1) **P**lasma,

2) **A** rapid uptake and removal compartment such as the kidney, and

3) **A** slow uptake compartment, reaching a maximum at approximately **4-5** hr, such as the lung.

The plasma level peaks early, usually within **1 hr** post-paraquat ingestion, followed by a rapid and steep decline due to its rapid redistribution from the circulation to other compartments. During this period, plasma concentration shows substantial variation with slight changes at different time intervals after ingestion.

- **Interpretation Of PARAQUATConcentration In Urine*:***

The diagnostic potential of a dithionite urine test, an indicator of the plasma paraquat level, to determine the severity of paraquat intoxication. The principle behind the dithionite test is that the absorbance of paraquat changes as a result of the blue color produced on reacting with dithionite.

This chemical reaction is facilitated in an alkaline environment. Therefore, the first step of the dithionite test is addition of dithionite to a fresh urine sample in a colorless container followed by alkalization with a weak alkalizing agent such as

sodium bicarbonate. The lowest detection level of Paraquat by high-performance liquid chromatography (HPLC) is 0.01 µg/mL, and by the dithionite paraquat detection test, approximately 1 µg/mL.

Despite its lower sensitivity, the dithionite test is a useful beside screening tool for paraquat intoxication because of its convenience and reproducibility.

A Foley catheter should be placed and the bladder should be fully emptied on immediate arrival of a paraquat intoxicated patient, at the emergency room. This urine sample represents urine production over the previous several hours. Dithionite urine test results from the first sample represent the average blood paraquat levels during the previous several hours. A second urine sample is collected after the first urine collection. The result of the dithionite test from the second urine sample represents the current blood paraquat level. An observation of higher levels in the first urine sample than the second urine sample can be interpreted as decreasing serum paraquat levels from the initial levels prior to patient hospitalization.

Sequential dithionite urine tests are conducted every **3-4 hr** after the second dithionite urine test, until the results are negative. The time to achieve a negative urine dithionite test is a reliable marker for predicting mortality and/or essential organ failure. The sensitivity and specificity for mortality are **71.4%** and **75.0%,** respectively with a cut-off value of **34.5** hr for the time to negative conversion of the urine dithionite test. The incidence of acute kidney injury and respiratory failure with a time>**34.5** hr is **100%** and **85.0%,** respectively.

- **Evaluation Of PARAQUAT-Induced Lung Injury By Imaging**

A simple chest radiograph has poor sensitivity and specificity for evaluating PARAQUAT-induced lung injury. We recommend **High-Resolution Computed Tomography (HRCT)** of the lungs on day 7 post-paraquat ingestion. We find HRCT as a best modality in fully evaluating the extent of acute paraquat lung injury.

Sequential measures on **HRCT** of the lung. A forty-three old woman intentionally ingested on paraquat in a suicide attempt. She presented to the hospital within **3 hr** of ingestion. Serum paraquat level was **2.63 µg/mL**. Note that the area of the lung lesion was not expanded in the sequential HRCT. The process of lung fibrosis completes by one month.

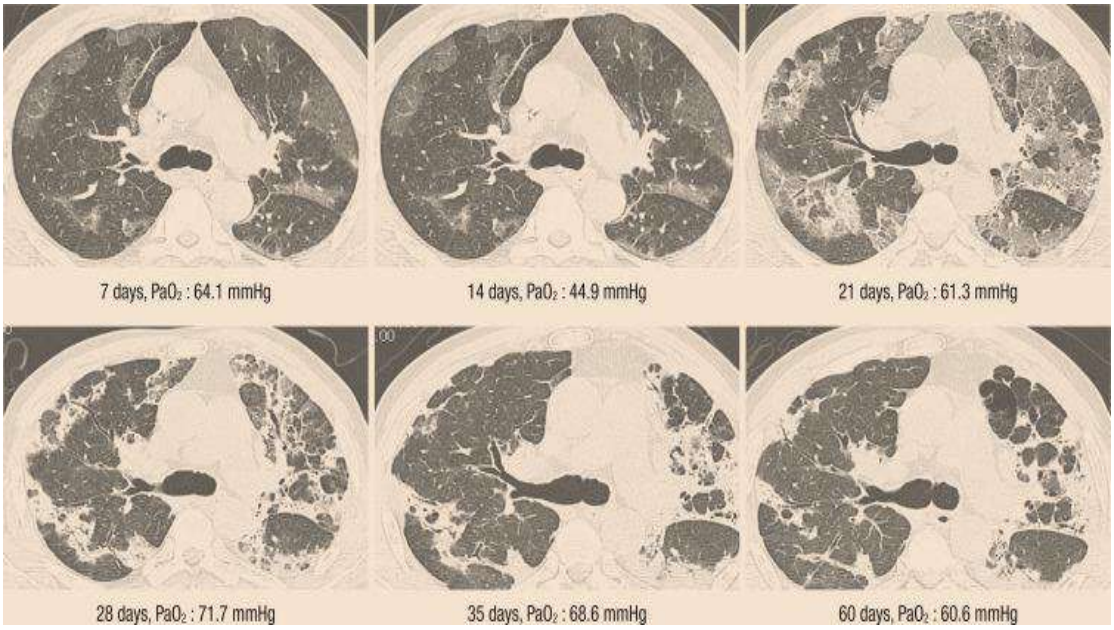


Fig.1.7 Induced lung injury by imaging

The initial pathology of the lung is an inflammation of the alveoli, i.e. alveolitis, which presents as **Ground Glass Opacity (GGO**) signal on **HRCT** imaging. The predilection site of **GGO** is the sub-pleural area. A **GGO** area **>50%** of the total lung volume is usually fatal, but all surviving patients have a **GGO** area **<20%** of the total lung volume on **HRCT** imaging at 7 days post-paraquat ingestion.

