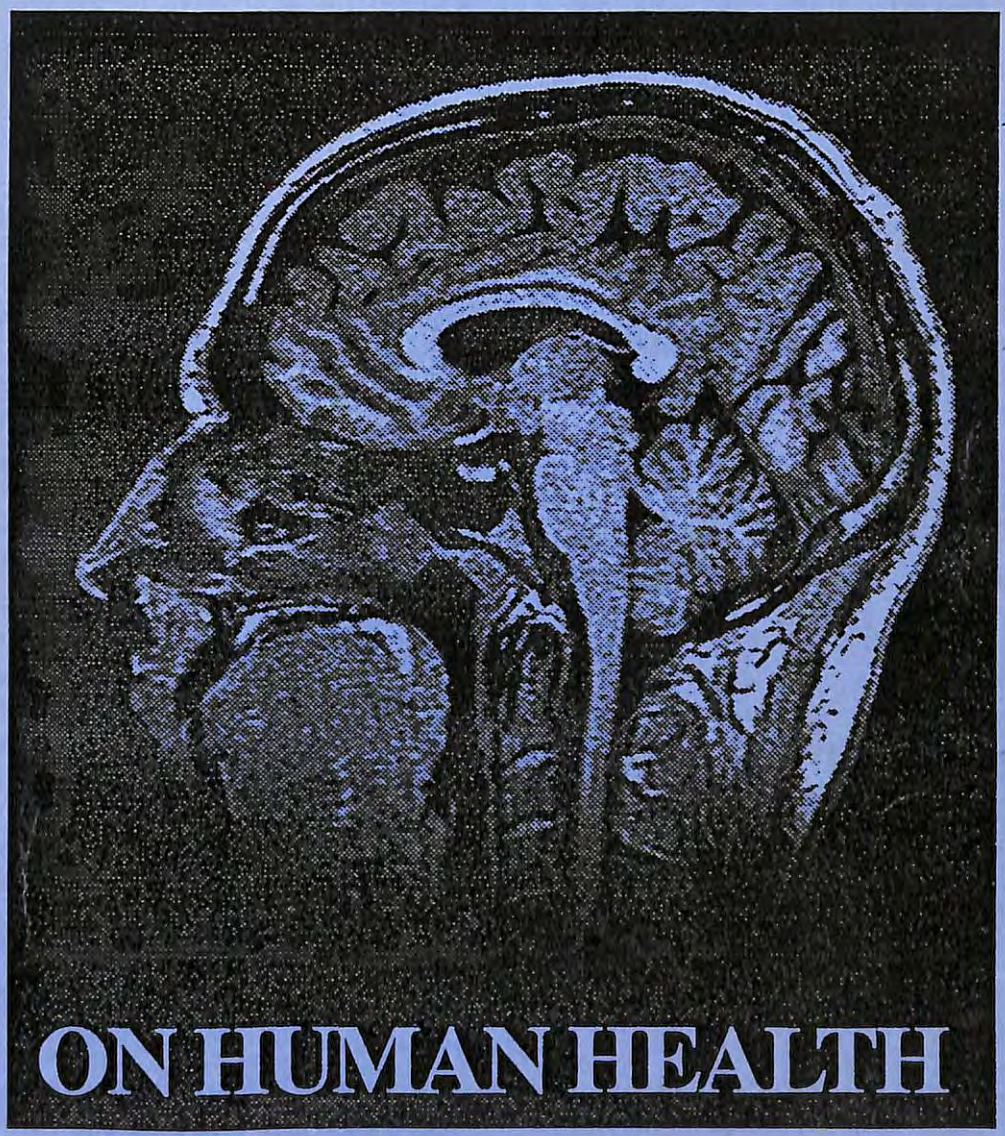
THE EFFECTS OF ORGANOPHOSPHOROUS PESTICIDES ON HUMAN HEALTH



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THE EFFECTS OF ORGANOPHOSPHOROUS PESTICIDES ON HUMAN HEALTH

Authors:

M. A. Allsopp
V. T. Jewell
P. A. Johnston

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THE HUMAN HEALTH EFFECTS OF ORGANOPHOSPHOROUS PESTICIDES

SUMMARY

The Mediterranean Action Plan (MAP) is part of the United Nations Environment Programme's (UNEP) Regional Seas Programme. Its legal component, the Barcelona Convention has black listed organophosphorous (OP) compounds in its protocol for the "Protection of the Mediterranean Sea Against Pollution from Land-based Sources". In 1991, the Mediterranean countries agreed:

> "to promote measures to reduce inputs into the marine environment and to facilitate the progressive elimination by the year 2005 of organophosphorous compounds hazardous to human health and the environment."

The Mediterranean countries agreed that measures should include integrated pest control (IPM) in agriculture and financial and technical support to train farmers in IPM "whereby non-chemical methods of controlling pests are emphasised." Contract Parties also agreed to immediately end the use of OP compounds unless it is proved that they have no direct effect on human and animal health. Despite these decisions, hazardous OP pesticides are still used widely in agriculture in the Mediterranean region.

This report examines the human health effects from the use of OP pesticides. Its objective is to emphasise the urgent need to implement the 1991 decision to eliminate hazardous OP compounds in order to protect the people's health and the environment.

Organophosphorous Compounds

The discovery of the adverse effects of OP compounds led to their synthesis and use as nerve gases during World War II. The insecticidal properties of OP compounds were found as a result of military nerve gas research, and since World War II they have been commercialised for agricultural use.

Use of Organophosphorous Pesticides in Mediterranean Countries

The banning of several organochlorine pesticides in Western countries in the 1970's and 80's, because of their persistence and toxicity in the environment, has led to an increased use of OP pesticides in many countries even though these compounds are also highly toxic. OP pesticides are now the main group of insecticides used both on staple and commercial crops in the Mediterranean region, especially olives and citrus fruits. As a result, many people are occupationally exposed to these chemicals and hundreds of tonnes enter the Mediterranean environment each year.

The Issue of Human Health

Most OP pesticides which are currently in use have not undergone adequate toxicity testing. This is especially true for neurotoxicity which is the major toxic effect of OP compounds. Even when OP pesticides have been tested for neurotoxicity, marked differences in toxicity have been found to occur between different animal species. Therefore, neurotoxicity in humans is hard to predict from animal experiments, and OP pesticides are presently used without adequate knowledge of human health effects.

This report discusses recent evidence which shows that occupational exposure to OP pesticides may cause long-term damage to the peripheral and central nervous systems in humans as well as other health threats. Damage to the nervous system may occur after only a single acute OP poisoning episode or after long-term (i.e. chronic) exposure or repeated exposure to small quantities of OP pesticides.

Since many people are routinely exposed to OP pesticides in their work in the Mediterranean region, and there are also many cases of acute OP poisoning reported each year, there could be vast numbers of people suffering from toxic effects to their nervous systems induced by OP pesticides. The extent of the problem is currently unknown but the growing body of evidence from recent studies suggests it could be very widespread.

In addition, OP compounds from agricultural use are present in the air, in water systems and on food. The health effects to the general population from this exposure are largely unknown.

The Way Forward

The Contracting Parties of the Barcelona Convention have agreed to eliminate OP compounds hazardous to human health and the environment.

There is already evidence that occupational exposure to OP pesticides can lead to long-term adverse effect on the nervous system. A previous submission to the Barcelona convention in May 1991 by Greenpeace also outlined environmental problems with OP pesticides. In the light of this evidence Greenpeace advocates that the only solution to human health and environmental problems from the use of OP pesticides is to phase out their production, import and use.

Reduction strategies for selected pollutants are difficult to implement and essentially unworkable. Greenpeace therefore advocates that implementation of a precautionary approach is interpreted as a shift in agricultural practices away from dependence on OP pesticides altogether. A precautionary approach means that the production and use of OP pesticides should be completely phased out.

An alternative strategy is the implementation of ecological farming methods in the Mediterranean. Such methods are already being successfully practised in parts of the region. Financial and technical support for research, development and implementation of ecological agriculture in the Mediterranean is now needed.

Some EC countries have banned the use of certain OP pesticides but still manufacture and export these compounds to Mediterranean countries. The import of such hazardous OP pesticides into the Mediterranean countries should be banned, and EC countries should end the production and export of these OP compounds.

Health Effects from Organophosphorous Pesticides

a. Acute OP pesticide poisoning

OP pesticides are responsible for causing many acute pesticide poisoning cases and some fatalities every year among exposed workers in Mediterranean countries. Studies in Greece, Tunisia and Morocco have reported that a large percentage (>60%) of hospitalisations from all types of pesticide poisoning occurred as a result of OP pesticides.

