EFFECT OF ORGANIC PHOSPHORUS INSECTICIDES ON CHOLINESTERASE ACTIVITY ENZYME

THESIS

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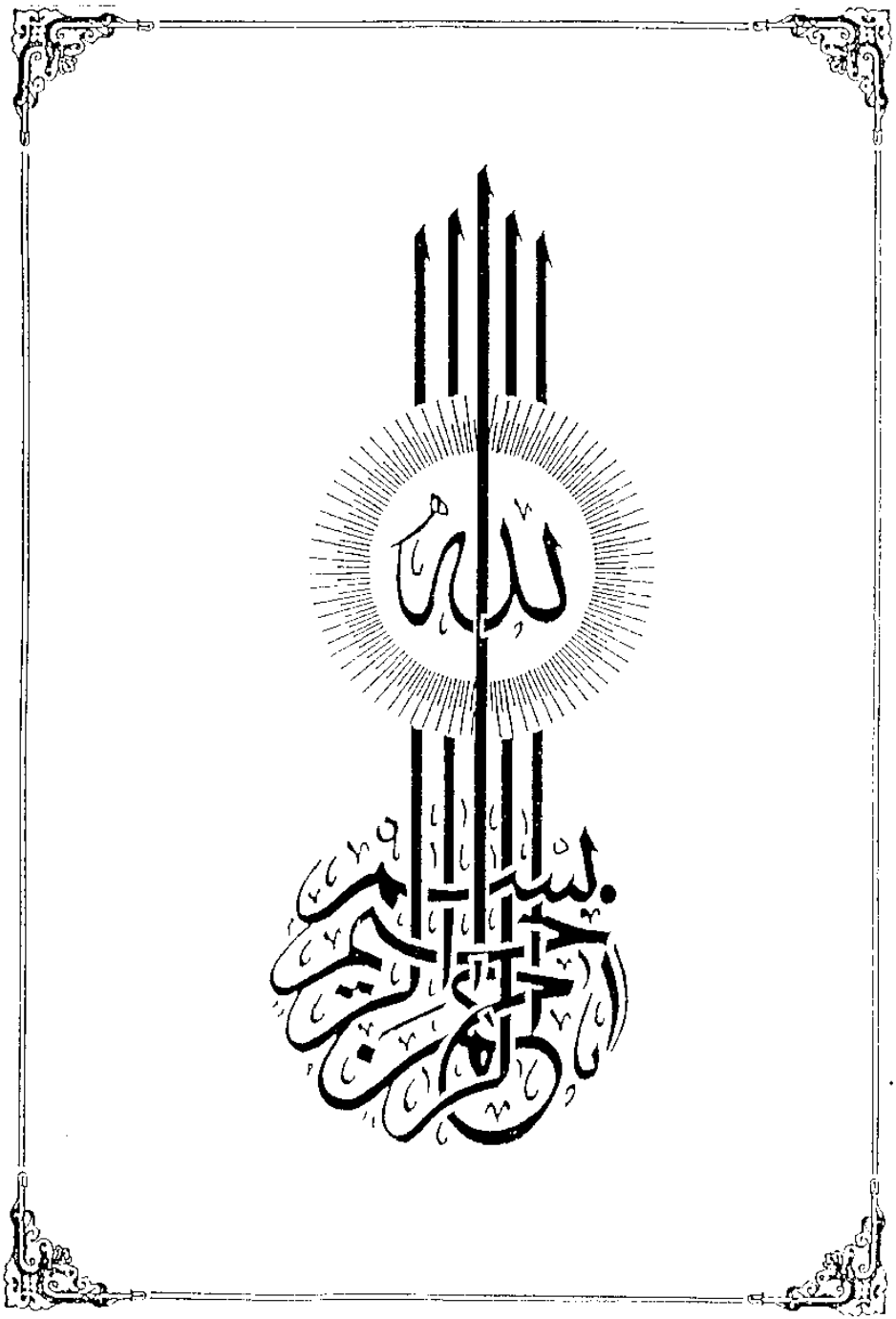

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INTRODUCTION

INTRODUCTION & AIM OF THE WORK

The first organophosphate insecticide was tetra ethyl pyrophosphate (TEPP). It was developed in Germany as a substitute for nicotine, which was in short supply in that country during world war II.

