REVIEW OF LITERATURE

The biomedical literatures were reviewed in every phase of this research work starting from formation of research question, protocol development and execution of work, data analysis, thesis formatting and publication. All the three types of literature resources namely primary, secondary and tertiary were used effectively and efficiently. Apart from the regular resources for literatures, IOWA Drug Information System (IDIS) and drug and poison information center located at the Government district headquarters hospital, Ooty were well used for updating the information.

The relevant information from such resources are summarized and presented in this section in the following subtitles.

1. Epidemiology
2. Parameters analyzed in epidemiological studies
3. Epidemiology of poisoning cases
4. Identification of poisoning agents
5. Agrochemical poisoning
6. Agrochemical poisoning in Udhagamandalam
7. Healthcare expenditure assessment
8. Organophosphate compounds
9. Clinical manifestations organophosphate poisoning
10. Management of organophosphate poisoning
11. Limitations of organophosphate poisoning management

EPIDEMIOLOGY

Epidemiology is the study of the patterns, causes, and effects of health and disease conditions in a defined population. It is the cornerstone of public health which shapes policy decisions and evidence-based practice by identifying risk factors for disease and targets for preventive healthcare. In epidemiological studies the occurrence of disease or condition are measured using rates. The rates tell us how fast the condition is occurring and spreading in a population. They can provide the idea of incidence rate, mortality rate and prevalence rate of a specific problem with respect to socio demographic characteristics in a given community. Apart from the illness, disability or death rates, the positive phase of a particular condition is counted in these studies and useful in improving the public health\(^{(1,2)}\).

PARAMETERS ANALYZED IN EPIDEMIOLOGICAL STUDIES\(^{(62)}\)

Incidence rate

Incidence rate is the measure of new events as well as the risk of developing the condition. These measurements are useful in identifying the population at risk with respect to age group, male or females, occupational group and so on.

Incidence rate = (Number of new cases of a disease occurring in the population during a specific period of time \(\div\) Number of persons who are at risk of developing the disease during that period of time) \(\times\) 1000.
Prevalence

Prevalence measures of frequency of health related events, which are already, exist in a specific community.

Prevalence rate = (Number of cases of a disease occurring in the population during a specific period of time ÷ Number of persons who are at risk of developing the disease during that period of time) × 1000. The denominator represents the number of people who are at risk for developing the condition.

Mortality rate

Mortality rate can serve as the measure of disease severity, and can help us to determine whether the treatment for a disease has become more effective over time. In addition mortality rates may serve as surrogates for incidence rates when the disease being studied is a severe and lethal one. The result obtained can be used to compare the risk for people in different geographic areas and sub groups in the population.

Mortality Rate = (Total number of deaths from all causes in 1 year ÷ Number of persons in the population at mid-year) × 1000.

Case-fatality rate:

Case fatality rate is the measure of the severity of the disease. This value represents chance of the patients dying in a specific condition even though mortality rate is very less.

Case fatality rate (%) = (Number of individuals dying during a specified period of time due to a specific condition ÷ Number of individuals affected with that condition) × 1000.

EPIDEMIOLOGY OF POISONING CASES

Shreemanta Kumar Dash et al evaluated the pattern of poisoning cases including death over a period of 2 years from 1999-2001 in Orissa. Organophosphate compounds were the most commonly abused substance. Males predominated in this study with male to female ratio 1.14:1. Peak incidence was observed in the age group 21-30 years. More than four-fifth of the cases belonged to medium socioeconomic status. Majority of the victims were literate and married outnumbered the unmarried cases. Occurrence of poisoning was more common in day time and during summer season.

A.D. Mahabalshetti was aimed to assess the pattern and outcome of acute poisoning cases in a tertiary care hospital in Karnataka. The study included 104 cases and data regarding age, sex, time elapsed after intake; circumstances of poisoning, name of the poisonous substance, chemical type, severity and outcome were collected in the prestructured proforma. A majority of poisoning cases were due to organophosphorous compound. Suicide by poisoning was the most common mode of poisoning for both male and female. Poisoning is more common in young individuals. The overall mortality is substantially high, mainly contributed by self-poisoning with pesticides.

M. Shoaib Zaheer et al determined the various parameters of poisoning such as mode and type of poisoning, relation to sex, occupation, marital status, vulnerable age group, outcome of patients with poisoning, and to find out the most common type of poison used in the North
Indian states. Organophosphates and aluminium phosphide constituted the majority of cases. The distribution pattern was statistically significant (P<0.001). Strict legislative measures over the sale of poison and increase in public awareness about the seriousness of the problem through health education should be undertaken.

Subash Vijaya Kumar(33) et al characterized the poisoning cases admitted to the tertiary care hospital, Warangal district, Andhra Pradesh. They reviewed data obtained from the hospital medical records and included the following factors: socio-demographic characteristics, agents and route of intake and time of admission of the poisoned patients. This study highlighted the lacunae in the services of tertiary care hospitals and the need to establish a poison information center for the better management and prevention of poisoning cases.

CH. Srinivas Rao(8) et al in their study aimed to describe frequency and distribution, assess quality of management and subsequent outcomes from pesticide poisoning in one large hospital at Warangal district in Andhra Pradesh, southern India. During 6 years, 8040 patients were admitted to the hospital with pesticide poisoning. The overall case fatality ratio was 22.6%. More detailed data from 2002 revealed that two-thirds of the patients were <30 years and 96% had intentionally poisoned themselves. Males outnumbered females. Two compounds, monocrotophos and endosulfan, accounted for the majority of deaths with known pesticides in 2002. Low fixed-dose regimens were used in the majority of cases for the most commonly used antidotes (atropine and pralidoxime). Inappropriate antidotes were also used in some patients. Even without an increase in resources, there appear to be significant opportunities for reducing mortality by better medical management and further restrictions on the most toxic pesticides.

Kiran N(69) et al evaluated the pattern of poisoning at a tertiary care hospital in South India, Bangalore and studied the sociodemographic profile also. In this study they found male patients predominated over female patients and young patients were affected more. Organophosphate pesticide was the most commonly used agrochemical for poisoning. The conclusion of the study was as follows. Establishing a poison information center (PIC) which should be networked with other PICs in India and also with developed countries can help in early identification of poisoning and also managing the cases by sharing the information. Awareness to the public regarding information on poison prevention has to be penetrated.