The health effects of acute OP poisoning are caused by the inhibition of an enzyme called acetylcholinesterase. This enzyme plays a key role in the transmission of nerve impulses. When the normal action of this enzyme is blocked by OP compounds, it becomes impossible to "switch off" nerve impulses. This results in a number of characteristic adverse symptoms and in severe cases respiratory failure or heart failure may result in death. Acute poisoning can be treated with drugs and the patient usually recovers within a few days. However, there is now evidence that acute OP pesticide poisoning may lead to long-term adverse effects on the nervous system.

b. Long Term Effects on the Nervous System

Recent studies on individuals who are occupationally exposed to OP pesticides suggest that both acute and long-term (chronic) exposure may cause long-term effects both on the peripheral and central nervous system. The number of people affected by such neurotoxicity is currently unknown but studies indicate that the problem could be very widespread.

(i) Damage to the Peripheral Nervous System

Severe cases of acute OP poisoning can cause long-term damage to the peripheral nervous system known as organophosphate-induced delayed neuropathy (OPIDN). Symptoms include muscle pain and weakness, and tingling/burning which begins in the hands and feet and may eventually progress to the limbs. Because symptoms start at the extremities the nerve damage is referred to as "distal" (i.e. distal axonal degeneration). If damage to the nerves is very extensive, paralysis may occur. The number of people reported to be suffering from OPIDN is relatively small. However, recent studies suggest that many individuals who are occupationally exposed to OP pesticides may suffer peripheral nervous system damage - both from incidents of acute poisoning or after repeated exposure to small quantities of OP pesticides. For example:

Acute poisoning - Tests on the hands and feet of individuals who had previously experienced only one case of acute poisoning from methamidophos, found chronic (long-term) sensory impairment, reflecting OPIDN.

Chronic Exposure - Recent studies suggest that long-term exposure to small repeated quantities of OP pesticides, with no episodes of acute poisoning, may cause OPIDN. Such repeated exposures may possibly cause cumulative damage to the nerves. Studies on farmers in the UK who use OP sheep dips (which contain OP pesticides - diazonon, chlorfenvimphos or propetamphos) have shown that symptoms reported by the farmers are characteristic of peripheral nerve damage. In addition, tests on 16 farmers who had been involved in sheep dipping for 4 years or more, revealed that they all had peripheral nerve damage in the form of distal axonopathy, which is characteristic of OPIDN. The same pesticides used in sheep dips in the UK are used on crops in the Mediterranean.

(ii) Damage to the Central Nervous System

Both acute OP intoxication or chronic exposure to OP pesticides may result in long-term damage to the central nervous system which involves changes in brain function. Symptoms include depression, anxiety, drowsiness, dizziness, fatigue, slurred speech and mental confusion.

Acute Poisoning - There is conclusive evidence that acute OP poisoning can cause long-term adverse effects on brain function. This may be due to a lack of oxygen supply to the brain during the poisoning episode caused by effects on the heart and respiratory systems.

A recent study which tested individuals two years after they had suffered from just a single episode of acute OP poisoning showed they had subtle, but clinically significant, declines in neuropsychological (i.e. brain) functioning.

Chronic Exposure - Recent studies have demonstrated that repeated exposure to small quantities of OP pesticides may cause long-term adverse effects on the brain. A study of farmers in the UK who used OP sheep dips reported that more than a third of them suffered from central nervous system effects synonymous with OP intoxication including fatigue, loss of concentration and depression.

In addition, a World Health Organisation epidemiological study of "healthy workers" who had chronic exposure to OP pesticides in their occupations in several European countries revealed that these individuals generally scored significantly less on neurobehavioural tests of well being and mood status (e.g. anxiety, depression, irritability). Thus symptoms of feeling less well and having mood problems in the workers were related to occupational exposure to OP pesticides.

c. Other Health Effects

Exposure to OP compounds may result in a number of other toxic effects including:

Cancer - Epidemiology studies have reported that exposure to OP pesticides is associated with an increased risk in a number of cancers including stomach, lung and bladder cancer and non-Hodgkin's lymphoma.

Saku Disease - Since 1965, crop spraying with OP pesticides in Japan has been reported to cause adverse effects on the eye, termed Saku disease, in populations living near to sprayed areas. Symptoms include short-sightedness, and children in particular have been affected.

Birth Defects - Animal experiments have shown that OP compounds cause toxic effects to the developing foetus resulting in birth defects. Limited evidence suggests that birth defects may also occur in humans following OP exposure.

Immunotoxicity - Animal experiments have shown that some OP pesticides are toxic to the immune system, and in particular cause allergic reactions. Aerial spraying of malathion in US cities was reported to cause allergic reactions in people. Experiments on mice support this phenomenon showing that malathion is toxic to cells of the immune system which cause allergic reactions at extremely low levels.

Effects on the General Population

In the case of immunotoxicity, Saku Disease and neurotoxicity it is possible that the general population can be affected by aerial spraying of OP pesticides. Similar effects on the general population may also occur from exposure to OP residues in foodstuffs. Monitoring of residues of OP pesticides on food in the Mediterranean region however is infrequent, but recent studies have found OP pesticide contamination of fruits and vegetables. One study detected levels of OP pesticides greater than those permitted by Italian law on 48% of oranges from Sicily which were being sold in Bologna, Italy. Thus in addition to the health of occupationally exposed individuals, the health of the general population may also be affected by OP pesticide exposure. Presently the extent of health effects in the general population from exposure to these highly toxic pesticides is unknown and should be of great concern.

1. INTRODUCTION

1.1 The Mediterranean Action Plan

The Mediterranean Action Plan (MAP) is part of the United Nations Environment Programme's (UNEP) Regional Seas Programme. Its legal component, the Barcelona Convention, has established a regional framework for the protection of the Mediterranean Sea against pollution. One of the protocols to the convention is the "Protocol for the Protection of the Mediterranean Sea Against Pollution from Land-based Sources". Organophosphorous (OP) compounds are included in Annex I (Black list) to this protocol (with the exception of those which are biologically harmless or rapidly converted into biologically harmless substances). OP pesticides categorised as potentially hazardous chemicals by the Commission of the European Union and as priority hazardous substances by the International Conference on the Protection of the North Sea are given in Annex II tables 3 and 4 respectively.

In 1991 at the Seventh Meeting of the Barcelona Convention, Contracting Parties agreed:

> "to promote measures to reduce inputs into the marine environment and to facilitate the progressive elimination by the year 2005 of organophosphorous compounds hazardous to human health and the environment." (UNEP 1991c)

The Mediterranean countries agreed that measures should include integrated pest control (IPM) in agriculture, and financial and technical support to train farmers in IPM "whereby non-chemical methods of controlling pests are emphasised." Contracting Parties also agreed to immediately end the use of OP compounds unless it is proved that they have no direct effect on human and animal health (UNEP 1991c).

There is already scientific evidence that OP pesticides can cause damage to environmental and human health. It is therefore essential that the 1991 decision on OP compounds be implemented to deal with the use of OP pesticides.

At present OP pesticides are used extensively in the Mediterranean region. Implementing the 1991 decision on OP compounds is possible by shifting away from agricultural practices which require large inputs of chemical pesticides to ecological farming methods which do not require the use of such chemicals (see Organic Citrus report - Buffa et al. 1995).

2. PESTICIDE POISONING

Pesticide poisoning is a worldwide problem of great magnitude. Recent estimates suggest that each year there are 3 million cases of acute severe pesticide poisonings resulting in 220,000 deaths (WHO 1993). Many such poisoning episodes occur in developing countries where 99% of fatal pesticide intoxications are thought to occur, and where the true number of severe pesticide poisonings is estimated to be 25 million (Jeyaratnam 1990).

2.1 Organophosphorous Pesticide Poisoning

No global estimate is available on the percentage of poisonings caused by specific types of pesticides, but OP pesticides are known to cause many acute poisoning episodes and some fatalities. Table 1 shows the number of cases of acute pesticide poisonings in three Mediterranean countries (studies commissioned for Greenpeace and submitted to the Barcelona Convention, May 1991; Besri and Chtaina 1990, Bouguerra 1991, Psomas 1991). Episodes of OP poisonings in Greece and Tunisia appeared to represent the main class of pesticide poisonings. For example, 67% of the pesticide poisonings in Greece, recorded between 1982 and 1985, were caused by OP intoxication. Similarly, in Morocco, 66% of pesticide poisoning cases were due to OP poisoning. In Tunisia, the number of fatalities from OP poisoning was very high. There were also reported to be numerous intoxications amongst agricultural workers from exposure to OP pesticides. This is mainly because these pesticides are easily attainable in Tunisia and little protection is provided for workers.

TABLE 1

PESTICIDE POISONING AND FATALITIES IN 3 MEDITERRANEAN COUNTRIES

Country/Reference	Pesticide Poisonings
Greece	1500 acute pesticide poisoning cases reported annually (Athens), leading to approximately 30 deaths. 67% of pesticide poisonings due to OP's (1982-85). 212 fatal pesticide poisonings in northern Greece (1982-85).
Tunisia	444 fatal poisonings from OP pesticides in the Tunis region alone (1976-86). In general, poisonings from OP pesticides were reported to be very common.
Morocco	112 cases of suspected pesticide poisoning at the Avicenna University Hospital Centre (1983-85). 39 of these cases (66%) due to OP pesticides.

