SOCIO-DEMOGRAPHIC PROFILING OF ORGANOPHOSPHORUS PESTICIDES POISONING REPORTED TO NATIONAL POISON CENTRE OF MALAYSIA BETWEEN YEAR 2006 TO 2015

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UNIVERSITI SAINS MALAYSIA

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By

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DECLARATION

I hereby declare that I am the sole author of this thesis; entitled "Socio-demographic Profiling of Organophosphorus Pesticides Poisoning Reported to National Poison Centre of Malaysia Between Year 2006 to 2015". I hereby declare that this research has been seen to Universiti Sains Malaysia (USM) for the purpose of the award of Master of Science (Health Toxicology). The dissertation is the result of my own research except as cited in the references. The dissertation has been accepted for the respective degree and is not concurrently submitted in candidature of any other degree.

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LIST OF ABBREVIATIONS

COPIDN	Chronic Organophosphate-Induced Neurological Damage
DOSM	Department of Statistic Malaysia
EPA	Environmental Protection Agency
GDP	Gross Domestic Product
JEPeM	Jawatankuasa Etika Penyelidikan(Manusia)
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NTE	Neuropathy Target Esterase
OP	Organophosphorous Compound
OPIDN	Organophosphate-Induced Delayed Neuropathy
UN	United Nations
USEPA	United States Environmental Protection Agency
USM	Universiti Sains Malaysia
WHO	World Health Organization

ABSTRAK

Keracunan dan kesan negatif terhadap kesihatan manusia akibat penggunaan racun makhluk perosak daripada bahan organofosforus telah dikaji secara meluas dan berterusan oleh para saintis. Racun makhluk perosak didapati memberi kesan akut dan kronik terhadap manusia dan persekitaran, juga memberi sumbangan terhadap kadar kematian global akibat bunuh diri, terutamanya di negara-negara pertanian yang berpendapatan rendah dan sederhana. Kajian ini telah dirangka bagi mendapatkan corak demografi kes-kes yang telah dirujuk dan disimpan di dalam pangkalan data Pusat Racun Negara, Malaysia bagi tempoh 10 tahun, bermula 1 Januari 2006 sehingga 31 Disember 2015. Kes keracunan akibat racun makhluk perosak daripada bahan organofosforus berjumlah 4029 kes, menyumbang kepada 28.4% daripada keseluruhan kes keracunan akibat racun makhluk perosak bagi tempoh kajian. Jumlah kes meningkat lebih dua kali ganda daripada 2006 hingga 2015. Racun rumpai glyphosate menjadi penyumbang terbesar, sebanyak 58.6% daripada jenis racun organofosforus yang terlibat. Perak, Selangor dan Johor merupakan antara penyumbang terbesar kes keracunan organofosforus, sejajar dengan keluasan tanah yang digunakan bagi aktiviti pertanian. Sebanyak 66.6% daripada kes keracunan organofosforus adalah lelaki dan 54.6% daripada keseluruhan kes adalah berbangsa India. Majoriti iaitu sebanyak 70.6% kes adalah dengan sengaja dan bertujuan bagi membunuh diri (93.7% daripada sebab keracunan yang disengajakan). Majoriti kes berlaku di rumah, sebanyak 95.1%. Terdapat hubungan yang signifikan di antara jantina dan bangsa terhadap kes keracunan organofosforus, juga terhadap kategori keracunan.

ABSTRACT

Toxicity of organophosphorus compound pesticides towards human health were widely researched by scientists and remain continuous. Organophosphorus pesticides pose both acute and chronic effects to environment and human, gave significant contribution to world suicide especially in low- to middle-income agricultural countries. This study was structured to get the demographic pattern of Organophosphorus compound pesticides poisoning cases which were captured inside the National Poison Centre registry database in Malaysia for 10 years period, starting from 1st of January 2006 till 31st of December 2015. Data analysis was done using the Statistical Program for the Social Sciences (SPSS) version 22. Organophosphorus pesticides poisoning with total number of 4029, contributed to 28.4% of all pesticides poisoning cases registered within that timeframe. The number of cases increased more than two folds from 2006 to 2015. Glyphosate, the herbicides accounted for 58.3%, become the commonest poison involved in organophosphorus pesticides poisoning. High contribution from Perak, Selangor and Johor to organophosphorus pesticides poisoning almost parallel to the agricultural contribution by these states. Male gender contributed 66.6% of organophosphorus pesticides poisoning and the Indian ethnic represents 54.6% of organophosphorus pesticides poisoning. Majority of the organophosphorus pesticides poisoning are intentional (70.6%) and suicidal is the main reason (93.7%). Majority of poisoning occur at home (95.1%). There were significant association between gender and race with organophosphorus pesticides poisoning as well as category of poisoning.

