INSECTICIDES

Savolainen Kai M.
Department of Industrial Hygiene and Toxicology, Finnish Institute of Occupational Health, Topeliuksenkatu, Helsinki, Finland

Vähäkangas Kirsi
Department of Pharmacology and Toxicology, University of Oulu, Finland

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Contents

1. Introduction

Insecticides are used all over the world, but especially in developing countries with tropical climates, which are ideal conditions for the growth of insects. However, large

quantities of insecticides are used in industrialized countries since certain insect species pose a major threat to growing plants in the field and greenhouses. Many insecticides have also played an important role over the years in the fight against the insects that spread malaria.

Even though most of the use of insecticides occurs in sub-tropical or tropical countries, these agents have been used around the world, for example in the United States, and in small quantities at the latitudes of the Nordic countries. Since most insecticides are highly toxic, a plethora of reports have been published on their effects on experimental animals and man (some of these are given in the Bibliography).

All of the insecticides used today are neurotoxic, and their most important acute effects are mediated via the central nervous system (CNS). In addition to the neurotoxic effects, insecticides also have other toxic effects, but neurotoxicity predominates. However, the organochlorine insecticides, such as DDT and lindane also possess teratogenic, genotoxic, and carcinogenic effects that will also be briefly dealt with in this article. The emphasis of this presentation is, however, on the neurotoxicity of compounds belonging to this class of pesticides.

Unfortunately, the mammalian and insect nervous systems have great similarities, for example, in their neurotransmitter receptors. Insecticidal compounds have been targeted to interfere with specific membrane proteins, usually the receptors. In the synapses, since the receptors may be virtually identified in mammals and insects, these neurotoxic compounds do not have any inherent specificity in their neurotoxicity toward insects. The three major classes of insecticides widely used today are organophosphates (OP), carbamates and the pyrethroids. Also, another group of insecticides, organochlorine compounds (e.g., DDT), have been extensively used in the past, and are still used today in the developing countries in the fight against malaria vectors.

The anticholinesterase insecticides, notably OPs and carbamates, have the highest acute toxicity of insecticides, often ranging from 1 and 10 mg/kg bw, and most of the acute insecticide-induced poisonings can be attributed to these compounds. Some of the OP insecticides may also induce long-term or persistent health hazards in exposed individuals, usually in their peripheral nervous systems. The acute toxicity of organochlorine compounds such as DDT is much less, around 100 mg/kg bw, but they are extremely persistent, and may pose carcinogenic hazards to humans, and a threat to the environment due to their resistance to biodegradation. The safest group of insecticides used today are the pyrethroids whose acute toxicity is low, but even those may cause slight neurotoxicity, and may sensitize exposed humans in the general or occupational environments.

In this article, emphasis will be placed on the OP and carbamate anticholinesterase insecticides, and the pyrethroids. However, the toxic properties of organochlorine insecticides will also be dealt with because of their previous extensive use. It needs to be noted that the usage of organochlorine insecticides continues, even if it has declined due to their prohibition in a number of industrialized countries. Table 1 provides information of the annual use of pesticides (herbicides, fungicides, and insecticides) in different countries, as estimated by the United Nations Food and Agriculture

Organization. Even if herbicides are internationally the most widely used pesticides, it is noteworthy that in developing countries in tropical areas, insecticides are probably the most important class of pesticides in terms of human poisonings. Also, in countries such as the USA and several Southern European countries, insecticides have been widely used. For example, in the USA the use of OP insecticides in 1994 was about 240 metric tons of active ingredients, with California accounting for more than 10 % of the total use.

Country	**Metric tons of active ingredient**	**Country**	**Metric tons of active ingredient**
Africa		**Oceania**	
Algeria	9 400	Australia	120 000
Cameroon	3 900	Total in Oceania	120 820
Morocco	9 400		
Zimbabwe	4 000	**Near East**	
Total in Africa	30 000	Iran	19 600
Latin America and Caribbean		Turkey	23 600
Brazil	57 000	Total in Near East	53 870
Chile	7 000		
Colombia	20 000	**North America**	
Costa Rica	10 000	Canada	30 000
Ecuador	14 000	USA	248 000
Honduras	6 700	Total in North America	278 000
Mexico	36 000		
Paraguay	3 000	**Europe**	
Venezuela	2 700	France	110 000
Total in Latin America	169 320	Germany	30 000
Asia		Hungary	17 400
China	240 000	Italy	80 000
India	72 000	Romania	20 000
Kazakhstan	10 000	Russia	27 000
Korea	26 400	Spain	42 000
Malaysia	40 000	Ukraine	15 000
Pakistan	5 600	United Kingdom	31 000
Sri Lanka	4 900	Total in Europe	454 200
Thailand	36 000		
Uzbekistan	1 000		
Total in Asia	442 000		

[1]see O'Malley (1997) *The Lancet* 349, 1161-1166.

Table 1. Annual pesticide use (herbicides, fungicides, and insecticides) estimated by the United Nations Food and Agriculture Organization[1].

The most critical period for exposure to insecticides occurs in the working environments during the production, transportation, and mixing of the insecticidal formulations,

though exposure can also occur during spraying of the compounds, and even when collecting sprayed crops, for example flowers, especially those grown in greenhouses. Consumers may also become exposed to insecticides through food items such as vegetables and fruits, and even through other food items. However, the skin is usually the most important exposure route in the occupational environment. Occasionally, exposure through inhalation may take place, and oral exposure due to poor occupational hygiene is possible. Consumer exposure through the oral route is usually insignificant, and does not pose either an acute or a long-term health risk to exposed individuals.