H Jaiprakash(9) et al in this study analyzed the pattern, cause and mortality rate of poisoning. The study was conducted in a rural area in South India. The data was analyzed using descriptive statistics. Among various poisoning cases male outnumbered females and young patients were affected more. The poisons consumed were as follows: Organophosphorus 135 cases, aluminum and zinc phosphide 50 cases, phenobarbitone 18 cases, benzodiazepines 7 cases, paracetamol 2 cases, miscellaneous 13 cases. Mode of poisoning came more was suicidal. Establishment of strict policies against the sale and availability of pesticides and over the counter drugs is an effective way to control organophosphorous and drug poisoning.

Bhoopendra Singh(5) et al characterized the poisoning cases admitted to the Government Wenlock Hospital at Mangalore, India. Data obtained from the hospital medical records and included the following factors: socio-demographic characteristics, agents and route of intake, and time of admission of the acutely poisoned patients. The poisons responsible for most of the mortality were organophosphate pesticides (65%) and aluminium phosphide (15%). In summary, the prevention and treatment of poisoning due to organophosphate and aluminium phosphide should merit high priority in the health care of the indigenous population of South India.
Vishwajeet Pawar\(^{(67)}\) *et al.* investigated the trends of poisoning cases at central India. During the study they observed more poisoning cases in male patients. Insecticides were the most common agent used for poisoning. Suicidal cases were more compared to accidental cases. More number of poisoning cases observed in winter season. Agriculture was the most common occupation and financial problem arised as the commonest reason for poisoning in married and unmarried peoples.

Tanuj Kanchan\(^{(68)}\) *et al.* evaluated the difference in pattern of suicidal poisoning among males and females to identify population at risk, and understand the problem status among both genders in Southern India. During this period, a total of 137 cases of suicidal poisoning related deaths were autopsied. Males were predominantly affected. Males usually consumed poison during evening and late night hours. Maximum male mortalities were noted during second quarter of the year in contrast to first quarter in females.

Alexander A. H. Lawson\(^{(69)}\) *et al.* reviewed all the acute poisoning cases admitted to an acute medical unit without special facilities for the treatment of poisoning. In this hospital set up experiences limitations in medical, nursing, and laboratory facilities for better treatment. Now they compared the results with that obtained from specialized units.

Bharath K. Guntheti\(^{(70)}\) *et al.* studied the patterns of poisoning cases admitted at Khammam, Andhra Pradesh. The common motive of poisoning was suicidal. The most commonly abused substance was organophosphate. The number of male patients outnumbered female patients. Peak incidence of poisoning was observed in younger age groups. The study observed increasing trend of suicide by organophosphate compounds and rat poison, whereas other poisons for committing suicide are less commonly used and here with—reflecting the pattern of poisoning in Khammam.

Anand Mugadlimath\(^{(71)}\) *et al.* carried out a retrospective analysis of all poisoning cases admitted in Bijapur, Karnataka. In this 12 month study they found male and married patients outnumbered females. Insecticides were the most common poison used for the suicidal purpose. The commonest agent used for poisoning was organophosphates. Younger patients were more prone to poisoning than old patients. They concluded that illiteracy and low economic status were responsible for this scenario.

Vijayamahantesh S.N\(^{(72)}\) *et al.* conducted a prospective study on Sociodemographic profile of poisoning cases of Gulbarga region. They found that majority of poisoning cases were seen in married people. Maximum number of poisoning was recorded in August. The most common poison responsible for death is organophosphate. Male patients overcome the females. Rural victims outnumbered urban. Majority of poisoning was seen with married and illiterate people.

Devendranath Sarkar\(^{(73)}\) *et al.* carried out a descriptive retrospective study on poisoned patients who were admitted to Rangpur Medical College Hospital. During the study they got the results as follows. Males slightly outnumbered females. Organophosphate was the most commonly used toxic agent for poisoning. Financial disharmony was the main cause of suicide. So they concluded that specific strategies should develop for prevention and educational programs against deliberate self-poisoning.

Satinder P. Singh\(^{(74)}\) *et al.* carried out the study to review the deaths related to poisoning in Malwa region of Punjab. They found that younger male patients were predominated more. Winter and summer months were having higher incidence of poisoning cases. Aluminium
phosphide and organophosphate compounds were the commonest agents causing poisoning. The results of the present study have been compared to those from India and around the world.

Tanuj Kanchan\(^{(10)}\) et al. was done a study to understand the magnitude and pattern of all poisoning fatalities in relation to the manner of death in Manipal region of Southern India. Males were predominantly affected. Organophosphate compounds were implicated in 68.7% of the total poisoning related fatalities. Males in the 3rd to 5th decades were prone to self-poisoning with organophosphate compounds. Accidental poisoning deaths were uncommon and poisoning was not a preferred method of homicide in this region. The study reveals that quantitative chemical (toxicological) analysis is required to further strengthen and improve the databases of epidemiology of poisoning in our region.

AK Batra\(^{(13)}\) et al. reviewed Autopsy records in fatal poisonings were studied for age, sex, residence, marital status, type of poison and manner of poisoning (accidental, suicidal or homicidal). Admission and death rates of acute poisonings were compared with those from other unnatural causes. Young, married, patients from rural area was affecting more compared to other patients. Insecticides were the commonest agent used for poisoning. Young married males of rural background with agricultural occupation and failure of monsoon is the risk factors associated with poisoning cases.

J. Jeyaratnam\(^{(12)}\) et al. done the sample survey of clinical records of patients admitted to the different hospitals in Sri Lanka. Mode of poisoning found more commonly was suicide. Young patients were affected more compared to older patients. Males predominated over females. Organophosphate compounds were found to be the commonest agents used for poisoning.

Emad M. Abdullat\(^{(75)}\) et al. A prospective autopsy study addressing fatal poisoning with agricultural and horticultural pesticides was undertaken in Jordan over a 4 year period. The main pesticide used was carbamate poisoning followed by organophosphate. Young patients were affected more. Enforcement of a new legislation addressing the availability of agricultural and horticultural pesticides for self-harm, especially carbamates and organophosphorus, is the most important strategy in the long term to prevent fatal pesticides poisoning in Jordan.