CHAPTER 1

INTRODUCTION

The Food and Agriculture Organization of the United Nation (UNFAO) 2014 defined pest as any species, strain or biotype of plant, animal or pathogenic agent injurious to plants and plant products, materials or environments and includes vectors of parasites or pathogens of human and animal disease and animals causing public health nuisance. Pesticide means any substance, or mixture of substances of chemical or biological ingredients intended for repelling, destroying or controlling any pest, or regulating plant growth (UNFAO, 2014).

Pesticides can be classified in many ways either by their toxicity effects, agricultural usage or based on its chemical families such as organochlorines, organophosphorus compounds to inorganic compounds (Garcia, Ascencio, Oyarzun, Hernandez & Alavarado, 2012).

Organophosphorus compound pesticides have been used worldwide for pest control for over 100 years. According to various studies, organophosphorus compound pesticides forms the commonest poisoning substance in Asia (Selvaraj & Sudharson, 2016), especially in countries with high agricultural activities (Tzeng et al., 2008; Patel & Tekade, 2011; Zhang et al., 2013).

Malaysia, located in South East of Asia, is a country with high agricultural activities. Agriculture has played a vital role in the development of modern Malaysia and continues to make a significant contribution to the national economy, as reported by the Malaysian Administrative Modernisation and Management Planning Unit (MAMPU), 2012. The Food and Agriculture Organization of the United Nation (2017) estimated that Malaysia agriculture area in 2014 is about 7839 thousand hectares out of its total land of 33080 thousand hectares. It was hypothesized that, due to Malaysia's high involvement in agricultural activities, poisoning cases due to pesticides, especially the organophosphorus compound group of pesticides might be parallel to many other studies conducted in different countries.

This study focused on sociodemographic profile of poisoning cases due to any organophosphorus compound that were used as pesticides, including the insecticides, herbicides, fungicides and etc, either in agriculture or as vector control in public health, which were captured by the poisoning registry database at National Poison Centre in Malaysia. Any poisoning cases involving organophosphorus compound beyond its usage as pesticides, such as organophosphorus compound used in pharmaceutical product and medicine or, as a chemical ingredient in industries were excluded from the analysis. The classification of the organophosphorus compound pesticides is based on the inventory report published by IPCS INCHEM (IPCS, 2006).

1.1 Problem Statements

Pesticides are recognized as a major contributor for suicide globally. However, there is still lack of attention given to its significant role as a chosen method to attempt suicide (WHO, 2014). There is lack of published data regarding epidemiology of pesticides poisoning in Malaysia, especially the data which specifically covered the organophosphorus compound pesticides poisoning.

This research helps to obtain and analyse the organophosphorus compound pesticides poisoning cases that were reported to NPC Malaysia. Although the referred cases were not covering all poisoning cases in this country, the results are still can be used as a baseline for further extensive study of organophosphorus compound pesticides poisoning in Malaysia.

1.2 Objectives of The Study

This study was designed to establish the sociodemographic profile of poisoning cases from organophosphorus compound pesticides which were referred for consultation and registered at National Poison Centre, Malaysia from 1st of January 2006 to 31st of December 2015.

In order to achieve the general objective, some specific parameters were considered to be analysed as listed below:

1. To determine the trend of poisoning in perspective of organophosphorus compound pesticides
2. To categorise the poisoning incidence of organophosphorus compound pesticides based on sociodemographic data
3. To determine the association between organophosphorus compound pesticides poisoning with the demographic data

1.3 Significance of The Study

This study can be the first step for further interventional study in our local health and emergency settings. The real picture about the prevalence of pesticides poisoning, or in this study referred to organophosphorus compound pesticides, in our country will be obtained and compared with the global situation. This study findings might benefit those who involved in patients care for example, the health care providers such as doctors, pharmacists and paramedics.

1.4 Scope of The Study

This study was designed just to get the sociodemographic profile of organophosphorus compound pesticides poisoning cases, however, not covering the clinical profile and outcome of the victims.

CHAPTER 2

LITERATURE REVIEW

2.1 Pesticides

Pesticides are group of chemicals that are designed to control unwanted pests. Pesticides may be classified in many ways either by their mechanism of action towards the pests, based on their major agricultural usage, by toxicity effects based on LD50 or by the chemical structures and ingredients available inside the formulation.

Pesticides may be catagorised based on their major agricultural usage into insecticides, herbicides and fungicides. Other groups may include rodenticides, nematocides, molluscides, acaricides, larvacides, miticides, pediculicides, scabicides, defoliants, desiccants, attractants (pheromones), plants growth regulator and repellants. Approximately, there are 1000 chemical compounds, biological agents and physical agents being marketed globally with multiples brand names and formulation (Snodgrass, 2010).