When a patient hesitantly ingests a large amount of undiluted **paraquat (>100 mL of 20%** paraquat) with multiple sips, there is a high chance of developing esophageal rupture and pneumomediastinum, with fatal consequences. **GGO** lesions progress to fibrosis after **2-3** weeks. Fibrosis is a progressive process, usually stopped within one month.

- **Evaluation Of PARAQUAT-Induced Lung Injury By Arterial Blood Gas Analysis *(*ABGA):-**

Tachypnea with low **$PaCO_2$** indicates the progression of hypoxia. **PaO_2**decreases progressively as the paraquat induced lung injury proceeds. Notably, in cases of **PaO_2<60 mmHg**, there is a significant rise in morality. Pulmonary fibrosis develops in the later stage of lung injury. A pulmonary function test after paraquat induced lung injury can demonstrate the restriction of lung volume, but the diffusion capacity of the remnant lung remains intact.

Identification of cases with acute paraquat intoxication those are treatable. The upper and lower limit of paraquat levels among survivors and non-survivors among **375** patients with acute paraquat intoxication. These levels can be divided into a dead zone (above the upper line, no survivors), gray zone (between the two lines; uncertain final outcome), and a safe zone (below the lower line, no deaths).

→ **Post Mortem Appearances:-**

- There are ulceration around the lips and mouth.
- The stomach may show erosions.
- The kidneys may show cortical pallor and diffuse tubular damage.
- The internal organs, brain and meninges are congested.
- The face is congested and there is cyanosis of the lips, fingers, toes.

1.1.3 RODENTICIDES:

Rodenticides are pesticides that kill rodents. Rodents include not only rats and mice, but also squirrels, woodchucks, chipmunks, porcupines, nutria, and beavers. Although rodents play important roles in nature, they may sometimes require control. They can damage crops, violate housing codes, transmit disease, and in some cases cause ecological damage.

	Oral	Inhalation	Dermal	Primary Eye Irritation	Primary Skin Irritation
Warfarin	**Moderate - High toxicity**	**Not significant**	**Not significant**	**No data**	**No data**
Chlorphacinone[4]	**High toxicity**	**High toxicity**	**High toxicity**	**Non-irritating**	**Non-irritating**
Diphacinone[4]	**High toxicity**	**High toxicity**	**High toxicity**	**Moderate irritation**	**Slight irritation**
Bromadiolone	**High toxicity**	**High toxicity**	**High toxicity**	**Low irritation**	**Minimally irritating**
Difethialone	**High toxicity**	**High toxicity**	**High toxicity**	**Mild irritant**	**Non-irritating**
Brodifacoum	**High toxicity**	**High toxicity**	**High toxicity**	**Minor irritation**	**Mild irritant**
Bromethalin	**High toxicity**	**High toxicity**	**Moderate toxicity**	**Slight irritation**	**Non-irritating**
Cholecalciferol	**High toxicity**	**Very low toxicity**	**Low toxicity**	**No data**	**No data**
Zinc phosphide	**High toxicity**	**High toxicity**	**Low toxicity**	**Slight irritation**	**Non-irritating**
Strychnine	**High toxicity**	**High toxicity**	**Low toxicity**	**Highly irritating**	**Non-irritating**

Table.1.6 Types of Rodenticides

CHAPTER -2

LITERATURE REVIEW

2.1 Organophosphate Poisoning At Chris Hani Baragwanath Academic Hospital 2012 – 2015:

A review of the literature showed differing results, with a female predominance in some studies, and a male predominance in others. Reasons given in the literature for these gender differences include farming practices, with the associated occupational exposures; gender-favoured methods of suicide; and gender-specific psychosocial stressors. With CHBAH(Chris Hani Baragwanath Hospital) being a predominantly urban hospital, farming practices most likely do not play as great a role as in some of the studies reviewed in the literature, which often covered hospitals in more rural areas. The findings in our study are more probably related to accessibility of the poison, especially in the context of those cases of deliberate self-harm, where impulsivity may result in the use of the most accessible agent in the circumstances, as well as being related to affordability of the poison in an area that comprises mainly lower income households. The mean age group affected most by organophosphate poisoning as reviewed in the literature, fell in the 25 -30-year-old range. The SA (South Asia) study from the Western Cape (WC) showed that 75% of the cases were less than 40 years of age. Our study showed a slightly younger population group with a median age of 30 years, highlighting the age group that is supposedly the most economically active subset of the population.

2.2 A randomized clinical trial to evaluate the efficacy of single versus multiple gastric lavage in the management of patients with acute organophosphorus Background:

Despite lack of supporting evidence Gastric Lavage (GL) is one of the most commonly used decontamination method for organophosphorus (OP) ingestion in developing countries.

This study was designed to evaluate the outcome of patients with OP pesticide poisoning treated with Gastric Lavage (GL) with regard to timing and frequency of the procedure.

In this study, Gastric Lavage (GL) was planned to be administered to patients with OP pesticide poisoning after initial stabilization irrespective of lavage given in peripheral hospitals. Therefore, some patients received one procedure (single Gastric Lavage) and some received more than one procedure (multiple Gastric Lavage). Early Gastric Lavage was defined as Gastric Lavage given within **2 h** of poison exposure and late Gastric Lavage was referred to performing the procedure after **2 h**.

During the study period, 40 patients with OP pesticide poisoning received GL comprising 11 who received early single, nine who received late single, 10 who received early multiple and 10 who received late multiple GL. Mortality, respiratory failure incidence, ICU admission and incidence of Mechanical Ventilation (MV) were not significantly different between patients receiving early single, late single, early multiple and late multiple Gastric Lavage. There was significant difference between patients who received early single, late single, early multiple and late multiple Gastric Lavage regarding the duration of Mechanical Ventilation (MV), hospital stay duration, and atropine and oximes ampoules needed.