Muhammad Nurul Islam\(^{(76)}\) et al. investigated the pattern, trend and incidence of unnatural poisoning deaths attended in Sir Salimullah Medical College Mortuary, Dhaka, Bangladesh. The main reasons behind taking poison were diseases, familial dispute, alleged insanity and marital discord. Organo-chlorine compounds were the main agents used for poisoning. Age group of 13-14 was affected more. Gender distribution shows males predominated over females. The attempt of suicide was done by the people mainly from urban areas.

Kambiz Soltaninejad\(^{(77)}\) et al. was assessed the effects of epidemiological variables on fatal pesticide poisoning. Among these medico legal autopsies, fatal poisoning cases were evaluated retrospectively by reports of toxicological analysis. The variables such as age, sex, job, residential location, educational level, type of pesticide and cause of poisoning were reviewed. The most common type of poisoning was suicidal and the agent used was Aluminium phosphide and organophosphate compound.

M. Ziya Kir\(^{(78)}\) et al. in this study, medico-legal deaths between the years 2001 and 2011 in Ankara and nearby cities in Turkey were investigated retrospectively. Insecticides were the most common (94%) cause of fatal pesticide poisonings, most of them (63%) being organophosphate insecticides. Intensive efforts to reduce occupational and intentional pesticide poisonings are urgently needed in Ankara and nearby cities.
Sadananda Naik B\textsuperscript{(79)} et al. evaluated the clinical and demographic profile of acute poisoning cases admitted to Alva’s Health Centre, Moodabidri, Karnataka. A total of 150 patients were admitted for acute poisoning during the study period and found female predominance. Most of the poisoning were intentional and the vast majority of whom consumed agrochemical poisoning.

B. Maharani\textsuperscript{(80)} et al. were reviewed information with regard to acute poisoning in adults at Salem, Tamil Nadu. It is a retrospective study conducted during Jan 2009-Jan 2012 in a tertiary care hospital. 150 cases of acute poisoning in adults due to drugs and chemicals were included. Data on age, sex, marital status, occupation, religion, locality, type of poison, time and month of intake, route of exposure, associated co-morbid conditions and outcome of poisoning were recorded and analyzed by descriptive method. Males outnumbered females. Organophosphorous compound was the most commonly used agent.

IDENTIFICATION OF POISONING AGENT

The poison information center is defined as the specialized unit providing all poison information including mechanism, diagnostic details, primary care required, management, interpretation of laboratory details, toxicovigilance and possible preventive methods. These services may helpful in the assessment of magnitude of poisoning cases in an area and enable the physicians to provide better management. The nature of the poison consumed by the patient can be suspected from the patient history, clinical symptoms and circumstantial evidences. The identification of poisoning agent by relying on this method cannot be used always. A large number of cases are observed with poor correlation between the patient clinical status and laboratory investigation reports\textsuperscript{(81,82)}.

AGROCHEMICAL POISONING

The prevalence of agrochemical poisoning is very high in India. This may be because of easy availability and low cost of agrochemicals. It is argued that restricting access to the most hazardous pesticides would be of paramount importance to reduce the number of severe acute poisoning cases and case-fatalities.

P.C. Abhilash\textsuperscript{(83)} et al review the technology of application of pesticides in India and recommend future strategies for the rational use of pesticides and minimizing the problems related to health and environment. Currently, India is the largest producer of pesticides in Asia and ranks twelfth in the world for the use of pesticides. The author has been observed that pesticide exposures are increasingly linked to immune suppression, hormone disruption, diminished intelligence, reproductive abnormalities and cancer.

Flemming Konradsen\textsuperscript{(84)} et al reviews the different options to reduce the availability of the most hazardous chemicals, focusing on issues in developing countries. The aim should be to achieve almost immediate phasing out of the WHO Classes I and II pesticides through national policies and enforcement. These short-term aims will have to be supported by medium- and long-term objectives focusing on the substitution of pesticides with safe and cost-effective alternatives, possibly guided by the establishment of a Minimum Pesticide List, and the development of future agricultural practices where pesticide usage is reduced to an absolute minimum.

Andrea Viviana Waichman\textsuperscript{(85)} et al investigates levels of understanding of pesticide handling among farmers by focusing on their ability to understand the information displayed on product
labels, which might affect risk reduction. The information displayed on product labels was not effective in promoting protective and safety measures. Farmers, in the main, do not read the labels, reporting that the fonts are too small, and that the instructions are too long and in overly technical language. They understood few of the pictograms, which are directed at the illiterate. In many cases, the inability to understand the information displayed led to the adoption of practices which actually increased exposure, risks to human health and environmental contamination. Farmers’ adopted practices and understanding of product labels is presented and possible alternatives discussed, including changes to the Federal law on pesticide product labeling.

Michael Eddleston\textsuperscript{(40)} et al reviews that use of pesticides is poorly regulated and often dangerous; their easy availability also makes them a popular method of self-harm. In 1985, the UN Food and Agriculture Organization (FAO) produced a voluntary code of conduct for the pesticide industry in an attempt to limit the harmful effects of pesticides. Unfortunately, a lack of adequate government resources in the developing world makes this code ineffective, and thousands of deaths continue today. WHO has recommended that access to highly toxic pesticides be restricted—where this has been done, suicide rates have fallen. Since an Essential Drugs List was established in 1977, use of a few essential drugs has rationalized drug use in many regions. An Analogous Minimum Pesticides List would identify a restricted number of less dangerous pesticides to do specific tasks within an integrated pest management system. Use of safer pesticides should result in fewer deaths, just as the change from barbiturates to benzodiazepines has reduced the number of deaths from pharmaceutical self-poisoning.

W. Van Der Hoek\textsuperscript{(86)} et al argued that the easy availability and widespread use of highly hazardous pesticides is the most important reason for this high number of poisoning cases. The frequent application of highly hazardous pesticides in high concentrations was often irrational and posed serious health and financial risks to the farmers. Sales promotion activities and credit facilities promoted this excessive pesticide use, which was not counteracted by an agricultural extension service. Hazardous practices when spraying pesticides were due to the impossibility of applying recommended protective measures under the local conditions, rather than to lack of knowledge. Current emphasis on programs that promote the safe use of pesticides through education and training of farmers will be ineffective in Sri Lanka because knowledge is already high and most poisoning cases are intentional. Instead, enforcement of legislation to restrict availability of the most hazardous pesticides would result in an immediate health benefit. Improved agricultural extension services to promote alternative non-chemical methods of pest control are the most important strategy, in the long term, to prevent acute pesticide poisoning.