2.2 The Real Extent of OP Pesticide Poisoning

In general, the majority of acute poisoning episodes which are actually recorded represent severe cases in which people have been hospitalised. No figures have been compiled however, for the many individuals who are not hospitalised who also suffer acute OP poisoning symptoms but to a lesser degree. Moreover, recent evidence suggests that long-term exposure to relatively low levels of OP pesticides may not cause acute poisoning symptoms, but can have long-term adverse effects on health (e.g. WHO 1993). At present there is no estimate of the true numbers of people who suffer from such health effects as a result of exposure to OP compounds. A great number of people could potentially be affected since it has been estimated that there are 50 million people who prepare or use pesticides intensely, and a further 500 million exposed to pesticides to a lesser extent (WHO/UNEP1989).

3. EXPOSURE TO ORGANOPHOSPHOROUS COMPOUNDS

3.1 Populations at Risk

The major occupational populations at risk from exposure to OP compounds include workers in agriculture (e.g. sprayers, mixers, harvesters, greenhouse workers), and workers in pesticide manufacturing and packaging. Community exposures may also result from ingestion of residues in sprayed fruits and vegetables and from non-occupational exposure to aerial spraying (WHO 1993).

3.2 Routes of Exposure

OP pesticides can enter the body by inhalation, ingestion and by penetration through the skin (dermal absorption). Dermal absorption is the most common route of exposure in agricultural workers. The ability of different OP pesticides to penetrate the skin varies from one compound to another, but is generally enough to produce acute intoxication if the operators are not adequately protected (Maroni 1986). Inhalation of OP compounds also results in exposure of workers. Small airborne particles from evaporation or larger particles from crop spraying can be inhaled into airways of the lungs, swallowed, or pass directly into the blood through membranes in the nose.

An epidemiological study of individuals exposed occupationally to OP pesticides in Bulgaria, Hungary and Poland (WHO 1993), concluded that the main route of exposure was dermal, with the extremities and head being especially vulnerable to deposition of the compounds. Although protective clothing substantially reduced exposure, it did not provide absolute protection. Inhalation from air exposure was found to represent a much lower route of exposure than absorption through the skin. However, air exposure to OP compounds by inhalation was significant in certain indoor environments including formulation and packaging of some OP compounds.

Results of a recent study on workers using organophosphate sheep dips in the UK suggested that inhalation in outdoor environments may also represent a significant route of exposure. To assess exposure of the workers, levels of the breakdown products of OP pesticides were monitored in urine. It was found that workers wearing good protective clothing had absorbed the same amount of OP compounds as those wearing no protective clothing (Niven et al. 1994). This suggested that the main route of exposure must be either inhalation and/or dermal absorption in uncovered areas such as the face.

3.3 Elimination of Organophosphorous Compounds From the Body

After absorption, OP pesticides and the products they are broken down to in the body (metabolites) distribute quickly into the body tissues. The highest concentrations are usually found in the liver and kidney (the organs which deal with detoxification and elimination of chemicals from the body). Extremely high concentrations of lipophilic OP compounds may also be found in nervous tissue and other lipid rich tissue. The rate at which OP compounds are detoxified and eliminated from the body varies from compound to compound. However, the process is usually quite rapid, taking about 48 hours to eliminate 80-90% of a dose. The remaining small amounts may take several days to clear (Maroni 1986).

3.4 Inadequate Testing of OP Compounds for Neurotoxicity

The major toxic effect on the body from exposure to OP compounds is neurotoxicity. It should be noted that many currently available OP pesticides have not been adequately tested for neurotoxicity because they were on the market before the requirements for neurotoxicity were implemented (Cherniack 1988). Also when OP pesticides have been screened for neurotoxic effects, the data is collected from animal experiments. However, there are marked differences between animal species in susceptibility to neurotoxic effects such as organophosphate-induced delayed neuropathy, and results from test animals may not be predictive of effects in humans (Johnson 1975).

4. HOW ORGANOPHOSPHOROUS COMPOUNDS EXERT TOXIC EFFECTS

Most of the toxic effects produced by OP pesticides in insects and mammals are caused by the inhibition of enzymes called esterases. The inhibition of one such enzyme, known as acetylcholinesterase (AChE), is responsible for the acute toxic effects seen in humans following OP poisoning (Maroni 1986). AChE is present in nervous tissue, red blood cells and muscles. It plays a key role in the transmission of nerve impulses within the autonomic nervous system[1] and parts of the central nervous system (Gallo and Lawryk 1991).

Footnote 1:

The autonomic nervous system is concerned with the innervation of smooth muscle, heart muscle and glands. It is composed of two parts, the parasympathetic nervous system which is concerned with normal function necessary to life, and the sympathetic nervous system which is concerned with reponse to emergencies.

4.1 Transmission of Nerve Impulses

Nerve impulses pass along neurons (nerves) in the form of electrical signals. When an impulse reaches a junction between two neurons (known as a synapse), or between a neuron and a muscle (neuromuscular junction) the impulse cannot cross the gap in the form of an electrical signal. Instead, a chemical substance called a neurotransmitter is released from the end of the neuron into the gap. The neurotransmitter acts as a bridge across the gap by stimulating receptors on the surface of the adjacent neuron or muscle which in turn passes on the signal.

The neurotransmitter which operates within the autonomic nervous system and parts of the central nervous system is acetylcholine (ACh). Neurons which release ACh are called cholinergic neurons. After ACh is released from the end of neurons, it is broken down by the enzyme AChE within milliseconds. This ensures that only the correct amount of ACh reaches the receptors on the adjacent nerve or muscle to pass on the impulse, because more ACh is released by neurons than necessary for transmission of each impulse. Thus by rapidly destroying the neurotransmitter ACh, the enzyme AChE allows each impulse transmission to be passed on correctly and then to end (Maroni 1986, Gallo and Lawryk 1991, Ballantyne and Marrs 1992).

TABLE 2

THE EFFECTS OF ANTICHOLINESTERASE AGENTS

Muscarinic Effects	Lacrimation (tears) Rhinorrhoea (nasal secretion) Excess Salivation Increased bronchial secretion and coughing Bronchoconstriction (constriction of air passages to lungs) Sweating Miosis (constriction of pupils) Blurred Vision Urination Diarrhoea
Nicotinic Effects	Tachycardia (rapid heart rate) High Blood Pressure Skeletal muscle twitching and Fasciculations Skeletal muscle weakness Skeletal muscle paralysis Pallor
Central Nervous System Effects	Headache Loss of Co-ordination Convulsions Respiratory Failure Coma

Source:
Perera (1993), Ballantyne and Marrs (1992), Overstreet and Schiller (1992)

4.2 Effect of Organophosphorous Compounds on Transmission of Nerve Impulses

OP compounds can form strong bonds with the enzyme AChE. The bond may be either broken in time (1-1000 hours), or not broken at all. This results in the enzyme AChE being taken out of action either temporarily or permanently (Manson et al. 1993, Maroni 1986). If this occurs, the ACh released by the cholinergic neurons cannot be broken down, and causes over-stimulation of the adjacent neuron or muscle. The effects of such abnormal stimulation are numerous as shown in Table 2 because cholinergic neurons are widely distributed throughout the body (Overstreet and Schiller 1992).

5. ACUTE TOXIC EFFECTS OF ORGANOPHOSPHOROUS POISONING

The effects of acute OP poisoning on health in humans can be categorised into 3 stages. The initial effects are known as the cholinergic crisis and have been well documented in many studies. Other health effects classified as the intermediate syndrome may follow the cholinergic crisis a few days later. If the patient survives these initial effects most of the clinical signs and symptoms are potentially reversible. However, a third stage of effects on health following OP poisoning can occur, which involves long-term adverse effects on the nervous system (Marrs 1993).

5.1 Cholinergic Crisis

The initial effects of acute OP poisoning are primarily the result of the accumulation of the neurotransmitter ACh (Marrs 1993). The many different signs and symptoms of poisoning are listed in Table 2. Since ACh receptors are not all identical they are classified as either nicotinic or muscarinic on the basis of their response to the chemicals nicotine and muscarine. Consequently, the acute signs and symptoms of OP poisoning, or exposure to any other anticholinesterase agent, are described nicotinic and muscarinic effects.

The rate of onset of symptoms of acute poisoning varies from a few minutes to several hours depending mainly on the chemical structure of the OP compound. In usual occupational cases of OP poisoning, relatively incapacitating symptoms including nausea, cramps, discomfort in the chest and muscular twitching, often follow the initial symptoms of giddiness, blurred vision and headache after a period of 2-8 hours. The onset of more serious symptoms for example on the respiratory system may be more rapid (Gallo and Lawryk 1991). Effects on the respiratory system are complex involving increased secretions of the respiratory tract, constriction of airways (bronchoconstriction) and muscle weakness. The most common cause of death in cases of OP poisoning is respiratory paralysis and consequent anoxia (oxygen deficiency) (Marrs 1993). Effects on the heart can also lead to death.