World Health Organisation (WHO), 2009 recommended pesticides classification based on their hazard effects or LD50 tested in experimental rats in laboratories. They are classified as Extremely Hazardous, Highly Hazardous, Moderately Hazardous and Slightly Hazardous. The hazard defined by the WHO Recommendation is the acute risk to health following relatively acute exposure(s).

According to its chemical structure, pesticides are classified into different families, ranging from organochlorines and organophosphorus compounds to inorganic compounds (Garcia et al., 2012).

Organophosphorus compound pesticides contain very broad variety of chemical structures. They shared the basic pentavalent phosphorus atom with 3 singly bonded constituents and a coordinate covalent bond to either a sulphur or an oxygen. A lot of chemical configurations and combinations were developed from this basic structure. Because of this, comprehensive classification of organophosphorus compound pesticides become difficult and the spectrum of usage of these compounds also become very wide. They can be used as insecticides, herbicides, fungicides and etc. (Chamber, Meek & Chambers, 2010).

Organophosphorus compound that were used as pesticides can be sub-grouped based on their basic structure and presence of chemical substituents bond to the phosphorus. The compounds can be subclassified into eight main groups named phosphate, phosphonate, phosphinate, phosphorothioate, phosphorodithioate, phosphonothioate, phosphoramidate and phosphorothioamidate (Marrs, 2001; Chamber et al., 2010).

2.2 Pesticides and Socio-economy

The Sustainable Development Goal launched by the United Nations in 2015 listed ‘no poverty’ and ‘zero hunger’ as the first two, out of the seventeen goals, with specific targets that need to be achieved within certain period of time (United Nation, 2016; United Nation, 2016[a]). Globally, about 795 million people in the world today are undernourished, majority of them live in developing countries. Asia, especially the Southern Asia faces the greatest hunger burden followed by sub-Saharan Africa (UN, 2016[a]).

The Food and Agriculture Organisation of the United Nations (UNFAO), 2017 revealed that agriculture provides livelihoods for 40 per cent of today’s global population. Agriculture is the single largest employer, source of income and jobs for poor rural. It was estimated that, to provide for a population of 9.7 billion in year 2050, food production will need to be increased from the current 8.4 billion tonnes to almost 13.5 billion tonnes a year (UNFAO, 2017).

Previous 50 years showed that intensification of agriculture become the backbone, to support the rapid growing population, reducing hunger and improving nutrition. The “Green Revolution” adapted by Asian countries in 1960s, increased cereal yields such as rice, saved millions of people from starvation. These were almost impossible without the increased in use of fertilizers as well as pesticides (Prabhu, 2012).

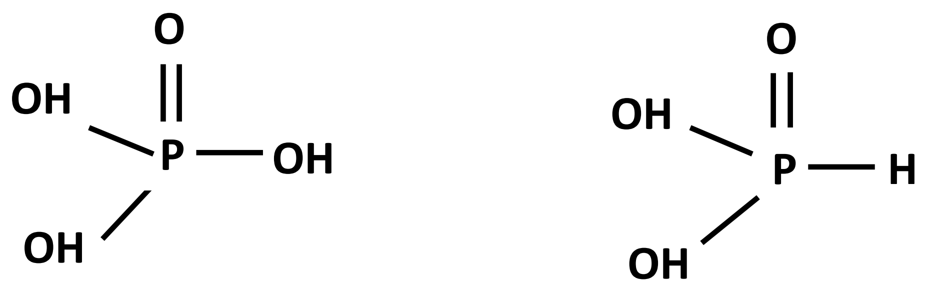
In general, pesticides use benefitted people in the world. However, along with their benefits that increase crops yield and food production, excessive pesticides usage also poses several adverse consequences to environment and human. Loss of biodiversity, land erosion and water pollution by the chemicals used as pesticides gave cost to society and environment (Pimentel, 2005). Effects to human health from acute, self-poisoning and chronic, long term toxicity should be put into account and considered as deleterious effects of pesticides use.

2.3 History and Chemistry of Organophosphorus Compound Pesticides

Organophosphorus chemistry began around 1820s with the esterification of alcohols to phosphoric acid. However, the potential toxicity remained unrecognised until 1930s. Sarin, soman and tabun, the highly toxic organophosphorus compounds with potential usage as chemical warfare agents were invented and introduced by group of scientists led by B. C. Saunders in England and Gerhard Schrader in Germany (Chamber et al., 2010).

The earliest commercial organophosphorus compound pesticides such as tetraethyl pyrophosphate (TEPP) in 1937, dimefox in 1940, schradan (octanomethyl pyrophosphoramide) in 1942 and parathion in 1944 were also produced by these groups of scientists. Research and interest in organophosphorus compound grew rapidly until now. It was estimated that, by 1960 more than fifty thousand compounds had been made. In 1970s, more than two hundred organophosphorus compound pesticides being commercially marketed worldwide (Chamber et al., 2010).