Carmen Freire\textsuperscript{(87)} et al carried out the review and suggested that high exposure to pesticides, including poisoning, experienced by agriculture workers and rural residents may result in an elevated risk of psychiatric disorders and suicidal behavior. An updated systematic review was conducted in epidemiologic literature on the relationship of pesticide exposure with depression and suicide published over the last 15 years by using MEDLINE database. Depression or other psychiatric disorders have shown increased risks associated with previous pesticide poisoning in 5 studies, with statistically significant odds ratios (OR) ranging from 2.08 to 5.95. Lower risk estimates have been found for chronic pesticide exposure. Among studies on suicide, 4 reports found increased suicide rates in areas with intensive pesticide use (OR between 1.60 and 2.61) compared to areas with lower pesticide use. Occupation in agriculture has shown a significant association with higher suicide risk than other occupational groups.
AGROCHEMICAL POISONING IN UDHAHAMANDALAM

S Ponnusankar et al conducted a survey on agrochemical poisoning at Ooty, South India. In this two year survey they have analyzed the poisoning cases and found that among the various poisoning cases agrochemicals were widely consuming. This study revealed the misuse of pesticides in Nilgiris region.

HEALTHCARE EXPENDITURE ASSESSMENT

Pesticides, economics and health have been intimately related since the inception of pesticide use for crop production. The increased incidence rate of poisoning and hospitalizations lead to financial burden to individual, hospital and government. The cost of government healthcare services for treating victims is substantial in most cases. The costs of treating self-poisoned patients are not well documented in low income countries, where the overwhelming majority of poisonings occur. Lack of documentation is unfortunate because studies on health costs can inform health policy and guide investment and management at different levels of the healthcare system for optimizing resources. Information on the economic burden of illness associated with pesticide use could help in economic justifications of health and agricultural programs that are aimed at poisoning surveillance in the monetarily controlled environment of developing countries. Thus, the healthcare expenditure data of a particular disease in a particular area can assist the health policy makers in management at different levels of the healthcare system by optimizing the resources.

Wickramasinghe K et al conducted a study to estimate the direct financial costs to the Sri Lankan Ministry of Health of treating patients after self-poisoning, particularly from pesticides, in a single district. The average total cost of treating a self-poisoned patient at the general hospital was US$ 31.83, with ward staff input and drugs being the highest expenditure category and only US$ 0.19 of this sum related to capital and maintenance costs. The average total cost of treatment was highest for self-poisoning with pesticides (US$ 49.12). The patients placed in the intensive care unit, who comprised 5% of the total, took up 75% of the overall treatment cost for all self-poisoned patients at the general hospital. The average total cost of treating self-poisoned patients at peripheral hospitals was US$ 3.33. The average patient cost per transfer was US$ 14.03. In 2006, the total cost of treating self-poisoned patients in the Anuradhapura district amounted to US$ 76,599, of which US$ 53,834 were comprised of pesticide self-poisonings. Based on the total treatment cost per self-poisoned patient estimated in this study, the cost of treating self-poisoned patients in all of Sri Lanka in 2004 was estimated at US$ 866,304. The cost of treating pesticide self-poisonings may be reduced by promoting the use of less toxic pesticides and possibly by improving case management in primary care hospitals.

Gulsum Kavalci et al designed a study to investigate the epidemiological, clinical and economical aspects of deliberate self-poisoning patients admitted to Yenimahalle State Hospital Intensive Care Unit. Exposed poisons were classified into one of three categories; pharmaceuticals, pesticides, and alcohols. Cost account was based on the medical invoices at patient discharge. There was no statistically significant difference between pharmaceutical agents in terms of hospital cost (P > 0.05). The mean length of hospital stay was 6.4 ± 4.3 days. There was a statistically significant difference between the lengths of stay of patients in terms of hospital cost (P < 0.05). The patient cost increased as the length of stay increased due to the policy of bundle pricing.
**Serinken M** et al. conducted a study to investigate hospital costs of deliberate self-poisoning (DSP) cases and relevant factors in a university-based emergency department (ED) in Turkey. Total costs showed statistically significant differences with respect to sex, type of intoxicants, and location of treatment. Venipuncture, monitoring, nasogastric tube insertion, and gastric lavage were the procedures most commonly applied. Activated charcoal was administered to 66.9% (n=146) of the study sample. The study sample had many differences in demographic and clinical outcomes of patients with DSP as well as hospital costs compared with global reports. Gender, ingestion of non-medical substances, and treatment location affected the total hospital costs of these patients. Strategies focusing on high-risk subgroups and conditions may help to reduce unnecessary expenses.

**Chiara MT** et al. assessed the risk associated with pesticide abuse. Pesticide use in agriculture poses several risks to both human health and non-target agro-ecosystems. Due to lack of information on the monetary value of reducing pesticide risks, it is difficult to perform an economic analysis that addresses social efficiency of policy and draws conclusions about the appropriate degree of regulation.

**Yeo HM** et al. in their study estimated the cost of treatment of an illness. The treatment cost of a case of deliberate self-harm (DSH) to a large University Teaching Hospital and reviewed the case notes of 190 consecutive cases of deliberate self-harm presenting to emergency department. On average, each attendance costs 425.24 pounds to hospital discharge.

**Pato Pato A** et al. made a financial estimate of the costs of epilepsy in adults. The direct costs included: treatment received, number of visits to neurology, primary care, and emergencies, number of days admitted to hospital, number and type of diagnostic tests, use of transport to and from hospital, and psych pedagogic and social support due to the epilepsy. The indirect costs were analyzed according to, loss of work productivity of the patients, taking into account families where the patient needed supervision due to epilepsy. The total costs were derived from the sum of the direct and indirect costs. The intangible costs were calculated according to QOLIE-10 questionnaire. The greatest percentage of costs associated to epilepsy is due to the work productivity loss by the patients. The costs of psychological and social suffering in epilepsy lead to a deterioration in the quality of life.