Related extremely toxic compounds such as ethyl N-dimethyl Phosphoroamido cyanidate (Tabun) and iso propyl methyl phosphoshono-fluoridate (Sarin) were kept secret by the German Government as Potential chemical warfare agents. These, and other extremely toxic compounds, are the so called nerve gas chemical warfare agents (TEPP), although an effective insecticide, was highly toxic to mammals and was rapidly hydrolyzed in the presence of moisture. Further efforts lead to find more stable compounds for use in agriculture for synthesis of Parathion (E605,O,O-diethyl O-P-nitrophenyl Phosphorothioate) and its oxygen analog paraxon (E600; O,O-diethyl O-P-nitrophenyl Phosphate). (Casarett. et al. 1975) .

Parathion become one of the most widely used organo-Phosphorus insecticides, because it is exhibited

a wide range of insecticidal activity & suitable Physical & chemical activity (i.e low volatility & sufficient stability in water a mild alkalinity).

Parathion has the dubious distinction of being the pesticide most frequently involved in fatal Poisonings. During the last two decades the agricultural chemical industry has developed many other organic triesters of Phosphoric acid and Phosphorothioic acid that have been registered for use as insecticides.

Shortly after Parathion became available for study its acute toxicity on experimental animals revealed signs of poisoning that resembled excessive stimulation of cholinergic nerves. These could be alleviated by atropine, a cholinergic agent.
This suggested inhibition of acetyl cholinesterase of nerves as the mechanism of toxic action, had been demonstrated for related organo phosphate triesters, and was confirmed by the finding that tissues of rats poisoned by parathion had markedly reduced cholinesterase activity and increased free acetyl choline in their brains (Du Bois et al., 1959). Thus, the biochemical basis for

acute poisoning by parathion in mammals, i.e., inhibition of the acetyl cholinesterase activity of nerve tissue, became known soon after its introduction as an insecticide.

Subsequent development and research on other organo-Phosphate insecticides have revealed that they all, in sufficient doses, inhibit acetyl cholinesterase in vivo and thus share a common mechanism of acute toxic action. The chemical mechanism of cholinesterase inhibition is discussed in moredetail later on (Casarett, et al, 1975.

The main effects of organo Phosphorus compounds are :

1 - Muscarine like effect which includes:
Bronchial tree, gastro-intestinal, sweat glands, salivary glands, lacrimal glands, heart, pupils, Eye urinary tract.

2 - nicotine like effect: which includes:
striated muscles & sympathetic ganglia

3 - its effects on the central nervous system .

So the aim of the present work is to know the effect of organo phosphorus compounds on the military individuals who are working in spraying & dusting of these compounds. (especially malathion & diazinon).

This study is also intended to diclose the effect of organophosphorus on the Blood activity of cholinesterase (Plasma & Erythrocyte).

REVIEW OF LITERATURE

During the second world war chlorinated hydrocarbons and organo phosphates were introduced as insecticides. These compounds enjoyed wide use, particularly DDT which has low toxicity. Although there is not enough evidence at Present that DDT or other chlorinated hydrocarbons in the tissues of human beings are harmful, there are opinions that the concentration may eventually became intolerably high. This concern was dramatically Portrayed by Rachil carsonin her book "Silent spring".

Since future and civilization are greatly dependent on insecticides in agriculture, forestry and vector Control, particularly in malaria Control, substitutes for chlorinated hydrocarbon insecticides are required. Presently organo phosphates insecticides are considered to be the most practical substitutes because they are potent insecticides and are relatively rapidly hydrolized after application, many organo phosphorus compounds have been synthesized in the last 30 years and many of them have been widely used as agricultural insecticides.

