ORGANO-PHOSPHATES

POST 122
note December 1998

Organophosphates (OPs) have been used as insecticides since the 1950s, finding a wide range of applications in both arable and livestock farming. However, recent years have seen concerns intensify over their potential adverse health effects on people (notably sheep farmers) exposed to low doses over long periods of time.

This report summarises the current state of research in this area and examines the issues that arise.

BACKGROUND OF OP USE

OPs were first introduced in the 1950s, but remained second choice pesticides behind organochlorines until concerns over the environmental persistence of these compounds (notably DDT) began to surface in the 1970s. As the use of organochlorines tailed off, OPs became the logical choice to succeed them, and UK sales increased during the mid 1980s (**Figure 1**). Throughout this time OPs became widely used both in livestock and arable farming. However, changes in the regulations on sheep dipping (only those sheep diagnosed as being infected with sheep scab now have to be dipped) mean that sales of OPs in the livestock sector have declined in recent years (Figure 1). Overall, OPs now account for some 38% of total pesticide use globally, although the figure for western Europe is somewhat lower than this (~26%).

FIGURE 1 UK SALES OF OP PESTICIDES

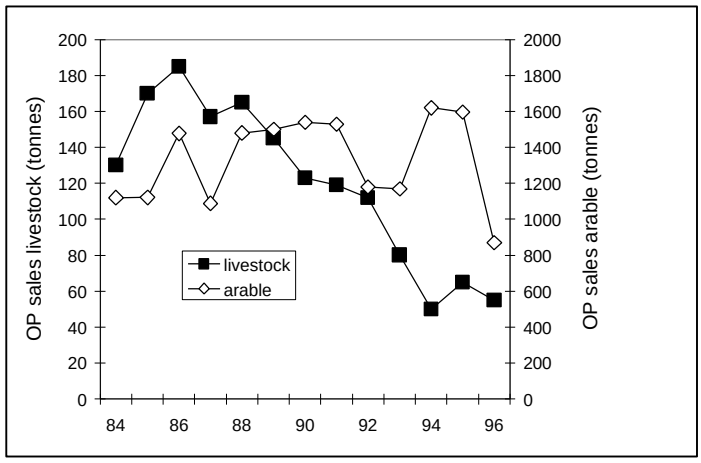


TABLE 1 OPs LICENSED FOR UK AGRICULTURAL USE

Main Use	OP Compounds
General insecticides	azamethiphos, chlorfenvinphos, chlorpyrifos, chlorpyrifos methyl, diazinon, dichlorvos, dimethoate, disulfoton, ethoprophos, etrimfos, fenitrothion, fosthiazate, heptenophos, malathion, mephosfolan, phorate, phosalone, pirimiphos methyl, quinalphos, thiometon, trichlorfon
Fungicides	pyrazaphos, tolclofos methyl
Sheep dips	diazinon, propetamphos

WHAT ARE OPs?

The Main Types of OPs

OP pesticides are part of a larger group of organophosphorus agents designed to inhibit the enzyme acetylcholinesterase (AChE), although recent research suggests that they also act on a number of other types of proteins (**Box 1**). As explained in more detail later, AChE is found in many animals, including insects and mammals (including humans) and plays a vital role in the transmission of messages between nerve cells. Some OPs have been specifically developed to form the basis of nerve agents such as Tabun and Sarin. While OP pesticides are closely related to such compounds and work in much the same way, they are designed to be less harmful to humans and other mammals, and to degrade quickly in the environment.

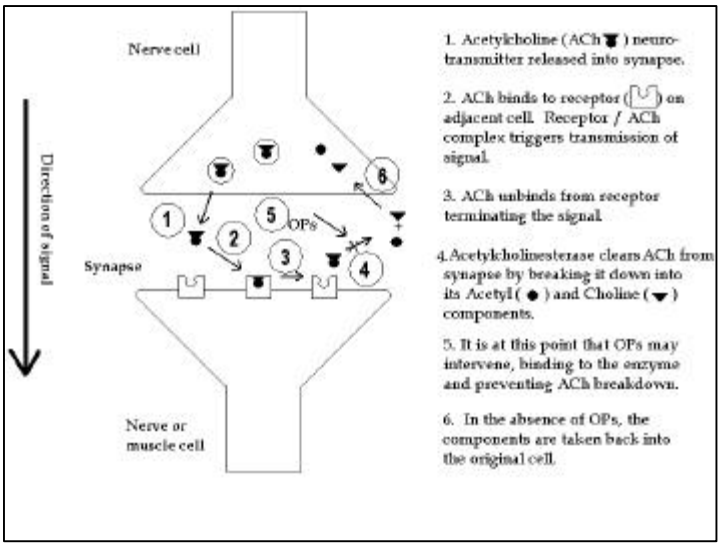
More than 20 different OP pesticides are currently approved for agricultural and horticultural use in the UK, and these are shown in **Table 1** (this list excludes veterinary medicines such as phosmet). Most are general purpose insecticides that are applied to plants to kill penetrating, chewing or sucking insects such as aphids, spider mites, etc. Some of these may also be incorporated into pet collars to control fleas, lice and other parasites. Others are used in other preparations (e.g. domestic, gardening, public health) to control flies, wasps, ants, etc. Only two (diazinon and propetamphos) OPs are currently approved for use as sheep dips although several more have in the past been licensed for this purpose.