**Fatma Mutlu Kukul Guven** et al. conducted a study to emphasize the cost-lowering effect of treatment and follow-up of such suicide cases in Emergency Departments instead of intensive care units. A total of 791 adult patients with suicidal attempts were retrospectively examined and their clinical and demographic data were included. In addition, the costs of their treatment in the ED, ICU and Psychiatric Clinic between 01/01/2007 and 31/12/2011 were compared. The study concluded that it would be profitable if the intoxication cases were followed-up in the ED observation units and that ED’s could be used more effectively than ICUs.

**ORGANOPHOSPHATE COMPOUNDS**

Organophosphates are the insecticide most commonly used worldwide in the pest control of the crop. Toxic exposure to these toxic chemical is serious health problem. The mode of entry is inhalation, dermal and intentional ingestion by workers. There are more than a hundred organophosphorous compounds in common use. These are classified according to their toxicity and clinical use.
1. Highly toxic organophosphates: (e.g. tetra-ethyl pyrophosphates, parathion).
2. Intermediately toxic organophosphates: (e.g. coumaphos, clorpyrifos, trichlorfon).
3. Low toxicity: (e.g. diazinon, Malathion, dichlorvos).

It crosses the blood brain barrier. They are potent inhibitors of acetyl cholinesterase and pseudo cholinesterase. This may lead to decreased hydrolysis of acetylcholine. The toxicological effects are due to accumulation of acetyl choline at synapses. The cholinergic synapses are present in CNS, somatic nerves, autonomic ganglion and parasympathetic nerve endings like sweat glands. The signs and symptoms which are due to muscarinic and nicotinic effects appear within a few minute to few hours (average: 6-8 hours) and the crucial period is first 24 hours.

M. Kazemi\( ^{95} \) et al evaluated that the use of OPs has a number of health advantages, including control of insect vector borne diseases and increasing the food and agriculture productions. However, the use of these toxic compounds on man, animals or in his immediate environment has caused potential hazards that seriously are baneful for public health. There has been increasing awareness and concern on the part of food and health officials and of the dairy industry about the presence OPs in milk and other milk products.

Paudyal BP\( ^{34} \) made a review on hazardous effects of organophosphate compounds. They are a group of pesticides that includes some of the most toxic chemicals used in agriculture. OP toxicity is due to the ability of these compounds to inhibit an enzyme, acetyl cholinesterase at cholinergic junctions of the nervous system. This review will deal with the history and composition, its uses and role in pollution, metabolism of OPs, health impacts, and clinical manifestations of its toxicity, diagnostic methods and treatment. It should concentrate on the optimization and monitoring of usage of OP compounds as pesticides and furthermore, encouraging the farmers to use natural pesticides and organic agriculture rather than chemical pesticides.

Eun Jung Kang\( ^{96} \) conducted a study to describe the clinical course, diagnosis and outcome of acute organophosphate (OP) insecticide poisoning. Lab investigations done included blood complete picture, urea, creatinine, ABG’s, and serum cholinesterase levels. Variables of the study included gender, mode of exposure, clinical course, management and complications. The majority of patients exhibited the classic clinical features of parasympathetic over activity. Patients received atropine, Pralidoxime and atropine along with Pralidoxime. Complications encountered during their treatment and stay in the hospital included aspiration pneumonia, hyperglycemia, respiratory failure, urinary tract infection, cellulitis, phlebitis. The study was concluded that the widespread use of organophosphates as a household and agricultural pesticide, in the absence of adequate regulations and education in their use is probably the most important reason for OP poisoning in an agricultural country like Pakistan. Despite severe toxicity in most of our cases, there were very few fatalities. This reflects the necessity of early diagnosis, treatment and the implementation of advanced supportive care in ICU.

Girish Thunga\( ^{37} \) et al were aimed to correlate the incidence of acute OP poisoning with the type of pesticides, its clinical characteristics and quality of management provided with subsequent outcomes in the patients. The most predominant of the affected age groups was 21-30 years (60.5%). The most common reason for poisoning was attempted suicide (98%). The most common OP compounds exposed were methyl parathion and Quinolophos. The most frequent clinical signs were salivation, miosis, fasciculation, respiratory system findings, tachycardia, and hypertension. The total mortality rate of the study population was found to be 25%. Medical management mainly involved administration of pralidoxime and atropine along with supportive management. There was always correlation with type of compound, pre-
hospitalization period and the type of management may be useful for preventing the mortality rate in developing countries like India.

Franz Worek\(^{(97)}\) et al reported that Organophosphate present a constant threat to the population. Sensitive and specific methods for the detection and verification of exposure to nerve agents are required for diagnosis, therapeutic monitoring, health surveillance and forensic purposes. Determination of acetyl cholinesterase and butyryl cholinesterase activity in blood remains a mainstay for the fast initial screening but lacks sensitivity and specificity.

**CLINICAL SYMPTOMS OF ORGANOPHOSPHATE POISONING**

Signs of organophosphate poisoning are classified into muscarinic, nicotinic, and central nervous system (CNS) levels. Helpful signs of poisoning include the pungent garlic like odour of organophosphorous in breath and vomitus, miosis, bradycardia and muscle fasciculations. Excessive salivation, excessive respiratory tract secretions and lacrimation are also indicating organophosphate poisoning. It should be remembered that some patients may present with the nicotinic effects of tachycardia, hypertension and mydriasis (rather that the anticipated bradycardia, hypotension and miosis)\(^{(6)}\).

The Poisoning severity score (PSS) is a classification scheme for cases of poisoning in adults and children\(^{(39,44)}\). This scheme should be used for the classification of acute poisonings regardless of the type and number of agents involved. The occurrence of a particular symptom is checked against the chart and the severity grading assigned to a case is determined by the most severe symptom(s) or sign(s) observed. Severity grading should take into account only the observed clinical symptoms and signs and it should not estimate risks or hazards on the basis of parameters such as amounts ingested or serum/plasma concentrations. The signs and symptoms given in the scheme for each grade serve as examples to assist in grading severity.

Similarly, the Peradeniya Organophosphorous Poisoning (POP) scale has identified clinical parameters which can grade severity without any laboratory investigations\(^{(42,43)}\). 5 common clinical manifestations of OP intoxication have been selected as the parameters. These are representative of muscarinic, nicotinic and central effects of acute cholinergic phase. The score is obtained at the initial presentation before any medical intervention.