Organophosphorus compound pesticides can be considered to be derivatives of either phosphoric acid (H3PO4) or phosphonic acid (H3PO3) in which the Hydrogen (H) atoms are replaced by variable organic components. Figure 2.1 shows the simplified structure of phosphoric acid and phosphonic acid (Marrs, 2001; Chamber et al., 2010).



Phosphoric Acid (H3PO4)

Phosphonic Acid (H3PO3)

Figure 2.1: Structure of Phosphoric Acid (H3PO4) and Phosphonic Acid (H3PO3)

Due to this replacement, many configurations of these pentavalent bonds developed. For example, in phosphate group of organophosphorus compounds, all the 'H' atoms were replaced to form a pentavalent of four phosphorus-oxygen (P-O) bonds whereas in phosphonate group of organophosphorus compounds, three phosphorus-oxygen (P-O) bonds together with one phosphorus-carbon (P-C) bond developed (Figure 2.2) (Chamber et al., 2010).

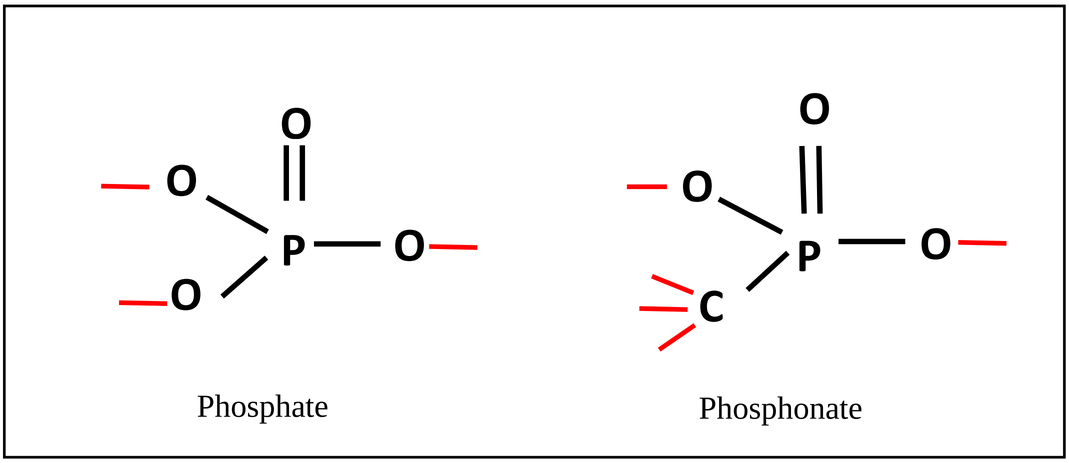


Figure 2.2: Basic structure of phosphate group and phosphonate group of organophosphorus compound pesticides

2.4 Organophosphorus Compound Pesticides

Organophosphorus compound pesticides classes contain diverse array of structures, all united by the presence of a pentavalent phosphorus(P) atom with three singly bonded constituents and a coordinate covalent bond to either a sulphur(S) or an oxygen(O) (Chamber et al., 2010). The structure can generally be described as the figure below (Figure 2.3).

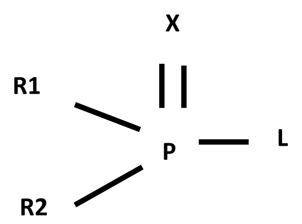


Figure 2.3: General structure of organophosphorus compound pesticides

‘L’ is the ‘leaving group’, can be considered as the most reactive and most variable constituent. This leaving group is the one that would be ‘displaced’ when the organophosphorus compound phosphorylates acetylcholinesterase, the primary target enzyme for its insecticidal activity. This group is also the most susceptible end to hydrolysis. As cited by Marrs (2001) in Organophosphates: History, Chemistry, Pharmacology, the structure of this leaving group provides one way in which organophosphorus compound can be classified.

‘X’ which develops coordinate covalent bonds to phosphorus (P), can be either oxygen (O) or sulphur (S). R1 and R2 are less reactive compared to the leaving group ‘L’. They are commonly alkoxy groups which can be alkyl-, aryl-, alkylthio- or alkylamino- group (Chamber et al., 2010). The following groups are examples on how organophosphorus compound pesticides being classified based on the chemical structures.

2.4.1 Phosphate Group

In phosphate group pesticides, their basic chemical structures derived from replacement of all the 'H' atom by the 'O' atom, which made the four phosphorus-oxygen bonds as the core structure (Chamber et al., 2010). Examples of pesticides fall under this group are dichlorvos, chlorfenvinpos, dicrotophos, crotoxyphos, heptenophos, mevinphos, trio-o-cresyl phosphate, naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) and many others (Marrs, 2001; Balalimood et al., 2012). Majority of these organophosphorous compound pesticides are used as insecticides, in agricultural sector and some are used as a public health control for vector-borne-disease such as naled (USEPA, 2016).