Studies which have monitored individuals exposed to OP compounds have shown that signs of poisoning do not usually appear until blood (plasma) levels of AChE are below 50%, while severe poisoning is usually associated with depression to below 30% (WHO 1986). Exposure of workers to OP compounds is sometimes checked by monitoring the blood levels of AChE, but these safety checks are rare in many countries.

Acute OP poisoning is usually treated using a drug called atrophine which blocks the action of the neurotransmitter ACh at muscarinic receptors, and thus stops the overstimulation of these neurons and muscles. Other drugs (pyridinium oximes) are used to reactivate the cholinesterase enzymes which have been inhibited by OP compounds (Marrs 1993, Ballantyne and Marrs 1992).

5.2 Intermediate Syndrome

Intermediate syndrome was first described by Senanayake and Karalliede (1987), who reported its occurrence in 10 individuals following OP poisoning. The syndrome occurs after the cholinergic crisis, 1-4 days after OP intoxication. It is characterised by muscular weakness of the limbs and neck.

Respiratory muscles are also affected which means there is a risk of death if respiratory support is not given. OP compounds most commonly associated with this syndrome are fenthion, monocrotophos and dimethoate .

6. LONG-TERM HEALTH EFFECTS OF ORGANOPHOSPHOROUS EXPOSURE

6.1 Effects on the Peripheral Nervous System

Long term adverse effects on the peripheral nervous system can occur following acute OP poisoning. One such condition which is known to be caused by certain OP compounds is called organophosphate-induced delayed neuropathy (OPIDN). This effect does not appear to be related to the inhibition of the enzyme AChE. Instead, it may be brought about by the OP compound binding to, and modifying the structure of another enzyme in the neurons called neuropathy target esterase (NTE) (Gallo and Lawryk 1991, Ballantyne and Marrs 1992, Marrs 1993). However, the mechanism is not clearly understood and other esterase enzymes apart from NTE may be involved (M. Johnson, personal communication). OPIDN results in damage to the peripheral nerves (called distal axonal degeneration). The neuropathy is known as a "distal" type because damage begins at the extremities of the nerves and therefore affects the feet and hands first (Barclay et al. 1993). In severe cases of poisoning the central nervous system can also be affected, causing damage to the spinal cord.

Onset of delayed neuropathy occurs one to several weeks after OP poisoning. Symptoms include tingling and burning sensations in the legs which progresses to cramping muscle pain and weakness. Paralysis in the legs may follow and the arms may subsequently be affected (Maroni 1986, Ballantyne and Marrs 1992). Improvement of symptoms may occur in mild cases. However, severe toxicity results in long-lasting neurological dysfunction reflecting spinal cord damage (Abou-Donia and Lapadula 1990).

6.1.1 Effects on the Peripheral Nervous System following Acute OP Poisoning

Most pesticides available on the market in Western countries are thought to be incapable of producing OPIDN (Marrs 1993). OP pesticides which have caused delayed neuropathy in humans after acute exposure in an occupational setting include mipafox (2 cases in Britain, 1952) leptophos (12 cases in USA, 1974-5), trichlorphon (4 cases in Rumania, 1984), methamidophos (9 cases in Sri Lanka, 1982) and fenthion (3 cases in USA, 1985) (Gallo and Lawryk 1991, Marrs 1993).

Although the number of people reported to be suffering from OPIDN after acute OP poisoning following occupational exposure is relatively small, there is now great concern that it may be more frequent among the users of OP compounds than previously thought. For example, a recent study in Nicaragua by McConnell et al. (1994) was undertaken to evaluate the long-term effects of acute OP poisoning. 36 male workers were tested 10-34 months after an episode of acute OP poisoning. One group consisted of workers who had been poisoned by methamidophos (a known peripheral neurotoxin) and the other group had been poisoned by OP pesticides other than methamidophos. Vibrotactile thresholds were measured in fingers and toes as a way of assessing OPIDN. Both groups had statistically significant abnormal vibrotactile thresholds compared to a control group of unexposed individuals. Differences were more pronounced among workers using methamidophos. The study concluded that chronic sensory impairment could be induced following only a single episode of acute methamidophos poisoning. It was suggested that the public health implications considering the results of this study are worrisome, because cases of OPIDN recorded in the medical literature to date may represent only the worst cases of a spectrum of neuropathy which may be more common than previously thought.

6.1.2 Effects on the Peripheral Nervous System following Chronic exposure to Organophosphorous Pesticides

Recent evidence suggests that chronic (long-term) exposure of individuals to small repeated doses of OP compounds may affect the nervous system. In such cases there may be no acute symptoms of poisoning. It is likely that chronic exposure could result in cumulative poisoning which may produce subclinical effects initially (i.e. nerve damage without any symptoms) but render the individual susceptible to further toxic insults with repeated exposures. This would produce progressive adverse effects on the nervous system (Jamal, personal communication).

6.1.3 Effects on the Peripheral Nervous System following Chronic Exposure to Organophosphorous Sheep Dips

In the UK, there have been many complaints by farmers of long-term health effects following the use of OP sheep dips. The sheep dips contain either one or a combination of the OP compounds called diazonon, propetamphos and chlorfenvinfos. Investigations of chronic health effects have been carried out, including studies by the National Farmers Union in 1991 and the National Poisons Unit (NPU) in 1992 (Perera 1993). These studies did not use sensitive measures to examine specific neural damage. However, the studies did show that symptoms reported by the farmers were consistent with damage to the nervous system.

In 1993 a study was undertaken by Dr. G. Jamal, Consultant Clinical Neurophysiologist at the Institute of Neurological Sciences, Glasgow, to assess peripheral nerve damage in farmers using OP sheep dips (Jamal 1993, personal communication). Sixteen farmers who had been involved in regular dipping of sheep over a period of 4 or more years were randomly selected to take part in the study from a list of 200 farmers. The time since their last exposure to sheep dip ranged from 4 months to 3 years. Several neurophysiological tests were used to find out if there was any peripheral and/or central nervous system damage in the farmers, and in a control group of individuals matched for age and sex. The tests used were extremely sensitive and can detect damage in the nerves even before symptoms are evident (i.e. subclinical signs of neurotoxicity can be detected).

Results of the tests showed there were statistically significant abnormalities in the peripheral nerve function of all 16 farmers compared to the control group. The abnormalities involved all types of nerve fibre in both sensory and motor systems and showed the characteristics of distal axonopathy (nerve damage beginning at the extremities). Central nervous system function was not affected in any of the farmers. It was concluded that the study showed convincing evidence of peripheral nerve damage in the form of distal axonopathy in a group of farmers who had been exposed to OP sheep dips. However, it is not possible to conclude that the sheep dip caused these effects, but the OP compounds in the sheep dip are the most obvious candidate. A future study is proposed to determine whether and how quickly nerve damage occurs as a result of repeated low dose exposure in a group of 30 farmers who are just starting to use OP sheep dips over a period of 5 years.

6.1.4 Organophosphorous Pesticides in Sheep Dips are Also Used for Crop Spraying

It is possible that OP sheep dips can cause OPIDN and have other effects on the central nervous system (see section 6.2). Two of the OP pesticides used in sheep dips (diazonon and chlorfenvinfos), are also used for spraying crops in many countries including the Mediterranean. The implications of this are of concern because many people are potentially exposed to these agents and could therefore suffer adverse effects to the nervous system.

Diazonon is known to contain an extremely toxic impurity called sulfotepp which is formed during the production process (Karr et al. 1985). Sulfotepp is also an OP compound. It is far more toxic than diazonon itself and is classified as a "highly toxic" substance by the US EPA and is more toxic than parathion (Meier et al. 1979). It is therefore probable that it could have adverse effects on human health. Sulfotepp is also relatively stable and may concentrate in the environment, causing ecological problems (Meier et al.1979). The amount of sulfotepp contained in diazonon preparations is not regulated and is extremely variable depending on the manufacturer (Karr et al. 1985). Diazonon is not labelled as containing sulfotepp so appropriate safety precautions may not be taken when handling the pesticide. The use of sulfotepp itself is banned in some countries.

6.2 Effects on the Central Nervous System

Several studies over the last 40 years have shown conclusively that acute intoxication with OP compounds can cause long-term effects on the central nervous system. These effects involve changes in brain function which may be irreversible.

Acute effects from OP poisoning such as convulsions, respiratory failure and cardiac arrythmias, can result in oxygen deficiency in the brain (cerebral anoxia). Since it is well known from other causes that oxygen deficiency within the central nervous system can have long-term effects on brain function, it is not surprising that OP intoxication also leads to these effects (Marrs 1993). In addition, there is some evidence which suggests that chronic exposure to small repeated quantities of OP compounds which does not cause acute intoxication, can result in effects on brain function.

6.2.1 Symptoms

Effects on the central nervous system from exposure to OP compounds involve behavioural and psychological disturbances. Such changes have been recorded in both animal experiments and human studies (Marrs 1993).