Khazi MA\(^{(98)}\) et al evaluated the correlation between the clinical score described by Peradenya Organophosphorous Poisoning (POP) scale, serum pseudo cholinesterase level at presentation, ventilator requirement and the outcome. The results shown that the severity of poisoning as measured by POP scale directly correlated with serum cholinesterase level (P<0.001). There were 50% patients in moderate poisoning score and only 5% patients in severe poisoning. A total of 18% of the patients died of which 85% belonged to moderate and severe group. POP scale directly correlated with death outcome (P<0.001). It was also seen that all the patients with pseudo cholinesterase level less than 50% of normal range were ventilated. Lower Pseudo cholinesterase level also directly correlated to death outcome (P<0.001).The study concluded that the POP scale and serum cholinesterase at presentation appeared useful to assess the severity of poisoning, particularly in terms of need for ventilator and prolonged duration of hospital stay.

Chen Chang Yang\(^{(99)}\) et al reviewed that cholinesterase levels are useful in predicting successful weaning of patients from mechanical ventilation. The clinical features of OP poisoning are bronchial secretions, altered conscious level, pneumonia, intermediate syndrome...
and flaccid paralysis. The APACHE II score may be used as an alternative index of severity in patients with OP poisoning. The Score of 26 or higher is a predictor of mortality.

P. Lee et al investigated the prognostic risk factors and the mortality of different organophosphates following acute organophosphate poisoning. In this retrospective study investigated patient survival according to initial parameters, including the initial Acute Physiology and Chronic Health Evaluation (APACHE) II score, serum cholinesterase level, and hemoperfusion and evaluated the mortality according to organophosphate types. The mortality was 0% for dichlorvos, Malathion, chlorpyrifos and profenofos. However, other organophosphates showed different mortality. The usefulness of hemoperfusion appears to be limited. From the study they concluded that the initial APACHE II score is a useful prognostic indicator, and different organophosphates have different mortality.

Hamid Noshad et al describes the respiratory failure in organophosphorous poisoning. Acute organophosphorous (OP) pesticide poisoning is a major clinical problem in the developing world. Textbooks ascribe most deaths to respiratory failure occurring in one of two distinct clinical syndromes: acute cholinergic respiratory failure or the intermediate syndrome. Delayed failure appears to be due to respiratory muscle weakness, but its pathophysiology is unclear. They assessed the clinical patterns of OP-induced respiratory failure, and to determine whether the two syndromes are clinically distinct.

MANAGEMENT OF ORGANOPHOSPHATE POISONING

The management should start with clearance of airway, breathing and circulation. High flow of oxygen should be given and placing the patient in left lateral position & head lower than feet and reduce the risk of aspiration of stomach contents. Gastric lavage is the most common form of decontamination for organophosphorous poisoning. Rate of absorption of organophosphorous from human bowels is not known. Ipecac induced emesis should not be used in organophosphorous pesticide poisoning. Atropine is effective against muscarinic manifestations but it is ineffective against nicotinic manifestations. Atropine can be given until heart rate is more than 80BPM, Systolic BP more than 80 mm Hg, chest is clear, stop sweating and pupil dilation. Pralidoxime is the antidote for organophosphate poisoning. Pralidoxime has three main actions

1. A direct reaction converting the organophosphate to a harmless compound.
2. A transient reaction protecting the enzyme from further inhibition.
3. Reactivation of the inhibited alkyl phosphorylated enzyme to free the active unit (if given early enough)

Blood pressure should be monitored during administration because of the occasional occurrence of hypertensive crisis. Organophosphate poisoning patients frequently develop agitated delirium. Diazepam is the first line therapy for seizures, seizures.

Alison Moffat et al made a retrospective study to evaluate the utilization of two antidotes, atropine and pralidoxime, in organophosphorous poisoning. Data was statistically analyzed in respect of demographic profile, signs of atropinization and the health outcome after treatment with antidotes. Nausea, vomiting, excessive salivation, sweating, meiosis (82.20%), blurred vision and disturbances of consciousness (7.93%) were the main presenting sign-symptoms. Following stomach wash, 17.12% patients improved; rest 82.88% received antidotes (atropine to all and pralidoxime to 58.66% cases). Cured patients were 41.33% treated with atropine only and 34.66% after pralidoxime addition; rest got referred to the higher centre. Positive responses
after atropinization were 83.33% for pupillary size and secretions and 80.66% for pulse rate. Majority of the OPP patients can be cured with atropine only in adequate doses without promoting for costly antidote (pralidoxime). Thus, cost of treatment can be reduced and suicidal death can be prevented.

Albuquerque et al studied the effectiveness of Galantamine in OP poisoning. 1.5 * LD 50 of Soman or sarin was administered to the guinea pigs. After 15 mt animals shown toxic symptoms of OP. Atropine was given to the animals and there was decrease in muscurinic symptoms. Then they have shown the life threatening symptoms and they have been euthanized. Animals pretreated with Galantamine did not show any toxic symptoms. According to the level of OP dose adjustments have to be done. Atropine will causes muscarinic blockade and this will increase the effectiveness of antidote. Galantamine and atropine is having some synergetic action. Effectiveness of Galantamine – atropine was compared with Pyridostigmine – atropine. The dose of Pyridostigmine which is required to produce the 100 % effect as Galantamine was very high and this is not favorable as it is suppressing Buch E, a plasma scavenger of OP. When it is compared with Huperazine – Atropine, again dose was the problem. At those doses Huperazine is showing some life threatening symptoms: Neurodegeneration in 3 areas of brain like Amygdale, hippocampus, pyriform cortex were the hallmark of OP. When Galantamine Pretreated and atropine post treated animals these symptoms were absent. So Galantamine is considered as the key antidote for OP poisoning because atropine alone can’t protect the brain.

H. Thiermann et al reported a case of organophosphate poisoning admitted with respiratory distress, pinpoint pupils and slurred speech. The symptoms appear after spraying the skin by insecticides. Plasma pseudo cholinesterase level appeared to be very low, consistent with acute intoxication with organophosphate insecticide. Management of organophosphate poisoning consists of airway management, administration of oxygen and fluid, as well as atropine in increasing doses and Pralidoxime. Decontamination of the patient’s skin and the removal of the patient’s clothes are mandatory in order to avoid recontamination of the patient as well as the surrounding healthcare personnel. Plasma pseudo cholinesterase analysis is a cheap and an easy indicator for organophosphate insecticides intoxications and could be used for diagnosis and treatment monitoring.