2. Organophosphate insecticides

2.1. Background

Today, the organophosphorus esters are the most widely used class of insecticides. Initially, OP compounds were discovered in Germany in the late 1930s, and parathion was the first compound of this class to be synthesized. Typical to all OP compounds is the presence of a phosphorus atom that is linked with a double bond with a sulfur or oxygen (the inactive parent compound is often activated by non-enzymatic desulfuration to a corresponding active oxon). Two alkyl chains are usually linked to the phosphorus with an oxygen bridge to a methyl, ethyl, or isopropyl moiety. The remaining bond of the pentavalent phosphorus atom is reserved for the so-called leaving group that is removed from the molecules upon its reaction with the target molecule, acetylcholinesterase (AChE), which also leads to aging of the enzyme, i.e., formation of a covalent bond between the OP compound and the enzyme. The leaving group, in turn, greatly varies between different OP compounds.

2.2. Mechanisms of Action

The toxic effects of OP compounds are due to the inhibition of AChE which represents the key-target of all OPs. OP-induced inhibition is due to the irreversible phosphorylation of the enzyme, AChE, and subsequent attenuation, or inhibition of the enzymatic activity. OP-induced inhibition of AChE leads to a dramatic accumulation of acetylcholine (ACh) at all sites where ACh serves as a neurotransmitter, notably the brain, sympathetic and parasympathetic ganglia of the autonomic nervous system, as well in the neuromuscular end-plate of striated or voluntary muscles. Normally AChE hydrolyzes ACh, and this hydrolysis leads to the formation of choline. Choline is removed from the synaptic cleft, into which ACh had been released by reuptake via a high affinity transport system back into the presynaptic nerve terminal where it is used in the synthesis of new acetylcholine molecules.

After OP exposure, ACh starts to accumulate in the synapse, leading to excessive stimulation of cholinergic receptors, both nicotinic (an ion channel) or muscarinic receptors (a family of 7 transmembrane domain receptors that are coupled to a GTP-binding protein). Stimulation of nicotinic receptors is associated with a dramatic increase of influx of sodium into the target cells. This, in turn, leads to neuronal depolarization and cellular activation. Activation of muscarinic receptors leads to activation through a G-protein linked to the enzyme, phospholipase C, that cleaves a membrane phospholipid, phosphatidylinositol-4, 5-bisphosphate, into diacylglycerol

and inositol-1,4,5-trisphosphate. These are two second messengers, and they cause elevations of free intracellular calcium and subsequent cellular excitation. Muscarinic receptor activation seems to be associated with cerebral activation and neuronal damage and ensuing death of neuronal cells in many brain regions after exposure to OPs. Neuronal cholinergic activation may lead to the increased formation of reactive oxygen species, possibly to changes in gene expression, and amplification of apoptotic events, i.e., increased likelihood of programmed cell death. It is of interest that glutamatergic rather than cholinergic muscarinic antagonists are able to antagonize the neuronal damage in experimental animals exposed to high doses of OP compounds and suffering from overt convulsions. These observations reflect the close interactions between these two classes of receptors.

2.3. Signs and Symptoms of Organophosphate Poisoning

In many cases, OP compounds cause acute intoxication at very low doses. Compounds such as parathion and mevinphos may cause death in humans at doses between 5-100 mg/kg, whereas very high doses of malathion, in the range of 12000 mg/kg, are required to cause serious problems, or death. Some OP agents which are used as nerve agents, such as soman *vs*. tabun, cause similar effects in the range dose 100-200 μg/kg. The signs and symptoms of an OP poisoning are those typical for cholinergic crisis, and reflect the excitation of both central nervous and peripheral as well as autonomic nervous systems. The onset of the clinical features of OP poisoning depends on the route and degree of exposure and re-exposure. However, the interval is generally less than 12-24 hours, but in some cases it may be several days, even weeks, because of initial lipid storage and subsequent redistribution of the compound. However, in some cases, especially after oral exposure of high doses or after exposure to cholinergic OP nerve agents, the onset of symptoms may be almost immediate, and may take place within minutes. The typical symptoms of a massive intoxication include excessive salivation, increased bronchial secretions, bronchoconstriction, muscle fasciculations, cardiovascular effects, miosis, confusion, tremors, convulsions, and ultimately death (Table 2). In some cases, however, even short-term exposure to high doses of OP compounds may induce chronic effects, which may be very difficult to diagnose. It may be even more difficult to diagnose the chronic effects induced by exposure to OP compounds at low doses, doses that do not elicit any clinical signs or symptoms.

Increased salivation and lacrimation
Increased bronchial secretion
Bronchoconstriction and respiratory difficulties
Bradycardia or tachycardia
Increased activity of gastrointestinal tract and increased urination
Muscle fasciculations, muscle tremors, and muscle weakness
Dizziness, confusion, headache, general weakness, convulsions, coma, and death

Table 2. Signs and symptoms of exposure to large doses of organophosphates

In cases of a massive exposure, death ensues because respiration is impaired due to bronchoconstriction and bronchial secretions, diaphragmatic contractions, as well as depression of the respiratory center in the brain stem.

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