OPs are not the only type of chemicals that inhibit AChE - other classes of pesticides (e.g. carbamates) also kill insects through their actions on this enzyme. The Food Safety Minister announced a review of anti-AChE compounds in May 1998, although this excludes veterinary medicines (toxicological information on such products is treated in a confidential manner for commercial reasons). Of the various different types of anti-AChE agents, it is the OPs that are of greatest concern to the general public.

How OPs Work

As noted previously, OPs work through their actions on AChE, an enzyme involved in the process by which messages transmit between nerve cells (and between

FIGURE 2 HOW OPs INHIBIT CHOLINESTERASE



nerve and muscle cells). The process is illustrated in **Figure 2**, which shows how AChE normally acts as the 'off switch' in the transmission of messages across the gaps (synapses) between cells, by breaking down the neurotransmitter (acetylcholine) after it has passed on the message. As explained in more detail in Box 1, OPs disable this enzyme by binding to it, so that transmission between cells continues in an unwanted fashion.

The exact consequences of OP-induced AChE inhibition will depend on a number of factors (see Box 1), but prolonged inhibition may lead to severe disruption of nerve transmission and neuromuscular functions. OPs are also known to inhibit other proteins in the nervous system and brain, including the enzyme neuropathy target esterase (NTE, the normal function of which is unknown).

Current knowledge allows attempts to explain the observed effects of OP poisoning only in terms of their actions on these two enzymes (AChE / NTE). However, as explained in more detail in Box 1, some researchers suspect that OPs may also exert effects on other neurotransmitter systems.

EXPOSURE TO OPs

Crop Spraying

OPs are used as pesticides on a variety of crops and animals so the possibilities for human exposure are many and varied. When used on crops, the main route of exposure for humans is from exposure to OP spray. In practice the risks from this route of exposure in the UK appear to be low, with only one confirmed incident being reported during 1996/97. Pesticides are regulated under the Control of Pesticides Regulations 1986 (see **Box 2**) which prohibit their storage, use, sale, supply or advertisement unless they are approved and certain obligations and conditions are met. The use of hazardous substances (including OPs) is also subject to health and safety legislation including the Control of Substances Hazardous to Health Regulations 1994, which provide measures to:

- assess the potential risks to human health and the environment of all pesticides prior to marketing;
- monitor, prevent or control exposure to pesticides (e.g. by specifying protective clothing, enclosed tractor cabs, etc.);
- protect other people who may be in the vicinity during or after spraying (e.g. by closing access to fields and erecting warning notices).

Sheep Dipping

OPs may be given to animals in various different ways. For instance, vets may give them orally, apply them locally to the infected area (e.g. the treatment of warble fly in cattle involves the local application of the OP phosmet), or inject them. However, safety concerns focus on sheep dips, which can cause poisoning (e.g. through accidental ingestion) or low-level exposure (e.g. via skin contact, either directly with the dip or indirectly through contact with sheep after dipping).

BOX 1 OPs IN THE BODY

OP-protein interactions

OPs are artificial substances that are designed to mimic the shape of certain naturally occurring chemicals (esters) and thus also interact with the enzymes (esterases) that normally process them.

One such system affected by OPs is the acetylcholine (ACh) / acetylcholinesterase (AChE) system (see Figure 2). OPs mimic the neurotransmitter ACh by binding to the enzyme AChE, disabling it for the duration of the binding process. While ACh is normally released very quickly from the enzyme, unbinding of OPs may take hours or days (depending on the type of OP involved). Furthermore, if the OP 'ages' (i.e. loses a chemical group) while it is bound to the enzyme, then unbinding cannot occur and the enzyme is permanently disabled. Some types of OPs are more likely to undergo an aging process than others.

While OP insecticides inhibit the AChE enzyme (this is what they are specifically designed to do), some also affect other esterases. These include NTE (neuropathy target esterase), the function of which is unknown, but is thought to be implicated in normal neuromuscular function. Scientists believe that certain specific OPs that act on NTE can cause some of the nerves needed for sensation and movement to die.