Multiple Gastric Lavage (GL) created insignificant reduction in overall mortality from OP poisoning; yet early and multiple GL proved and to be more effective than single GL in reducing the incidence of respiratory failure, ICU admission and MV and in decreasing hospital stay duration and atropine and oximes therapy amount significantly.

2.3 Clinical features and prognosis of paraquat poisoning in French Guiana: A review of 62 cases

Paraquat is a nonselective contact herbicide of great toxicological importance, being associated with high mortality rates. Because of its high toxicity, the European Union withdrew it from its market in **2007**. The aim of this study is to analyze all cases of paraquat poisoning hospitalized in French Guiana in order to assess their incidence and main characteristics. Medical records of all paraquat intoxicated patients hospitalized from **2008** until **2015** were reviewed in this retrospective study. Demographics, clinical presentation, and laboratory data were evaluated. A total of **62 cases** were reviewed. The incidence of paraquat poisoning was **3.8/100,000** inhabitants/year. There were **44** adults and **18** children younger than **16** years of age. The median ages were **31** years [**18.08– 75.25**] in adults and **13.4** years **[0.75–15.08**] in children, respectively. The median duration of hospitalization was longer in children [**15.5 days (1–24**)] than in adults [**2 days (1**–**30**)], **P < .0**1. The majority of cases were due to self-poisoning (**84%**). Children had ingested a lower quantity of paraquat [**48.8 mg/kg (10–571.1**)] than adults [595.8 mg/kg (**6–3636.4**), P = **.03**]. There were more deaths among adults (65%) than in children (**22%**), P = **.004.** The severity and outcome was determined primarily by the amount of paraquat ingested. In conclusion, French Guiana has the largest cohort of paraquat poisonings in the European Union. The major factor affecting the prognosis of patients was the ingested amount of paraquat. The administration of activated charcoal or Pemba, in situ, within the first hour after ingestion of paraquat is essential.

2.4 Comparison of the Respiratory Toxicity and Total Cholinesterase Activities in Dimethyl Versus Diethyl Paraoxon-Poisoned Rats

The chemical structure of organophosphate compounds (OPs) is a well-known factor which modifies the acute toxicity of these compounds. We compared ventilation at rest and cholinesterase activities in male Sprague-Dawley rats poisoned with dimethyl paraoxon (DMPO) and diethyl paraoxon (DEPO) at a subcutaneous dose corresponding to **50%** of the median lethal dose (MLD).Ventilation at rest was recorded by whole body plethysmography. Total cholinesterase activities were determined by radiometric assay. Both organophosphates decreased significantly the respiratory rate, resulting from an increase in expiratory time. Dimethyl-induced respiratory toxicity spontaneously reversed within **120** min post-injection.

Diethyl-induced respiratory toxicity was long-lasting, more than **180** min post-injection. Both organophosphates decreased cholinesterase activities from **10** to **180** min post-injection with the same degree of inhibition of total cholinesterase within an onset at the same times after injection. There were no significant differences in residual cholinesterase activities between dimethyl and diethyl paraoxon groups at any time. The structure of the alkoxy-group is a determinant factor of the late phase of poisoning, conditioning duration of toxicity without significant effects on the magnitude of alteration of respiratory parameters. For same duration and magnitude of cholinesterase inhibition, there was a strong discrepancy in the time-course of effects between the two compounds.

2.5 Acute Pesticide Poisoning and Related Factors among Farmers in Rural Western Iran

Although **Acute Pesticide Poisoning** (APP) is known to be a major health concern among farmers in developing countries, knowledge of its prevalence and risk factors is limited. The purpose of this study was to investigate the prevalence and a broad range of potential work-related risk factors of APP among Iranian farmers

and farm workers. This cross-sectional study was conducted in rural areas of the Twiserkan County in Iran. In this study, there were **474** farmers and farm workers who had used pesticide 1 week before data collection. Participants were selected from **104** villages. Data were gathered using a questionnaire and analyzed using STATA. Binary logistic regression and multinomial logistic regression were employed. The results of this study showed that **286 (60.3%)** farmers and farm workers who applied pesticides suffered from work-related APP. Most frequent APP symptoms were runny nose **(29.8%)** and headache **(25.1%).** Five risk factors were identified, including annual income **($p < 0.05$)**, number of farming years (Odds Ratio (OR) = **0.31**), number of spraying years (OR = **2.40**), place of pesticide storage (OR = **2.69**), and type of sprayer ($p < 0.05$). The results of this study indicated that APP is prevalent among the studied farmers. Some work-related factors play an important role in APP among Iranian rural farmers. In addition, the magnitude of these risk factors differed significantly by severity of acute and somatic pesticide poisoning.

CHAPTER-3

AIM AND OBJECTIVES

3.1 AIM:-

- **A** study on Suicide cases due to Consumption of Pesticides

3.2 OBJECTIVES:-

- **T**o conduct statistical study for the total number of pesticide suicides that have occurred between January 2018 to December 2019 studied at Govt. General Hospital, Kakinada.
- **P**ostmortem appearances of the particular pesticide.

CHAPTER-4

MATERIALS AND METHODOLOGY

Among all the medico-legal case registered at the Government General Hospital, Kakinada, only the poisoning cases are taken into consideration. The study is carried out for the period of one month. All cases of poisoning, irrespective of age, sex, type and mode of poisoning, ingredients of poisons and the status of patients after poisoning are recorded in the proforma. Data collection is performed according to hospital regulations after approval by the hospital authorities.

All the poisoning cases are registered in the years of 2018 and 2019 are collected. This is a retrospective hospital based cross-sectional study conducted among a total of 208 cases that are registered as poisoning from 1st January 2018 to 31st December 2019.All the details of the cases are collected from the Medico-legal forms. The study is conducted in two phases.