Willemijn Van Heel et al found that the successful management of organophosphate compounds strongly depends on the speed of medical help and the ability helpers to react properly. Though the general principles of clinical toxicology, such as decontamination, stabilization, patient valuation and symptomatic treatment are similar for many toxicants, chemical warfare agents deserve special attention because of their very high inhalative and cutaneous toxicity, rapid onset of the disease and multiple organ failures. This article describes the medical management of mass casualties with blister agents, nerve agents and blood agents from the viewpoint of a clinical toxicologist.

Munidasa UA et al conducted a study to evaluate the outcomes and predictors of mortality in patients with acute OP poisoning requiring intensive therapy at a regional center in Sri Lanka. Mortality following OP poisoning remains high despite adequate respiratory support, intensive care, and specific therapy with atropine and oximes. One-third of the subjects needing mechanical ventilation and reaching intensive care units die within the first 72 h of poisoning. Systolic blood pressure of less than 100 mmHg and the necessity of a FiO2>40% to maintain adequate oxygenation are predictors of poor outcome in patients mechanically ventilated in the ICU.
Bhattarai\textsuperscript{(106)} et al reported a case of organophosphate poisoning who recovered after requiring almost 1000 mg of atropine, 10 gm of PAM and ventilatory support for 7 days is presented here. The overview of organophosphate poisoning and its management was given. With the approach adopted, the mortality reported in the general medicine unit in the central hospital in Nepal is 7.4%.

LIMITATIONS IN THE MANAGEMENT OF ORGANOPHOSPHATE POISONING

The major problem associated with oximes is ageing process. Ageing can be explained that the response to reactivating agents declines with time and the process is based on the type of organophosphate compounds. If larger substituents are attached with organophosphate compound, the reactivation rate may be extremely slow. Thus, administration of oximes is time dependent and the treatment should be started as early as possible. Generally this time period is 48 to 72 hours. Oximes may not reactivate the muscarinic symptoms of organophosphate poisoning\textsuperscript{(107)}. Similarly atropine does not have any effects on nicotinic receptors. The improper usage of atropine can cause iatrogenic atropine toxicity and in some cases the drug induces hypersensitivity reactions also\textsuperscript{(108)}.

The normal value of cholinesterase enzymes in healthy people depends on race, region, malnutrition, liver and renal diseases. The presence of alcohol, nicotine and caffeine can also induce alterations in the levels of cholinesterase. So, the establishment of a baseline value for cholinesterase enzymes in a particular region is very essential\textsuperscript{(109)}. The quantitative estimation of the cholinesterase from the blood samples can be analyzed using colorimetry\textsuperscript{(44)}. These markers can be used for diagnosis and monitoring of the treatment prognosis. The renal and hepatic markers also indicate the severity of organ toxicity. The management, based on these severity grades, may enable the physicians to provide an optimized treatment pattern to each patient. These practices provide a better quality of life to the patient and cause a reduction in the healthcare expenditure burden.

Establishing the provision to detect cholinesterase enzyme can solve many issues. The identification of inhibition of cholinesterase can be used as a diagnosing tool for organophosphate poisoning. Based on the severity of poisoning drug regimen can be fixed. The treatment prognosis can be monitored and the endpoint for the usage of antidotes can be fixed.

Lucio G. Costa\textsuperscript{(110)} et al estimated the 10 years of experience in assessing the severity of Organophosphate poisoning. The severity of organophosphate poisoning was assessed using the grading system of Bardin et al. Muscarinic effects were observed and the most frequent symptom was bronchial hyper secretion. Among these three different severity groups, prolonged length of stay, higher infection rates, and higher mortality were found in the life threatened group. Low serum AChE Levels support the diagnosis of OPP. Initial serum an acute phase reactant, had significant value in assessing the severity of the OPP. Although the management of acute OPP is supportive and the recovery rate is high, anti-cholinergic therapy should be used as soon as possible to counteract muscarinic effects.

Jong Rung Tsai\textsuperscript{(111)} made a review of the literature and consideration of three illustrative cases shows misunderstandings in the pathophysiology of the enzyme and in procedures for effective testing and monitoring of AChE levels. A 23 percent variance in AChE levels exists among normal patients. It is necessary to establish baseline levels to overcome individual variance. The practice of measuring of AchE levels in acute poisoning is limited. In employees who have been monitored and for whom baseline AChE levels have been established, a diagnosis of poisoning
can be made by comparing post exposure AChE levels with baseline levels. If there is no baseline level recorded, and if the offending chemical is in question, the clinician must base treatment on the clinical signs and symptoms. (J Am Board Fam Pract 1999;12:307-14.)

Milan Jokanović et al. focused on the relationship between the trend in serum cholinesterase activity & its clinical outcomes in acute OP poisoned patients. They collected data on following. Demographical factors like poisoning history, clinical manifestations, Glasgow Coma Scale, APACHE-II score, all SchE data within 48 hrs hourly 2PAM dosage, intubation & mortality. They examined the relationship between the trend of SchE activity and mortality. They concluded that the absence of elevating SchE activity level within 48 hrs of poisoning appears to associate with higher mortality in acute organophosphate poisoning patients.

V Siva Prabodh et al. conducted a study to determine whether serum cholinesterase levels have any diagnostic and prognostic value in acute organophosphorous poisoning. Serial measurement of Serum Cholinesterase levels in all patients – 4 times, at the time of admission before administration of PAM, 24hrs after administration of PAM, 48hrs after administration of PAM, 72hrs after administration of PAM. Results shown that serum cholinesterase levels were significantly decreased in acute organophosphorous poisoning cases when compared to controls and also there was regeneration of serum cholinesterase levels after administration of PAM by 22 %, 45% and 73% after 24hrs, 48hrs and 72 hrs. Thus, serum cholinesterase levels have diagnostic value as their levels are significantly decreased in organophosphorous poisoning cases and also prognostic value as there is regeneration of serum cholinesterase levels after administration of PAM.