The most frequently reported long-term behavioural and psychological disturbances include symptoms of depression, anxiety, irritability, drowsiness, fatigue, dizziness, mental confusion, reduced concentration, slurred speech, emotional instability and schizoid reactions (Maroni 1986, Ballentyne and Marrs 1992, Dille 1964). In addition, during recovery from poisoning, psychiatric disorders have been described including delirium, aggression, hallucinations, depression and psychosis (Blain 1992). Electroencephalograph (EEG) is used as a diagnostic tool to assess neurobehavioural effects on the brain. Changes in EEG have been reported to occur in individuals in some studies following OP poisoning (see Marrs 1993).

6.2.2 Effects on the Central Nervous System Following Acute Organophosphorous Poisoning

The long-term neurobehavioural and neuropsychological effects following acute OP poisoning have been discussed recently in two different epidemiology studies which used sensitive and reliable measures of behavioural assessment (Savage et al. 1988, Rosenstock et al. 1991). The study by Savage et al. (1988) investigated long-term effects in 100 individuals who had experienced previous acute OP poisoning. These individuals were compared to a control group of 100 matched individuals who had not been poisoned. Significant differences were apparent in neurobehavioural measures of memory, abstraction and mood, and even more so in neuropsychological tests including intellectual functioning, academic skills, abstraction and flexibility of thinking. Twice as many cases as controls (24 vs 12) had scores in one group of tests which were characteristic of individuals with cerebral (brain) damage or dysfunction. The study concluded that there were chronic neurological sequelae to acute OP poisoning. It reported however that these sequelae are sufficiently subtle that the clinical neurological examination, clinical EEG and ancillary laboratory testing cannot discriminate poisoned subjects from controls.

Since there was no definitive information on the severity of poisoning episodes of individuals in the study, it is possible that the behavioural and psychological effects seen were due in some cases to severe acute poisonings (Marrs 1993).

A study by Rosenstock et al. (1991) was carried out to see whether single episodes of acute organophosphate intoxication could lead to chronic central nervous system effects. The study took place in Nicaragua where OP compounds are the leading cause of pesticide poisoning. 36 men were tested approximately 2 years after an episode of acute OP poisoning. Compared to a matched control group, the "poisoned" group did significantly less well on a number of neuropsychological tests. These tests included 5 out of 6 of the WHO neuropsychological test battery (tests on verbal attention, visual memory, visuomotor and motor functions) and on several other neuropsychological tests. The study concluded that even single episodes of clinically significant OP intoxication are associated with a persistent decline in neuropsychological functioning.

The implications of results from both of these studies should be of great concern considering the large number of individuals who are poisoned each year by OP pesticides. The study by Rosenstock et al. (1991) is of particular concern because the decline in neuropsychological functioning recorded was attributable to only a single episode of acute poisoning.

6.2.3 Effects on the Central Nervous System Following Repeated Exposure to Small Quantities of Organophosphorous Compounds

The issue of whether relatively low level OP exposure causes long-term effects on the central nervous system is controversial. Some studies have shown behavioural, psychological or EEG changes after such exposure while others have shown nothing. For example, Levin et al. (1976) found elevated levels of anxiety ($p<0.005$) in commercial sprayers, but not in farmers who were regularly exposed to OP pesticides. However, this study has been criticised because the study population had been potentially exposed about 2 weeks before testing (Marrs 1993). Another study by Rodnitzky et al. (1975) carried out psychometric testing on 23 individuals (12 farmers and 11 pesticide sprayers) following long-term OP exposure and found no abnormalities.

6.2.4 Organophosphorous Sheep Dips

In the UK in 1991, the National Farmers Union carried out a study on farmers in the South West region in response to growing publicity about ill health caused by sheep dips (Perera 1993). Questionnaires were given to a randomly selected group of 213 farmers to assess chronic health effects. 35% of the group reported adverse reactions including fatigue, aching limbs, loss of concentration and depression. Acute symptoms of headache, dizziness and nausea were also reported. The study concluded that more than a third of sheep farmers suffer *"ill effects"* as a result of dipping which *"appear to be associated with the OP constituent in the dip"* (cited in Barclay et al. 1993). The NFU stated that *"There is some evidence to suggest that the effects are cumulative, and that with every year of sheep dipping that passes more farmers will report adverse symptoms"* (cited in Perera 1993). Although the NFU survey can only be regarded as anecdotal evidence, it does suggest that a large number of farmers do suffer from long-term health effects from sheep dipping and many of these effects are consistent with known neurotoxic and psychological effects from exposure to OP compounds.

In 1987 the British Health and Safety Executive (HSE) addressed the subject of chronic exposure to OP pesticides in a set of guidance notes on the biological monitoring of workers exposed to these compounds (HSE 1987). The document stated *"that acute and subacute exposure to OP pesticides can produce harmful effects in man, and repeated exposure at lower doses may cause insidious cumulative toxicity"* (HSE 1987). The HSE is currently funding a large epidemiological study on the chronic neurobehavioural and neuropsychological effects after long-term, non acute

exposure of farmers to OP sheep dips. This follows the growing body of evidence that there may be chronic health effects from sheep dipping and after a study by the National Poisons Unit (NPU) in 1992 on acute health effects which reported there was *"a medical problem from occupational exposure to sheep dip"* which needed further investigation.

6.2.5 Other Studies

In 1993, the World Health Organisation (WHO 1993) published a multinational, epidemiology study on long-term health effects from low level exposure to OP compounds. The work was carried out between 1983 and 1986, and involved a total of 752 individuals from Belgium, Czechoslovakia, Hungary, Israel, Poland, Turkey and Yugoslavia. The study population consisted of agricultural, manufacturing and packaging workers, who were exposed to one or more of the following OP compounds: azinophos-methyl, chlorphenvinophos, dimethoate, Dursban (chlorpyrifos), fenitrothion, malathion, methiadathion, methyl-parathion, parathion, phorate, phosalone, Phosdrin (mevinphos), pirimiphos, Pirimor, quinalphos, tetrachlorvinphos, thiometon, tricholphon and vamidothion.

The study population were all deemed to be "healthy workers". None of the workers were acutely poisoned during the 2-3 year study period or had suffered recent acute OP poisoning episodes. The study population were thus considered to represent a group who could have potential chronic health effects from low level OP exposure. Alcohol consumption and exposure to other types of pesticide were monitored since such factors could influence the susceptibility of workers to OP compounds.

Assessment of long-term health effects was carried out using the WHO Neurobehavioural Core Test Battery. EEG and other tests to assess nerve functioning were also used in some countries.

For the study as a whole, results of tests assessing nerve functioning varied between different countries. For example, in Bulgaria there was a significant adverse effect on conduction of nerve impulses in exposed workers compared to controls, but this result was not seen with workers in Israel. Similarly, results of neurobehavioural tests varied between different countries. However, a most important finding of this study is that in general, neurobehavioural tests on well being and mood status showed that compared to controls, many exposed individuals did not feel well and had mood problems. The WHO hypothesised that this data may provide evidence of neurotoxic effects in individuals who are well enough to work. It was also noted that because the study was limited to current "healthy workers" and ex-workers were not examined, this may have operated against detection of neurotoxic or other illnesses severe enough to result in slight impairment, disability or death.

The study concluded that nothing in the data indicates that *"current work conditions and exposures to organophosphates are without risk to real-life populations. The evidence from these studies suggests that the exposures of these individuals, while perhaps too low to produce acute toxic episodes, produced symptoms and signs warranting preventative action to reduce exposures"*.

A study in Israel by Richter et al. (1992) which was undertaken in conjunction with the above WHO study, showed that not only agricultural workers were affected by OP pesticide crop spraying of cotton, but that local residents were also affected by the spray drift. During the peak season for OP spraying, test scores of mood status and symptoms (including anxiety, depression and anger) were significantly poorer (>10%) than post-season scores. The effects did appear to be reversible during the post season.

6.3 Recent Political and Policy Information on Long-Term Neurotoxicity

In recent years there have been an increasing number of complaints of ill health from farmers in the UK relating to neurotoxic effects caused by chronic exposure to sheep dips. In response to this, on 30th November 1994 the European Commission (EC) "Scientific Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds" released a paper on EC opinion of "the health risk related to the use of OP compounds in sheep dipping solution", (EC 1994). The paper tentatively admits that there is a possibility of chronic damage from minimal exposures to OP compounds in sheep dips.

For example,

"The Committee accepts the possibility that there might be long-lasting non-specific neuropsychiatric effects of subchronic or repeated low dose exposure to organophosphorous pesticides, such as those used in sheep dipping or for other agricultural purposes"; and

"Depending on the nature and the dose of the exposure, including unintentional contamination, workers may show acute systemic effects and neuropsychiatric disturbances, or a delayed neuropathy".

The paper also states,

"It would be advisable whenever possible to avoid the use of organophosphorous compounds known to inhibit neuropathy target esterase".

All these statements clearly show that there is now concern at a political level that OP compounds are responsible for the adverse long-term health effects of OPIDN and neuropsychological disturbances experienced by many farmers who have been exposed to sheep dips in the UK.