4.1 PHASE –I:-

→ ***Step 1: Study The Type Of Poisoning Cases:-***

- In this, different type of pesticide poisoning cases are studied from the medico-legal forms at Government General Hospital, Kakinada

→ ***Step 2: Design Of The Study:-***

- Study period: The study is planned to be carried out for a period of 1 month consent from the hospital authority.

→ ***Step 3: Defining Criteria, Standards And Design Of Data Entry Format:-***

- **Inclusion criteria**: Persons who are died due to consumption of pesticides i.e. mainly insecticide and herbicide. In insecticides mainly due to organophosphorous compounds and in herbicides due to paraquat dichloride.
- **Exclusion criteria**: Persons who are died due to hanging, strangulation corrosive acids and metallic poisons.

4.2 PHASE II:-

→ ***Step 1: Literature Survey:-***

- **T**he literature supporting the study is collected and analyzed. The different sources used to collect the literature review that is about different pesticides and various websites such as **www.googlescholar.com, www.sciencedirect.com.**

→ ***Step 2: Data collection:-***

- **A**ll the data is collected from the Medico-legal forms.

CHAPTER-5

RESULTS AND DISCUSSION

A total of **413** cases are registered as poisoning cases from **01st** of January **2018** to**31st**of December**2019**.All the results are tabulated and given at the end this article.

In this percent study, maximum percentage of poisoning cases are among males **(76.19%**), whereas it is **33.81%** among females. The incidence of poisoning cases are high among the age group of **21-30** years (**35..99%**),which is the most emotionally unstable group followed by the age group of **31-40** years(**30.80%**).

The data in the table **3** depicts that the poisoning by organophosphorous compounds are most common **(44.91%).** This in turn increases more considerably when we view it as pesticides as a whole to about **57.44%**of total burden of poisoning cases. The major contribution of the people of East Godavari District is farming. Farmers have easy accessibility to pesticides than any other poisons in the market.

Moreover, the profession of farming of farming is becoming increasingly difficult due to various factors such as lower rainfall, increase in cost of fertilizers and labour, which ultimately result in continuous loss, followed by increasing debt eventually leading them to commit suicide.

After the organophosphorous compound poisoning, the poisoning cases due to Herbicide poisoning are second highest according to table **5.1 and 5.2** as one of the previous study of profile of poisoning cases.

Among the pesticide poisoning cases, organophosphorous poisoning is about **78.18**% as mentioned in the table no.**5.1 and 5.2**. Monocrotophos is the most common known organophosphorous compound to cause poisoning (**14.73%** of total OPC poisoning), as it is the commonest OPC available in the market in the state of Andhra Pradesh.

Even though only one case of ethyl alcohol intoxication along with organophosphorous poisoning is reported in whole study period.

In our study, incidence of rat killer poisoning i.e., Rodenticide is **1.41** (4 cases).The self-consumption of rat killer poison with intension to die is more common among the literate and middle class, salarised individuals than illiterate and downtrodden.

Recent studies have shown that a high mortality is due to depression leading to suicide. It has been established that consistent exposure, especially to Organophosphate Pesticides, produces a distinct pattern of physical symptoms and hasPsychological and Neurobehavioral effects such as anxiety, depression and cognitive impairement.