In addition to their actions on esterases, there is also evidence that OPs can interact with other proteins in the body. For instance, studies have shown OPs acting on a range of different receptors (proteins that sit on the outer surfaces of cells and receive in-coming messages) involved in various different biological pathways. Some scientists believe that these proteins may be related to the chronic effects on the peripheral and central nervous system.

OP metabolism

OPs are removed from the body, being broken down mainly by the liver and then excreted in urine. This process is normally rapid and most OPs are broken down over hours or days. A few very fat-soluble OPs may persist longer in body fat but almost invariably long-term or repeated exposure is needed to produce long-term (sustained) esterase inhibition.

Sheep dipping has been common practice since the 1970s to control pests such as sheep scab, lice, ticks and blowfly. Controls on dipping have changed so that now only sheep diagnosed with a pest infection need to be dipped. OPs have been the main pesticides used for such purposes for many years, and their use is strictly controlled (see Box 2). For instance, anyone wishing to purchase OP sheep dips must have a Certificate of Competence, and all dippers have a responsibility to follow the Control of Substances Hazardous to Health Regulations (which cover the design of dipping facilities, protective clothing, disposal of the dip, etc.).

Levels of compliance with these controls are known to be variable and the resulting exposure via skin contact can lead to a set of acute symptoms commonly referred to as dipper's flu (see later). Information on this and other **suspected** adverse reactions (SARs) in humans to veterinary products (dips, vaccines, drugs, etc) is collected by the Veterinary Medicines Directorate (VMD) and figures for 1985-96 suggest that nearly half (48%) of these may have been caused by OP sheep dips. However, the Veterinary Product Committee's Appraisal Panel has been able to fully confirm OP sheep dip as the cause of a suspected adverse reaction in only one of these cases. Trends in SARs for this period are given in **Figure 3** and show a pronounced rise in (unconfirmed) OP-related reports in the early 1990s (coinciding with increased publicity over the health effects of OPs) followed by a more recent decline.

Pesticide Residues

A third potential route of exposure to OP pesticides is via residues in food or drinking water. While individual levels of exposure from such residues may be very low, public health concerns stem from the fact that very large numbers of people may be exposed. Levels of OPs and other pesticide residues in foods are monitored by the Pesticides Safety Directorate (PSD) advised by a Working Party on Pesticide Residues (WPPR) which reports to the Advisory Committee on Pesticides (ACP) and the Food Advisory Committee (FAC). For each approved pesticide, the following may be set:

- an Acute Reference Dose (ARfD), an advisory maximum 'safe level' in a single portion of food;
- an Acceptable Daily Intake (ADI), an advisory 'safe' intake level for consumption throughout life;
- a Maximum Residue Level (MRL), a legal standard representing the maximum level of a pesticide allowed in a food product, set so that somebody consuming a large amount of a contaminated food will not exceed the ADI for that particular pesticide.

The WPPR spends around £1.7M each year analysing pesticide residues in some 2-3,000 food samples involving more than 80,000 tests. In 1997, no residues were detectable in 70% of these tests, while the levels found in a further 29% fell below the MRL. Only around 1% of the tests yielded levels of pesticides exceeding the MRL, a figure in line with those seen in previous surveys. In recent years, OP pesticides have been detected in a number of different foods including:

- Carrots - in the mid-1990s, tests revealed an unexpectedly wide variation in OP residues in carrots, with individual roots exceeding MRLs. More recent surveys confirm that farmers are moving away from the use of OPs on such crops.
- Winter Lettuce - results of surveys since the early 1990s suggest that a minority of UK lettuce growers have used certain pesticides (including an OP fungicide) illegally, resulting in abnormally high

BOX 2 OP LEGISLATION

Different parts of the regulatory system deal with different types of OP products. There are two main categories of agricultural OP products:

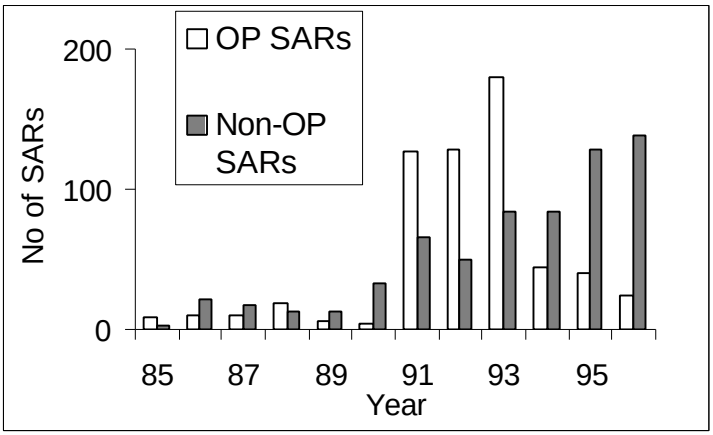
- **Plant protection products** - approved by the Pesticides Safety Directorate (PSD), on behalf of Ministers (who are advised by the Advisory Committee on Pesticides - ACP).
- **Animal (veterinary) products** - approved by the Veterinary Medicines Directorate (VMD) advised by the Veterinary Products Committee (VPC).