2.4.2 Phosphonate Group

Phosphonate groups pesticides can be found as insecticides, herbicides, fungicides and plant growth regulators. Their chemical structures shared the core structure of three phosphorus-oxygen bonds and one phosphorus-carbon bond (Chamber et al., 2010). Examples of phosphonates used as pesticides are glyphosate, which is mainly used as herbicides and trichlorfon, as insecticides (Marrs, 2001; IPCS, 2006; Farmer, 2010; Naydenova, Todorov & Troev, 2010; Larsen, Lifschitz, Lanusse & Virkel, 2016).

Metrifonate, the drug that was previously used to treat glaucoma, is the same as trichlorfon, the insecticides. The only thing is, when used as pharmaceutical product for human, the chemical need to be registered differently and following different registration and regulation pathway or system. These made the chemical obtained the new, different name (Marrs, 2001).

2.4.3 Phosphinate Group

In this group, two oxygen(O) atoms were replaced by carbon (C). Glufosinate is one of the examples of pesticides fall under this group. Although the main function is as herbicide (IPCS, 2006), glufosinate also showed some acaricidal, insecticidal, bactericidal and fungicidal activities (Marrs, 2001; Ujvary, 2010).

2.4.4 Phosphorothioates Group

In phosphorothioates group pesticides, one of the oxygen (O) atom had been replaced by the sulphur (S) atom, either at the covalent bond or at the monovalent bond. Examples of pesticides with sulphur atom replacing the oxygen atom at the covalent bond are diazinon, parathion, bromophos, fenithrothion, chlorpyriphos, fenchlorphos, coumaphos and etc. These organophosphorous compound pesticides are mainly used as insecticides (Marrs, 2001; Balalimood et al., 2012).

The VG (2-diethoxy-methylphosphorylsulfanyl-N, N-diethylethanamine), one of the chemical warfare agents also fall under this group. However, the sulphur (S) atom replaced or become a substitute to oxygen atom at the leaving group, 'L' position (Marrs, 2001; Hulse et al., 2014).

2.4.5 Phosphorodithioates Group

Pesticides that fall under this group shared the core structure similarity by presence of two sulphur (S) atom, replacing the oxygen atoms. The replacements can be at combination of the covalent bond and any monovalent bond, or involved only any two of the monovalent bonds. Examples of the pesticides are malathion, azinphos-ethyl, azinphos-methyl, mecarbam, menazon, morphothion, phenthoate, dimethoate, disulfoton, sulprofos and many others. They are mainly used as insecticides (Marrs, 2001; Balalimood et al., 2012).

2.4.6 Phosphonothioates Group

In this group, two oxygen (O) atoms were replaced by one sulphur (S) atom and one carbon (C) atom. Leptophos, EPN (*O*-ethyl *O*-*p*-nitrophenyl phenylphosphonothionate) and EPNO (*O*-ethyl *O*-*p*-nitrophenyl phenylphosphonate) are examples of insecticides that can be found under this group. In addition, the VX nerve agent, one of the most potent chemical warfare agent, is also come from this group (Marrs, 2001; Hulse et al., 2014).

2.4.7 Phosphoramidate Group

Tabun, one among the earliest chemical warfare agents fall under this group. An example of insecticide that come from same group, the phosphoramidate group of organophosphorous compound is fenamiphos. In this group, one of the phosphorus-oxygen bond was replaced by phosphorus-nitrogen bond (Marrs, 2001; Chamber et al., 2010; Balalimood et al., 2012).

2.4.8 Phosphorothioamidates Group

In this group, two oxygen (O) atoms were replaced by one sulphur (S) atom and one nitrogen (N) atom. The sulphur replaced the oxygen either at the covalent bond, or become a substitute at monovalent bond, the ‘L’ position. Examples of insecticides fall under this group are isofenphos and propetamphos (Marrs, 2001; Chamber et al., 2010; Balalimood et al., 2012).

2.5 Organophosphorus Compound Pesticides and Health

2.5.1 Exposure and Metabolism

Organophosphorus compound pesticides can enter human body through ingestion, inhalation, ocular and skin absorption. Exposure to the chemicals can be either acute or chronic. Acute exposure involving single, high dose of the substances usually associated with acute effects. Whilst in chronic exposure, the substances usually repetitively exposed to the victims at low dose, and sometimes not being realized by the victims. Chronic exposure usually produced chronic, nonspecific effects at the beginning.