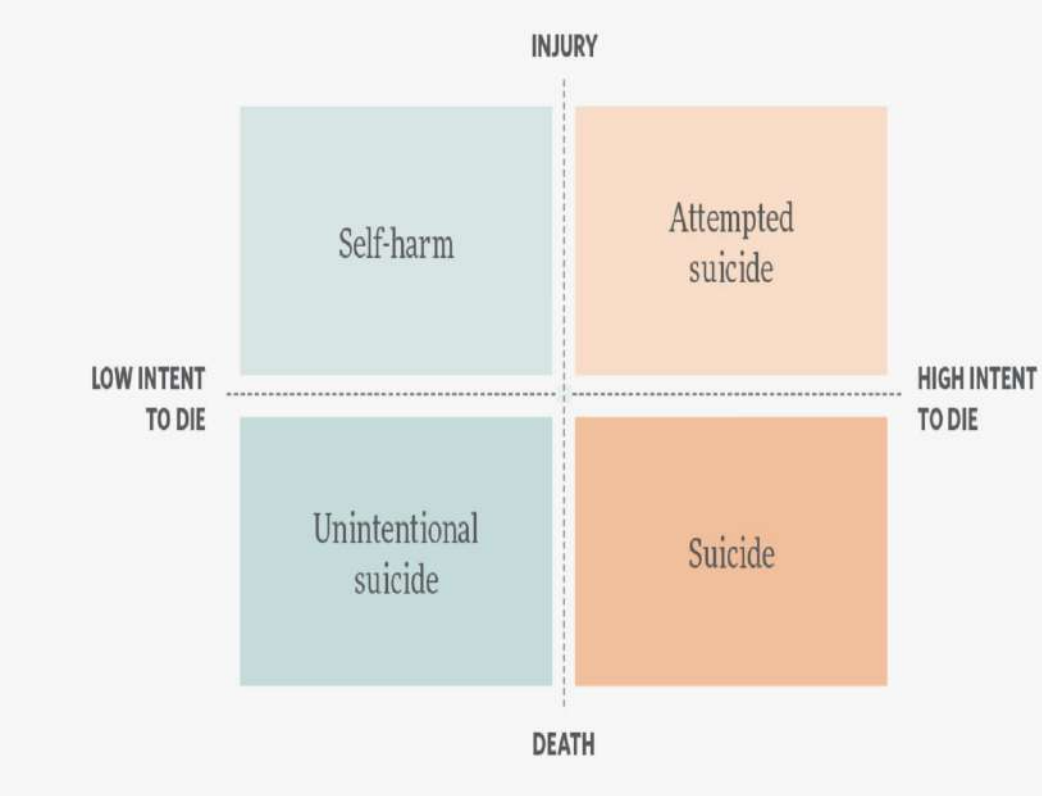
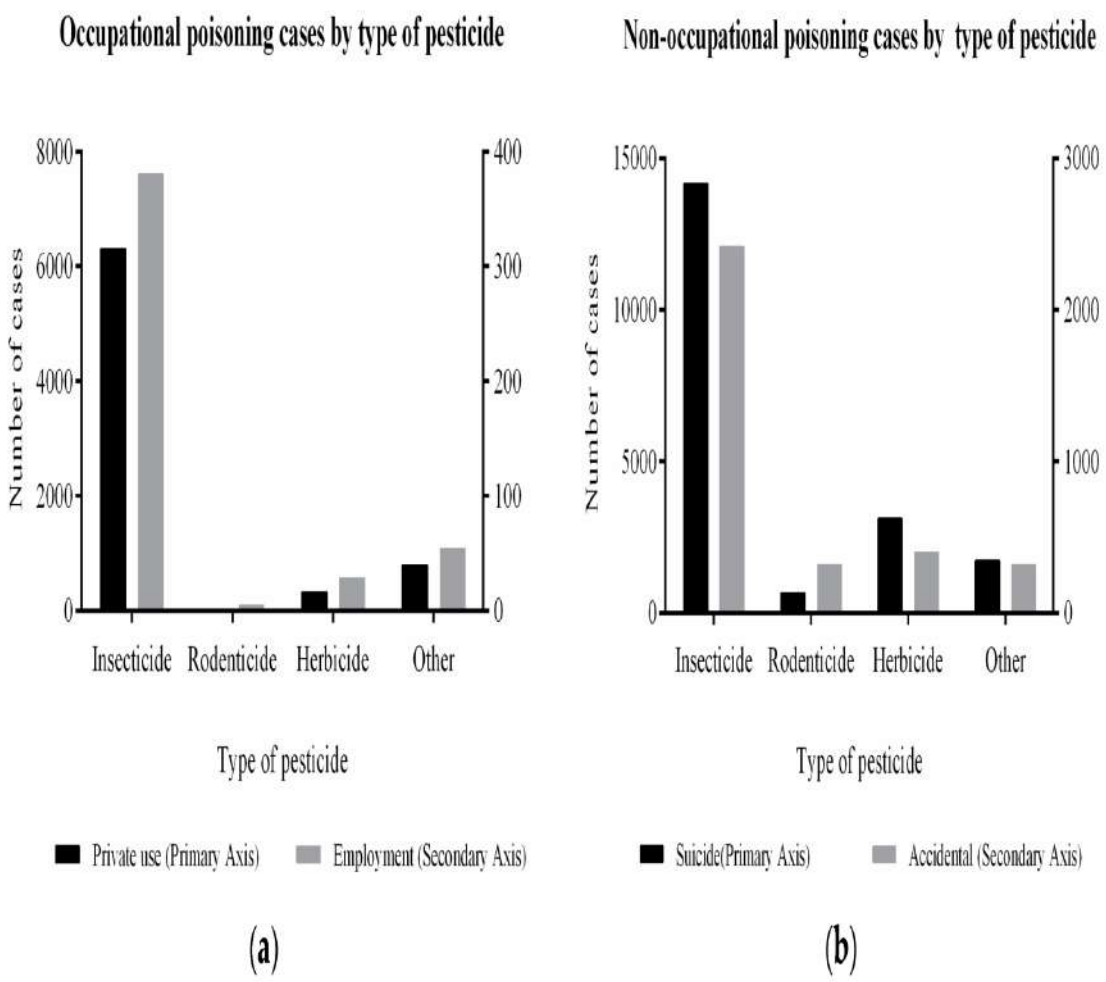