OPs also have uses as human medicines (e.g. for eradicating head lice) and such uses are licensed by the Medicines Control Agency, advised by the Committee on Safety of Medicines reporting to DH. Non-agricultural (e.g. public health) applications of OPs (except home garden uses) are licensed by the Health and Safety Executive advised by the ACP, reporting to DETR, DH and MAFF. Other relevant legislation includes:

- The Food and Environment Protection Act 1985;
- The Control of Pesticides Regulations 1986 (as amended);
- Pesticides (Maximum Residue Levels in Crops, Food and Feeding Stuffs) Regulations 1994;
- The Plant Protection Products Regulations 1995 (as amended);
- The Plant Protection Products (Basic Conditions) Regulations 1997;
- The Control of Substances Hazardous to Health Regulations 1994.

In addition, there are various codes of practice to help users to fulfill their legal obligations under the legislation shown above. These codes are not legally binding but may be considered as a statement of what is good practice in legal proceedings.

FIGURE 3 SARs FROM VETERINARY PRODUCTS 1985-1996



levels on some lettuces. Although the WPPR emphasised that the levels detected did not pose a health risk, several growers have been prosecuted. More recent (1996/97) surveillance has shown improvement but some misuse is still being detected.

- Infant Food - recent surveys of infant formulae and breastmilk showed no evidence of a range of OPs, although one OP pesticide was detected at low levels in a survey of fruit-based infant foods
- Other foods - low levels of OP pesticides are sometimes detected in foods such as bread, potatoes and broccoli.

Another potential route of exposure is through drinking water, and levels of OPs and other pesticides in water are monitored by the Department of Environment, Transport and the Regions and the Drinking Water Inspectorate. In general however, the fact that OPs are rapidly broken down in the environment makes them less of a problem in this respect than the more persistent pesticides such as organochlorines or pyrethroids.

EFFECTS OF OPs

As discussed in more detail below, scientists agree that single high doses of OPs can cause a number of well established effects in the short-, medium- or long-term (see **Table 2**). However, no such consensus exists regarding the effects arising from lower doses or from long-term (multiple) exposure.

Single High Doses of OPs

A single high dose of OPs can cause immediate **short-term** symptoms (acute syndrome) in humans and animals, typically lasting 1-5 days (but sometimes up to weeks depending on the type of OP and the dose). These symptoms are well characterised and include headaches, eye irritation, tiredness, sweating, muscle twitching, shortness of breath, weakness, memory and concentration problems, anxiety and depression. In severe cases, hospitalisation and immediate treatment may be required to prevent death. These acute symptoms are thought to result from the specific inhibition of AChE by OPs, since research has shown that a more than 30-50% reduction in this enzyme's activity in the blood is sufficient to produce the symptoms described above (see **Box 3**).

This type of exposure to OPs may also cause **longer-term** symptoms associated with various neuropsychiatric conditions. It may also lead to the condition known as 'OP induced delayed polyneuropathy' (OPIDPN), characterised by symptoms such as numbness and weakness in the hands and feet that may develop into a spastic paralysis. Such symptoms may start to occur 10-14 days after exposure to OPs and are thought to result from OP inhibition of the enzyme NTE (see Box 3). Whereas all OPs inhibit AChE, only some also act on NTE, and this means that:

- cases of OPIDPN are generally preceded by the short-term symptoms associated with AChE inhibition (outlined above);
- scientists are able to predict with reasonable accuracy whether an OP will cause OPIDPN by assessing its effects of NTE in animal studies - those shown to cause OPIDPN in such studies are not licensed for use in the UK.

Single high dose exposure can also lead to another class of symptoms that may take up to 4 days to develop. This so-called **intermediate** syndrome is characterised by muscle weakness, especially in the neck and respiratory muscles, and can lead to respiratory failure in severe cases. Although not understood, it is thought that such symptoms are caused by temporary loss of muscle connections, probably as a result of excessive excitation.

Lower Doses / Longer-term Exposure

While the above-described effects of OPs are not contentious, the effects of lower doses (i.e. insufficient to cause acute poisoning) or longer term exposure to OPs is the focus of much research and debate. Studies in this area are hampered by a number of factors - e.g. difficulty measuring actual exposure levels, range of different OPs, length of time between exposure and appearance of symptoms, and the diverse nature of the symptoms.