The UK government also acknowledged that OP sheep dips may cause health effects in chronically exposed workers in December 1994, when they publicly advertised that money was available for epidemiology research to investigate the effects of sheep dips on central nervous system and peripheral nervous system function (see *New Scientist*, 17 December 1994).

Finally, the recent concern at a political level is hardly surprising when so many farmers in the UK are fighting for financial compensation for the long-term neurotoxic effects caused by OP compounds in sheep dips. One of the farm managers has recently been granted industrial injury benefit backdated to 1979 for category C3, which refers to "exposure to organophosphorous compounds". This is surely an admission of the existence of chronic neurotoxic effects of OP compounds (*Tribunal*, 1994).

7. OTHER ILLNESSES ASSOCIATED WITH EXPOSURE TO ORGANOPHOSPHOROUS COMPOUNDS

Prolonged illnesses which occur after acute OP poisoning include complications such as liver dysfunction, heart dysfunction and delayed convulsions. There is evidence to suggest that these complications occur as a result of hypoxia (lack of oxygen) during the cholinergic crisis (Gallo and Lawryk 1991).

There are other illnesses which may result from exposure to OP compounds which may or may not be associated with effects on the enzyme ChE. These include toxicity to the eye, kidneys and immune system, as well as endocrine (hormonal) changes and effects on development (Marrs 1993).

7.1 Effects on the Eye

7.1.1 Impaired Vision and Increased Accidents

The eye contains relatively high amounts of cholinesterase enzymes and therefore can be affected by anti-cholinesterase agents such as OP compounds (Erickson-Lamy and Grant 1992). Following acute exposure to OP compounds, the pupils may contract (a condition known as miosis) and are unable to dilate as they normally would in conditions of dim light. Blurred vision may result and is often a symptom of acute OP poisoning. This effect was thought to be partly responsible for the increased number of accidents in the 1970's in pilots when crop spraying with OP pesticides. For example, in Israel in 1978 there were 4 fatal aircraft crashes during crop spraying with parathion. Studies later revealed that exposed pilots complained of blurred vision, headache, nausea, dizziness and chronic fatigue as the spraying season progressed (Richter et al. 1992). Safety conditions for pilots have since been improved in Israel. Miosis can also be very dangerous if localised contamination from an OP pesticide occurs in one eye. This interferes with the ability to judge distances which may result in accidents when driving vehicles (Gallo and Lawryk 1991).

7.1.2 Saku disease in Japan

In Japan there have been many reports that the increased use of OP pesticides in agriculture since 1965, is associated with the increased incidence of myopia (short-sightedness) and a more advanced visual disease syndrome called Saku disease. Saku disease is characterised by myopia, narrowing of the visual field, reduced visual acuity and other physiological effects on the eye. Children are especially vulnerable to the disease. It was named after the Saku region in Japan where people were reported to develop the syndrome after large amounts of OP pesticides were sprayed on agricultural land (Erickson-Lamy and Grant 1992).

From 1960-66 only malathion had been sprayed in the Saku district, but its use was subsequently heavily increased along with parathion. One study between 1960 and 1972 showed that in the district, which had a population of about 310,000, the number of patients (children) increased from 5 in 1966 to approximately 117 per year in 1970-71 (Tamura and Mitsui 1975). Other studies in Japan also showed that there appeared to be an association between OP use and myopia and Saku disease. In addition, studies in animals performed in Japan have clearly demonstrated the adverse effects of OP compounds on the visual system.

In a recent review of the many population studies in the Japanese literature, the US EPA (1994) suggested that the human population data alone does not provide conclusive evidence of the unique effect of OP compounds on the visual system (Dementi 1994). However, when definitive evidence from animal studies was also considered together with the human data, the EPA state that *"a much more compelling case exists that the association is real."* In addition, the report comments that studies which are currently in progress at the EPA's research facility appear to be substantiating much that has been reported in Japan. There have been no detailed studies on the effects of OP pesticides on the visual system in countries other than Japan so it is not surprising that there are no reports of Saku disease in other countries (Erickson-Lamy and Grant 1992).

7.2 Carcinogenicity of OP Compounds

Annex 2, Table 6 lists OP pesticides which have been classified as suspected carcinogens by the US EPA (1990). Classification of human carcinogens is based on evidence from *in vitro* tests for genetic damage (genotoxicity and mutagenicity) together with data from animal experiments. When available, evidence from epidemiology studies on occupationally exposed individuals may also be used.

In a recent study by Garret et al. (1992), 24 OP compounds were tested for ability to produce genetic damage (to DNA, chromosomes and mutations in certain genes). Results showed that the most potent OP compounds which are used in agriculture for which nearly all the tests were positive included cyclophosphamide, triethylenephosphoramide (TEPA) and trichlorofon. Other OP compounds were positive in some, but not all tests. These included the commonly used agricultural OP compounds malathion, dimethoate, monocrotrotophos, dichlorovos, parathion-methyl, disulfoton, demeton and azinphos-methyl. It was clearly shown that these compounds can produce certain sorts of genetic damage, although further evidence would be required, for example from animal studies, to show that these OP pesticides are carcinogens.

The epidemiological data on the carcinogenicity of OP compounds is very limited. According to a summary of previous studies by Palady et al. (1988), general use of pesticides including OP pesticides has been implicated in an increased incidence of stomach, bladder and lung cancer.

A large population-based study in eastern Nebraska found a twofold increase in the incidence of non-Hodgkin's lymphoma (NHL) (a cancer of the lymphatic system) in the general population. The area is characterised by intense agricultural activity. Use of the organochlorine herbicide 2,4-D was associated with a 50% increased risk of NHL in men, but OP pesticides were also associated with an increased risk of 10% (Weisenburger 1990).

7.3 Developmental Toxicity

There have been a few reported cases of birth defects following maternal exposure to OP pesticides during pregnancy. However, it is difficult to prove a cause and effect relationship in such cases. Nevertheless, there is conclusive evidence from animal experiments that OP compounds have adverse effects on the developing organism. An area of particular concern is the neurotoxic effects of exposure *in utero* and further studies are planned to investigate this. It has been suggested that human pregnancy may represent a time of increased risk to OP compounds even though there is no conclusive evidence from human studies (Tyl 1992).

7.4 Immunotoxicity

Suppression of the immune system in humans can increase susceptibility to viral, bacterial and parasitic infections, increase the incidence of tumours and possibly lengthen the course of an infection. Conversely, enhancement of the immune system (e.g. increasing the number of certain cells in the immune system) can lead to exacerbation of autoimmune diseases and general malaise or lethargy (Rodgers et al. 1992).

Some epidemiology studies have indicated that exposure to OP compounds causes toxic effects on the immune system, especially allergic reactions, but the extent and mechanism of the effects has not been conclusively ascertained. Experimental work on animals and *in vitro* studies have clearly shown that parathion and several other OP compounds can be immunosuppressive (Sharma and Tomar 1992, Rodgers et al. 1992). Malathion has been shown to both suppress or enhance immune function depending on the size of the dose and the route of exposure (Rodgers et al. 1992).

In some urban areas of the US, for example Los Angeles and California, aerial spraying of malathion is used in an attempt to control the Mediterranean fruit fly. There have been complaints of allergic reactions from people in these areas after spraying (Swadener 1992). Recent research on mice by Rodgers and Ellefson (1992) indicates that it may not be just individuals who are sensitive to chemicals who suffer from such allergic reactions. The study showed that when malathion was given to mice, it affected certain cells in the immune system involved in allergic reactions. Moreover, this effect on the immune system occurred at levels 1000 times lower than levels which cause inhibition of the neurotransmitter AChE. The study implies that similar changes could occur in the human immune

system after exposure to low levels of malathion (Swadener 1992). In addition, the experiment used pure malathion. Technical grade malathion used for spraying is known to contain impurities which can make it even more toxic to the immune system (Rodgers et al. 1992, Swadener 1992).

7.5 Chemical Sensitivity

Some individuals are hypersensitive to various chemicals including OP compounds. According to Mutch et al. (1992) it is possible that variations in sensitivity to the toxic effects of OP compounds can be explained by differing activity of certain esterase enzymes in the human population. A study has shown that the activity of certain of these enzymes, including AChE in the plasma and red blood cells and NTE, differs between individuals. This variation could have profound effects on susceptibility to OP toxicity (Mutch et al. 1992).

It has been hypothesised that individuals with depression are hypersensitive to the effects of ACh. Rosenthal and Cameron (1991) suggested that this could explain the sensitivity of such individuals to OP compounds. As a consequence, Overstreet and Schiller (1992) suggested that individuals with a history of depression should probably avoid exposure to agricultural pesticides.

