CHAPTER I

INTRODUCTION

Problem Statement

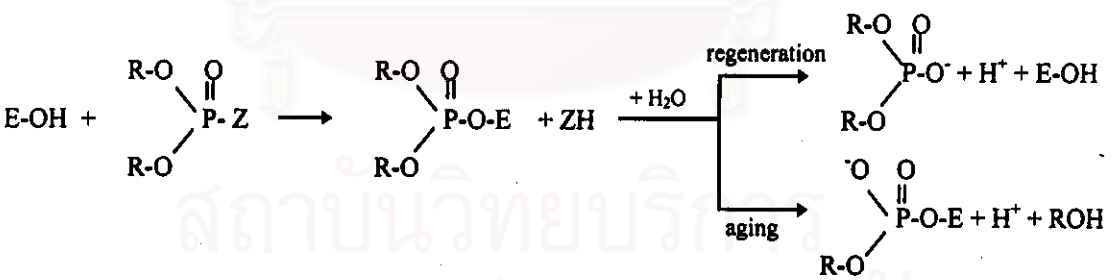
Thailand is an agricultural country where pesticides are widely used for controlling pests. Pesticides have caused a significant problem, pesticide poisoning (Jeyarathnam, 1990). The organophosphate and carbamate insecticides are often cited as causative agents. The five mostly used pesticides in Thailand were listed in Class IA (extremely hazardous) and Class IB (highly hazardous) pesticides classified by WHO (WHO, 1986). These insecticides are anticholinesterase inhibitors. The pharmacological effects of acetylcholinesterase inhibition are due to stimulation of muscarinic receptors and nicotinic receptors within both peripheral and central nervous system by acetylcholine which accumulates at the preganglionic synapses in both parasympathetic and sympathetic ganglia, parasympathetic postganglionic neuroeffector junctions and a few sympathetic neuroeffector junctions, and all somatic motor end-plates on skeletal muscle. Their signs of toxicity are summarized as shown in table 1.

However, there are significant difference between organophosphates and carbamates in their pharmacokinetics of enzyme inhibition. The reaction between some organophosphates and the active site in the acetylcholinesterase enzyme may result in the formation of a transient intermediate complex that is partially hydrolyzed, leaving a stable, phosphorylated and largely unreactive inhibited enzyme that, under normal circumstances, can be reactivated only at a very slow rate. This mechanism is called "aging mechanism" (figure 1). On the contrary, carbamates will not undergo this reaction and their enzyme complex are mostly reversible in a relatively shorter period. The dephosphorylation or decarbamoylation of the inhibited enzyme is the rate-limiting step in forming free enzyme (Ecobichon, 1996; Sullivan and Blose, 1992).

Table 1. Toxic signs of acetylcholinesterase inhibition (Chan and Hayes, 1989).

Muscarinic effects	Nicotinic effects	CNS effects
Bronchoconstriction	Muscular twitching	Giddiness
Increased bronchosecretion	Fasciculation	Anxiety
Nausea and vomiting	Cramping	Insomnia
(absent in rats)	Muscular weakness	Nightmares
Diarrhea		Headache
Bradycardia		Apathy
Hypotension		Depression
Miosis		Drowsiness
Urinary incontinence		Confusion
		Ataxia
		Coma
		Depressed reflex
		Seizure
		Respiratory depression

A. Organophosphates



B. Carbamates

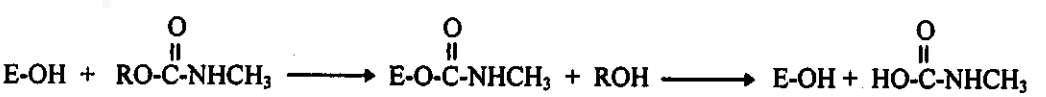


Figure 1. The interaction between an organophosphate or carbamate with the serine hydroxyl group in the active site of the enzyme acetylcholinesterase (E-OH) (adapted from Ecobichon, 1996).

The commonly used biomarkers in the diagnosis of the anticholinesterase related poisoning are the reduced level of cholinesterase enzymes. Details on different types of esterases inhibited by these compounds are found elsewhere (Chatonnet and Lockridge, 1989; Lotti, 1995). These biomarkers are used widely and considered as valuable diagnostic tools. However, as mentioned earlier, the carbamylated enzyme complex is spontaneous reversible and rapidly excreted. Therefore, the failure of sample collection within the appropriate time or the disturbances of cholinesterase enzyme complex such as shaking, mixing during sample preparation may cause underestimation or misinterpretation of pesticide poisoning cases.

Objectives

1. To investigate the toxicity of methomyl, total LDH activity, and LDH isoenzymes in the serum of rats treated with single and repeated dose administration protocol.

2. To assess the possible correlation between the alterations of total LDH activity, LDH isoenzymes, hematological values, and histopathologic findings in rats treated with single and repeated dose protocol.

3. To investigate the target organ of methomyl toxicity.

Hypotheses

1. Alterations of total LDH activity and LDH isoenzymes are observed in the serum of methomyl-exposed rats and can indicate the target organ of methomyl toxicity.

2. LDH isoenzymes is responsive as a marker of methomyl toxicity.

Contributions of the study to the field of pesticide toxicity

1. More understanding of the effects of methomyl in rats.

2. More understanding of the relationship between the alterations of total LDH activity and LDH isoenzymes in serum of rats and histopathologic findings.

3. Consideration of the most appropriate marker for monitoring the adverse effects of methomyl.