Deliberate ingestion, which strongly associated with suicidal intention contributed to one third of suicidal causes over the world (World Health Organisation, 2016). Accidental ingestion usually affected children due to improper storage of pesticides at home and the children's characteristic of immaturity, illiteracy and inability to assess risk, together with nature to explore new things (United Nations Environment Programme, 2004). Inhalation and skin absorption may occur mainly in occupational settings (Ye, Beach, Martin & Ambikaipakan, 2013), during handling and spraying of the pesticides, mainly due to improper techniques and inadequate protective equipment.

Metabolism of organophosphorus compound inside human body varies among groups and substances, strongly associated with the chemical structures. For example, the double or covalent bond atom, which can be either oxygen (O) atom or sulphur (S) atom, gave different intrinsic stability of the substance. The phosphorus=sulphur form is more stable compared to phosphorus=oxygen form, led to many insecticides manufactured in phosphorus=sulphur form. (Karalliedde & Senanayake, 1989).

These made the phosphates more volatile and directly toxic, compared to phosphorothioates whilst, phosphorothioates are converted to the biologically active oxon, paraxon by microsomes in liver (Karalliedde & Senanayake, 1989).

After absorption, organophosphorus compound pesticides and their metabolites distributed quickly in all tissues. Level of lipophilicity of the substances determined the level of concentration in neural and other lipid-rich tissues. The plasma half-life also differs between compounds, ranged from a few minutes to a few hours (Karalliedde & Senanayake, 1989). Metabolism of organophosphorus compound pesticides or their metabolites basically involved the Phase I (oxidation, reductions, hydrolysis) and Phase II (conjugations) reactions (Chamber et.al., 2010). Some compounds, such as phosphorothioates group are converted to biologically active oxon by the liver microsomes, via oxidation.

Detoxification occurs either through structural biochemical modification or by linkage to binding sites without exerting effects. Elimination of the organophosphorus compound and their metabolites occurs mainly through urine and faeces, 80-90% of most compounds being eliminated within 48 hours. Some are eliminated unchanged and some compounds remained in body for longer periods such as fenthion and fenitrothion (Karalliedde & Senanayake, 1989).

2.5.2 General Toxicology

Majority of organophosphorus compound used in agriculture are insecticides, only a few names are recognised as herbicides, fungicides, defoliant and growth regulators. The basic toxicological activity of organophosphorus compound in human is by acting as enzymes inhibitors, especially the esterases. These pesticides also affected some other enzymes such as the trypsin, chymotrypsin and lipases (Karalliedde & Senanayake, 1989).

In general, cholinesterases can be grouped into B-esterases, enzymes inhibited by the organophosphorus compound pesticides; the acetylcholinesterase, butylcholinesterase, carboxylesterase and A-esterases; arylesterases, paraoxonases, diisopropylfluorophosphatase is a different group of enzymes that catalytically hydrolysed the organophosphorus compound, important in term of detoxification (Wilson, 2010).

Based on their anticholinesterase activities, Marrs (2001) in his writing, Organophosphates: History, Chemistry, Pharmacology classified the effects of organophosphorus compound pesticides in human into four syndromes. These classifications were based on the onset and duration of symptoms exerted by the victims, divided into acute cholinergic syndrome, intermediate syndrome, organophosphate-induced delayed neuropathy (OPIDN) and chronic organophosphate-induced neurological damage (COPIND).

Acute cholinergic syndrome appeared immediately after exposure, can last after a few days. Intermediate syndrome commenced a few days after poisoning episode and can last a few days later. Organophosphate-induced delayed polyneuropathy (OPIDN) usually started a week or two after poisoning and can last longer and sometimes, persistent. COPIND is usually persistent.

This system was used by many authors to describe the clinical sequalae of organophosphorus compound pesticides poisoning in many organ systems for examples, by Hulse et al. (2014) in Respiratory Complication of Organophosphorus Nerve Agent and Insecticide Poisoning, by Karalliedde & Senanayake (1989) in Organophosphorus Insecticide Poisoning and, by Balalimood et.al. (2012) in Health Aspects of Organophosphorous Pesticides in Asian Countries.

2.5.3 Neurotoxicity

Organophosphorus compound pesticides especially the insecticides, were formulated to be neurotoxic. They should be able to acutely disrupted the neurotransmitter to alter the insects behaviour and survival. This may affect untargeted species such as human. For examples, as cholinesterase-inhibitor, the organophosphorus compound pesticides act as competitive substrates to acethylcholinesterase, a B-esterase-types of enzymes (Wilson, 2010).

Acetylcholinesterase was found at synapses of neuromuscular junctions, myotendineous junction, in cerebrospinal fluid, central nervous system neuron cell bodies, axons, skeletal muscles, smooth muscles and even blood cells such as red blood cells, megacaryocytes, lymphocytes and platelets. Acethylcholinesterase helped in reuptake of acethylcoline into the neurons (Wilson, 2010).