Allergic Rhinitis (nasal problems and headaches) and multiple chemical sensitivity syndrome (MCS) in some individuals are associated with exposure to environmental chemicals, including OP compounds. MCS occurs when individuals become sensitive to low level chemical exposures after an initial exposure, and may cause symptoms of headaches, depression and anxiety. Recent evidence has shown that the nervous system may be predominantly involved with this syndrome rather than the immune system. Inflammation of various tissues which cause the reactions is thought to be brought about by the nerves themselves, a process known as neurogenic inflammation. (Meggs 1993, Meggs and Cleveland 1993).

8. ORGANOPHOSPHOROUS PESTICIDE USE IN THE MEDITERRANEAN AND HEALTH EFFECTS

Annex I shows OP pesticides which are widely used in the Mediterranean region and the health threats of these compounds. Some of these pesticides have been banned in other countries because of their threat to human health or the environment (see Annex 2, Table 2). Apart from the risk of causing acute poisoning in humans, several of these OP pesticides have been mentioned in this report in relation to other known health effects. For example, malathion is associated with Saku disease, immunotoxicity and is known to cause genetic damage. Parathion is no longer authorised for use in some countries because it is highly toxic. Methamidophos is a known neurotoxin and recent evidence indicates it can cause OPIDN (McConnell 1994). This study recommended that methamidophos should be substituted with other pest control methods because it could potentially cause neurotoxic effects in many people (McConnell 1994). In a large epidemiology study on the chronic exposure of individuals to OP pesticides (including azinophos-methyl, chlorpyrifos, malathion and parathion), it was shown that well being and mood were adversely affected, reflecting neurotoxic effects (WHO 1993).

9. RESIDUES IN FOODS

The major source of OP residues on edible crops are from agricultural pesticides, while those in meat and other animal products arise from the use of veterinary medicines containing the products, such as those to control animal parasites. In addition to spraying crops with pesticides during the growing season, OP pesticides may also be applied to crops after harvesting to help preserve the crop during storage, transport and marketing. On an international scale, residues in foods are examined by the Codex Alimentarius Committees (Codex) and its commission on the Joint Food and Agricultural Organisation (FAO)/World Health Organisation (WHO) Food Standards Programme. Codex proposes Maximum

Residue Levels (MRLs) for pesticides in food. These levels are below the proposed acceptable daily intake (ADI) levels which are set from animal toxicology experiments (Woodward 1992). National levels of allowable pesticide levels in foods are also set by some countries.

Poisoning from OP residues in foods is uncommon. The outbreaks which have been documented indicate that food poisoning was mainly due to contamination during transport or storage, or resulted from bad agricultural practice, that is spraying close to harvest time. Nevertheless, there are concerns about contamination of foods with OP residues, because of their long-term toxicological effects (Overstreet and Schiller 1992).

In a recent study in Denmark, the dietary intake of anti-cholinesterase agents (OP pesticides and carbamates) from sprayed fruits and vegetables was estimated in 331 school teachers during the spraying season (Lander et al. 1992). The teachers were divided into groups of high, low or no exposure based on their consumption of sprayed fruits and vegetables. The levels of plasma cholinesterase (ChE) were measured in each individual at the beginning and end of the spraying season. In the high exposure group the mean ChE level was depressed by 2% ($p=0.04$), but in the low and no exposure groups there was no difference in ChE levels between the start and end of the spraying season. It was therefore concluded that an ordinary ingestion of agriculturally grown fruits and vegetables during the spraying season is enough to depress plasma ChE levels, although the effects of such chronic exposure from diet on human health are unknown.

A preliminary study of the levels of OP compounds in human milk in Italy found that OP compounds were present in breast milk on day 4 after giving birth (Bianchi et al. 1988). The source of the OP compounds was thought to be from fruit and vegetables grown under glass in Northern Italy. This is of concern because the developmental stages of life appear to be the most vulnerable to environmental chemicals such as OP compounds and organochlorines.

9.1 Residues in Food Produce From Mediterranean Countries

In the Mediterranean countries, there is generally very little information on pesticide residues in food since official monitoring varies from non-existent to infrequent. Studies in Morocco, Tunisia, Egypt and Greece however, have all found OP residues in olive oil. For example, a study in Greece in 1988-89 detected fenthion, azinphos-ethyl, methidathon and paramethyl in some samples of olive oil (Psomas 1991). Of these, azinphos-ethyl presented a significant problem in a few areas where it is used in the autumn, in violation of the official recommendation that oil-soluble insecticides should only be used on olive trees until the end of August. Monitoring of fenthion residues showed that for the first and second years of the study, 50% and 79% of the samples respectively contained detectable levels of fenthion residues. Significantly, 4% and 6% of these samples respectively had residue concentrations which exceeded the Codex MRL.

Other fruit and vegetable produce has also been found to be contaminated with OP residues in Mediterranean countries. For example, analysis of foods in local markets in Tunisia showed that 57% of citrus fruit samples were contaminated with malathion, 30% with methidathon and 4% with parathion, despite the fact that parathion is banned from use in Tunisia. 43% of carrot and 17% of artichoke samples were also contaminated with parathion. High concentrations of parathion residues, which is an oil soluble compound, have been found in citrus oils. The concentrations were reported to be higher than levels found either on the peel or in the fruit (FAO/WHO 1991).

A recent study in Italy was carried out on fruit and vegetable products of Bologna market. An alarming 48% of oranges, mostly from Sicily, had greater concentrations of pesticide residues than permitted by Italian law (Buffa et al. 1995).

The persistence of OP pesticides on fruit and vegetables has been reported in a number of studies. In Portugal, relatively high levels of parathion were detected on lemons (0.22mg/kg) and oranges (0.38 mg/kg) 21 days after spraying, although these levels are less than the MRL (WHO 1991). In another study, parathion was reported to persist on the skin of citrus fruits for several months (Buffa et al. 1995). Other studies have shown that Surin (a mixture of chlorfenvinphos and cypermethin), pirimiphos-methyl, fenthion, dichlorovos and monocrotrophos can persist on various fruits for 1-3 weeks after spraying before they degrade (Barba et al. 1988, Sendra et al. 1985, Prasad and Awasthi 1986).

9.2 Livestock

Animals are treated with OP pesticides for parasites, for example, cattle in Europe are treated for warble fly and sheep are treated for sheep scab in the UK. Following treatment, residues can be found in the milk for up to 3 days and in meat for 1 to 2 weeks after. (Woodward 1992). OP compounds can have adverse effects on the animals themselves. For example, sheep have been reported to become ill or die after dipping (Perera 1993), cattle have become ill after ingestion of an OP soil insecticide (Boermans et al. 1985), and bison have died following treatment with famphur for a parasite (Schillhorn-van-Veen et al. 1991). In addition, a recent study has suggested that treatment of cattle in Britain with OP insecticides against the warble fly plays an important part in the development of bovine spongiform encephalopathy (BSE), (mad cows disease), in cattle which are already rendered susceptible to the disease due to genetic factors and mineral deficiencies (Purdey M 1992).

9.3 Economic Considerations

Residues of OP pesticides on export crops can cause consignments to be turned away from importing countries. This is becoming more of an economic risk to Mediterranean countries as the health conscious markets of the North adopt more stringent laws on residues in foods. For example, Greek olive oil has been found to have residues of OP compounds higher than EEC standards which resulted in rejection of the oil from countries of exportation (Psomas 1991). Monitoring of Greek-Cypriot produce in 1989 revealed that 40% of one crop of Cypriot strawberries contained pesticide residues in excess of EC limits. A number of other crops including cucumbers, tomatoes, green beans, lettuce and potatoes also contained high residue levels. This was of concern to the Greek-Cypriot government since the EC is the principle importer of Greek-Cypriot produce (AGROW 1990).

The destruction of non-target organisms can also have an economic impact. Laboratory experiments have shown that OP pesticides are highly toxic to honey bees at doses many times lower than those suggested for crop treatments (Arzone and Patetta 1987 and 1989). A survey of honey bee colonies in Hungary between 1962 and 1987 found that crop spraying was responsible for the poisoning of 355-946 colonies each year, and in a total of 6005 of the known cases, OP pesticides caused 87% of the poisonings (Koltai 1988). In Tunisia, use of fenitrothion during the 1988 anti-locust campaign wiped out large numbers of honey bee colonies. Apiculture is an important sector of the economy and bees are also important pollinators of fruit trees. Heavy cattle and sheep losses were also reported as a result of the spraying programme (Greenpeace International and the Pesticides Trust 1993).

10. CONCLUSIONS

The Barcelona Convention Land Based Sources Protocol has black listed OP compounds, with the exception of those which may be considered to be biologically harmless or which are rapidly converted to biologically harmless substances. More specifically, Contracting Parties have agreed to ensure that products containing OP compounds shall not be used in their territory unless it is proved that there is no direct effect on human and animal health or unacceptable impact on the environment. There is no scientific certainty that any of the OP compounds are environmentally benign. A previous report submitted by Greenpeace to the Barcelona Convention in May 1991 highlighted problems of OP pesticide contamination in the environment. The evidence discussed in this report has demonstrated that there are human health problems associated with exposure to OP pesticides.