BOX 3 MEASURING OP EXPOSURE

A number of methods have been developed in order to assess the extent to which an individual has been exposed to OPs. These fall into three main categories:

- Estimates - e.g. deducing the likely exposure from the severity of the symptoms, or from information about the type of OP, concentration/formulation, duration of exposure, etc.
- Measurements of esterase activity in the blood. The drawbacks with this method are that the observed levels ideally should be compared to a pre-exposure sample from the same individual (since normal esterase levels vary greatly between people), and that measurements on blood do not necessarily correlate to the inhibition levels inside the central nervous system. In addition, such tests reveal nothing of the effects on other OP targets such as NTE.
- Measurements of OP breakdown products in urine. This method is more sensitive than blood esterase tests for determining if exposure has occurred, but less accurate at assessing the extent of exposure.

TABLE 2 TYPES OF EXPOSURE AND CONDITIONS

Condition	Exposure	
	Single high dose	**Multiple/low dose**
Short-term	Acute syndrome	Dippers flu
Medium-term	Intermediate syndrome	
Long-term	OPIDPN / other chronic effects	Chronic effects?

Information on potential chronic effects comes from three main sources. First, are epidemiological studies of people whose occupation exposes them to OPs (sheep dippers, orchard sprayers, etc.). There are many such studies but their quality varies considerably and, evaluating the relative merits of each involves assessing them against a number of criteria (**Box 4**) concerning study design, size, adequacy of controls, etc. The nature of such studies means that even where they are well designed, they will not deliver proof of cause and effect. Rather, they indicate whether or not there is a statistical link between OP exposure and the outcome(s) measured (symptoms, performance in neurological tests, etc.).

Second, are clinical reports on patients with histories of OP exposure. These are often published as case studies in the medical literature, usually involving small numbers of people. They allow an insight into the types of symptoms/conditions suffered by such people but, again, proof of causation is not always easy. Third, are studies on the effects of OPs on the central nervous system of animals. Such studies are still at an early stage, but may eventually provide a more fundamental understanding of OP action at the molecular level.

Recent years have seen several comprehensive reviews of these various sources of information that attempt to clarify the question of whether low-level, long-term exposure to OPs is linked with adverse effects on human health. These are summarised in **Table 3** and include reviews by the Medical Research Council (MRC), a joint review by the Royal College of Physicians and the Royal College of Psychiatrists (RCPs), as well as reviews by individual specialists.

Conclusions from these reviews vary. In their most recent report (November 1998) the Royal Colleges of Physicians and Psychiatrists[1] were not asked to directly address the issue of cause and effect, but rather to advise on clinical management of patients with symptoms that **may be** attributable to chronic OP sheep dip exposure. They called for specialist treatment centres to be set up in appropriate areas and recommended that GPs should be informed about the symptoms associated with OP sheep dipping, classifying these into four categories:

- behavioural and cognitive complaints - e.g. loss of concentration and poor memory;
- affective disturbances - e.g. anxiety, irritability, depression and suicidal feelings;
- chronic fatigue;
- neurological complaints e.g. muscle twitching or weakness, headaches, dizziness, abdominal pain and sweating.

BOX 4 EVALUATION OF SCIENTIFIC STUDIES

Evaluation of the merits of scientific research is crucial to resolving the question of whether OPs have long-term effects in humans after chronic exposure. Among the main criteria by which studies may be judged are:

- **Adequacy of controls** - does the study include an appropriate control (unexposed) group.
- **Sample size/statistical power** - does the study include sufficient people to give statistically meaningful results.
- **Selection bias** - are the people selected for study representative of the population under study, or has the selection process introduced some form of bias.
- **Overall study design** - there are pros and cons associated with the various different study designs. For instance, case studies tend to involve very small numbers and are less powerful than larger cross-sectional studies. However in both cases, assessment of exposure is retrospective. Studies that follow people over long periods of time (longitudinal studies) get round this problem, but obviously have the disadvantage of taking many years to complete.

TABLE 3 SUMMARY OF REVIEWS OF CHRONIC OP EXPOSURE

Review	Comments
MRC (1998)	6 epidemiological studies selected as being the most reliable. Conclusion was that any positive effects of OPs as a class were small enough not to be subjectively apparent.
Jamal (1997)	16 studies selected investigating neuropsychiatric effects. Conclusion was that long-term exposure is potentially serious and a growing concern.
RCPs (1998)	Examined evidence on OP sheep dips from sufferers, support groups and doctors. Concluded that these patients were often seriously ill, that existing NHS services were unsatisfactory and that proper treatment was essential.
Davies (1995)	Concentrated on reviewing the effects on mental health from 46 studies and first-hand experience. Concluded that there was sufficient evidence for OPs causing severe effects on mental health.
COT (1999)	Review of all available evidence due next year.