Cholinesterase inhibitor agents serve as an alternative substrate for acetylcholinesterases, prevent the reuptake process, resulting in accumulation of acetylcholine at the neuronal junction. As a result, an exposed individual will present the symptoms of cholinergic syndrome. Organophosphorus pesticides poisoning can be acute or chronic, depends on the volume, concentrations and dosage frequency, as well as route of exposure. Excess of acetylcholine overstimulated the muscarinic neuroeffectors of parasympathetic system at autonomic ganglia. Parasympathomimetic effects will be seen such as bradycardia, hypotension, miosis (constricted pupil) and blurred vision, diarrhea, urinary incontinence, excessive lacrimation and salivation. Victims might also have cough, rhinorrhea, bronchorrhea, bronchospasm and respiratory depression (Pope, 1999; Wilson, 2010; Balalimood et al., 2012).

The acetylcholine excess might also overstimulate the motor end plate of skeletal nicotinic neuromuscular junctions and caused sweating, muscle fasciculation, jerky movement and paralysis. The muscle fibres around the junction might also turn to necrosis, victims might suffer from myopathy presented with prolonged muscle weakness. The excessive acetylcholines affected the neurons inside central nervous system and caused headache, anxiety, hypothermia, tremors, convulsion, coma and even death (Pope, 1999; Wilson, 2010; Balalimood et al., 2012, Hulse et al., 2014).

Pesticides, specifically organophosphorus may also act on Neuropathy Target Esterase (NTE), another B-esterase (Karalliedde & Senanayake, 1989; Marrs, 2001; Wijeyesakere & Richardson, 2010). Although these enzymes physiologic functions are not conclusively identified, NTE can act as phospholipase which is responsible in hydrolysis of phosphatidylcholine to glycerophosphocolin, or as lysophospholipase, responsible in hydrolysis of lysophosphadylcholine to glycerophosphocholine and fatty acids. Inhibition of the second activity by pesticides caused excess of lysophosphadylcholine, lead to axonal disruption which is associated to delayed neuropathy, especially Organophosphate-induced-delayed-neuropathy (Wijeyesakere & Richardson, 2010). The victims might experience progressive lower limb myopathy, distal numbness or paraesthesia, loss deep tendon reflex, foot drop and high stepping gait.

Intermediate syndrome is characterised by delayed involvement of muscles supplied by cranial nerves, flexors of neck, respiratory and proximal limb muscles (Harshad, Abhish, & Vikhe, 2016).

2.5.4 Respiratory Toxicity

Acute respiratory problems from organophosphorus pesticides poisoning may occur during and after the acute cholinergic crisis which come from the anticholinesterase effects (Hulse et al., 2014; Harshad et al., 2016). During the acute poisoning, respiration may be affected through pulmonary parasympathetic muscarinic effects featured by bronchospasm, bronchorrhoea and alveolar oedema. Involvement of neurons inside the brain medulla and hindbrain, can cause depression of respiratory centre. Nicotinic involvement caused paralysis to respiratory muscle.

Exposure of the organophosphorus pesticides through inhalation can cause direct disruption of the pulmonary endothelial-epithelial barrier (Hulse et.al., 2014). Nausea and vomiting also increased the risk of aspiration pneumonitis. Almost similar respiratory complications might also be seen in intermediate syndrome cases, a state of muscles paralysis, often seen one to four days after poisoning, affecting conscious persons without cholinergic crisis (Karalliedde & Senanayake, 1989).

Organophosphorus pesticides might also cause respiratory problems following chronic low or sub-lethal dose exposure. Pesticides can behave as a Volatile Organic Compound; an organic compound that, when released to atmosphere, reacted with sunlight and nitrogen oxides to form tropospheric (ground level) ozone (O3). (Marty, Spurlock & Barry, 2010). The ozone is responsible to cause toxicity especially towards human respiratory system and immunological system. Ozone, the radical can react to membrane lipid, induced lipid peroxidation, caused depletion of antioxidants and lead to cells damage and death (Marty, Spurlock & Barry, 2010).

At same time, the initial inflammatory process may trigger the epithelial cells and macrophages to produce many cytokines that may induce asthma or exacerbated the asthmatics. The high concentration of cytokines may influx excessively into the alveolar and bronchioles interstitial space and caused tissue injuries. The ciliated cells may be damaged and lost their functions, tissues injury may lead to collagen synthesis and lungs fibrosis (Ale & Maibach, 2010; Brundage & Barnett, 2010; Marty, Spurlock & Barry, 2010).

2.5.5 Immunotoxicity

In general, the immune system gave response to foreign materials either through innate mechanism or adaptive mechanism. Innate response is the first response to foreign material invasion, produced by local physical barriers such as skin or mucosa. Adaptive response is when the antigen induced immunologic memory in immune system (Brundage & Barnett, 2010).