Fig.5.1 Types of suicides



Graph 5.1 Occupational and Non occupational Poisoning

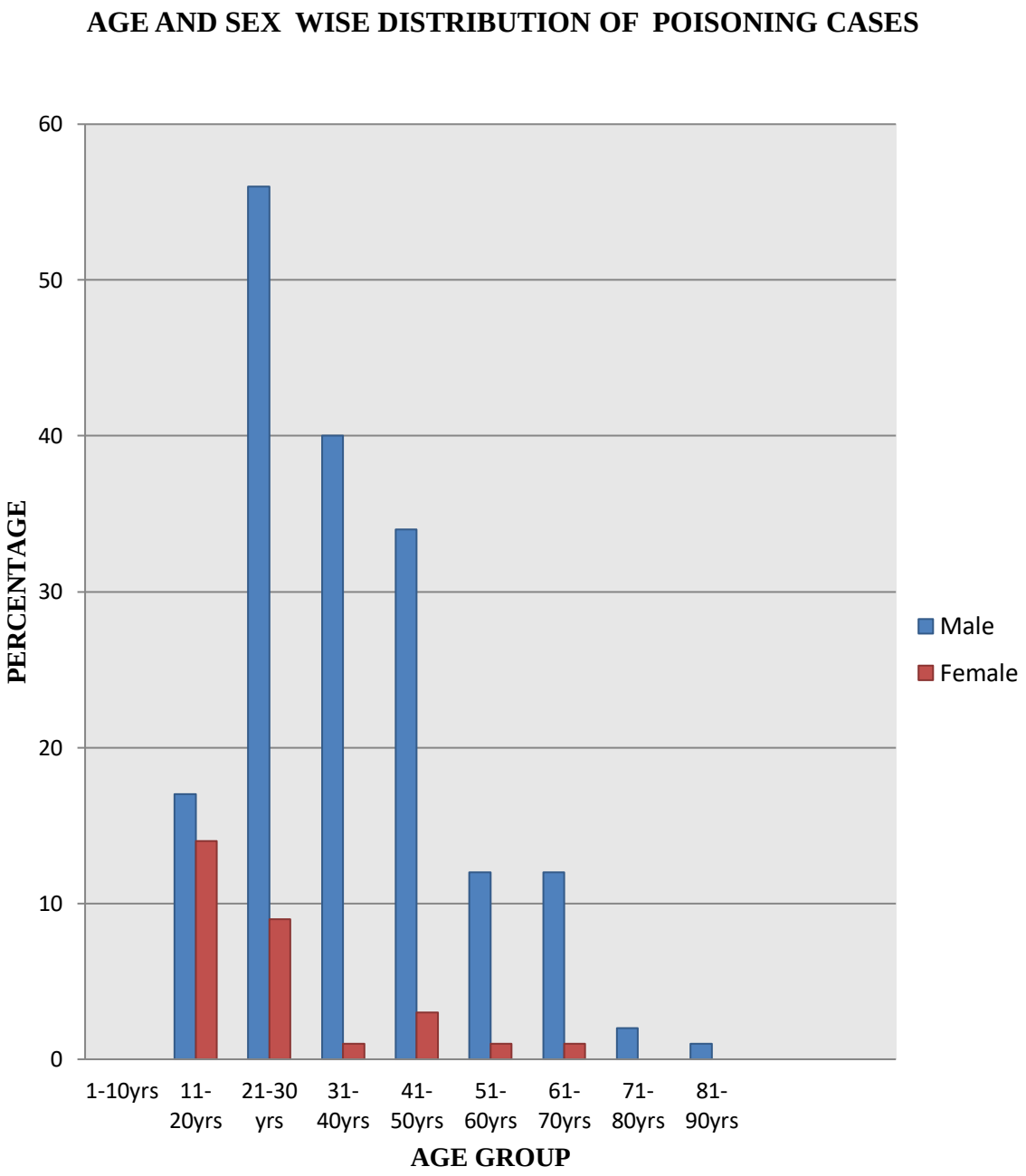
5.1 According To 2018 Statistical Analysis from 1st January to 31stDecember:

→ ***Age And Sex Wise Distribution Of Poisoning Cases:***

AGE GROUP	MALE		FEMALE		TOTAL
	NO.OF CASES	%	NO.OF CASES	%	
1-10 Yrs	0	0	0	0	0
11-20 Yrs	17	9.77	14	48.27	31
21-30 Yrs	56	32.1	9	31.03	65
31-40 Yrs	40	22.9	1	3.44	41
41-50 Yrs	34	19.5	3	10.34	37
51-60 Yrs	12	6.89	1	3.44	13
61-70 Yrs	12	6.89	1	3.44	13
71-80 Yrs	2	1.14	0	0	2
81-90 Yrs	1	0.57	0	0	1
TOTAL	174	100	29	100	203

Table.5.1 Age and Sex Wise Distribution of Poisoning Cases

→ ***GRAPH:-***



Graph.5.2 Age and Sex Wise Distribution of Poisoning Cases

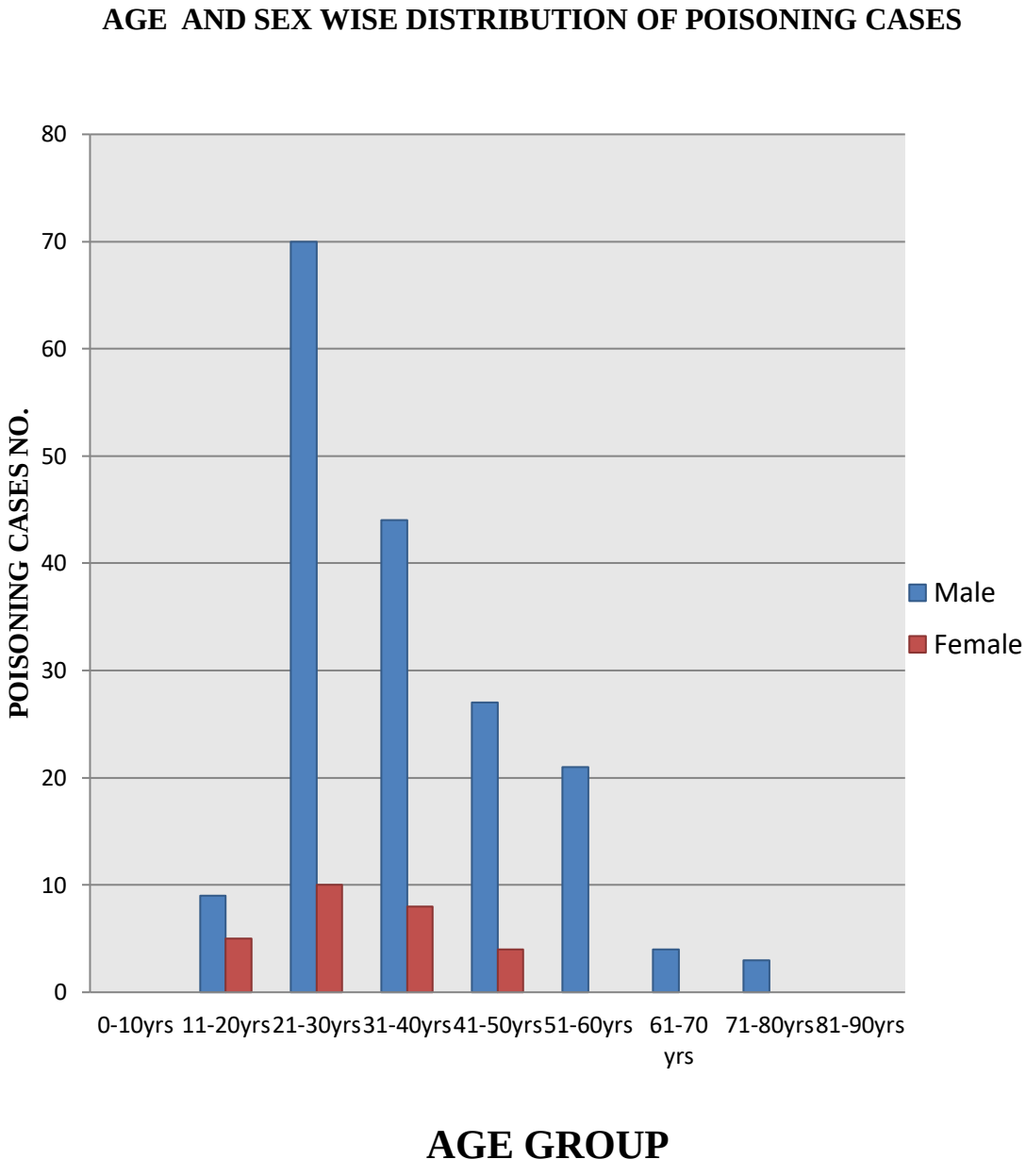
→ **5.2According To 2019 Statistical Analysis From 1st January To 31st December:**