I.M. Abdullat et al. evaluated the benefits of using serial measurements of plasma cholinesterase activity in the management of cholinesterase inhibitor insecticidal poisoning. After establishing and validating BuChE activity test, and making it available for clinical service in the toxicology laboratory at Jordan University Hospital. The results of serial measurement of BuChE obtained from each patient’s samples were used to draw a curve; three different types of curves were obtained from all patients samples. The obtained curves were found to follow our three proposed curves, which support our point view regarding the importance of the proposed curves in the differential diagnosis and treatment of cholinesterase inhibitor pesticides poisoning. This study pointed out the importance of utilizing serial measurements of BuChE activity in the diagnosis and the management of organophosphates and carbamates poisoning. The BuChE activity results were used to support diagnostic and prognostic criteria that guided patient management and follow up. Applying those curves to large number of patients’ samples will enhance its credibility. The study also demonstrated the importance of direct contract between toxicologist and physician in treatment of the pesticides poisoned patients.

Venkateshraru et al. evaluated the challenges of organophosphorous Poisoning treatment in clinical situation. One hundred cases of OP poisoning were analyzed. The severity was accessed clinically and by serial estimation of serum cholinesterase levels. Most of our patients had severe poisoning requiring mechanical ventilation; atropine and PAM (Prolidoxime) form the main stay of treatment. Good nursing care apart from medicines and artificial ventilation is needed for speedy recovery of the ailment. Serum cholinesterase depression is a good indicator for severity and diagnosis of the disease though improvement in levels of it may not be to the extent of that of clinical improvement.

HW Yun et al. conducted a study with the aims to identify the relationship between the dynamics of serum cholinesterase activity and mortality. In this retrospective study, medical records of all patients with acute organophosphate poisoning were reviewed from January 2001
to December 2009. Clinical features, SChE activity, Glasgow Coma Scale, laboratory findings, electrocardiogram finding, management and their outcomes were examined. Results: A total of 169 patients were included in this study. A total of 55 patients were enrolled. Deceased patients were 8 in number. Absence of an increase in SChE activity was related with mortality in organophosphate poisoned patients (p value=0.036; odds ratio, 5.445; 95% confidence interval, 1.121-26.551). The absence of an increase in SChE activity is associated with higher mortality in organophosphate poisoning. The SChE dynamic activity can provide a guide to physicians in the evaluation and management of organophosphate poisoned patients.

Malathi Prabha(117) et al evaluated the clinical presentation, lab investigation, complication, management and outcome of 30 organophosphate poisoning patients. The study concluded that Pseudo cholinesterase assay is a sensitive tool for the diagnosis of organophosphate poisoning.

DS Rao(118) et al evaluated 30 organophosphate poisoning patients at SVRRGG hospital from January to June 2001. Pseudo cholinesterase levels were estimated in them. Serum electrolytes and pseudo cholinesterase levels were estimated within 24 h of admission even before gastric lavage. Pseudo cholinesterase levels were decreased in 63% of patients with statistical significance, when compared to normal controls of non-OP poisoning. They concluded that the decreased levels of pseudo cholinesterase are highly specified for diagnosis of OP poisoning and particularly useful in suspected organophosphate poisoning patients.

Zawar(119) et al conducted a study in organophosphate poisoning in 37 patients at Indira Gandhi Medical College Nagpur. Serial estimation of pseudo cholinesterase was carried out in 37% of day1, day3 and day5 of hospitalization based on clinical features as on reported by Namba el al 1971. The Pseudo cholinesterase in healthy volunteers was found to be 6990+ 2137 U/L. Progressive rise of mean PChE was observed from D1 to D5 in all. But, it was significantly reduced on day 5 in moderate and severe poisoning. The study demonstrated a definitive correlation between plasma cholinesterase activity and severity and prognosis in patients with organophosphate poisoning.

Yamashitha M(120) conducted a study in 130 organophosphate poisoning patients. Fenithion malathion Dichlorovos, trichlorofen were commonly involved organophosphate compounds. The study concluded that better respiratory management will increase the outcome. The close observation of clinical symptom or changes in the levels of serum cholinesterase is essential for the proper management of organophosphate poisoning.

Coye MJ(121) et al. conducted a study among agricultural workers with history of exposure of organophosphate pesticides. They evaluated the utility of sequential post exposure acetyl cholinesterase analysis to confirm organophosphate intoxication in the absence of baseline cholinesterase values. The author has concluded that the sequential post exposure acetyl cholinesterase analysis confirm the diagnosis of organophosphate poisoning as well as helpful in better management.

Aunha JP(121) et al. conducted a study in 52 organophosphate poisoning patients. They evaluated the values of serum cholinesterase on monitoring the clinical course. The study concluded that acetyl cholinesterase is useful in organophosphate poisoning diagnosis and monitoring clinical course. The recovery of serum ChE values in > 10 % in organophosphate poisoning patients indicates a good prognosis.

G Avasthi(123) et al conducted a study in 29 organophosphate poisoning patients at Dayanand Medical College hospital, Ludhiyana with prospective evaluation of correlation between serial
clinical findings and serum ChE, electro diagnostic abnormalities with confirmed OP. The author concluded that clinical weakness confirming intermediate syndrome. The ChE level less than 200 ml U/L at admission is a predictor of intermediate syndrome.

Supreeti(124) et al conducted a study to evaluate the utilization of two antidotes, atropine and pralidoxime, in Organophosphorus poisoning (OPP). Majority of the OPP patients can be cured with atropine only in adequate doses without promoting for costly antidote (pralidoxime). Thus, cost of treatment can be reduced and suicidal death can be prevented.

THE MAJOR POINTS FROM LITERATURE ARE SUMMARIZED BELOW.

- The toxicocpidemiological studies are helpful in finding the lacuna in the knowledge of a particular health issue by framing better health policies.
- The high prevalence rate of poisoning cases was obtained from many parts of India.
- The tendency of deliberate self-harm in India is growing and ranks 10th in world.
- Agrochemical poisoning was the most common of all poisoning cases and among them organophosphorous compound was the commonest agent used for poisoning.
- The reason for agrochemical abuse may be because of easy availability and low cost.
- The cost of management of poisoning cases is substantial to individual as well as the Government.
- The data on cost of poisoning management can be used to frame the policies for better management of poisoning cases and prevention of occurrence.
- The fatal issue is often related to delay in diagnosis or difficulties in management.
- Even without an increase in resources, there appear to be significant opportunities for reducing mortality by better medical management and further restrictions on the most toxic pesticides.