The MRC review[2] (May 1998) did address the issue of cause and effect, and looked at all the available evidence in the literature. Of all the epidemiological studies reviewed, just 6 were considered to be sufficiently powerful and reliable (see Box 4). Only one of these (considered to be the best designed study[3]) showed small but significant long-term effects, with sheep dippers performing less well in tests of reaction time, neurological performance and reasoning compared with a matched group of quarry workers. MRC concluded that this study "*provides clear evidence of subtle, low-level cognitive differences between two study groups, which may be linked with one having an occupation that involved exposure to OP pesticides*". Taking the totality of the evidence into account (e.g. including the lack of observed effects in well designed studies using less sensitive clinical measures), the review concluded that chronic exposures "*are not likely to be responsible, in themselves, for any adverse health effects large enough to be subjectively apparent*".

[1] Report of a Joint Working Party of the Royal College of Physicians and Royal College of Psychiatrists, 1998. RCP, London.

[2] Ray, D, 1998. MRC Institute for Environment and Health, Leicester.

[3] Stephens, R *et al*, 1995. HSE Contract Research Report 74/1995, HSE Sheffield.

Other reviewers - for instance Jamal[4] and Davies[5] - have also considered a range of evidence from clinical, animal and epidemiological studies. While acknowledging weaknesses in some of the studies considered, both reviews drew stronger conclusions than the MRC. Thus Jamal identified 16 studies investigating possible links between low-level exposure to OPs and chronic neuropsychiatric effects, noting that only 3 of these failed to find such effects, compared with 13 studies where effects were observed. Furthermore, he considered that studies showing such effects were "*generally of a better design and higher quality*" than those giving negative results. Overall, Jamal concluded "*there seems to be a reasonable case for the existence of*" neurological/neurobehavioural effects arising from chronic exposure to OPs.

The Davies review included detailed consideration of clinical studies, focusing in particular on low-level exposure to OPs as a potential factor behind affective disorders (depression, mood swing, anxiety, etc.) and suicide. It concluded that "*there appears to be ample evidence from the molecular to the population level to suggest that long-term exposure to OP pesticides has a profound and deleterious effect on mental health*". A key theme of both the Davies and Jamal reviews was that studies on mental ill-health in OP exposed individuals have tended to be discounted because they are not readily explained in terms of OP interactions with esterases such as AChE and NTE. All three (Jamal, Davies and the MRC) reviews cited animal studies suggesting that OPs may act on other targets (e.g. enzymes, receptors) within the central nervous system, and pointed to these interactions as being the most likely mechanism behind the claimed effects on mental health.

Thus, while none of the reviews rejects the idea that that OPs can cause chronic adverse health effects in humans, there is still disagreement over the seriousness of such effects. This will be one of the main factors considered by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in its current evaluation of the evidence (due in Spring 1999).

Dipper's Flu

OPs may also cause a variety of flu-like symptoms (headache, fever, aching, etc.) - the dipper's flu mentioned earlier - that can sometimes occur immediately after a bout of sheep dipping and may persist for several days. Many of the people suffering from chronic conditions registered on the OPIN database recall such symptoms, although few experienced the acute syndrome discussed earlier. The biological basis by which OPs might cause such symptoms is not understood, although some scientists believe the condition represents a 'watered down' version of the acute syndrome.

ISSUES

It has long been accepted that single, large doses of OPs cause adverse health effects in humans, and such effects are relatively well characterised and understood. They are thought to arise largely through the actions of OPs on esterases such as AChE and NTE, and cause a range of conditions relating to abnormal neuromuscular function. Current regulations are largely aimed at preventing/minimising such effects by limiting exposure from sheep dipping, crop spraying, etc.

However, the question as to whether OPs cause chronic adverse health effects remains unresolved. Some experts see ample evidence of a link between OPs and psychiatric conditions such as suicide, anxiety, depression, etc., suggesting that they cause these effects through their actions on neurotransmitter/receptor systems. Others are less convinced, arguing that there is little hard evidence to support such a link and that any effects that do occur are too small to be of much significance. Given that chronic effects are, by their very nature, difficult to study, it is perhaps not surprising that the scientific evidence in this area is open to different interpretations. While this question will ultimately be resolved only through further research, the continued uncertainty raises a number of other important issues concerning the extent of the risk to public health and the best ways of reducing exposure to OPs.

Assessing the Risks

Concern over the possible chronic effects of OPs has prompted a number of recent developments. To ensure **effective co-ordination** between Government departments a Group on OPs was convened in autumn 1997, consisting of high level officials from all appropriate departments and agencies (MAFF, DH, DETR, HSE, VMD, PSD, Medicines Control Agency, Cabinet Office, Ministry of Defence, Welsh Office, Scottish Office and the Department of Agriculture Northern Ireland). This Group's 1998 Report to Ministers[6] considered the MRC review on the health effects of OPs, and recommended that it receive detailed consideration by the COT. It posed a number of specific questions for COT including:

- What evidence is there that people can develop chronic symptoms to low level exposure to OPs?
- Does the Committee agree that a number of the

[4] Jamal, GA, 1997. Adverse Drug Reactions and Toxicology Review, 16 (3) **, 133-170**

[5] Davies, DR, 1995. Journal of Nutritional and Environmental Medicine, 5, 367-374.