Modern methods for the control of insect include the use of insecticides in which the active substances

are organic compounds of phosphorus. The first work on these compounds was carried out in Germany 1939. Since 1945 there have been major advances in the united kingdom, U.S.A and elsewhere but nearly all of this stemmed from the work schrader in Germany (Hunter, 1975) preparations in common use contain tetra-ethyl-Pyrophosphate (TEPP), Hexa-ethyl-tetraphosphate (HETP) and diethyl-Para-nitro Phenyl thio phosphate (Parathion, E605F, DPTF, or bladan) which act as contact insecticides. Octamethyl Pyrophosphoramide (Schradan or OMPA), bis-(mono-iso propylamino)-Fluorophosphine oxide (mipafox), bis-(dimethyl-amino) Fluorophosphine oxide (dimefox) and diethyl thiophosphate of ethyl mercaptoethanol (demeton) act as systemic insecticides. They are related in chemical structure and Physiological action to di-iso propyl fluorophosphonate (DFP) which is a powerful cholinesterase inhibitor used in the treatment of myasthenia gravis, paralytic ileus and glaucoma. The insecticidal properties of TEPP, HETP and Parathion are similar to those of nicotine The effects of HETP are almost certainly due to contamination of manufactured product by TEPP.

These compounds may be used in the form of a spray or by dusting. Poisoning can occur from inhalation, ingestion and absorption through the unbroken skin. The poisonous effects may be cumulative .

The site of action is said to be the myoneural junctions and synapses of ganglions. Adrop in activity of cholinesterase to 30 per cent of normal or lower is associated with toxic symptoms:

Classification of organophosphorus Compounds

1) Most Dangerous:

Tetraethyl Pyrophosphate-Phorate-Disulfoton-Parathion-Demeton (systox)-Mevinphos-Ethyl P-nitro phenyl thionobenzene phosphonate (EPN). Schradan-Methyl Parathion-Azinphosmethyl-Dicrotophos .

2) Dangerous:

Dichlorvos-Diazinon-Dioxothion-Methyl demeton-Dimethoate-Naled-Phostex-Trichlorfon .

3) Least Dangerous:

Malathion-Ronnel.

Biologic action of organophosphorus compounds:

Acetyl choline (Acch), the natural substrate of this enzyme is a primary neurohumoral transmitter substance of the nervous system and is necessary for impulse transmission between:-

(1) Preganglionic and Post ganglionic fibres of the sympathetic and parasympathetic autonomic system;
(2) Post ganglionic parasym pathetic (cholinergic) nerves and secretory cells, smooth muscle, and cardiac muscle;
(3) Motor nerves and motor end Plates of striated muscle;
(4) Certain components of the central nervous system.

The normal transmission of an impulse by Acch is followed by the rapid hydrolysis of the transmitter by the enzyme and limitation of the duration and intensity of the stimulus.

Organophsphorus compounds of suitable configuration, because of certain structural similarities to Acch, become oriented to the surface of Acch esterase molecules and undergo changes analogous to those undergone by Acch, the natural substrate. In the case of the organo

phosphorus compounds, however the bond to the enzyme is abnormally stable, and the phosphorylated enzyme loses its normal function as an Acch esterase. Acch consequently accumulates and causes sustained stimulation, increased function, and finally decreased function with greater accumulation.

There is a wide variation in the mammalian toxicity shown by members of this group. Certain sulfur substituted organophosphorus compounds require metabolic oxidation before toxicity develops. Since this in vivo reaction occurs more rapidly in insect than in man, this chemical property is useful in increasing mammalian safety while maintaining insecticidal potency. The oxidative conversion occurs in man but is offset to a vriable degree by metabolic inactivation of biologically significant portions of the insecticide molecule. As long as the inactivation processes are capable of keeping up with the activation (oxidation) processes, intoxication does not occur. The body deals effectively with small doses of parathion an agent of this type which requires metabolic oxidation to become toxic. When the inactivation mechanism can not handle the amount of toxic compound presented to it,