→ ***Age And Sex Wise Distribution Of Poisoning Cases***

AGE GROUP	MALE		FEMALE		TOTAL
	NO.OF CASES	%	NO.OF CASES	%	
0-10 Yrs	0	0	0	0	0
11-20 Yrs	9	4.91	5	18.5	14
21-30 Yrs	70	38.25	10	37.03	80
31-40 Yrs	44	24.04	8	29.6	52
41-50 Yrs	27	14.7	4	14.8	31
51-60 Yrs	21	11.47	0	0	21
61-70 Yrs	4	2.18	0	0	4
71-80 Yrs	3	1.63	0	0	3
81-90 Yrs	0	0	0	0	0
TOTAL	183	100	27	100	210

Table.5.2 Age and Sex Wise Distribution of Poisoning Cases

→ ***GRAPH:-***



Graph.5.3 Age and Sex Wise Distribution of Poisoning Cases

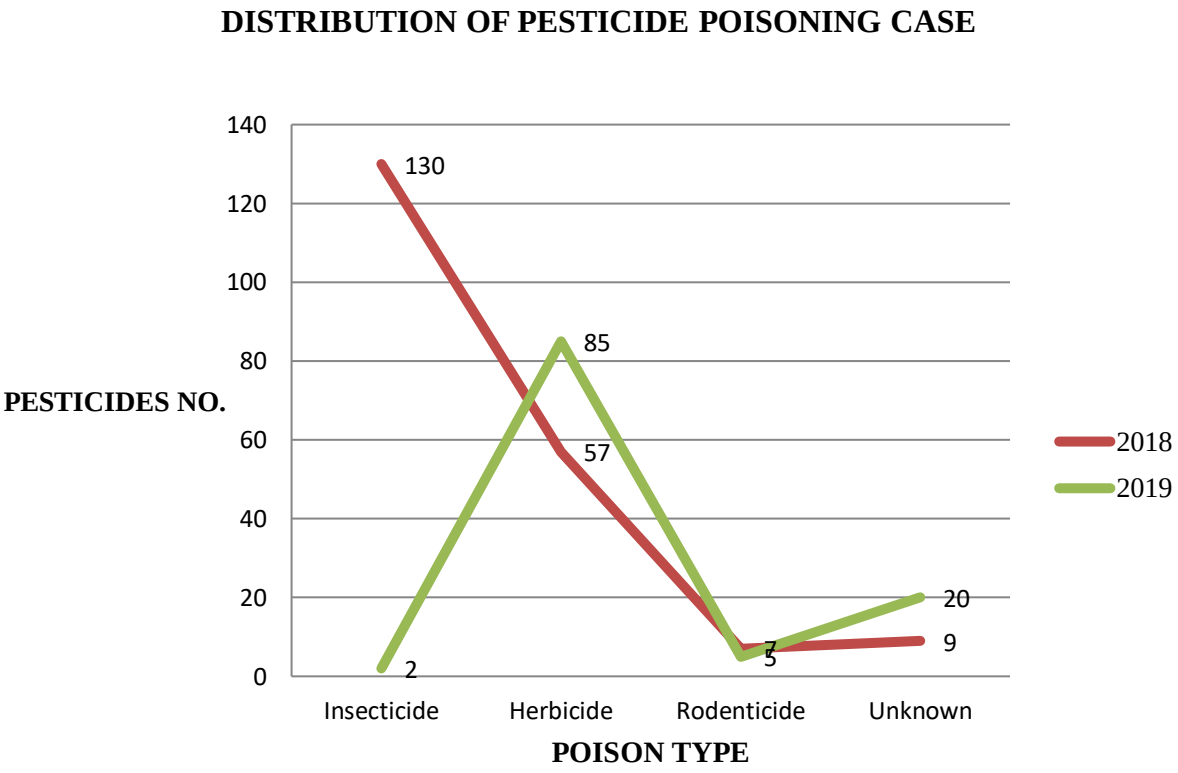
5.3According to 2018 and 2019 statistical analysis:-

→ ***Poison Wise Distribution Of Pesticide Poisoning Case:-***

TYPE	POISON	2018	%	2019	%
INSECTICIDE	ORGANOPHOSPHOROUS	130	64.03	100	47.61
HERBICIDE	PARAQUAT DICHLORIDE	57	28.07	85	40.47
RODENTICIDE	ZINC PHOSPHIDE	7	3.44	5	2.380
UNKNOWN	-	9	4.43	20	9.52
TOTAL		203	100	210	100