Pesticides can affect the immune systems by many ways. Activation of the immune system as a defence mechanism at same time can create the potential of developing autoimmunity. Immune system can also be suppressed or depressed by the pesticides which make the person susceptible to certain infection or diseases. The pesticides introduction may also cause hypersensitivity reaction with wide range of clinical presentations (Brundage & Barnett, 2010). Organophosphorus compound pesticides are potential to alter the immune systems.

2.5.6 Dermatotoxicity

Pesticides exposure can cause wide range of dermatitis, from irritant dermatitis to hypersensitivity reactions until anaphylactic symptoms (Ale & Maibach, 2010; Flores & Maibach, 2010; Langer, Maibach & Maier, 2010). It can be due to local or systemic exposure to pesticides. Photosensitivity refers to abnormal cutaneous reaction to solar ultraviolet reaction with presence of certain etiological factors (Langer, Maibach & Maier, 2010). Contact of exogenous factors in agriculture such as the pesticides, the sunblock application and the plants products is one of the etiological factors to this condition.

Photosensitivity cutaneous reaction can be either photo-irritant, or photo-allergy. Photo-irritant dermatitis is the commoner type, occur quick within minutes to hour, mimic sunburn at area exposed to sunlight and chemical. The chemicals absorbed the UV light and caused direct tissue damage. It may resolve spontaneously after stopping the exposure.

Photoallergic dermatitis occurs when the allergens being activated by the UV light, triggering the cell-mediated-hypersensitivity-reaction and released the IgE. This condition is uncommon, affect only 1% of population. The allergens can be locally contact to the skin such as sunblocks, plants and fragrances or systemic drugs such as NSAIDS, Tricyclic Antidepressants, antimalarial and many other sulfur-containing products (thiazides diuretics, sulfonylurea etc.). Pruritus is the prominent feature together with eczematous type skin reaction. Repeated contact may cause dry scale patch and plaque lesions, and may persist for months after discontinuing the exposure (Ale & Maibach, 2010; Flores & Maibach, 2010; Langer, Maibach & Maier, 2010).

Another type of pesticides dermatotoxicity is contact dermatitis, without UV light dependent. Smith and Hotchkiss, 2001 as cited by Flores & Maibach, 2010 mentioned that contact dermatitis contributed to 15-20% of all cases of occupational skin diseases. This condition can also be divided to irritant contact dermatitis, which is localized and allergic contact dermatitis which involved the immunological mechanism. Allergic contact dermatitis differed from photo allergen dermatitis in form of presence or absence of UV light contribution, however a person can get overlapping dermatitis reactions. Allergic contact dermatitis happened as a result of delayed-type-hypersensitivity, a Type IV hypersensitivity reaction (Ale & Maibach, 2010; Flores & Maibach, 2010; Langer, Maibach & Maier, 2010).

This condition is mediated by T-cells, requires previous sensitization to specific allergens. The allergens which are small enough to penetrate the skin barrier will bind to keratinocytes and attracted the Langerhans cell to perform phagocytosis. This combination will trigger the T-cell that will start its clonal expansion and division, produced the cytokines (interleukin-I, IL-II, interferon, tumor necrosis factors) and at same time developed the memory towards the allergens (Ale & Maibach, 2010; Flores & Maibach, 2010; Langer, Maibach & Maier, 2010).

When the exposure was repeated, the process will be repeated at local area, at same time may induce reaction to another organ system. This condition was described as contact urticaria syndrome. This syndrome is a broad spectrum, immune-mediated dermatitis, associated with Type I and Type IV hypersensitivity. The affected persons may be presented with collection of symptoms, either restricted to cutaneous or additional extracutaneous symptoms. It can be stages into Stage I, II, III and IV (Ale & Maibach, 2010).

In Stage I, the person had localized urticarial dermatitis, itchiness and tingling sensation. In Stage II, the urticarial lesions become generalized. In Stage III, besides generalized urticarial lesion, the symptoms also involved other systemic organs. The persons might have rhinoconjunctivitis, orolaryngeal symptoms, bronchial asthma and gastrointestinal symptoms. In Stage IV, the person may develop anaphylactic shock (Ale & Maibach, 2010).

2.5.7 Endocrine Disruption

Endocrine systems consisted of central organs and peripheral organs. Organs involved are the hypothalamic-pituitary axis, thyroid, parathyroid, adrenal, pancreas, ovary and testis. Their functions are mainly for synthesis, store and release of hormones which further regulate the functions of various organs. Main functions of hormones are regulating the body haemosthasis and control developmental processes. Steroid hormones such as oestrogen and androgen may be affected by the endocrine disruptor agents either by excitatory or inhibitory process towards the