[6] Group on OPs, 1998. Report to Ministers, MAFF, London

studies discussed in the MRC Report had methodological flaws? If so, what were the flaws and how serious were they?

- Is it possible, nonetheless, to deduce anything from these 'flawed' studies?
- Does the Committee agree with the evaluation of the studies selected by the MRC as being most reliable?
- Is it possible that the chronic symptoms and signs from low-level exposure could be different from delayed symptoms from acute exposure?
- Have the epidemiological studies that have been carried out on the effects of low-dose exposure to OPs been of the right design and of sufficient statistical power to detect a biologically significant effect?
- Are there indications of possible mechanisms other than the inhibition of AChE at work?
- Is it the Committee's view that the animal models being used to investigate mechanisms of effects of OPs are the right ones to predict how OPs will affect humans?

The Group also expressed a wish to see the MRC review referred to other Committees with appropriate expertise such as the ACP, VPC and CSM, and it is anticipated that the various Committees will report to Ministers shortly after they receive the COT advice (Spring 1999).

A second recent development was the announcement by the Food Safety Minister of **a review of the safety** of anti-cholinesterase compounds in May 1998. This will involve the PSD reviewing all agricultural products (including OPs and carbamates) licensed for agricultural use and HSE assessing other such products (veterinary medicines such as sheep dips are excluded from these reviews but are subject to on-going reviews by the VPC). The deadline for admission of data is September 1999. Following evaluation the ACP will consider the results of this review and advise Ministers accordingly with possible outcomes including:

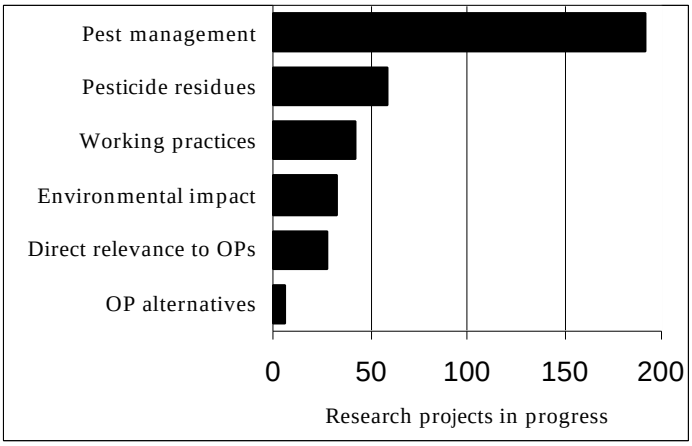
- revocation of licenses (if significant concerns are identified), either entirely or for specific uses;
- amendments to the conditions of approval;
- additional studies may be required.

Research Issues

While the reviews and re-evaluations outlined above may help to clarify the situation, they are unlikely finally to resolve the issue of whether OPs cause long-term adverse effects. However, this question may be informed by a number of current or proposed studies:

- An Institute of Occupational Medicine study jointly commissioned in 1995 by HSE, MAFF and DH (due to end in 1999). This is a comprehensive cross-sectional study looking at the effects of chronic OP exposure on a group of farmers matched with suitable controls over a number of years. It aims to determine a method of measuring OP exposure, classify any effects clinically and make a risk assessment.
- A study based in Glasgow which has identified clinical neurological indices that can define ill health caused by chronic OP exposure. These indices are now being used to compare groups of farmers at varying OP exposure levels.
- The MRC Toxicology Unit investigation to identify brain proteins other than AChE and NTE that OPs interact with. Studies to date have identified some potential targets (proteins that bind certain OPs at low doses more tightly than AChE does).
- A proposed questionnaire study on people (who claim occupational exposure to OPs) registered on a database maintained by the OP Information Network (OPIN).

FIGURE 4 GOVERNMENT FUNDED RESEARCH ON OPs



In addition to the on-going studies outlined above, Government funds a wide range of other research on OP pesticides (**Figure 4**) including studies on environmental risks, human exposure, alternatives, etc. For instance, since 1991, MAFF has funded 360 projects on OPs and related issues in disciplines ranging from epidemiology to psychology (including on-going joint research with the Institute of Food Research into the communication of risk and factors determining the perception of risks associated with use of OP sheep dips).

The need for further research is also one of the areas that the inter-departmental Group on OPs asked COT and the other advisory committees to assess in its 1998 Report. While the current concerns have focused on the effects of OPs on the nervous system, there have been suggestions that they may also exert wider effects. For instance, OPs have been suggested as a possible cause of BSE (see **Box 5**), and the Group on OPs have also asked COT and the other Committees to consider whether they may also be linked with impairments of the immune system or with bone disorders.