Table.5.3 Poison Wise Distribution of Pesticide Poisoning Case

→ ***Graph:-***



Graph.5.4 Poison Wise Distribution of Pesticide Poisoning Case

CHAPTERR-6

CONCLUSION

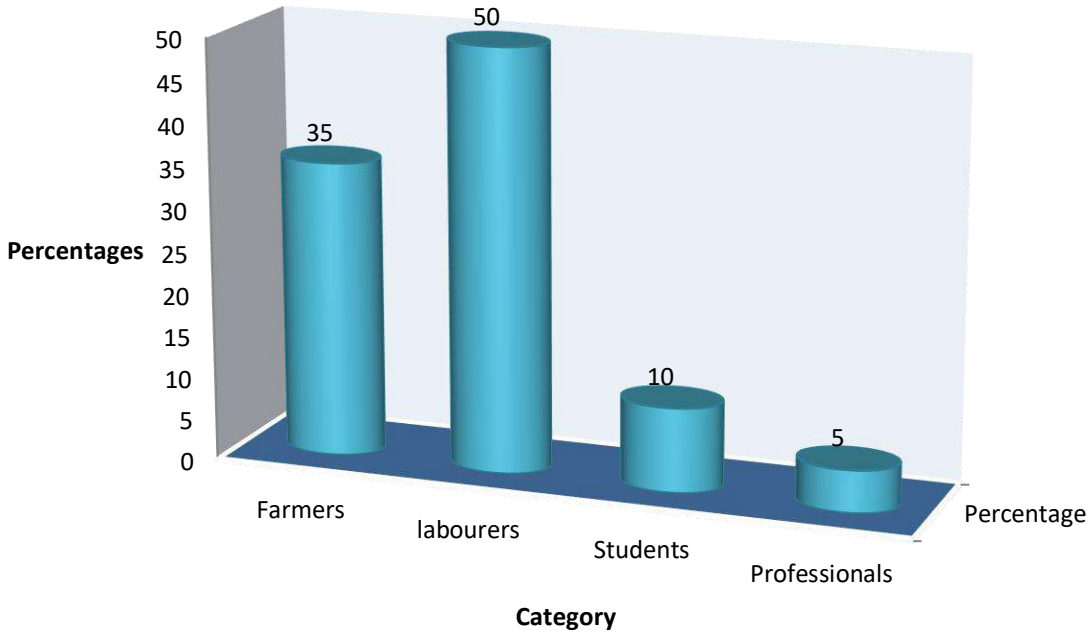
6.1 CONCLUSION:

Pesticide poisoning is the commonest mode of poisoning. Farmers are the most affected in both the top ranking poisoning cases as they have the highest occupational exposure (total of **68.31%**) of poisoning cases.

Poisoning by Organophgosphorous compounds are observed in **2018** is (**64.03%**) and in **2019** is (**47.61%**)and then followed by Paraquat dichloride in **2018** is (**28.07%**) and in **2019** is (**40.47%**) in cases of poisoning males are more affected than females and the people of age group **21-30** years are the most affected irrespective of their sex.

Farmers & Labourers are most affected by poisoning than other professionals.Organophosphorous compound is the most chosen pesticide for poisoning with intention to end their life.

Final conclusion, Pesticide suicide rates increased dramatically once the Green Revolution brought highly hazardous pesticides into poor rural households, leads to many deaths annually. Effective prevention will require better data and should rely on pesticide regulation to remove all highly hazardous pesticides from small scale farming since improved pesticide storage is unlikely to be effective.



Graph.6.1 Percentage of category

REFERENCE

1. Latha KS, Bhat SM, D'Souza P. Suicide attempters in a general hospital unit in India: their socio-demographic and clinical profile - emphasis on cross-cultural aspects. Acta Paediatrica Scand. 1996;94:26–30. [PubMed] [Google Scholar]
2. Phillips MR, Yang G, Zhang Y, Wang L, Ji H, Zhou M. Risk factors for suicide in China: a national case-control psychological autopsy study. Lancet. 2002;360:1728–1736. [PubMed] [Google Scholar]
3. Singh S, Wig N, Chaudhary D, Sood NK, Sharma BK. Changing pattern of acute poisoning in adults: experience of a large north-west Indian hospital 1970-1989. Journal of the Association of the Physicians of India. 1997;45:194–197. [Google Scholar]
4. Maniam T. Suicide and parasuicide in a hill resort in Malaysia. British Journal of Psychiatry. 1988;153:222–225. [PubMed] [Google Scholar]
5. Hettiarachchi J, Kodithuwakku GC. Pattern of poisoning in rural Sri Lanka. Int.J Epidemiol. 1989;18:418–422. [PubMed] [Google Scholar]
6. Eddleston M. Patterns and problems of deliberate self-poisoning in the developing world. QJM. 2000;93:715–731. [PubMed] [Google Scholar]
7. Somasundaram DJ, Rajadurai S. War and suicide in northern Sri Lanka. Acta Psychiatr.Scand. 1995;91:1–4. [PubMed] [Google Scholar]
8. Hutchinson G, Daisley H, Simeon D, Simmonds V, Shetty M, Lynn D. High rates of paraquat-induced suicide in southern Trinidad. Suicide Life Threat.Behav. 1999;29:186–191. [PubMed] [Google Scholar]
9. Cantor CH. Suicide in the Western World. In: Hawton K, van Heeringen K, editors. The International Handbook of Suicide and Attempted Suicide. Chichester: John Wiley and Sons Ltd.; 2000. pp. 9–28. [Google Scholar]
10. Forensic Medicine And Toxicology-V.V Pillay