The major health problem with OP pesticides is neurotoxicity. The available data suggest that acute OP poisoning can result in long-term neurological effects (e.g. OPIDN), changes in behaviour, a decrease in neuropsychological performance and alterations in EEG (Blain 1992). Moreover, a recent study (Rosenstock 1991) reported that only one episode of acute OP poisoning could result in a persistent decline in neuropsychological functioning.

There is also a growing body of evidence which suggests that low dose chronic exposure to OP compounds can cause adverse effects on the peripheral and central nervous systems. Studies on sheep farmers in the UK and a large multinational epidemiological study by WHO (1993) provide evidence that chronic exposure to OP pesticides in an occupational setting can have adverse neurotoxic effects.

These studies show that the number of people affected by long-term neurotoxic effects after either acute or chronic exposure to OP compounds is much greater than previously thought (e.g. Rosenstock et al. 1991, McConnell et al. 1994, WHO 1993). Individuals may suffer permanently or for many years from such neurotoxic effects since no known therapies are available. The number of individuals affected in the Mediterranean area alone is potentially huge, since so many people are routinely exposed to OP pesticides occupationally and many cases of acute poisonings are recorded annually. The extent of the problem is currently unknown and should be of great concern. In addition, the health of the general population may be threatened by exposure to OP pesticides from contamination of food, air and water.

Implementing reduction strategies to deal with the human health and environmental problems from use of OP pesticides were shown in a previous Greenpeace report to the Barcelona Convention (May 1991) to be essentially unworkable. The only practical solution to the problem is to adopt the precautionary approach and shift agricultural practices to ecological methods.

Greenpeace strongly supports the Mediterranean countries' decision to adopt measures to promote the phaseout of OP pesticides. Greenpeace urges that emphasis is placed on immediately banning the import and use of the most dangerous OP pesticides. At the same time financial and technical support must be provided to train farmers in integrated pest management with an emphasis on non-chemical methods of pest control. This would achieve the direct benefits of protecting the health of occupational workers, the general population and safeguarding the environment.

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ANNEX I

ORGANOPHOSPHATE PESTICIDES COMMONLY USED IN THE MEDITERRANEAN REGION[1] AND THEIR ENVIRONMENTAL AND HEALTH THREATS (numbers refer to corresponding tables on toxic impacts in Annex II)

PESTICIDE	Toxic Highly 1	Moderately 2	Banned In at least one country 3	EU Priority Substance 4	North Sea Priority Substance 5	Leaches to ground water 6	Suspected Carcinogen 7
AZINPHOS-METHYL	•			•	•		
CHLORPYRIFOS		•				•	
DICHLORVOS		•		•	•		•
DIMETHOATE		•				•	
FENITROTHION		•		•	•		
FENTHION		•		•	•		
MALATHION		•					
METHAMIDOPTOS	•		•	•			
PARATHION	•		•	•			•
PHENTHOATE		•					

ANNEX II

ENVIRONMENTAL AND HEALTH EFFECTS OF ORGANOPHOSPHATE PESTICIDES

TABLE 1: ORGANOPHOSPHATE PESTICIDES ACCORDING TO TOXICITY

HIGHLY TOXIC*: tetraethyl pyrophosate [TEPP], dimefox, phorate, disulfoton+, fensulfothion, demeton+, terbufos, mevinphos, ethyl parathion, azinphos-methyl, fosthietan, chlorthiophos, fonophos, prothoate+, fenamiphos, phosfolan+, methyl parathion, schradan, mephosfolan+, chlorfenvinphos, coumaphos, phosphamidom, methamidophos, dicrotophos, monocrotophos, methidathion, EPN, isofenphos,endothion, bomyl, famphur, fenophosphon, dialifor, cyanofenphos, dioxathion, mipafox.

MODERATELY TOXIC*: bromophos-ethyl, leptophos, dichlorvos, ethoprop, demeton-S-methyl+, triazophos, oxydemeton-methyl+, quinalphos, ethion, chlorpyrifos, edifenphos, oxydeprophos+, sulprophos, isoxathion, propetamphos, phosalone, thiometon, heptenophos, crotxyphos, phosmet, trichlorfon, cythioate, phencapton, pirimiphos-ethyl, DEF, methyl trithion, dimethoate, fenthion, dichlofenthion, bensulide, EPBP, diazinon, prophenofos, formothion, pyrazophos, naled, phenthoate, IBP, cyanophos, crufomate, fenitrothion, pyridaphenthion, acephate, malathion, ronnal, etrimphos, phoxim, merphos, pirimiphos-methyl, iodofenphos, chlorphoxim, prpyl thiopyprophosphate, bromophos, tetrachlorvinphos, temephos.

* Compounds are listed approximately in order of descending toxicity. "Highly toxic" organophosphates have listed oral LD50 values [rat] less than 50 mg/kg; "moderately toxic" agents have LD50 values in excess of 50 mg/kg.

+These organophosphates are systemic; they are taken up by the plant and translocated into foliage and sometimes into fruit.

SOURCE: Morgan, D.P., 1989. Recognition and Management of Pesticide Poisonings. United States Environmental Protection Agency (EPA), Washington D.C.

TABLE 2: ORGANOPHOSPHATE PESTICIDES THAT ARE BANNED IN ONE COUNTRY OR MORE BECAUSE OF THEIR THREAT TO HUMAN HEALTH OR THE ENVIRONMENT

Azinphos-ethyl 2; Azinphos-methyl 3,6,9; Carbofenothion 6; Chlorthiophos 7; Demeton (O and S) 2,8,9; Demeton-S-Methyl 5,9; Dialifos (Dialifor) 7,8; Dichlofenthion 9; Dicrotophos 7,9; Disulfoton 2,5,6,9; Endothion 9; Fensulfothion 2; Fonofos 7,8,9; Mephosfolan 6; Methamidofos 1; Methidathion 9; Methomyl 1; Mevinphos 2,6,9,12; Monocrotophos 1; Omethoate 7,8; Parathion ethyl 1; Parathion methyl 4,11; Phorate 2,7,8,9; Phosphamidon 1; Prothoate 7,8; Sulfotep 2,8,9; Sulprofos 7,8; Tetraethylpyrophosphate (TEPP) 8,9,10; Thiameton 9; Triazophos 9; Zinophos 9.

NOTES

1. Pesticides that are covered by or are candidates for the FAO/UNEP joint Prior Informed Consent (PIC) procedure which includes substances banned in five countries or more or are considerd particularly hazardous under conditions of use); 2. Belize; 3. Bulgaria, 4. Ecuador, 5. Hungary; 6. India; 7. Malaysia; 8. Panama; 9. Russia; 10. Thailand; 11. Tunisia; 12. United States of America.

SOURCES: Dinham, B. 1993. The Pesticide Hazard. Zed Books, London. United Nations, 1991. Consolidated List of Products whose Consumption and/or Sale have been Banned, Withdrawn, Severely Restricted or not Approved by Governments. UN, New York.

TABLE 3: ORGANOPHOSPHATE PESTICIDES ON THE EUROPEAN UNION PRIORITY CANDIDATE LIST OF POTENTIAL HAZARDOUS CHEMICALS

Azinphos-ethyl; Azinphos-methyl; Demeton; Dichlorvos; Disulfoton; Fenitrothion; Fenthion; Malathion; Methamidophos; Mevinphos; Omethoate; Oxydemeton-methyl; Parathion ethyl; Parathion methyl; Triazophos.

SOURCE: Comission of the European Union, Substances on the List of 129 substances (Directive 76/464/EEC).

TABLE 4: ORGANOPHOSPHATE PESTICIDES CATEGORISED AS PRIORITY HAZARDOUS SUBSTANCES BY THE INTERNATIONAL CONFERENCE ON THE PROTECTION OF THE NORTH SEA.

Azinphos-ethyl; Azinphos-methyl; Dichlorvos; Fenitrothion; Fenthion; Malathion; Parathion ethyl; Parathion methyl.

SOURCE: Ministerial Declaration, 1993. Third International Conference on the Protection of the North Sea. The Hague.

TABLE 5: ORGANOPHOSPHATES PESTICIDES CLASSIFIED AS PROBABLE OR TRANSIENT LEACHERS

Chlorpyrifos; Dimethoate; Fenamiphos; Oxydemeton-methyl.

SOURCE: Fielding, M., D. Barcelo, A. Halweg, et al., 1991. Pesticides in Ground and Drinking Water. Water Pollution Research Report 27. Commission of the European Communities, Directorate-General for Science, Research and Development, Brussels.

TABLE 6: ORGANOPHOSPHATE PESTICIDES THAT ARE SUSPECTED CARCINOGENS.

Acephate; Dichlorvos; Dimethoate; Methidathion; Methomyl; Parathion-ethyl; Phosphamidon.

SOURCE: US Environmental Protection Agency (US EPA), 1990. List of Chemicals Evaluated for Carcinogenic Potential. US EPA, Washington D.C.

Greenpeace International
Keizersgracht 176
1016 DW Amsterdam
Tel: 31-20-523-6222
Fax: 31-20-523-6200

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