BOX 5 MIGHT OP USE BE LINKED WITH BSE?

In addition to the documented effects of OPs on esterases there has also been a suggestion that OPs may be the cause of bovine spongiform encephalopathy (BSE), although this goes against the generally held scientific view that BSE is caused by prions. The suggestion is based on:

- evidence that OP usage (specifically phosmet) and BSE incidence are linked (within the UK) in both time and place;
- a biochemically plausible hypothesis for a mechanism by which OPs might cause or predispose towards BSE.

This has been considered by the Spongiform Encephalopathy Advisory Committee (SEAC), which found no reason, based on available data, to provide funding for research into the hypothesis. SEAC argued that any link between OP use and BSE incidence was statistically unlikely, and noted that the hypothetical mechanism lacked any experimental corroboration.

BOX 6 POSSIBLE OP REPLACEMENTS IN SHEEP DIPS

Potential replacements for OP pesticides in sheep dips include:

- Non-OP pesticides such as pyrethroids. However, these do not kill the same broad range of pests as OPs do and thus proved to be relatively ineffective in trials. Another concern is that while relatively harmless to humans, they are extremely toxic to freshwater fish, shrimps, etc. and thus pose a substantial additional environmental risk.
- Vaccines - although vaccines could be used to control pests such as sheep scab, such approaches are still at the research stage and thus not commercially available.
- Biological control of pests using, amongst other things, natural insect attractants or pheromones have been successfully deployed as pesticides in greenhouses. So far they have not been developed beyond enclosed horticulture.

Minimising Exposure to OPs

Scientific uncertainty over the potential chronic effects of OPs raises the question of how best to reduce exposure to these compounds in the meantime. Sheep dippers remain the chief concern, and options here include:

- a moratorium on sheep dipping;
- use of alternative (non-OP) control methods;
- tighter enforcement of existing protection measures.

Proponents of a moratorium point out that New Zealand, Denmark and other countries do not use sheep dips but have no serious problems with pests such as sheep scab. Opponents of such an approach however, point to the potentially devastating economic implications for farmers of any widespread return of sheep scab. As far as alternative control measures are concerned, there are several potential approaches (outlined in **Box 6**) although none appears to be an ideal replacement (non-OP pesticides are either ineffective, or too environmentally damaging, whereas vaccines and biological controls are not commercially available). Finally, there are practical limits to the extent to which dipping regulations can be enforced - inspectors can ensure that farmers possess all the protective clothing and equipment, but cannot supervise all dips to make sure they are correctly used.

Other concerns focus on the possibility that the very low levels of OP residues on foods might constitute a long-term risk to members of the public. As outlined earlier, the WPPR monitor levels of OPs and other pesticides in foods to ensure that they stay below safe levels (MRL, ADIs, etc.). Any shift in scientific thinking suggesting that low levels of OPs might be more harmful than previously thought and the implications of this for the various safety levels would need to be considered by the ACP. Under such circumstances, consideration would also have to be given to reducing the overall use of OPs in agriculture. Limiting inputs from pesticides in general is one of the principles of Integrated Crop Management, and the Pesticides Forum (established in 1996) is currently considering ways of promoting the responsible use of pesticides in the UK.

Other Issues

Science (in the form of COT's review of the evidence and the results of on-going research) is not the only factor shaping attitudes and policy to OPs. Recent years have seen several court cases abroad (including one in Hong Kong and one in Australia) where people seeking compensation for conditions they claim to be linked to OP exposure have won damages. A recent UK case where a shepherd claiming to be suffering from fatigue, mood swings, tingling, numbness, memory problems, etc. caused by exposure to OP sheep dips sought compensation from his employers (Lancashire County Council) ended with an out of court settlement of £80,000. Although the lack of a court ruling means that the case has not set a legal precedent, other cases are in the offing. Any legal ruling that low levels of OPs were responsible for such conditions could have significant implications for other employers or for MAFF.

Another problem identified by groups such as OPIN is that GPs do not always have the required expertise to manage patients claiming exposure to OPs, and may not refer such cases to appropriate specialists. OPIN thus sees a need for measures to ensure that such patients are automatically referred to specialists familiar with complaints affecting the nervous system. This proposal is in line with the joint Royal Colleges Report which called for specialist treatment centres to be set up and for GPs to be better informed about OP-related symptoms.

Overall, few doubt that a number of individual sheep dippers and other farmers suffer from symptoms such as depression, mood swings and other ill-defined but debilitating conditions (OPIN currently have over 600 such cases on their database). However, the question as to whether OPs are the cause of such conditions is only likely to be resolved by more research.